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Mind-body medicine and its impacts on psychological networks, quality of life, and health, volume II

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Mind-body medicine and its impacts on psychological networks, quality of life, and health, volume II

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Editorial: Mind-body medicine and its impacts on psychological networks, quality of life, and health, Volume II

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Editorial on the Research Topic
Mind-body medicine and its impacts on psychological networks, quality of life, and health, Volume II

This Research Topic is the second volume of the series "*Mind-body medicine and its impacts on psychological networks, quality of life, and health*" (Schulz et al., 2023a,b).

The improvement in living conditions, particularly in industrialized countries, has resulted in a substantial increase in life expectancy over recent decades. Concurrently, the prevalence of chronic diseases is escalating. These include cardiovascular diseases, chronic pain, inflammatory bowel diseases and cancer. The manifestation and chronification of disease is precipitated by a combination of detrimental lifestyle factors, including but not limited to: cumulative stress, inadequate exercise, and suboptimal nutrition. These factors, when compounded by an imbalance between exertion and recovery, can have a profound impact on health outcomes. There has been a marked increase in the level of awareness regarding the interconnection between the human mind, emotional state, lifestyle choices and physical health. The understanding of body and mind interaction is increasing, and this is supported and confirmed by evidence demonstrating a high level of clinical relevance. The development of mind-body medicine (MBM) is intimately associated with this field of research.

MBM is a holistic approach that integrates psychological and physical methodologies with the objective of enhancing health and wellbeing. This field encompasses practices such as meditation, yoga, and biofeedback and many more, which aim to enhance the mind's capacity to affect bodily functions and symptoms. Recent research has demonstrated that MBM can significantly influence neural networks, leading to improved mental health outcomes. The efficacy of these practices in reducing stress, anxiety and depression has been demonstrated, thereby enhancing overall quality of life. Moreover, MBM interventions have been demonstrated to exert a favorable influence on physical health, as evidenced by a reduction in blood pressure, enhancement of immune function, and alleviation of chronic pain. MBM offers a variety of benefits for mental and physical health. Some of the main ones are stress reduction, improved mental health, increased quality of life, physical health benefits, promoting self-awareness and takes a holistic approach to health promotion, addressing both the mind and body for more comprehensive healing.

The MBM approach is predicated on the premise that there is an interplay between the body, mind, emotions and behavior. This interplay extends to the regulation of vegetative physiological signaling pathways. The objective of MBM is to utilize scientifically-based knowledge on the interactions between the body, mind and emotions to promote salutogenetically-based resources. In this theoretical framework, the body, mind and emotions are regarded as operating in unison, with illnesses being conceptualized as inducing a state of imbalance within complex bio-psychological systems. A fundamental tenet of MBM emphasizes the necessity for lifestyle modifications. The psychological aspects of MBM have been demonstrated to exert an influence on lifestyle factors, and thus exert an indirect effect on a wide range of areas of the mind-body connection. A range of techniques are employed within MBM, including but not limited to: mindfulness-based stress reduction, meditation, active movement, relaxation, mindfulness, stress management, relaxation and habits of perception and evaluation. These interventions are designed to target multifaceted bio-psychological and social systems, encompassing diverse domains of lifestyle, with the objective of enhancing self-efficacy and promoting health. The therapeutic approaches employed by MBM comprise a variety of methods that frequently facilitate the provision of cost-effective preventive or therapeutic options. As demonstrated by the existence of relevant evidence-based data, this field has the potential for significant scientific and clinical growth in relation to lifestyle change and the prevention of some of the most significant health issues. MBM interventions are employed within both conventional medicine and complementary medicine, with their application arising from emotional, mental, social, spiritual and behavioral factors. These treatments are also often combined to influence health. The analysis of these signaling pathways has revealed three distinct mechanisms: structural, dynamic and regulatory. The information transfer in both healthy and diseased states provides insights into the physiological structures and functions of the whole integrated system, with its different types of interaction (Schulz et al., 2018, 2019).

The second volume of the series "*Mind-body medicine and its impacts on psychological networks, quality of life, and health*" focuses on the evidence-based investigations on physical exercise, integrative strategies for self-care, applications from traditional Chinese medicine, hypnotherapy, Ayurveda, relaxation, meditation methods, yoga practice, qigong, tai chi, biofeedback interventions, implementation of digital health tools, evaluation of behavioral change techniques, mindful stress relief, cognitive restructuring, autogenic training, and health-impacting social support. The present Research Topic has amassed a wide array of research content, encompassing multidisciplinary contributions within the domain of MBM. This includes comprehensive data analysis and clinical practice applications. The present volume II includes 40 articles and comprises 26 original research articles, one methods article, one hypothesis and theory article, two perspective articles, one mini review and 9 systematic reviews. Participating journals were Frontiers in Integrative Neuroscience, Frontiers in Behavioral Neuroscience, Frontiers in Medicine, Frontiers in Network Physiology, Frontiers in Psychiatry, and Frontiers in Public Health.

The content of the second volume of the series "*Mind-body medicine and its impacts on psychological networks, quality of life, and health*," can be clustered within four main categories.

Interventions for mental health and wellbeing: This category comprises studies that investigated diverse interventions or factors that significantly influence mental health, emotional states, stress, and overall wellbeing, frequently incorporating a mind-body component or emphasizing resilience. The following key issues were addressed by this category: physical exercise and emotional wellbeing; self-reflection and stress reduction; integrated physical-mental therapies; mindfulness and wellbeing in adolescents; mindful movement for mental health; Yoga for stress and emotional wellbeing; mind-body exercises and quality of life; creative arts and emotional regulation; patient consciousness in therapy; health and wellness coaching; and group meditation for public health.

Specific conditions and symptoms: depression, anxiety, stress, and fatigue: This category encompasses studies that addressed specific mental health disorders or key symptoms, frequently exploring their prevalence, interconnections, risk factors, or targeted interventions. The following key issues were addressed by this category: The following studies have been conducted on the subject of cancer-related fatigue and stress: eurythmy therapy, activity-based stress release, psychosomatic health in students, depression in cancer patients, automated stress detection, sex differences in diabetes patients' symptom networks, anxiety, depression, sleep in university students, BMI and depressive symptoms, mental health literacy and psychological status, Traditional Chinese Medicine (TCM) and depression, adolescent suicide attempters, exercise for COVID-19 patients' mental health, and mind-body therapies for adolescent depression.

The connection between physical health, pain and quality of life and mental health: This category includes studies that focused on physical wellbeing, pain management, and general quality of life, often exploring their connections to psychological factors, social support, or mind-body interventions. The following key issues were addressed by this category: sleep duration and chronic musculoskeletal pain, Tai Chi vs. water aerobics and brain connectivity, social support and quality of life in cancer patients, health-related quality of life assessment in alopecia areata, placebo effects and appetite/satiety, physiological markers for social and physical pain, social alienation and emotional intelligence, placebo in mindfulness-based interventions for pain, exercise enjoyment in overweight/obese individuals, breakfast consumption and handgrip strength, Qigong for COVID-19 rehabilitation, mind-body exercise for stroke patients, outdoor interventions for myopia, and inter-organ regulation of affective states.

The connection between physical and mental health in an educational context: This category specifically includes studies in which the study population is comprised of students, often addressing their unique challenges, academic expectations, or specific interventions relevant to their developmental stage. The following key issues were addressed by this category: doctoral students' expectations, physical exercise and emotional states in university students, mindful movement for kinesiology and sport students, psychosomatic health in TCM university students, Yoga for university students' wellbeing, mental health symptoms and health-promoting lifestyles in Chinese university students, and Qi states and depression in college students.

Interventions for mental health and wellbeing

Qian et al. investigated the psychophysiological effects of NaiKan Therapy, a self-reflection method, on salivary oxytocin and cortisol release in 60 participants over a period of 5 days. A significant increase in oxytocin levels and a decrease in cortisol levels were observed post-therapy, suggesting that NaiKan Therapy enhances social bonding and reduces stress reactivity. These findings offer novel insights into the neuroendocrine mechanisms of this introspective practice and its potential for improving mental wellbeing. Singh et al. introduced a Budo group therapy for psychiatric in- and outpatients, incorporating martial arts, mindfulness, and breath work to enhance physical and mental health. Over a 14-month period, 215 individuals participated, demonstrating good retention and high self-reported satisfaction, motivation, and improved physical and psychological wellbeing. The study concludes that Budo group therapy is a feasible, well-accepted, and promising transdiagnostic treatment approach that combines physical activation with resilience enhancement for a broad spectrum of mental health needs. Ecker et al. investigated the immediate effects of a single mindfulness intervention on healthy adolescents aged 12–19, using both subjective and physiological measurements. Contrary to the prevailing expectations, no significant immediate improvements in wellbeing, state mindfulness, heart rate, or heart rate variability were observed in comparison to an active control group. However, the findings indicated that a generally mindful attitude (trait mindfulness) was positively correlated with better subjective wellbeing and reduced mental burden in this age group, suggesting its potential as a resilience factor. Spaccapanico Proietti et al. evaluated the short-term impact of an 8-week mindful movement programme (Movimento Biologico) on 38 Kinesiology and Sport Sciences students. The programme led to a marked enhancement in the positive mental health of the participants, as well as in several interoceptive awareness subscales, including emotional awareness. Furthermore, the autonomy subscale of psychological wellbeing demonstrated a significant enhancement, indicating an improvement in body sensation recognition, emotional-physical links, and self-confidence. Castellote-Caballero et al. analyzed, in a randomized controlled trial, the efficacy of a 12-week yoga intervention on stress, emotional wellbeing, and anxiety in 129 university students. The experimental group demonstrated significant enhancements in perceived stress, emotional wellbeing, and both state and trait anxiety, in comparison to the control group. Their finding indicated that yoga can play a substantial role in the reduction of stress and anxiety, and the enhancement of emotional wellbeing in university students. Yang et al. investigated the impact of mind-body exercises on the quality of life in 1,087 older adults, exploring the chain mediating effects of perceived social support and psychological resilience. They found a significant and positive correlation between quality of life and mind-body exercises. Their findings indicated that perceived social support and psychological resilience exhibited a chain mediating effect, signifying that mind-body exercises enhance quality of life by fortifying these factors. Barnett and Vasiu investigated, in a hypothesis and theory paper, the neural mechanisms of creative arts' therapeutic effects on mental and physical health, with a specific focus on the medial prefrontal cortex (mPFC) and amygdala. Preliminary findings indicate that both active and passive engagement with creative arts consistently activate neural circuits involved in adaptive emotional regulation. The study concludes that creative arts have the potential to function as a complementary therapeutic strategy by engaging shared neural mechanisms with emotional regulation, thereby enhancing understanding of their role in mental health. Shirbache et al. introduced "Ultra-Overt Therapy" (UOT), a novel medical approach that emphasizes patient consciousness and awareness of medication's physiological processes to improve drug efficacy. Their non-systematic review explored evidence from the mind-body relationship, placebo response, neuroscience, and complementary medicine, suggesting theoretical promise for UOT. It is recommended that future research be conducted to ensure a comprehensive understanding of the global impact of this method on medical treatment and patient care. Wolever and Weinand presented the Health and Wellness Coaching (HWC) as an evidence-based approach to address chronic disease, integrating mind-body science and autonomy-promoting lifestyle interventions. The Vanderbilt Health Coaching Program's process is detailed, highlighting the integration of mindfulness, the Wheel of Health, and guided visualization with motivational interviewing. Additionally, structural tools like the Vanderbilt Health Coaching Funnel and IVA Funnel are introduced to foster sustainable behavior change and clarify true coaching strategies. Schneider et al. underscored, in a perspective paper, the pressing need for novel public health strategies to avert collective stress, violence, and war, examining the role of evidence-based meditation from Ayurveda and Yoga in this context. The programme under scrutiny is that of Transcendental Meditation, which has been demonstrated to be effective in reducing collective stress and conflict while improving quality of life, as evidenced by empirical studies across cultures. The mechanisms by which group meditation mitigates collective violence are explored through the lenses of public health models, neuroscience, and quantum physics principles. This suggests that group meditation has the potential to enhance societal wellbeing and peace.

Specific conditions and symptoms: depression, anxiety, stress, and fatigue

Timm et al.b investigated in a prospective observational study the online implementation of eurythmy therapy (ERYT), a mindful-movement therapy from anthroposophic medicine, for cancer-related fatigue (CRF), stress, and mindfulness. Study 1, which utilized a mixed sample, demonstrated enhancements in emotional and physical wellbeing, with a concomitant reduction in stress and an increase in mindfulness. However, the study did not reveal a significant effect on fatigue. Study 2, which focused on subjects diagnosed with cancer, revealed a substantial enhancement in CRF, stress, and mindfulness scores. These findings imply that online ERYT may offer benefits for these indicators in cancer patients and underscore the accessibility advantages of the online format. In another study (Timm et al.a) they appraised the practicability and efficacy of an 8-week online Activity-Based Stress Release (ABSR) programme, a pioneering mindfulness-based intervention (MBI) derived from anthroposophic medicine, on perceived stress and mindfulness. A large-scale observational study with 830 participants was conducted, and the results demonstrated a significant decrease in self-reported stress and a substantial increase in mindfulness scores over the course of the intervention. These benefits were sustained at follow-up. They suggested that this AM-based intervention effectively cultivates mindfulness and is adaptable to an online format, offering a diverse approach within MBIs. Byun et al. evaluated the feasibility of automated stress detection in patients diagnosed with major depressive disorder (MDD), panic disorder (PD), and healthy controls (HCs) using machine-learning algorithms based on heart rate variability (HRV) features. A total of 147 subjects participated in the study, during which HRV data was collected during stress and relaxation tasks. The highest classification accuracies were observed in healthy controls (HCs), however, personalized longitudinal scaling significantly improved accuracies across all groups to over 0.90. They suggested that HRV metrics have the potential to serve as biomarkers of stress; however, the altered autonomic responses observed in psychiatric patients necessitate the development of tailored approaches for stress monitoring. This emphasizes the value of longitudinal scaling for the development of personalized technologies. Wu et al. investigated sex differences in the symptom network structure of depression, anxiety, and self-efficacy among 413 diabetes patients. The prevalence of depression and anxiety was found to be higher in female subjects than in male subjects. The strongest symptom connections exhibited variation by sex; nevertheless, "worry" and "nervousness" were found to be central to both groups. They found a strong negative association between "guilt" and self-efficacy in females, suggesting the need for targeted interventions to promote psychological wellbeing. Jafari et al. investigated, in a cross-sectional study, mental health literacy (MHL) and depression literacy (D-Lit) and their relationship with psychological status and quality of life in 400 Iranian patients with type 2 diabetes mellitus (T2DM). They revealed inadequate levels of MHL and D-Lit, with only 5.8% of respondents answering D-Lit questions correctly. Their findings indicated a robust correlation between low MHL and D-Lit with elevated symptoms of depression, anxiety, and stress, as well as a diminished quality of life. This underscores the imperative for targeted mental health interventions. Tomaszek et al. examined, in a retrospective cohort study, the demographic and clinical profiles of 425 adolescent suicide attempters (aged 11–17 years) who were admitted to an emergency department during the period of the COVID-19 pandemic. The majority of participants were female, aged between 15 and 17, and resided in urban areas. The most prevalent method was self-poisoning, frequently involving antidepressants or paracetamol, followed by self-harm. It is noteworthy that approximately 70% of visits were linked to mental disorders, primarily depressive disorder, thereby underscoring the pandemic's enduring repercussions on youth mental health. Tang et al. assessed, in a systematic review and meta-analysis, the impact of exercise therapy on anxiety and depression in patients with COVID-19. A meta-analysis of six studies involving 461 patients with confirmed cases of the disease found that those who engaged in regular exercise demonstrated significantly reduced anxiety levels, depression levels, PHQ-9 scores, and sleep quality when compared to non-exercising individuals. The research provides evidence that exercise therapy can effectively help patients with confirmed cases of the novel coronavirus (SARS-CoV-2) to experience reduced symptoms of anxiety and depression, and to achieve better sleep quality. Luo S. et al. investigated, in a systematic review and network meta-analysis, the effectiveness of different mind-body therapies (MBTs) in alleviating depression among adolescents. A comprehensive review of the extant literature was conducted, encompassing nine randomized controlled trials with a total of 955 subjects. Their findings indicated that yoga, dance therapy and Tai Chi were more effective in reducing depressive symptoms. Specifically, yoga was identified as the optimal intervention, followed by dance therapy and Tai Chi, demonstrating positive effects on adolescent depression. Moshfeghinia et al. investigated, in a systematic review and meta-analysis, the association between depression and keratoconus (KC), a chronic corneal disease. A comprehensive analysis encompassing 83 KC patients and 3,186 controls yielded a conspicuously elevated depression score in the KC cohort. However, a meta-analysis of four studies comparing depression rates found no increased overall risk of depression among KC patients. Their findings suggest a complex relationship between KC and mental health, warranting further investigation.

The connection between physical health, pain and quality of life and mental health

Li et al. investigated in a cross-sectional study the relationship between sleep duration and chronic musculoskeletal pain (CMP) in 3,904 US adults using NHANES data. The study revealed a U-shaped association, indicating that both short (<7 h) and long (≥9 h) sleep durations were associated with an increased prevalence of CMP, with 7 h of sleep exhibiting the lowest odds ratio. These findings underscore the importance of maintaining optimal sleep duration for the promotion of musculoskeletal health. Port et al. made a comparison between the functional brain connectivity of older adults who practice Tai Chi and those who practice Water Aerobics in a case-control fMRI study. They demonstrated that practitioners of Tai Chi exhibited stronger connectivity in the Salience Network during periods of rest. Furthermore, increased correlations were observed in brain regions associated with memory, attention, and cognitive control during the performance of the N-Back and Stroop tasks. In contrast, the Water Aerobics group demonstrated enhanced connectivity in areas associated with motor actions and object mirroring during the Stroop task, suggesting the presence of distinct neural mechanisms for these activities. Mandato et al. conducted a longitudinal study with a view to evaluating the impact of medical history, perceived physician-patient communication, and perceived social support on quality of life (QoL) in 98 endometrial cancer (EC) patients during their 1st year following surgery. They found that elevated perceived social support was associated with enhanced emotional wellbeing (EWB) at 1 month and 1 year following surgery. Furthermore, support from a significant other was found to be associated with improved physical functioning, reduced pain, and diminished fatigue at 1 year. The study concludes that multifaceted social support is a pivotal factor in bolstering psychological wellbeing and enhancing overall QoL for EC patients, emphasizing its importance in comprehensive care. Muhetaer et al. utilized a network approach to explore the inter-relationship between depression and health-related quality of life (HRQOL) dimensions in 1,735 Chinese cancer patients. The prevalence of depression, a central symptom that manifested alongside symptoms such as nausea/vomiting, pain, and physical function, was found to be nearly two-thirds of patients. The impact of depression on health-related quality of life (HRQOL) is predominantly through its effect on emotional function, pain, physical function and sleeplessness. This underscores the significance of timely treatment for depression in enhancing overall HRQOL. Caldarol et al. conducted a multicentric study with the aim of evaluating the psychometric properties of the Italian Skindex-16AA in patients diagnosed with moderate-to-severe Alopecia Areata (AA). The analysis yielded a two-factor, eight-item structure, designated Skindex-8AA, which exhibited satisfactory psychometric properties, including internal consistency, convergent validity, and test-retest reliability. The Skindex-8AA was proposed as a suitable instrument for the assessment of HRQOL in AA patients. Cui et al. analyzed, in a cross-sectional study, data from 10,686 Chinese adults in order to investigate the relationship between body mass index (BMI) and depressive symptoms. They demonstrated a substantial U-shaped correlation, suggesting that both underweight and obesity elevated the risk of depression. This association was particularly pronounced in younger, highly educated, single, and employed subgroups, suggesting that maintaining a normal body weight is a crucial strategy for preventing depression and promoting overall physical and mental health. Lanz et al. tested the hypothesis, in a double-blind study, if placebo-induced changes in appetite and satiety could influence attentional bias toward food cues in a group of 63 healthy participants. Participants received a placebo capsule with specific expectancy manipulations for enhanced appetite or satiety, followed by a visual probe task to measure attentional bias. The results demonstrated that placebo-induced satiety effectively hindered attention allocation toward food in healthy women, as evidenced by significantly elevated reaction times for food cues in comparison to non-food cues. This process may be mediated by a reduction in hunger and food craving. Lopes et al. examined the role of placebo effects and expectations in mindfulness-based interventions (MBIs) for pain, given their established effectiveness but unclear mechanisms. A total of 19 studies were included in the review, but only a small number of these specifically focused on MBI-related placebo effects. However, the studies indicated a clear role for placebo and expectations in MBI outcomes for both acute and chronic pain. They emphasized the necessity for these factors to be considered routinely in future experimental designs and further research to be conducted in order to achieve a comprehensive understanding of the connection between MBIs, placebo/expectations, and pain relief. Jang et al. (2024) compared multimodal physiological responses to social and physical pain in a group of 73 healthy participants. The study found that social pain induced increased heart rate (HR) and skin conductance, and decreased blood volume pulse, pulse transit time, respiration rate (RR), and finger temperature (FT). The physical pain induced an increase in heart rate variability and skin conductance, as well as a decrease in blood volume pulse and pulse transit time. However, no change was observed in FT. The presence of these distinct patterns indicates that HR, HRV indices, RR, and FT can serve as markers to differentiate physiological responses to social and physical pain stimuli. Diao et al. evaluated the levels of social alienation experienced by patients undergoing peritoneal dialysis. In addition, their investigation sought to ascertain the mediating factors that contribute to this phenomenon, namely personal mastery and perceived social support. The results indicated a mean social alienation score of 42.01 ± 3.15. Elevated emotional intelligence levels were found to be significantly correlated with reduced social alienation. The mediation model demonstrated that personal mastery and perceived social support fully mediated this effect, highlighting their importance for interventions. Luo Y. et al. evaluated and compared, in a meta-analysis, the effects of High-Intensity Interval Training (HIIT) and Moderate-Intensity Continuous Training (MICT) on enjoyment and affective responses in overweight or obese individuals. Including 16 articles with 537 participants, the study analyzed enjoyment using the Physical Activity Enjoyment Scale and affective responses via the Feeling Scale and Felt Arousal Scale. The review concluded that HIIT generally yields a better pleasure response than MICT in this population, though no significant difference in emotional response was found. Ren et al. elucidated, in a systematic review and meta-analysis, the conflicting evidence regarding the association between the frequency of breakfast consumption and handgrip strength, as well as standing long jump. The meta-analysis, which incorporated a total of six studies on grip strength and three on standing long jump, revealed a significant positive association between regular breakfast consumption and higher handgrip strength levels in women, though not in men. No significant differences were observed in standing long jump performance based on breakfast consumption frequency for either sex. Antonelli and Donelli investigated, in a systematic review, Qigong's potential as integrative support for COVID-19 and Long-COVID-19 rehabilitation. The review of pertinent clinical studies revealed beneficial effects of Qigong, an ancient Chinese practice combining movements, breathing, and meditation, on persistent respiratory issues, dizziness, sleep disturbances, and health-related quality of life. Further investigation is crucial to quantify and standardize Qigong's contribution, aiming to integrate this accessible practice into public health strategies and comprehensive treatment regimens. Dong et al. systematically evaluated, in a systematic review and meta-analysis, the effects of mind-body exercise on physical ability, mental health, and quality of life in stroke patients. A total of 33 randomized controlled trials with 1985 participants were included, revealing significant improvements in balance, upper and lower limb motor ability, overall exercise capacity, depression, and quality of life. However, the impact of mind-body exercise on walking ability was not found to be statistically significant. Notably, Qigong (Baduanjin) with specific intervention parameters was found to be particularly effective in improving balance and quality of life. Mei et al. evaluated, in a systematic review, and meta-analysis the overall efficacy of outdoor interventions for myopia in children and adolescents. Analyzing seven randomized controlled trials with 9,437 subjects, the meta-analysis demonstrated significant improvements in spherical equivalent refraction, axial length, and reduced myopia incidence following outdoor interventions. The study concludes that outdoor interventions effectively prevent and control myopia with low risk and high therapeutic benefits, making them a preferred or adjuvant approach to medication. Arinel and Abdelaal synthesized, in a mini-review, empirical finding on the rapidly developing field of inter-organ regulation of affective and internal states, focusing on the bidirectional communication between the brain, gut, and heart. These conserved mechanisms are crucial for aligning reward states with physiological needs, thereby optimizing survival behaviors such as resource acquisition and adaptation. The review under discussion emphasizes the significance of comprehending the mechanisms and circuits of both gut- and heart-mediated reward processes for the purpose of investigating unconscious and conscious reinforcement, affective disorders, and mind-body interventions.

The connection between physical and mental health in an educational context

Stock-Schröer and Lange conducted a cross-sectional survey of doctoral students in medicine and health sciences in Germany online to ascertain their expectations for graduate school, with a particular focus on complementary and integrative medicine (CIM). The participants expressed a primary desire for individual personal support, networking opportunities, and mutual support. Medical students placed a higher value on scientific guidance, while non-medical students indicated a preference for personality development and networking. Doctoral students with CIM topics also expressed a desire for improved final grades, with these results being of crucial importance for curriculum development. Cao and Luo explored in a longitudinal study the causal link between physical exercise and emotional states in 1,215 university students, mediated by Sense of Coherence (SOC). Results showed that SOC significantly predicted positive affect (PA), and PA, in turn, predicted physical exercise. Physical exercise also indirectly influenced PA through SOC, underscoring SOC's vital role in promoting emotional wellbeing and the reciprocal relationship between physical activity and positive emotions. Yi et al. investigated the psychosomatic health of 665 TCM university students, revealing high prevalence of depression (41.65%) and anxiety (36.69%), alongside common somatic symptoms. Network analysis identified "worrying too much," "uncontrollable worries," and "weakness" as central symptoms within the comorbid network. The identification of "little interest or pleasure," "feeling down," "dyssomnia," and "sighing" as bridging symptoms suggests that these are crucial targets for intervention to prevent mutual symptom transmission. Sun et al. employed network analysis to identify core and bridge symptoms within comorbid anxiety, depression, and sleep problems, and to explore their interconnections with health-promoting lifestyles (HPLs) among 3,896 Chinese university students. The study identified "low energy," "daytime dysfunction," and "trouble relaxing" as core symptoms, while "physical activity," "spiritual growth," and "stress management" emerged as key health-promoting behaviors. Their findings indicated that the targeting of these core/bridge symptoms and the promotion of specific HPLs can significantly enhance the mental health of university students. Xinzhu and Yuanchun ascertained the correlations between the following three variables: Qi stagnation, Qi deficiency, and depression levels. The study population comprised 403 college students. Their findings indicated the presence of mild depressive symptoms, low levels of Qi stagnation and deficiency, and a strong positive correlation between the two Qi states. They found a moderate and positive correlation between both Qi stagnation and Qi deficiency with depression, thereby providing support for the traditional Chinese medicine theory and suggesting that physical therapy may be an effective intervention for alleviating symptoms.

In summary, the thematic content and focus of the series was primarily on the following areas: the mind-body connection, mind-body networks and mindfulness-based approaches; mental health and wellbeing (in a general sense and with regard to symptoms); physical health and physiology; social aspects and support; methodology and diagnostics; neurobiological and psychophysiological mechanisms; and specific populations and contexts. The clinical questions focused on specific research questions or hypotheses, such as the effectiveness of interventions, prevalence, associations and correlations, mechanisms and biomarkers, development and validation of measurement tools, and feasibility and acceptability. The diseases/conditions under scrutiny encompassed a wide range of ailments, including, but not limited to, mental health and mood disorders, such as depression and anxiety, stress and panic disorders, suicide attempts, social alienation, affective disorders, and sleep problems. In addition to physical illnesses, the following conditions have been observed: chronic musculoskeletal pain, pain (general/specific), endometrial cancer, cancer (general/Chinese cancer patients), alopecia areata, diabetes (type 2), long-term effects of severe acute respiratory syndrome (SARS-CoV-2) infection, stroke, myopia, overweight/obesity and chronic diseases (general). The studies under review in this series make reference to a number of interventions, including but not limited to mind-body therapies such as Yoga, Tai Chi, Qigong, mindfulness-based interventions, eurythmy therapy, Budo group therapy, NaiKan therapy (self-reflection), dance therapy, transcendental meditation, creative arts, health and wellness coaching, and ultra-overt therapy; physical activity and exercise such as general physical exercise, water aerobics, high-intensity interval training, continuous moderate-intensity exercise, exercise therapy, and outdoor interventions. The following factors have been identified as playing a role in the provision of psychosocial support and lifestyle interventions: social support, maintaining normal body weight, maintaining optimal sleep duration, health-promoting lifestyles, targeted psychological interventions, physiotherapy, placebo effects and expectations (as intervention factors); and technological and personalized approaches, such as automated stress detection and personalized technologies (based on HRV).

The second volume of the series "*Mind-body medicine and its impacts on psychological networks, quality of life, and health*," primarily focused on the mind-body connection and mindfulness-based approaches, examining mental and physical health, social aspects, and related mechanisms. Clinical inquiries addressed intervention effectiveness, prevalence, and underlying mechanisms. A wide array of conditions were investigated, including mental health disorders (e.g., depression, anxiety) and various physical ailments (e.g., chronic pain, cancer, diabetes, SARS-CoV-2 long-term effects). Interventions reviewed encompassed diverse mind-body therapies (e.g., Yoga, Tai Chi, mindfulness), physical activity (e.g., exercise, HIIT), psychosocial support (e.g., social support, lifestyle changes), and technological approaches (e.g., automated stress detection).

Author contributions

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Conflict of interest

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A network approach to investigating the inter-relationship between health-related quality of life dimensions and depression in 1735 Chinese patients with heterogeneous cancers

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Background: We aimed to explore the inter-connection between depression and HRQOL dimensions in cancer patients using a network approach, which might provide new insights for precise interventions to improve cancer patients' overall HRQOL.

Methods: Between June 1, 2016, and August 31, 2017, a total of 1735 eligible patients with heterogeneous types of cancer were recruited. The Zung Self-Rating Depression Scale (SDS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) were used to measure patients' depression status and HRQOL, respectively. A regularized partial correlation network was established. Central and bridge symptoms/functions were identified using expected influence and bridge expected influence. A directed acyclic graph (DAG) was used to explore the possible causal relationship between depression and HRQOL dimensions.

Results: In this study, depression and 15 dimensions of the EORTC-QLQ-C30 scale were highly inter-correlated and could be represented as a network. We found that nearly two-thirds of cancer patients experienced various degrees of depression, and depression was consistently the central symptom in the network, in addition to nausea/vomiting, pain, and physical function. DAG and bridge symptoms indicated that depression might influence overall HRQOL in cancer patients mainly through emotional function, pain, physical function, and sleeplessness, particularly in cancer patients with moderate-to-severe depression. The disparity in network structures between mild and moderate-to-severe depression suggested that the relationship between depression and HRQOL dimensions might be bidirectional.

Conclusion: The prevalence of depression remained high in Chinese patients with cancer, and depression may influence various symptoms and functions within the HRQOL network. Screening and early treatment of depression were warranted to improve the overall HRQOL of cancer patients, in addition to adequate treatment of pain and nausea/vomiting and improvement in physical function.

KEYWORDS

health-related quality of life, depression, network analysis, directed acyclic graph, inter-correlation

1 Introduction

Cancer remains one of the most significant public health issues globally (1). Although the incidence and mortality remain high in most countries, improvements in treatment, cancer prevention, and early detection have led to a growing prevalence of cancer survivors (2). As more and more cancer patients live longer, the health-related quality of life (HRQOL) of cancer survivors has become equally important (3). Multiple factors, including demographic characteristics of cancer patients, cancer type, treatment and its side effects, comorbidity, emotional disorders, social support, etc. may impact the HRQOL of cancer survivors (3–5). Among them, emotional disorders were often overlooked although their prevalence among cancer patients was high (6). Depression was one of the most common emotional disorders among cancer patients (7) with a prevalence of 7.9–32.4% (8). There was a wealth of evidence indicating a strong correlation between depression and overall HRQOL of cancer patients (9, 10). However, HRQOL is a multidimensional construct encompassing multiple symptoms and functions, and these functions/symptoms might correlate and interact with each other. The exact nature of the complex inter-correlations between depression and HRQOL symptoms/functions and their causal mechanisms is still unknown.

Network analysis offers a new perspective in this regard. Network analysis is a method to study the relationships, interactions, and structure of various elements within a system (11). By constructing a symptom network and identifying symptoms with high centrality and their correlation, we may find the most influential symptoms in the network and manage symptoms more precisely (12, 13). In addition, the network analysis can be used to assess the complex interactions between symptoms of comorbid psychiatric disorders (e.g., depression and anxiety) or systems (e.g., quality of life and pain) and identifies the bridge symptoms between them, which are priority targets for clinical intervention (14–16). Network analysis was also applied in psychometric analysis of HRQOL data in previous studies (17–19).

Most network analysis studies used cross-sectional study design and built undirected partial correlation networks, which did not provide information about causal mechanisms. However, recent studies used Bayesian learning and directed acyclic graph (DAG) to explore the potential causal relationships between symptoms (20–23). DAGs can uncover possible directions of conditional dependency relationships between variables and provide important insights into possible causal relationships in cross-sectional designs.

In this study, we aim to investigate the complex interaction between 15 HRQOL dimensions and depression by constructing an HRQOL-depression network in heterogeneous cancer patients, identify the central symptoms/functions in the network and the bridge symptoms/functions connecting HRQOL dimensions and depression, and explore the possible causal relationship between HRQOL dimensions and depression. This may provide implications for precise intervention on the HRQOL of cancer patients with emotional disorders.

2 Materials and methods

2.1 Study settings and participants

All cancer patients who were admitted to the Third Hospital Affiliated to Xinjiang Medical University (Affiliated Cancer Hospital) between June 1, 2016, and August 31, 2017, and who met the inclusion and exclusion criteria were selected as study participants. The inclusion criteria were cancer patients based on clinical diagnosis (breast, colorectal, cervical, gastric, head and neck, esophagus, and lung cancers), aged 18 years or older, and providing written consent. The exclusion criteria were being unable to complete the self-rating scale, incomplete medical records, no evaluation of HRQOL and depression, and written consent not being obtained.

2.2 Data collection

We extracted basic and clinical data from patients' medical records; these data included age, gender, cancer types, time since first diagnosis, tumor-node-metastasis (TNM) staging, treatment received since diagnosis (surgery, chemotherapy, radiotherapy), and comorbidity (type-2 diabetes mellitus, chronic heart disease, and hypertension). In addition, the HRQOL and depression status of patients were assessed using the Zung Self-Rating Depression Scale (SDS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

2.3 Measures

2.3.1 The Zung self-rating depression scale

SDS was developed by William W.K. Zung in 1965 and used to assess an individual's depressive symptoms in terms of emotions, cognition, and physiology through self-reporting. The scale consists of 20 items, with scores ranging from 1 (none or a little of the time) to 4 (most or all of the time). The final index score was converted by multiplying the raw score by 1.25 and then rounding off decimal places. The severity of depression was categorized according to the index score: nil depression (index score < 50), mild depression (index score 50–59), moderate depression (index score 60–69), and severe depression (index score ≥ 70) (24).

2.3.2 The European organization for research and treatment of Cancer quality of life questionnaire

EORTC QLQ-C30 was used to measure the HRQOL of cancer patients. The questionnaire consists of 15 domains, including five functional domains, namely, physical functioning (PF), role functioning (RF), cognitive functioning (*CF*), emotional functioning (EF), and social functioning (SF); nine symptom domains including dyspnea (DY), nausea and vomiting (NV), loss of appetite (AP), fatigue (FA), pain (PA), sleeplessness (SL), constipation (CO), diarrhea (DI), and financial difficulties (FI); and one global health status (QL). A high functional score represents high HRQOL, and a high symptom score indicates severe physical symptoms (25).

2.4 Statistical analysis

2.4.1 Network estimation

The network estimation was completed in R 4.2.1 and the R packages qgraph (26) and mgm (27). We constructed the SDS and HRQOL network which consisted of nodes represented by depression and 15 subscales of EORTC QLQ-C30 using the Gaussian graphical model (GGM) with regularized partial correlations (28). The nodes in the network are interconnected by edges, which signify a regularized partial correlation between two nodes while controlling for all other nodes in the network. Each edge is assigned a weight that is regularized using a graphical lasso (least absolute shrinkage and selection operator, LASSO) to guarantee the high specificity of the connections. This process leads to the creation of a concise and easily interpretable model (29). Thicker edges represent stronger connections, with blue edges indicating positive connection and red edges indicating negative connection. The layout of the presented networks was based on the Fruchterman-Reingold algorithm (30).

To identify the central (influential) symptoms in the network, the expected influence (EI) was calculated. EI is a more accurate centrality measure that represents the cumulative weight of all its edges, accounting for both positive and negative associations with its neighboring nodes in the network. In other words, EI accounts for the sign of the association between two nodes (i.e., negative or positive partial correlation) by summing the absolute values of the edges connected to the node (31). Additionally, the role of symptoms/functions as bridges between depression and HRQOL dimensions was assessed using the bridge expected influence (bEI) of each symptom/dimension. The bEI of a node was determined by summing the edge weights to the nodes of all other symptoms, indicating the importance of an individual symptom in linking different clusters of disorders or systems (32).

2.4.2 Network stability

To assess the accuracy of edge weights, the 95% confidence interval was plotted for each edge in the presented networks, using 1,000 bootstrap samples. The stability of EI and bEI was evaluated by calculating the Correlation Stability (CS) coefficient through a case-dropping bootstrap approach (1,000 times). As per the recommended guidelines (27), an ideal CS coefficient is above 0.5 and should not fall below 0.25. Furthermore, bootstrapped difference tests were conducted for both edge weights, EI and bEI (1,000 times). All these procedures were performed using the R-package bootnet (28).

2.4.3 Network comparison

We investigated whether the network characteristics differed between gender, age groups, TNM stages, months from diagnosis, depression severity, and treatment types. The Network Comparison Test (NCT) was performed to assess differences in the network structure, global strength, and each edge between the two networks using Holm-Bonferroni correction of *p*-values due to multiple tests (33). These tests were performed with the R-package NetworkComparisonTest (34).

2.4.4 Directed acyclic graph

DAG can encode the conditional independence relationships between nodes in cross-sectional data and identify acceptable causal relationships among them. The R package bnlearn and the Bayesian hill-climbing algorithm were used (35, 36). The algorithm calculates the structure of the network model by adding, deleting, and reversing the direction of edges, ultimately optimizing the goodness-of-fit score (i.e., the Bayesian information criterion). To ensure the stability of the resulting DAG, we then bootstrapped 10,000 samples (with replacement). When determining the direction of each edge, if the direction of the directed edge is present in more than 51% of the DAGs in the 10,000 bootstraps, the directional edges would be represented in the final DAG (37).

Statistical analysis was performed using R 4.2.1. Categorical variables were expressed as proportions or percentages. Mean ± standard deviation ($\bar{x} \pm s$) was used to describe normally distributed continuous variables. One-way ANOVA was used to compare normally distributed continuous variables between multiple independent groups, and the Bonferroni method was used for pairwise comparisons. Pearson's correlation was used to examine the relationship between depression severity and HRQOL dimensions. A *value of p* of less than 0.05 was considered statistically significant.

3 Results

3.1 Characteristics of participants

Among 1864 cancer patients who were admitted to The Third Hospital Affiliated to Xinjiang Medical University (Affiliated Cancer Hospital) during the study period, 1735 met the inclusion and exclusion criteria (112 patients refused to participate in the study, and 17 patients had incomplete medical records) and were included in the final analysis. The mean age of the eligible patients was 53.91 ± 11.42 years, ranging from 18 to 85 years, and 67.55% (1,172/1735) were women. A total of 1,217 (70.14%) were diagnosed with cancer for less than 12 months. The most prevalent cancer type in the 1735 patients was breast cancer (26.6%, 462/1735), followed by colorectal cancer (17.1%, 297/1735), cervical cancer (16.5%, 287/1735), gastric cancer (12.5%, 217/1735), head and neck cancer (11.0%, 191/1735), esophagus cancer (10.9%, 189/1735), and lung cancer (5.3%, 92/1735). The characteristics of cancer patients are shown in Table 1.

3.2 Depression and HRQOL subscale scores in patients with seven cancer types

The overall prevalence of depression in cancer patients was 67.3% (1,167/1735). A higher prevalence of depression was observed among patients with cervical (80.5%), esophagus (87.8%), and lung cancers (80.4%). The prevalence of other common symptoms in cancer patients is shown in Supplementary Table S1. The mean scores of SL and FA were higher in all and specific cancer patients compared to other symptoms, indicating they had higher sleeplessness and fatigue burden. The mean scores of EF and SF were lower in all and specific cancer patients compared to other function scores, indicating they had worse social and emotional functions (Table 2). The associations and correlations between HRQOL dimensions and severity of depression are shown in Table 3. All dimensions of HRQOL except DI were

TABLE 1 Basic characteristics of cancer patients (*n*,%).

	Total (*n* = 1735)	Breast (*n* = 462)	Colorectal (*n* = 297)	Cervical (*n* = 287)	Gastric (*n* = 217)	Head and neck (*n* = 191)	Esophagus (*n* = 189)	Lung (*n* = 92)
Sex								
Men	563(32.45)	6(1.30)	175(58.92)	3(1.05)	159(73.27)	35(18.32)	124(65.61)	61(66.30)
Woman	1,172(67.55)	456(98.7)	122(41.08)	284(98.95)	58(26.73)	156(81.68)	65(34.39)	31(33.70)
Age								
<65	1,407(81.10)	424(91.77)	218(73.40)	248(86.41)	157(72.35)	171(89.53)	132(69.84)	57(61.96)
≥65	328(18.90)	38(8.23)	79(26.60)	39(13.59)	60(27.65)	20(10.47)	57(30.16)	35(38.04)
Months from diagnosis, median(range)	3.31[0.66,15.10]	7.93[1.81,27.51]	3.87[0.69,17.41]	1.02[0.20,3.44]	2.59[0.43,7.87]	5.41[0.84,23.43]	2.89[0.49,9.41]	3.36[0.80,14.32]
<12 Month	1,217(70.14)	266(57.58)	203(68.35)	241(83.97)	172(79.26)	125(65.45)	146(77.25)	64(69.57)
≥12 Month	518(29.86)	196(42.42)	94(31.65)	46(16.03)	45(20.74)	66(34.55)	43(22.75)	28(30.43)
TNM Staging								
T1-T2	772(44.5)	296(64.07)	104(35.02)	177(61.67)	52(23.96)	73(38.22)	50(26.46)	20(21.74)
T3-T4	963(55.5)	166(35.93)	193(64.98)	110(38.33)	165(76.04)	118(61.78)	139(73.54)	72(78.26)
Surgery								
Yes	1,183(68.18)	451(97.62)	233(78.45)	108(37.63)	130(59.91)	150(78.53)	84(44.44)	27(29.35)
No	552(31.82)	11(2.38)	64(21.55)	179(62.37)	87(40.09)	41(21.47)	105(55.56)	65(70.65)
Chemotherapy								
Yes	1,254(72.28)	415(89.83)	210(70.71)	187(65.16)	172(79.26)	98(51.31)	100(52.91)	72(78.26)
No	481(27.72)	47(10.17)	87(29.29)	100(34.84)	45(20.74)	93(48.69)	89(47.09)	20(21.74)
Radiotherapy								
Yes	655(37.75)	226(48.92)	57(19.19)	215(74.91)	13(5.99)	51(26.70)	64(33.86)	29(31.52)
No	1,080(62.25)	236(51.08)	240(80.81)	72(25.09)	204(94.01)	140(73.3)	125(66.14)	63(68.48)
Any comorbidities*								
Yes	321(18.50)	56(12.12)	68(22.90)	66(23.00)	48(22.12)	30(15.71)	28(14.81)	25(27.17)
No	1,414(81.50)	406(87.88)	229(77.10)	221(77.00)	169(77.88)	161(84.29)	161(85.19)	67(72.83)
Depression								
No	568(32.74)	217(46.97)	126(42.42)	56(19.51)	61(28.11)	67(35.08)	23(12.17)	18(19.57)
Mild	564(32.51)	165(35.71)	95(31.99)	88(30.66)	64(29.49)	60(31.41)	61(32.28)	31(33.70)
Moderate	465(26.80)	68(14.72)	58(19.53)	115(40.07)	62(28.57)	51(26.70)	77(40.74)	34(36.96)
Severe	138(7.95)	12(2.60)	18(6.06)	28(9.76)	30(13.82)	13(6.81)	28(14.81)	9(9.78)

*Type 2 diabetes mellitus, and/or chronic heart disease, and/or hypertension.

associated with the severity of depression. The severity of depression was positively correlated with all symptom dimensions of HRQOL except DI (r ranged from 0.241 to 0.509, all $p < 0.001$) and negatively correlated with all functions of HRQOL (r ranged from −0.561 to-0.382, all $p < 0.001$).

3.3 Network structure and centrality

As shown in Figure 1A, we constructed a network of 15 HRQOL symptoms/functions and depression and found that depression was negatively connected with EF (weight = −0.22), PF (weight = −0.20), QL (weight = −0.11), RF (weight = −0.08), and SF (weight = −0.07) and positively connected with PA (weight = 0.16), SL (weight = 0.10), AP (weight = 0.09), FI (weight = 0.08), and CO (weight = 0.07) (Supplementary Table S2).

As shown in Figure 1B, NV and PA had the highest positive EI values (1.81 and 1.70, respectively), while SDS and PF had the highest negative EI values (−1.10 and − 1.41, respectively). EF, PF, PA, and SL were bridge symptoms/functions connecting depression and HRQOL dimensions, with bEI of −0.22, −0.20, 0.16, and 0.10, respectively (Figure 1C). Additionally, we also constructed depression and HRQOL dimensions networks among patients with different severity of depression and seven types of cancer, separately (Supplementary Figures S15-S20). NV was consistently the central symptom in patients with mild depression (EI = 1.76), moderate-to-severe (EI = 1.92), and no depression (EI = 1.30).

TABLE 2 Mean scores and SDs of depression and EORTC-QLQ-C30 symptoms/functions scales by cancer type.

Symptoms/ Functions	total (n = 1735)	Breast (n = 462)	Colorectal (n = 297)	Cervical (n = 287)	Gastric (n = 217)	Head and neck* (n = 191)	Esophagus (n = 189)	Lung (n = 92)
Depression	55.66 ± 10.98	51.29 ± 9.90	52.98 ± 10.83	59.72 ± 9.72	57.76 ± 11.49	54.73 ± 11.23	61.20 ± 9.37	59.13 ± 10.18
PF	74.6 ± 17.47	80.09 ± 13.78	76.30 ± 17.03	71.06 ± 16.10	72.23 ± 18.49	77.73 ± 16.89	67.11 ± 20.79	67.05 ± 19.68
RF	79.88 ± 21.34	88.17 ± 18.92	80.25 ± 20.15	75.38 ± 19.02	74.35 ± 22.16	83.17 ± 19.97	72.64 ± 23.10	72.10 ± 25.09
EF	69.83 ± 22.27	75.46 ± 18.88	74.41 ± 22.11	62.40 ± 24.92	68.47 ± 21.16	69.12 ± 22.03	62.79 ± 22.94	69.11 ± 20.77
CF	79.51 ± 15.23	82.83 ± 13.35	81.26 ± 15.14	75.32 ± 16.77	77.50 ± 15.1	81.33 ± 15.21	76.46 ± 16.12	77.54 ± 12.94
SF	69.84 ± 19.15	75.05 ± 19.16	71.66 ± 19.62	66.09 ± 16.57	66.05 ± 17.34	72.00 ± 20.75	64.83 ± 18.58	64.13 ± 19.13
QL	63.61 ± 15.81	68.03 ± 15.86	65.94 ± 14.53	61.13 ± 14.93	59.68 ± 15.02	64.2 ± 17.94	57.51 ± 15.11	62.23 ± 13.04
FA	27.69 ± 19.88	21.57 ± 19.26	24.95 ± 18.37	33.1 ± 19.51	32.67 ± 20.95	25.83 ± 19.34	33.10 ± 18.90	31.4 ± 18.75
NV	6.36 ± 13.50	4.08 ± 10.51	5.11 ± 12.07	8.54 ± 14.87	10.29 ± 17.47	4.89 ± 11.70	7.05 ± 13.21	7.43 ± 16.82
PA	15.63 ± 19.42	9.63 ± 13.86	12.29 ± 17.90	22.42 ± 20.46	16.82 ± 21.46	15.27 ± 20.04	23.1 ± 21.97	17.93 ± 21.00
DY	12.81 ± 19.52	11.54 ± 18.67	11.22 ± 18.00	11.27 ± 18.93	13.06 ± 18.94	11.87 ± 18.70	15.17 ± 22.40	25.72 ± 22.16
SL	34.64 ± 29.69	33.69 ± 28.58	33.11 ± 29.25	32.17 ± 30.64	36.25 ± 29.86	33.86 ± 28.51	40.74 ± 31.39	37.32 ± 30.80
AP	15.73 ± 24.52	8.66 ± 18.42	12.91 ± 21.62	20.33 ± 26.76	25.50 ± 29.66	12.91 ± 24.34	21.34 ± 25.90	17.39 ± 24.45
CO	16.96 ± 25.08	12.34 ± 21.27	16.50 ± 24.83	19.05 ± 26.76	22.12 ± 26.3	14.31 ± 23.04	23.10 ± 29.40	15.94 ± 24.94
DI	6.97 ± 16.15	3.39 ± 10.78	10.89 ± 20.44	10.22 ± 19.41	8.76 ± 17.57	5.76 ± 13.95	5.47 ± 13.73	3.62 ± 11.54
FI	29.03 ± 30.05	20.78 ± 28.48	21.89 ± 26.49	44.13 ± 31.96	33.03 ± 29.4	24.43 ± 28.96	39.86 ± 28.53	24.28 ± 23.23

PF: Physical Functioning; RF: Role Functioning; CF: Cognitive Functioning; EF: Emotional Functioning; SF: Social Functioning; FA: Fatigue; NV: Nausea/Vomiting; PA: Pain; DY: Dyspnea; AP: Appetite; SL: Sleeplessness; CO: Constipation; DI: Diarrhea; FI: Financial hardship; QL: General health status.
Head and Neck*: Nasal cancer; Laryngeal cancer; Thyroid cancer; Oral cancer; Tongue cancer; Lip cancer.

Table 3 Association of depression severity with HRQOL subscale scores in cancer patients.

Symptoms /Functions	No depression	Mild depression	Moderate depression	Major depression	F	P	r
PF	83.59 ± 10.92$^{\dagger\zeta}$	74.80 ± 13.46$^{*\zeta}$	64.25 ± 17.21*†	43.59 ± 21.10$^{*\dagger\zeta}$	535.51	<0.001	−0.561**
RF	89.53 ± 16.16$^{\dagger\zeta}$	79.76 ± 18.85$^{*\zeta}$	68.74 ± 19.82*†	48.41 ± 22.77$^{*\dagger\zeta}$	412.29	<0.001	−0.491**
EF	81.96 ± 16.05$^{\dagger\zeta}$	67.96 ± 19.97$^{*\zeta}$	55.02 ± 21.81*†	42.11 ± 16.62$^{*\dagger\zeta}$	507.57	<0.001	−0.544**
CF	84.92 ± 12.44$^{\dagger\zeta}$	79.42 ± 14.26$^{*\zeta}$	72.47 ± 16.26*†	64.35 ± 15.70$^{*\dagger\zeta}$	246.10	<0.001	−0.382**
SF	78.45 ± 17.49$^{\dagger\zeta}$	67.84 ± 16.99$^{*\zeta}$	60.94 ± 16.66*†	49.09 ± 16.97$^{*\dagger\zeta}$	346.89	<0.001	−0.439**
QL	70.80 ± 14.66$^{\dagger\zeta}$	62.03 ± 13.57$^{*\zeta}$	56.65 ± 13.86*†	44.44 ± 12.16$^{*\dagger\zeta}$	409.42	<0.001	−0.441**
FA	18.03 ± 16.39$^{\dagger\zeta}$	28.02 ± 16.83$^{*\zeta}$	39.42 ± 17.64*†	56.28 ± 16.17$^{*\dagger\zeta}$	466.15	<0.001	0.509**
NV	2.47 ± 8.62$^{\dagger\zeta}$	5.95 ± 12.52$^{*\zeta}$	10.92 ± 15.92*†	21.30 ± 21.36$^{*\dagger\zeta}$	238.74	<0.001	0.331**
PA	6.98 ± 12.50$^{\dagger\zeta}$	15.08 ± 17.14$^{*\zeta}$	26.42 ± 19.94*†	44.91 ± 23.73$^{*\dagger\zeta}$	439.23	<0.001	0.487**
DY	8.67 ± 15.55$^{\dagger\zeta}$	11.90 ± 18.51$^{*\zeta}$	17.72 ± 22.43*†	31.17 ± 25.49$^{*\dagger\zeta}$	121.77	<0.001	0.241**
SL	25.17 ± 26.54$^{\dagger\zeta}$	39.85 ± 29.01*	40.82 ± 30.81*	51.54 ± 31.04$^{*\dagger\zeta}$	137.69	<0.001	0.289**
AP	6.18 ± 15.94$^{\dagger\zeta}$	14.46 ± 22.20$^{*\zeta}$	27.74 ± 27.22*†	51.85 ± 27.85$^{*\dagger\zeta}$	391.53	<0.001	0.294**
CO	10.14 ± 19.02$^{\dagger\zeta}$	15.70 ± 24.32$^{*\zeta}$	24.89 ± 27.84*†	46.60 ± 28.80$^{*\dagger\zeta}$	207.25	<0.001	0.283**
DI	6.27 ± 15.32$^{\zeta}$	6.69 ± 15.46	8.65 ± 18.28*	9.26 ± 18.70	6.51	0.0892	0.076
FI	17.89 ± 26.02$^{\dagger\zeta}$	31.18 ± 29.04$^{*\zeta}$	43.25 ± 30.17*†	50.62 ± 28.64$^{*\dagger\zeta}$	238.55	<0.001	0.367**

* Indicates $p < 0.05$ compared to no depression; † indicates $p < 0.05$ compared to minor depression; ζ indicates $p < 0.05$ compared to moderate depression; * *indicates $p < 0.001$.
PF: Physical Functioning; RF: Role Functioning; CF: Cognitive Functioning; EF: Emotional Functioning; SF: Social Functioning; FA: Fatigue; NV: Nausea/Vomiting; PA: Pain; DY: Dyspnea; AP: Appetite; SL: Sleeplessness; CO: Constipation; DI: Diarrhea; FI: Financial hardship; QL: General health status.

PF was consistently the bridge function connecting depression and HRQOL dimensions in patients with mild and moderate-to-severe depression (Figure 2). Depression was the central symptom in all specific cancer types except gastric cancer. EF, PA, and PF were bridge symptoms connecting depression and HRQOL dimensions in most cancer types.

3.4 Network stability

The case-dropping bootstrap procedure showed that EI and bEI remained stable after dropping different proportions of the sample (Supplementary Figure S1). The CS-C for EI and bEI was 0.75. The

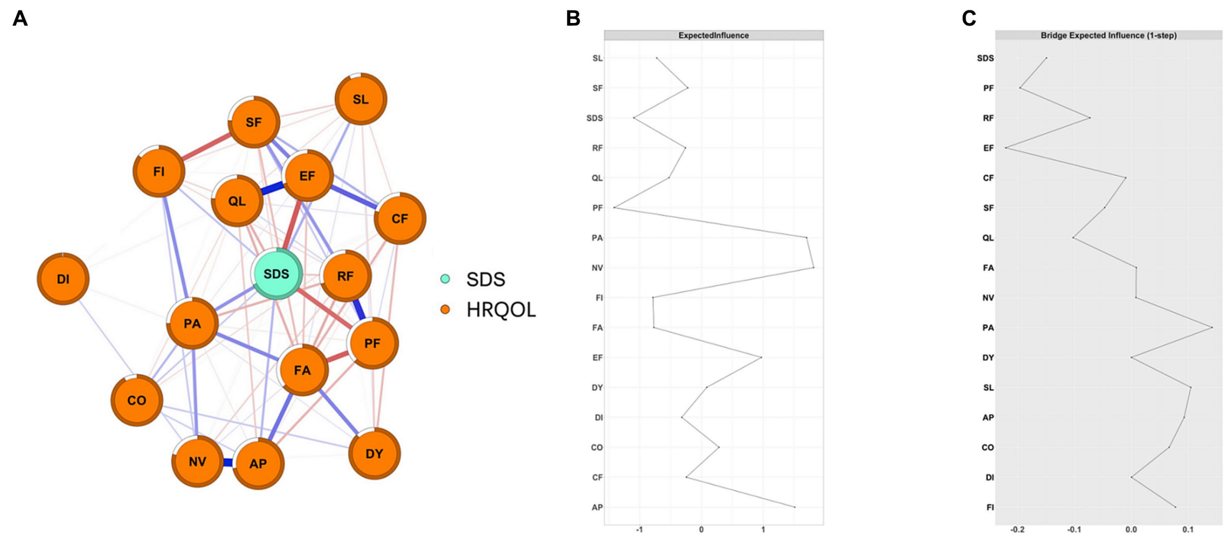

FIGURE 1
The network structure of depression and HRQOL in cancer patients and the EIs and BEIs of the nodes in the network. **(A)** network structure of depression and HRQOL in cancer patients; The blue edge represents positive connections and the red edge represents negative connections; the thickness and saturation of the edge represent the strength of the connection; **(B)** the Centrality plot depicting the Expected Influence of each node in the network; **(C)** the Bridge Centrality plot depicting the Bridge Expected Influence of each node in the networkPF: Physical Functioning; RF: Role Functioning; *CF*: Cognitive Functioning; EF: Emotional Functioning; SF: Social Functioning; FA: Fatigue; NV: Nausea/Vomiting; PA: Pain; DY: Dyspnea; AP: Appetite; SL: Sleeplessness; CO: Constipation; DI: Diarrhea; FI: Financial hardship; QL: General health status).

bootstrapped 95% CIs for estimated edge weights indicated that most edges were stable and accurate (Supplementary Figures S2–S5).

3.5 Network comparison test

The network comparison test showed that the overall network structure was significantly different between patients aged ≥65 years and those aged <65 years (M = 0.215, p = 0.006), while the difference in global strength was not significant (S = 0.447, p = 0.181). We further analyzed the specific edges whose strengths were different between age groups and found that the edge EF-FA was significantly stronger in patients aged ≥65 years than in patients aged <65 (edge difference: 0.22; $p < 0.001$), and other edges such as EF-*CF* (difference: 0.16; $p = 0.007$) and EF-SF (difference: 0.13; $p = 0.019$) were significantly stronger in patients aged <65. No difference was observed between edges involving depression in all age groups (all $p > 0.05$) (Supplementary Figures S6-S14).

Both network structure (M = 0.22, p = 0.003) and global strength (S = 2.54, $p < 0.001$) were significantly different between the mild depression group and the moderate-to-severe depression group (Figure 2). Further analysis showed that the edges between SDS-EF (difference: 0.16; $p < 0.001$), between SDS-*CF* (difference: 0.16; $p < 0.001$), and between SL-FI (difference: 0.18; $p < 0.001$) were significantly stronger in the moderate-to-severe depression group compared to that in the mild depression group. The global strength showed that the network constructed in patients with moderate-to-severe depression was more densely connected compared to that in patients with mild depression.

Neither network structures nor global strengths were significantly different between TNM stages, genders, treatment types (surgery, chemotherapy, and/or radiotherapy), and months from first diagnosis (Supplementary Figures S6-S13).

3.6 Directed acyclic graph (DAG)

Figure 3A displays the importance of each edge to the entire DAG structure. The edges that were most important for the network structure included SDS-PF (with a change in BIC of −373.95), AP-NV (with a change in BIC of −330.54), and SDS-EF (with a change in BIC of −155.93). Meanwhile, the edges that were least important for the network structure included SL-QL (with a change in BIC of 0.07) and SF-QL (with a BIC change of −0.54) (Supplementary Table S3).

In Figure 3B, an edge is thicker if it points from one node to another in a greater proportion of the bootstrapped networks. Structurally, SDS was at the top of the DAG, which directly activated a total of 11 symptoms/functions of HRQOL, including PF (BIC: −373.95; Direction: 0.60), EF (BIC: −155.93; Direction: 0.76), AP (BIC: −45.47; Direction: 0.58), FA (BIC: −31.49; Direction: 0.69), QL (BIC: −19.99; Direction: 0.94), SL (BIC: −18.68; Direction: 0.97), FI (BIC: −13.22; Direction: 0.99), PA (BIC: −12.78; Direction: 0.94), RF (BIC: −8.19; Direction: 0.92), CO (BIC: −5.79; Direction: 0.97), and SF (BIC: −5.77; Direction: 0.93) (Supplementary Table S3).

Using DAG analysis, we further analyzed the potential causal relationship between depression and dimensions of HRQOL in patients with mild depression and moderate-to-severe depression, separately. In patients with mild depression, SDS was downstream of DAG and indirectly activated by FA through AP, RF, and PA. In patients with moderate-to-severe depression, SDS was upstream of DAG and directly activated PA and FA but indirectly activated RF and AP through FA (Figure 4). In patients with no depression, FA was

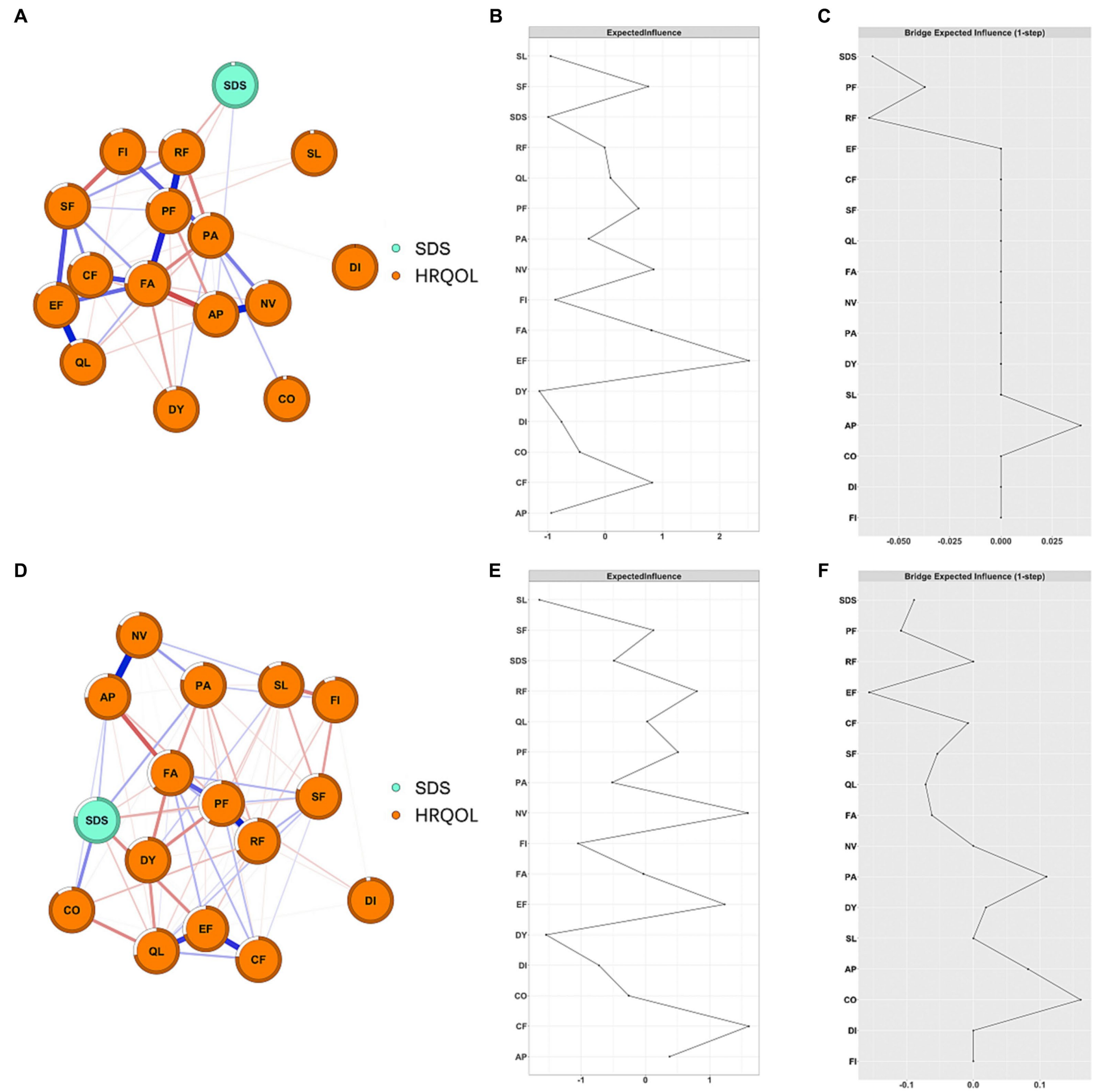

FIGURE 2
Network structure and EI of depression and HRQOL in cancer patients among different severities of depression. **(A)** Network structure of mild depression patients; **(B)** EI of mild depression patients; **(C)** bEI of mild depression patients; **(D)** network structure of moderate to severe depression patients; **(E)** EI of moderate to severe depression patients; **(F)** bEI of moderate to severe depression patients.

upstream of DAG and directly activated PA, QL, NV, AP, RF, SF, DY, and SL (Supplementary Figure S14).

4 Discussion

To the best of our knowledge, this is the first study to utilize network analysis to investigate the interrelationship between different dimensions of HRQOL and depression among cancer patients. In this study, we constructed a depression and HRQOL dimensions network in heterogeneous cancer patients. Our study results showed that depression and 15 dimensions of the EORTC-QLQ-C30 questionnaire were highly intercorrelated and could be represented as a network, indicating the validity of the EORTC-QLQ-C30 questionnaire. Cancer patients may experience symptoms, such as pain, nausea, vomiting, fatigue, loss of appetite, depression, anxiety, constipation, shortness of breath, insomnia, etc. due to cancer itself, its treatment, and co-morbid conditions (38, 39). In this study, we found that NV, depression, and PA were the central symptoms in the network while the PF was the central function, and they remained central in patients with specific types of cancer. In the network structure, nodes with high EI acted as important intermediaries or connectors within the network, facilitating the flow of information, spreading influence, or affecting the overall network structure and function (30). Therefore, NV, depression, PA, and PF may play a crucial role in determining overall HRQOL in cancer patients, which might be important targets for clinical intervention to improve overall HRQOL.

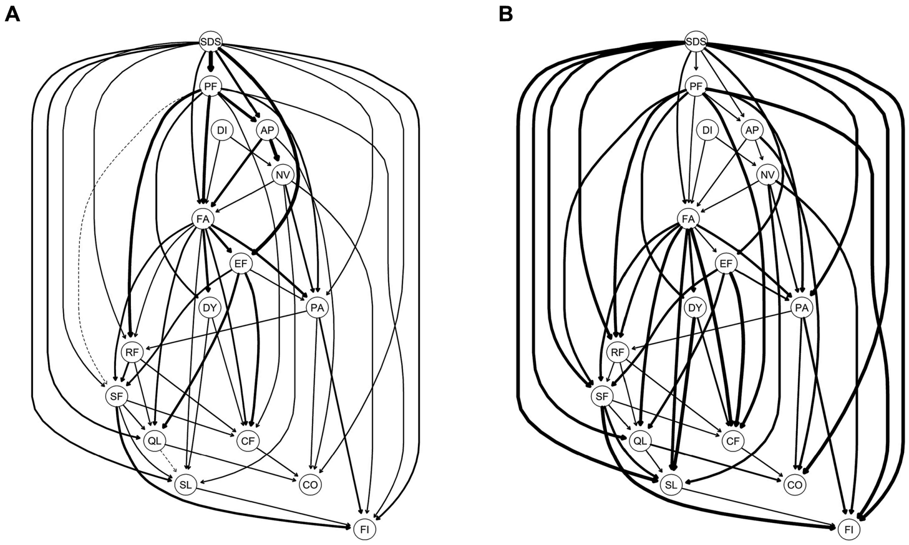

FIGURE 3
Directed acyclic graph (DAG) for symptoms of Quality of Life and depression; **(A)** the edge thickness represents the importance of that edge to the overall DAG structure; **(B)** the edge thickness represents the directional probability. **A**: Presence of edges: Edge thickness indicates the importance of that edge to the overall network structure, with greater thickness signifying that an edge is more crucial to the model fit. Thickness reflects the change in the Bayesian Information Criterion of the model when that edge is removed. For this graph, solid lines represent that the presence of an edge improves the model fit (a dashed line would represent an edge whose presence worsens the model fit). **B**: Direction of edges: the edge thickness indicates directional probability, or in what percentage of the fitted networks the edge went in that direction. Edge thickness is drawn proportionately such that a thicker arrow indicates a higher directional probability. For this graph, a solid line represents that an edge was present in its current direction in at least 51% of the 10,000 bootstrapped networks, while a dotted line represents an edge present in its current direction in less than 51%. For both **A,B**, exact edge weights can be found in Supplementary Table S1 in the supplementary materials.

In our study, 68% of cancer patients had depression, and nearly half of them were moderate-to-severe depression. Furthermore, our study showed that the severity of depression was associated with almost all dimensions (symptoms/functions) of HRQOL in cancer patients except diarrhea; this was similar to results in previous studies (9, 40, 41). However, previous studies did not account for complex interactions between symptoms/functions, and the potential causal association between symptoms/functions was not investigated. In this study, we used EORTC QLQ-C30 questionnaire to assess HRQOL of cancer patients, and we found that depression was the central symptom in HRQOL-depression networks, and EF, PF, PA, and SL were bridge symptoms/functions linking depression and HRQOL dimensions. Additionally, DAG analysis showed that depression was at the top of DAG and directly activated 11 symptoms/functions of HRQOL dimensions, particularly EF, PF, and PA, which further triggered other symptoms/functions of HRQOL. Our study illustrated the direction and pathway of the impact of depression on HRQOL for the first time. These results suggested that screening and early treatment of depression in cancer patients was vital to improve the mental and physical health of cancer patients and improve overall HRQOL.

In this study, we found that the relationship between depression and HRQOL dimensions might be bidirectional. In stratified analysis, depression was downstream of DAG and was mainly activated by RF and AP in patients with mild depression, while depression was upstream of DAG in patients with severe depression, which influenced other symptoms and functions of HRQOL. Recent studies indicated that PA might worsen depressive symptoms in cancer patients (42–44), while treatment of depression might facilitate effective management of pain in cancer patients (45). This indicated that the relationship between PA and depression might be bidirectional. However, this result should be interpreted with caution. Although we used DAG analysis to show the potential direction between symptoms/functions, still the study design we applied was cross-sectional. Therefore, further longitudinal studies are needed to establish a more definitive understanding of the causal dynamics between depression and pain.

5 Limitation

There were several limitations in this study. First, the data we used were all derived from a cross-sectional survey; therefore, the dynamic changes between depression and HRQOL dimensions could not be examined. Second, although we used the DAG network to explore the predictive (and potentially causal) priority of these symptoms, we were unable to establish a definitive causal relationship due to the constraints imposed by our cross-sectional design. Third, the results should be interpreted with caution as the generated networks were based on group-level analysis, and whether group-level results can represent individuals remained unclear. Finally, our study was conducted in a single medical center, which might have selection bias.

6 Conclusion

Our study explored inter-connection, bridge symptoms, and potential causal relationships between depression and different

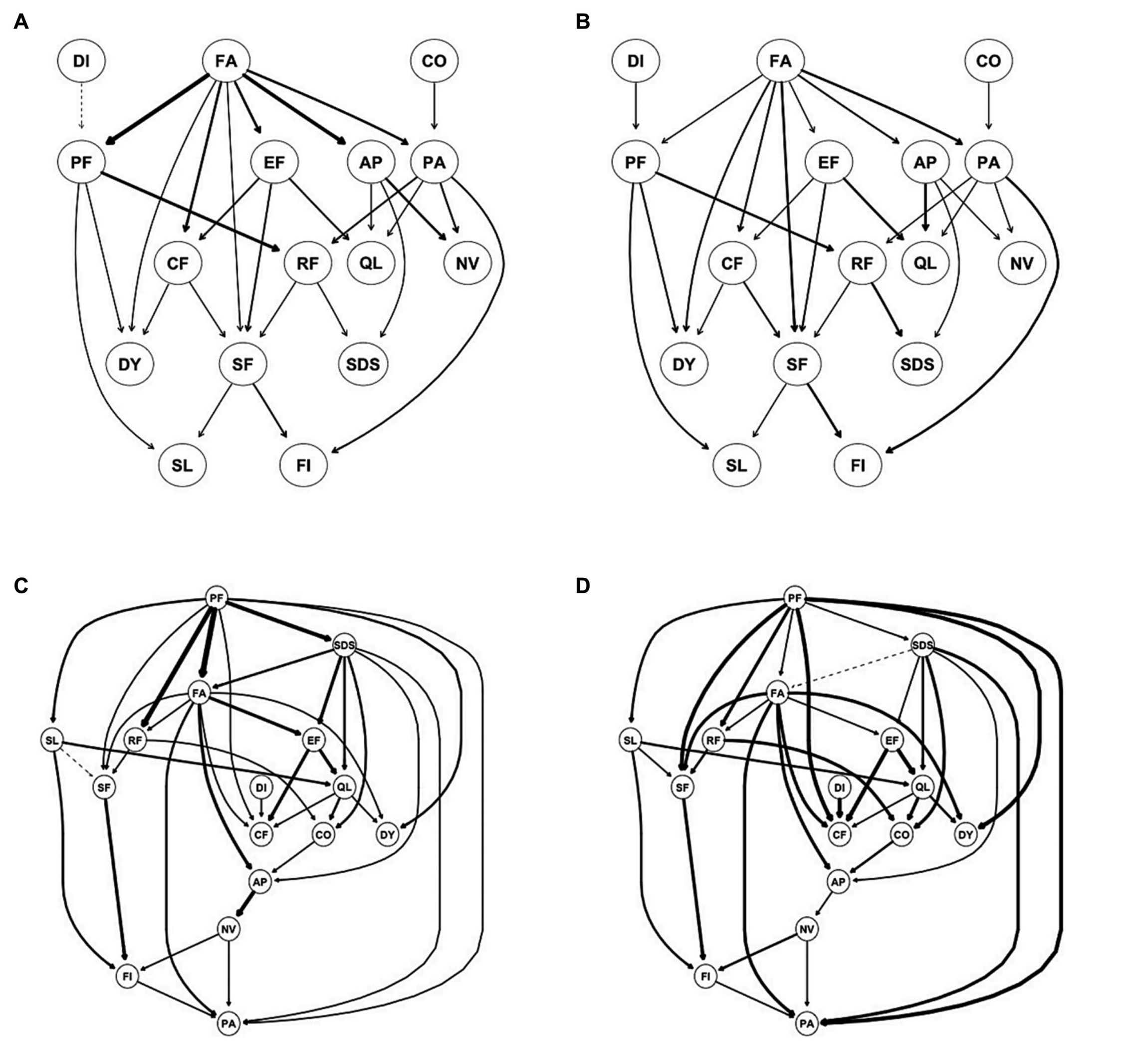

FIGURE 4
Directed acyclic graph (DAG) for symptoms/dimensions of HQOL and depression for mild depression **(A,B)** and moderate to severe depression **(C,D)**. **(A,C)** Edge thickness represents the importance of that edge to the overall DAG structure; **(B,D)** edge thickness represents the directional probability.

dimensions of HRQOL in Chinese cancer patients. We found that nearly two-thirds of cancer patients experienced various degrees of depression, and depression was the central symptom in the depression-HRQOL dimensions network, in addition to NV, PA, and PF. DAG and bridge analysis indicated that depression might influence overall HRQOL in cancer patients through EF, PA, PF, and SL, particularly in patients with moderate-to-severe depression. The disparity in network structures between mild and moderate-to-severe depression suggested that the relationship between depression and HRQOL dimensions might be bidirectional. Screening and early treatment of depression were warranted to improve the overall HRQOL of cancer patients, in addition to adequate treatment of PA and NV and improvement in PF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the study was approved by Xinjiang Medical University ethnic committee (Number: XJYKDXR20230208001). All sensitive and private information of patients were kept confidential. All participants provided written consent.

Author contributions

SM: Data curation, Formal analysis, Investigation, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. PM: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. KA: Funding acquisition, Project administration, Resources, Visualization, Writing – review & editing HZ: Data curation, Formal analysis, Methodology, Writing – review & editing. WT: Conceptualization, Data curation, Methodology, Writing – review & editing. KT: Data curation, Methodology, Writing – review & editing. YL: Data curation, Methodology, Writing – review & editing. QS: Data curation, Methodology, Writing – review & editing. WJ: Conceptualization, Investigation, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1325986/full#supplementary-material

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Implementation of a Budo group therapy for psychiatric in- and outpatients: a feasibility study

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Introduction: Physical exercise has been shown to have numerous health benefits on co-morbid somatic conditions in psychiatry and can also enhance mental health. Thus, it is not difficult to recommend physical training programs as part of an integrated and holistic treatment approach for mental health disorders. However, getting patients to participate and keeping them engaged is a major challenge. Programs based on martial arts training could be interventions improving physical and mental health with higher attachment rates. The structured discipline, holistic approach integrating physical and mental elements, and empowering activities, may explain higher participant attachment rates.

Methods: Thus, the main objective of this feasibility study is to describe a newly established group therapy program incorporating interventions from martial arts training with its physical and philosophical parts including mindfulness and breath work.

Results: During the 14-month study period from April 2021 to May 2022, a Budo group therapy was used by 215 individual persons with a total of 725 group therapy participations. Retention in the program was good across all settings and very good for persons who participated as outpatients. The mean age of the participants was 33.5 years with a range from 14 to 69 years of age, and about 41% of the participants were female. The therapy program was able to address patients over the whole spectrum of psychiatric diagnoses. Satisfaction and motivation were uniformly self-reported as very good. Patients self-reported improved mental and physical health after participating in a Budo session compared to pre-session.

Discussion: Budo group therapy thus can be seen as a feasible, well-accepted and promising new transdiagnostic treatment approach, combining physical activation with resilience enhancement. With minimal contraindications, a broad spectrum of individuals seeking mental health support can engage in this group therapy.

KEYWORDS

mental health, physical exercise, martial arts, group therapy, resilience

Introduction

Individuals with mental health problems often also have somatic illnesses with a lifetime prevalence of up to 46.6% for any comorbidity (1). Comorbidities can arise as somatic health issues increase in the general population. In particular, cardiovascular disease and ischemic events have been increasing in the general population over the last few decades (2). The same is observable for metabolic syndrome with its defining factors obesity, elevated blood-glucose, insulin resistance, hyperlipidaemia and hypertension (3). Both metabolic syndrome and cardiovascular disease are also leading causes for the premature all-cause mortality in psychiatric patients. These conditions can also arise because of known behavioural risk factors such as smoking, alcohol consumption, poor nutritional diet, poor sleep hygiene and physical inactivity. The risk factors are often observed among psychiatric patients accompanying or independent of the underlying psychiatric conditions (4). In addition, adverse effects of psychopharmacological medication can also contribute to the development or worsening of these comorbidities (5, 6). Vice versa, there are also studies showing that impaired physical health may lead to psychiatric conditions (7).

In this context, physical exercise has been shown to have numerous health benefits. Positive effects can be seen in, e.g., enhancing cardiovascular and cardiorespiratory fitness, preventing or improving metabolic disorders such as insulin resistance, strengthening the immune system and increasing life expectancy (8, 9). According to guidelines for patients with chronic conditions such as cardiovascular disease and metabolic syndrome, the recommended approach for prevention and treatment is increasing regular physical exercise to at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic physical exercise per week (10, 11). In patients with an elevation in cardiovascular risk, physical exercise has been shown to be advantageous compared to management of cardiovascular disorders and risk factors by medication, leading to an improvement in all-cause-mortality and fewer side effects (12).

However, regular physical activity can also enhance mental health, even having potential benefits equal to psychotherapy (13). Advantageous behavioural changes caused by physical activity and their mechanisms of action are being studied extensively. After single bouts of exercise a decrease in negative and increase in positive mood has been reported lasting up to 24 hours (14). Differing from many health improvements where effects are not observable instantly, e.g. weight loss or cardiovascular fitness, improvements in sleep parameters can be observed the following night directly after the bout of exercise. Furthermore, attending to regular exercise can lead to significant subjective and objective benefits comparable to other interventions used to treat insomnia (15). Emotion regulation is the ability of an individual to influence the occurrence, experience and expression of emotions and therefore includes the awareness of ones feelings. It is a main target of cognitive-behavioural therapy and has been shown to improve through physical activity (16). Delayed gratification by allowing short-term discomfort for long-term benefits is crucial for impulse control and it is imitated and trained by regular physical activity. Many important self-regulatory processes are combined when attending to physical activity such as setting goals, activity planning and self-monitoring (17). In a meta-analytic review on physical exercise and its effects on cognitive performance, the positive influence of different levels of exercise intensities was described. Lower intensities were linked with improvements in cognition immediately following the bout of exercise, whereas after more strenuous bouts beneficial effects were observable for longer durations (18). Another behavioural amelioration that has been reported due to exercise is in cognitive flexibility (17), i.e., the capacity of a person to adjust their thoughts and actions according to varying circumstances (19). These benefits can be further strengthened by incorporating, e.g., mindfulness-based interventions and meditation into the physical training program (16, 20, 21). Finally, due to the interdependence of physical and mental health and the high degree of comorbidities, benefits in one health area are also suitable to improve health in the other (17, 22).

In light of the vast positive impact of physical exercise on many risk factors and overall health, it is evidence-based to recommend physical training programs as part of an integrated and holistic treatment approach for mental health disorders. However, getting people to participate and keeping them engaged in regular physical activity is a major challenge, making this a main obstacle for the success of training programs (23).

Training programs based on martial arts could be interventions improving physical and mental health with higher attachment rates. In a systematic review on the effect of combat sports in middle-aged and older people, the authors observed an adherence rate of greater than 80% in ten different studies. Furthermore, they found an adherence rate between 71 and 96% in 5 different studies in which one was investigating the benefits of boxing, one of judo and three of karate programs (24). Martial arts training seems suitable as an intervention in persons with mental health problems. It has been described to not only bring physical benefits such as improvements in strength, mobility, flexibility and aerobic endurance (25), some forms of training also incorporate mindfulness (26). In a cross-sectional study Miyata et al. showed that practitioners of traditional Japanese martial arts have a proclivity to mindfulness and to better mental health outcomes (27). Other studies show an association of martial arts training and improvement in mindfulness, self-control and wellbeing, and in depressive and anxiety disorders (28). In particular, Budo – known as Japanese martial arts – is getting more attention in the medical field due to its effects on physical and mental health. There are many different subcategories in Budo and the term is not closely defined. It is also used to describe a culture of spirituality and moral values (29). Some subcategories of Budo use weapons and some are solely depending on the capabilities of the human body. However, every Budo -style has the same underlying principles in which it differs from other western recreational sports; Japanese martial arts are moulded by tradition and religion (30). By focussing on calming the mind on the basis of *Fudoshin* (unmoving mind, immovable heart) which is seen as equanimity in Japanese tradition, Budo also encompasses meditational components of Buddhism and Shintoist and Taoist concepts (31, 32). Although having many similarities with other sports, Budo is seen as a method to develop human character and emphasizes on educational aspects (33).

However, and despite the evidence for their suitability for psychiatric patients, literature on combined physical and mental health interventions based on martial arts training in psychiatry is sparse and further research is needed. Following this line of thought, we established a Budo group therapy targeting physical and mental health improvement. By integrating physical exercise, meditational introspection, mindfulness and its moral teachings, we wanted to improve physical health, alleviate psychiatric symptoms and improve the course of the psychiatric conditions of our in- and outpatient participants.

Aim of the study

Thus, the main objective of the current paper is to describe a newly established Budo group therapy program incorporating interventions from martial arts training with its physical and philosophical parts including mindfulness and work of breathing. We want to assess patients' usage behaviour and satisfaction with the group therapy, examine the subjective impact on the mental and physical wellbeing of the participants, and gain insight into patient preferences regarding form and frequency of service delivery.

Subjects and methods

General framework

The Department of Psychiatry, University of Basel (Universitäre Psychiatrische Kliniken, UPK) in Switzerland is the only psychiatric university hospital of northwestern Switzerland. It provides in- and outpatient services for the city of Basel and the surrounding area with a population of over 200,000 persons. There are around 300 beds available to patients at the UPK Basel in four specialized clinics: the adult psychiatric clinic (UPKE), the private clinic (UPKP), the clinic for children and adolescents (UPKKJ), and the forensic psychiatric clinic (UPKF) for adolescents and adults. The adult psychiatric clinic is organized following a track concept and includes a department for outpatient care, diagnostics and crisis intervention (ZDK), a department for psychotic disorders (ZPE), a department for psychosomatic medicine and psychotherapy (ZPP), a department for affective disorders (ZASS), a department for substance use disorders (ZAE), and a gerontopsychiatric department (ZAP). Apart from psychopharmacological, biological, and psychotherapeutic treatment, the therapy of in- and outpatients consists of various other treatment options, such as occupational therapy, art and gestalt therapy, music therapy, aromatherapy, physiotherapy, and nature-oriented therapy with animals or with gardening activities. In order to improve treatment options, different group therapies are established and evaluated routinely. In April 2021, Budo was implemented in the general therapeutic setting at the UPK as a new therapy group.

Budo group therapy

The two key elements of Budo – building physical strength and developing spiritual and mental well-being – represent the fundamental basis of each therapy session. Every session has a therapeutic theme that is integrated into the individual training parts. Up to 10 participants were allowed per therapy session. Each training is run by two trainers and is structured in four parts beginning with a greeting, and then a warm-up, followed by theme-oriented exercises. The sessions end with a short debriefing.

Greeting: The participants stand side by side and the trainers position themselves in front of them. The trainers signal the start of the session with the first exercise. Everyone closes their eyes, and concentrates on the here and now and on their own body. The participants should allow themselves to feel their current emotions and observe how they feel in their body. This introspection lasts for approximately one minute and is followed by a greeting, brief description of the program and the rules of the group session. These rules can be derived from the main principals of "Syugyo" (life training/self-cultivation) (33) as well as the Japanese etiquette "reigi" (34), and are especially important in the psychiatric setting. The Japanese philosopher Yuasa Yasuo elaborates on this concept of self-cultivation in his book "*The Body, Self-Cultivation, and Ki Energy*" (35). The key rules are: every interaction needs to be polite and respectful; everybody has to pay attention to tidiness and hygiene; everyone has to pay attention to their emotional and physical wellbeing and if they worsen the trainer must be informed; participants are asked to act in a calm attentive manner, heed the advice of the trainer, and never act vengefully. These listed rules should also guide the participants in their day-to-day life even after the therapy session.

Warm-up: The warm-up consists of various short mobility and aerobic exercises followed by 15 to 20 minutes stretching. First, the participants have to jog or jump rope for several minutes to stimulate their cardiovascular system. Afterwards they practice their mobility by moving different body parts such as hips, arms, spine, head in a coordinated circular motion thus loosening the big joints and the surrounding muscle groups. Depending on the program, the participants are instructed to imitate the gait of different animals. The trainer demonstrates how this should look and the participants try to re-enact the motion. Shortly before the stretching, the basic kickboxing posture and stances as well as basic kicks are focused on. In a playful manner, participants learn how to move and position themselves. Kickboxing was chosen for its effectiveness in providing a comprehensive physical workout, including cardiovascular exercise and strength training. The dynamic and engaging nature of kickboxing, along with its potential to empower individuals and boost confidence, aligns with many of the goals of the Budo group therapy program. The adaptability of kickboxing to various fitness levels and its popularity as a contemporary fitness activity was thought to maybe have a broad appeal for a wide audience. The warm-up ends with 15 to 20 minutes of static stretching. The body parts that are mainly focused on are the legs and hip region targeting the flexors and extensors as well as the neck, upper back and shoulder musculature. Each stretch is held for at least 30 seconds and is accompanied with breathing instructions.

Theme-oriented exercises: The themes of every therapy session can differ. The trainer decides prior to planning a training on what they want to focus. Concentration and attentiveness, tension and relaxation, perceiving and regulating emotions or self-efficacy and self-confidence are themes implemented on a regular basis in each course session. An example for this part on concentration and attentiveness might look like this:

The participants are briefly given a short theoretical background for the exercises. For example: "In some mental illnesses, but also in situations that we are all familiar with from everyday life, concentration and attention can be impaired." The group is then asked whether anyone has already experienced problems with concentration and attention in their day-to-day life. If so, what was the reason? Afterwards, the task is explained step by step using a flipchart. After the instruction, there is time for questions.

Participants are told that an exercise is being carried out in groups of two and that it should have a positive effect on attention and concentration. Afterwards, the group can share how their experience of the exercise was. One person takes on the role of the coach and takes a large punching pad. The second person starts as the pupil and walks loosely in a circle around the coach. The coach can give three different instructions.

When the coach says "1", the pupil runs to the punching pad as quickly as possible and performs three punches. When the coach says "2", the pupil runs as fast as possible to the punching pad and performs a front kick. When the coach says "3", the pupil runs as fast as possible to the punching pad and jumps as high as possible in front of it. The instructors demonstrate these movements.

The coach has the task of calling out the numbers in any order and at different intervals to check whether the pupils are focusing, and they have to check if they are performing the task correctly. The task takes three minutes, after which the roles are swapped.

If someone notices that they are very tired or not feeling well, they can take a break at any time. They can also ask for help at any time if difficulties arise. They are told that it is important to reduce distractions. The participants are informed about the time frame of the exercise and that there is a break zone. If there are no more questions, the participants are asked to briefly think of the numbers 1, 2 and 3 and to visualize which movement belongs to which number. After the introduction, the exercise begins.

Debriefing: The end of the session is structured similarly to the beginning. The participants line up in front of the trainers and everyone closes their eyes at the trainers' signal. The room gets quiet and everyone visualizes what they learned and practiced in the session. Participants are asked to think of the things they appreciated during the training and their achievements, if there were new techniques or inputs they especially liked or if they maybe feel more energized. They get encouraged that even if they experienced hardships during the day, they finished a strenuous training. Once again, they get the time for introspection, to focus on how they feel and to monitor if there are changes in their self-perception. The debriefing lasts for approximately five minutes. Afterwards, the trainers thank the patients for their participation and the session ends.

Study population

All in- and outpatients of the adult psychiatric clinic (UPKE/UPKP), the forensic psychiatric clinic (UPKF), and the child and youth psychiatric clinic (UPKKJ) were eligible for participation in the group therapy. The responsible physician had to approve an individual patient's suitability to be enrolled in the Budo group. The study population was not restricted to patients with specific diagnoses. Exclusion criteria were recent cardiovascular or orthopaedic interventions, and general medical illness, e.g., flu-like symptoms. Patients with any sort of acute somatic pain, except for muscle tension, were also excluded.

Participant survey

On the basis of our clinic-wide quality management concept following the PDCA (Plan – Do – Check – Act) cycle in implementing, monitoring, and improving new therapies, the participants were able to fill in a survey after each session. They were able to answer questions about their wellbeing and whether or not they see an additional benefit by attending the Budo group. Details on the questionnaire are available in the online-only supplement to this article. Participants had the option to provide identifying data, enabling the tracking of participating multiple times in the survey and the pseudo-anonymized extraction of routine clinical data, or to participate anonymously. The survey was conducted from April 2021 until May 2022 using EFS Survey/Unipark (Tivian XI GmbH, Cologne, Germany).

Documentation and management of clinical data

Clinical and treatment data were continuously documented using the Medfolio software (current version: 2.2.0.2539, release sr27qs1.0sp_kged32_560; NEXUS AG, Villingen-Schwenningen, Germany) and extracted using HCe® Analytics software (Business Intelligence Connector 3 (BIC 3) for patient controlling; TIP Management AG, Dübendorf, Switzerland). Data on age, gender, diagnoses according to the International Classification of Diseases, 10th revision (ICD-10 (WHO, 1992)), and legal status were documented by the psychiatrists responsible for the respective patient.

As data was documented during routine treatment and anonymized during data extraction, and as the survey was performed within the clinic's routine quality management assessments, data collection and analyses were exempt from ethics committee approval. Publishing the results was not pre-planned, but decided on afterwards to facilitate the transfer of our experiences into clinical practice. The local ethics committee (EKNZ; Ethik-Kommission Nordwest- und Zentralschweiz) has provided a written confirmation that no ethics committee vote was needed for this publication (Req-2023-00460).

Statistical analysis

Participation in the group therapy, clinical and sociodemographic characteristics, and variables from the survey are given in total numbers and percentages for nominal scaled variables as well as mean and standard deviation (SD) for ordinal and interval scaled variables. This being a feasibility study, and because of the relatively modest sample size of the survey, supportive explorative statistical analyses are reported for descriptive purposes only. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0 (Released 2020. IBM Corp. Armonk, NY) as well as R-Studio, Version 2023.03.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the 14-month study period from April 2021 to May 2022, the Budo group therapy was used by 215 individual persons with a total of 725 group therapy participations. Patients took part in different treatment settings (i.e., inpatient or outpatient treatment) and each admission to a treatment setting is documented as a separate case, resulting in 236 treatment cases. Of these, 214 cases took part during inpatient treatment and had 2.6 ± 2.2 (mean ± SD) treatment sessions (range: 1 – 13 sessions); 16 during outpatient treatment with 7.2 ± 14.2 treatment sessions (range: 1 – 49); and six took part both during in- and outpatient treatment with 9.4 ± 3.0 treatment sessions (range: 6 – 13).

Clinical and sociodemographic data of group therapy and survey participants are presented in Table 1. With 87%, most group therapy participants were patients from the adult psychiatric clinic (UPKE). About one in ten participants was a patient from the private clinic (UPKP) attended, and single participants from the clinic for children and adolescents (UPKKJ) as well as from the forensic psychiatric clinic (UPKF). Within the UPKE, all diagnostic departments contributed patients with the exception of the department for gerontopsychiatry (ZAP). Mean age of the participants at entry was 33.5 years with a range from 14 to 69 years of age, and about 41% of the participants were female. About 4% of the participants had been involuntarily admitted to general or forensic psychiatric inpatient treatment and the same percentage of participants had been subjected to seclusion or involuntary treatment. Most participants had a main diagnosis of affective disorders (37%) or substance use disorders (23%).

While survey participants were – in general – comparable to group therapy participants, no patients from the UPKKJ and the UPKF took part in the survey. Also, persons with involuntary entry, exposed to seclusion or involuntary treatment, or diagnosed with schizophrenia spectrum disorders were missing from the survey.

Exploratory analyses showed no evidence for significant statistical correlations between the frequency of group therapy attendance and gender, age, and duration of inpatient treatment (all $r < |.12|$; $p > .110$).

74 participants filled in the survey in the study period of April 2021 to May 2022. Results are presented in Table 2. Using a 5-point Likert scale with a rating of 1 indicating lowest rating or agreement

TABLE 1 Clinical and sociodemographic data of group therapy and survey participants.

	Group therapy (n = 215)	Survey (n = 46)
Psychiatric clinic or department[a,b]		
Adult psychiatric clinic (UPKE)	187 (87%)	40 (87%)
UPKE Department for outpatient treatment and crisis intervention (ZDK)	23 (10.7%)	5 (10.9%)
UPKE Department for psychotic disorders (ZPE)	26 (12.1%)	3 (6.5%)
UPKE Department for substance use disorders (ZAE)	44 (20.5%)	7 (15.2%)
UPKE Department for psychosomatic medicine and psychotherapy (ZPP)	40 (18.6%)	12 (26.1%)
UPKE Department for affective disorders (ZASS)	54 (25.1%)	13 (28.3%)
UPKE Department for gerontopsychiatry (ZAP)	0 (0%)	0 (0%)
Private clinic (UPKP)	22 (10.2%)	6 (13%)
Clinic for children and adolescents (UPKKJ)	1 (0.5%)	0 (0%)
Forensic psychiatric clinic (UPKF)	5 (2.3%)	0 (0%)
Duration of inpatient treatment (mean ± SD)[c]	81.1 ± 132.3	73.7 ± 62.1
Involuntary measure		
Involuntary entry	8 (3.7%)	0 (0%)
Seclusion and/or involuntary treatment	8 (3.7%)	0 (0%)
Sociodemographic data[a,d]		
Age at entry (mean ± SD)	33.5 ± 11.9	31.9 ± 10.4
Female gender (%)	89 (41.4%)	20 (43.5%)
Main diagnosis (ICD-10)[e,f]		
Organic, including symptomatic, mental disorders(F0)	1 (0.5%)	1 (2.2%)
Mental and behavioural disorders due to psychoactive substances (F1)	49 (22.8%)	10 (21.7%)
Schizophrenia, schizotypal and delusional disorders (F2)	17 (8%)	0 (0%)
Mood, affective disorders (F3)	80 (37.2%)	19 (41.3%)
Neurotic, stress-related and somatoform disorders (F4)	30 (14%)	7 (15.2%)

(Continued)

TABLE 1 Continued

	Group therapy (n = 215)	Survey (n = 46)
Behavioural syndromes with physiological disturbances and physical factors(F5)	3 (1.4%)	0 (0%)
Disorders of adult personality and behaviour (F6)	28 (13%)	6 (13%)
Mental retardation (F7)	0 (0%)	0 (0%)
Disorders of psychological development (F8)	1 (0.5%)	0 (0%)
Behavioural and emotional disorders, onset in childhood or adolescence (F9)	4 (1.9%)	1 (2.2%)

[a]no missing data; [b]in general, about 88% of all cases are treated in the UPKE, 6% in the UPKP, 4% in the UPKKJ, and 2% in the UPKF, missing data; [c]missing data for 11 group therapy participants (for involuntary entry variable only) and for one survey participants; [d]with about 48% of all patient cases being of female gender; [e]missing data for two group therapy participants and for two survey participants; [f]distribution of main diagnoses for all patients in the hospital in 2022 was: F0: 1.5%, F1: 24.5%, F2: 17.6%, F3: 25.7%, F4: 15.4%, F5: 0.5%, F6: 11.5%, F7: 0.5%, F8: 0.3%, F9: 1.4%, others: 1.2%.

and 5 indicating highest rating or agreement, participants showed high values for satisfaction (4.9 ± 0.3, range 4 – 5) and motivation (4.8 ± 0.4, range 4 – 5).

Patients self-reported that they felt markedly better physically (4.3 ± 0.9, range 1 – 5) and psychologically (4.1 ± 0.8, range 2 – 5) after group therapy participation. While most participants reported an improvement, there was a small number of participants who felt worse physically (3.3% rated "physically, I feel a lot worse") or psychologically (6.7% rated "psychologically, I feel worse"). Comparing female and male participants, exploratory analyses indicated that male participants might report better subjective improvement physically ($t(23)$ = 2.01, p = .056) and psychologically ($t(23)$ = 4.30, p = <.001) compared to female participants. Furthermore, Pearson analyses indicated a positive correlation of psychological (r = .544, p = .036), but not physical improvement (r = -.172, p = .540) with participant age. Feeling psychologically better was highly correlated with feeling physically better (r = .609, p <.001).

Concerning future use of the group therapy, survey participants indicated that they felt Budo was an important addition to the therapeutic programme (4.8 ± 0.4, range 3 – 5), that they were interested in partaking multiple times a week (4.6 ± 0.8, range 2 – 5), and that they would like to continue participating after discharge from an inpatient setting (4.6 ± 0.7, range 2 – 5).

Discussion

In this feasibility study, we investigated the practical implementation of a Budo group therapy program in a subset of psychiatric in- and outpatients. In addition to information on group therapy participation and retention, a modest retrospective observational analysis was conducted to provide further information on satisfaction and motivation, subjective self-reported intervention effects, and perspectives on future use. Strengths of this study are the novelty of the treatment approach, presenting naturalistic usage data from a large psychiatric university hospital covering the whole spectrum of patients, and the inclusion of subjective participant feedback.

Usage data show that the Budo group therapy could be successfully introduced and was accepted very well. A considerable number of patients participated in the sessions. Although most patients participated from an inpatient treatment setting, some patients started to participate in an outpatient treatment setting or continued to participate after discharge from inpatient treatment. Retention in the program was good overall with a mean of over three participations per person, and very good

TABLE 2 Survey on self-reported satisfaction and motivation, intervention effects, and perspectives on future use.

	Participants		Male[a]		Female[a]		p-value
	n	$M \pm SD$	n	$M \pm SD$	n	$M \pm SD$	
Satisfaction and motivation							
How satisfied were you with the Budo group therapy?	73	4.9 ± 0.3	36	4.9 ± 0.2	27	5.0 ± 0.2	p = .738
How motivated were you during the Budo therapy session?	73	4.8 ± 0.4	36	4.8 ± 0.4	27	4.9 ± 0.4	p = .638
Intervention effects							
How do you feel physically?	30	4.3 ± 0.8	14	4.6 ± 0.6	11	4.0 ± 0.8	p = .056
How do you feel psychologically?	30	4.1 ± 0.9	14	4.6 ± 0.5	11	3.6 ± 0.7	p <.001
Perspectives on future use							
Do you think that the Budo group therapy is beneficial in the therapeutic setting?	72	4.8 ± 0.4	35	4.9 ± 0.4	27	4.8 ± 0.5	p = .354
Would you like to use the Budo group therapy multiple times per week?	72	4.6 ± 0.8	36	4.8 ± 0.6	26	4.4 ± 0.9	p = .081
Do you think that the Budo group therapy would be beneficial even after discharge from inpatient treatment?	67	4.6 ± 0.7	34	4.6 ± 0.7	24	4.6 ± 0.6	p = .838

All ratings were made on a 5-point Likert scale, with 1 indicating lowest rating or approval and 5 indicating highest rating or approval; [a]self-identified gender.

in persons who participated as outpatients (with a mean of over seven participations) or as in- and outpatients (with a mean of over nine participations). This is further supported by the responses in the patient survey concerning perspectives of future use, indicating favourable ratings regarding the importance of the treatment approach, the interest in continuing to participate after discharge, and the interest in partaking multiple times a week. These results are compatible with findings of a high adherence to martial arts based exercise therapy (24). Thus, Budo group therapy could be a promising candidate for a combined therapeutic intervention aimed at mental and physical health with high adherence after hospitalisation and could help integrate physical exercise in patients' lives in the long run.

The group therapy program was able to address patients from all parts of the hospital with the exception of the department of gerontopsychiatry. Considering the overall case distribution in the hospital (as provided in detail in the legend for Table 1), there seems to be an overrepresentation of participants from the private clinic and an underrepresentation of patients from the clinic for children and adolescents. As apt for a transdiagnostic treatment approach, participants had main diagnoses covering the whole spectrum of psychiatric disorders. Considering the overall case distribution in the hospital (as provided in detail in the legend for Table 1), there seems to be a descriptive underrepresentation of patients with schizophrenia spectrum disorders and a descriptive overrepresentation of patients with affective disorders. No patients with mental retardation took part, which is unsurprising as they are rarely admitted to this institution. Both male and female patients used the Budo group therapy program, with numbers suggesting only a slight descriptive underrepresentation of female participants. As – in theory – a group therapy including elements from martial arts training might attract a predominantly male audience, this is, however, quite encouraging. While mean age suggests that younger persons were descriptively overrepresented, participants in general covered a broad age range from 14 to 69, suggesting that the Budo group therapy might also be suitable for older adult persons. Nevertheless, missing participation from patients from the department of gerontopsychiatry indicates that appropriateness of the therapy program for persons with an age of 70 and upwards, with a diagnosis of dementia and with severe somatic co-morbidities should be further assessed.

Judging from the data of persons allowing identification of their clinical information, survey participation seems to be in general representative of the participant group. However, no participants from the forensic clinic, the clinic for children or adolescents, diagnosed with a schizophrenia spectrum disorder or having been involuntarily admitted or subjected to seclusion or coercive medication could be identified. It remains unclear if these patient groups did not participate in the survey or if they are part of the about one third of the participants that did not allow linking their clinical data.

Satisfaction and motivation were uniformly rated very highly by all patients participating in the survey, with ratings only indicating either high or very high satisfaction and motivation. This has to be seen in the context that the group therapy was not mandatory and might have primarily attracted persons that were prone to exercise and therefore to positive ratings. However, the large number of participants and the missing of any negative or neutral ratings suggest that the positive ratings may not only be due to participant self-selection. An increase in life satisfaction in people engaging in other martial arts has been observed as well. In a systematic review on Brazilian jiu-jitsu and its effects as social and psychological therapy the author elaborated on increased satisfaction and pro-social behaviour and reduced symptoms of various psychiatric conditions in participants of Brazilian jiu-jitsu. Furthermore, he describes a social benefit with a sense of community and belonging (36). The participants of the Budo group therapy may experience similar effects, which could explain these high ratings. Intervention effects were self-reported as generally positive in mental and physical health, with favourable mean ratings and most patients reporting improvement of their health. Only one in 30 participants described feeling worse physically, and about one in 16 participants did feel worse psychologically.

Exploratory analyses suggest that male participants might subjectively experience more physical and psychological improvement from the therapy sessions than female participants, and that higher age might be connected with increased psychological improvements. Our findings on a putative difference could be between female and male participants' subjective physical and psychological improvements are compatible with the current literature. For example, Tiggemann and Williamson showed that men who engage in high intensity exercise report greater psychological improvements especially in self-esteem compared to women (37). Furthermore, the gender difference is associated with different motives to engage in exercise. Craft et al. illustrated that unrelated to the underlying reason for physical exercise, men showed a higher quality of life whereas in women the motive for exercising was important in the context of quality of life (38). Nonetheless, the number of female participants and their subjective improvements show the positive potential of this group therapy in male and female participants. As Kavoura et al. discussed, there are numerous factors for underrepresentation of female martial artists in psychological research such as historical bias, gender stereotypes and many more (39). Therefor it is crucial not to disregard the results of the female participants. However, given the preliminary nature of the survey and the small sample size, our findings have to be interpreted very cautiously.

The effects of physical exercise and of mindfulness based interventions on stress are well known (13). Budo based therapy combines both and may therefore also help prevent or reduce stress, agitation and aggression, which can lead to involuntary measures in psychiatry (40, 41). In a review on social-psychological outcomes of martial arts practise among youth contrasting findings were discussed concerning the effects of martial arts training on aggression. Some studies described positive outcomes with decreases in hostility and aggression and better self-control, whereas others reported negative effects such as more antisocial behaviour (42). In that review, however a different age group was focused on with no known psychiatric conditions, which makes it difficult to draw conclusions for the participants of the Budo group therapy. While the Budo group therapy was able to successfully address patients with main diagnoses often associated with aggression and coercion in psychiatry (i.e., ICD-10 main diagnoses from chapters F0, F1, F2, F3, and F6), patients from forensic psychiatry settings, and patients subjected to involuntary admission, seclusion, and involuntary medication, the number of these participants was limited, and no outcomes addressing stress levels, agitation and aggression were available. Therefore, the potential of Budo group therapy sessions to aid in dealing with agitation and aggression in psychiatry remains to be seen and should be explored in future research.

Limitations

There was no pre-established study protocol, therefore resulting in limited depth of information available for analysis. The survey data primarily relied on self-reported responses from individuals who had participated in the program and hence experienced the new treatment, potentially introducing a bias towards more favourable assessments. Nonetheless, the substantial interest and engagement of the patients indicated a widespread interest in this new treatment approach. However, future research should consider the use of randomized allocation and establishment of a control group to address potential biases and provide comparisons that are more robust. Regardless, it is worth noting that the novelty of the treatment option and the results indicating its high potential emphasise the need for further research in this area.

Conclusion

Budo group therapy is feasible in an inpatient and outpatient psychiatric setting and offers a unique approach in the possibilities of therapeutic interventions in mental health. Its ability to combine physical activation with resilience enhancement provides a powerful instrument for the promotion in mental well-being. Furthermore, it has a transdiagnostic applicability allowing patient participation across a wide range of psychiatric conditions. With minimal contraindications, a broad spectrum of individuals seeking mental health support can engage in the group therapy. Most notably, Budo has a capacity to motivate patients, fostering a sense of empowerment and self-improvement. As research continues to search for innovative interventions in mental health treatment, the integration of martial arts stands as a compelling option, worthy of further investigation and incorporation into therapeutic practices.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The Ethics Committee Northwest Switzerland EKNZ declared that no ethic committee approval was needed for the current study (Req-2023-00460). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JS: Writing – original draft. KJ: Conceptualization, Writing – original draft. MJ: Formal analysis, Writing – original draft. LI: Data curation, Writing – review & editing. FR: Project administration, Writing – review & editing. JM: Supervision, Writing – review & editing. AN: Supervision, Writing – review & editing. UL: Supervision, Writing – review & editing. CH: Conceptualization, Supervision, Writing – original draft.

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Sex differences in symptom network structure of depression, anxiety, and self-efficacy among people with diabetes: a network analysis

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Aims: The present study aims to explore the relations between symptoms of depression and anxiety and self-efficacy among people with diabetes. At the same time, we also examined the sex difference between network structures.

Methods: This study recruited 413 participants with diabetes, and they completed Generalized Anxiety Disorder Scale (GAD-7), Patient Health Questionnaire (PHQ-9), and the Self-efficacy for Diabetes (SED). Symptom network analysis and network comparison test were used to construct and compare the depression-anxiety symptom network models of the female and male groups. Finally, we conducted flow diagrams to explore the symptoms directly or indirectly related to self-efficacy.

Results: The strongest edges in the depression-anxiety symptom networks are the edge between "GAD3" (Excessive worry) and "GAD4" (Trouble relaxing) and the edge between "PHQ1" (Anhedonia) and "PHQ4" (Energy) in the female and male groups, respectively. Most of the symptoms with the highest EI and bridge EI are related to worry and nervousness. Additionally, in the flow diagram of the female group, "PHQ6" (Guilt) has a high negative association with self-efficacy.

Conclusion: Females with diabetes are more vulnerable to depression and anxiety. Interventions targeting key symptoms in the network may be helpful in relieving the psychological problems among people with diabetes.

KEYWORDS
diabetes, depression, anxiety, self-efficacy, sex difference, network analysis

1 Introduction

Diabetes is a group of serious, long-term, and metabolic disorders that will have a major impact on not only individuals' physical health but also their mental health (1, 2). Previous research suggests that individuals with diabetes are twice as likely to suffer from depression and anxiety as the general population (3, 4). Developing depression or anxiety will affect an individual's job performance, quality of life, and even cause suicidal ideation (5–7). Additionally, suffering from mental health problems may also have a negative association with the self-efficacy of the diabetes population (8). Lower self-efficacy for diabetes may affect self-management behaviours in diabetic patients, exposing diabetic patients to the risk of diabetes-related morbidity and mortality (9). In other words, mental health problems may also affect the way individuals cope with diabetes, forming a negative circle. Things will get worse if individuals with diabetes have a comorbidity of depression and anxiety (10, 11).

Although a wealth of research about individuals with diabetes focuses on the relations between depression, anxiety, and self-efficacy, the symptom-level and detailed knowledge are relatively unknown. Considering the limitations of previous literature, the current study employed symptom network analysis to explore the symptom-level relation between depression, anxiety, and self-efficacy among people with diabetes. The present research can provide us with information on key symptoms that can be targeted when intervening in the mental health problems of people with diabetes and improving self-efficacy.

1.1 Depression and anxiety among individuals with diabetes

Diabetes is a kind of metabolic disorder characterised by high blood glucose levels (1). The results of the International Diabetes Federation (IDF) show that the global diabetes prevalence among people aged 20–79 years old in 2021 is about 10.5%, and this prevalence may rise to 12.2% in 2045 (12). The high prevalence and severe negative outcomes (i.e., financial burden, disability, and mortality) of diabetes make it an illness of worldwide concern (13, 14). China also has a large diabetes population, roughly 24% of the world's diabetes population (13, 15). A large sampled cross-sectional study showed that the estimated overall prevalence of diabetes in mainland China in 2018 was 12.4% (16). These data highlight the significance of paying attention to the individuals with diabetes in China.

The mental health of individuals with diabetes deserves attention. The long-term dietary restrictions required to manage glycemic levels and the impact of diabetes on social and family functioning can contribute to mental health issues like depression and anxiety (4, 17). A burgeoning body of literature has identified the association between diabetes, depression, and anxiety (7, 18). The analysis of Li et al. (19) showed that the prevalences of depressive and anxious symptoms among individuals with type 2 diabetes in China were 37.8 and 28.9%, respectively, which were higher than the prevalences in the general population. Mental health problems such as depression and anxiety have negative effects on people's quality of life and are even associated with suicidal ideation (6, 7). What's more, it is documented that mental health problems are also related to reductions in self-efficacy for diabetes, which may have an impact on the physical health of the diabetes population (8, 9). Individuals who suffer from a co-morbidity of anxiety and depression may face more serious negative consequences (10, 11). In sum, considering the high prevalence and the detrimental outcomes of depression and anxiety in individuals with diabetes, the issues of mental health problems in the diabetes population warrant attention.

1.2 Depression, anxiety, and self-efficacy for diabetes

Effective diabetes treatment needs changes in the patient's daily routine (i.e., insulin injections, blood glucose testing, and diet), which means that the self-management of individuals plays a significant role (20). Self-efficacy, the perception of one's capability to overcome difficulties and perform specific behaviours to achieve his or her goals (20), is a key factor that affects the self-management behaviours of diabetes individuals (21). Jiang et al. (22) employed a meta-analysis containing 1,308 participants, finding that enhancing self-efficacy-focused education on diabetes would enhance self-management behaviours and improve the quality of life. Consistently, other studies also supported the high association between self-efficacy and self-management behaviours among people with diabetes (21, 23), highlighting the significance of improving self-efficacy of the diabetes population.

Research showed that negative mood states would have a negative effect on self-efficacy (24). It was identified that depression and anxiety share a negative association with self-efficacy in people with diabetes (8, 25, 26). Additionally, the relationship between depression, anxiety and self-efficacy may differ in males and females. The prevalences of depression and anxiety among the diabetes population (27) and the level of self-efficacy (28) are related to sex. The research of Cherrington et al. (25) showed that negative associations between depression and self-efficacy existed in males with diabetes but not females with diabetes. Shakeel et al. (29) found that the relation between anxiety and self-efficacy of patients with chronic illness varied across genders. Thus, it is necessary to consider sex when analyzing the relationship between depression, anxiety, and self-efficacy among the diabetes population.

1.3 The current study

Reviewing previous literature, several gaps need to be closed. Firstly, even though previous research has identified the relationship between mental health problems (i.e., depression or anxiety) and diabetes, few of them take the perspective of network analysis to examine the symptom-level relation between the comorbidity of depression and anxiety among individuals with diabetes. Secondly, although studies have found that psychological problems are associated with lower self-efficacy, the evidence about which symptoms of anxiety and depression are more strongly associated with self-efficacy for diabetes is limited. Thirdly, current knowledge of sex differences in the relationship between depression, anxiety, and self-efficacy is limited to the symptom levels, which warrant further exploration.

To address the aforementioned deficits, symptom network analysis, a popular method in the clinical psychology area to provide detailed information on symptom-level relations between different variables (30), is suitable. The current study applied network analysis to examine the symptom-level relation between depression, anxiety, and self-efficacy, considering the sex difference. There are three aims in the present study. First of all, we aim to construct the depression-anxiety symptom network models of the diabetes population, identifying the key symptoms in the network structures. Second, we constructed the flow diagrams including self-efficacy and symptoms of depression and anxiety. Through this procedure, we can find the important symptoms that are related to self-efficacy. Third, we aim to examine whether sex differences existed in the depression-anxiety symptom network models and the flow network models.

2 Method

2.1 Measures

2.1.1 Generalized anxiety disorder scale

The Generalized Anxiety Disorder Scale has 7 items, which is used to measure the level of anxiety of individuals (31). Each item scored on a 4-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). The total score of this scale ranges from 0 to 21 and a higher score of GAD-7 represents more severe anxious symptoms. Previous studies show the applicability of its Chinese version (32). With a Cronbach's α score of 0.943, GAD-7 shows great internal consistency in the present study.

2.1.2 Patient health questionnaire

The 9-item Patient Health Questionnaire is applied to measure the severity of depressive symptoms (33). Each of the items is rated from 0 (not at all) to 3 (nearly every day) and the higher total scores of this questionnaire indicate the more severe depressive symptoms. The Chinese version of PHQ-9 shows good psychometric properties (34). In the current study, the Cronbach's α score of PHQ-9 is 0.884.

2.1.3 The self-efficacy for diabetes

The current study applied the Chinese version of SED to measure the level of self-efficacy in people with diabetes to cope with diabetes (35). This scale has 9 items and each scored from 1 (no confidence at all) to 5 (with complete confidence), with higher total scores indicating a higher level of self-efficacy. The Cronbach's α score of SED is 0.890.

2.2 Participants and procedure

This survey used a convenience sampling method to collect the data, which was conducted in June 2023 in Bengbu, Anhui Province, China. For the fact that most of the subjects participating in the current study are the older and less educated individuals, it was hard for them to complete the questionnaire independently. Therefore, in this study, after obtaining informed consent from the participants, the nursing staff read the questions to the subjects, asked them for their answers and recorded their answers on a paper questionnaire. After completing the questionnaire, one insulin was given to each participant as payment. Finally, the staff converted these paper-based questionnaires into an electronic version data. This study recruited 413 individuals with diabetes ($Mean_{age} = 50.68$, $SD_{age} = 13.31$) to complete the questionnaire. The average duration of their diabetes of them is 7.40 years. To further examine the symptom network differences between males and females, we divided them into two different groups according to their sexes. The female group has 147 individuals ($Mean_{age} = 50.32$, $SD_{age} = 14.54$) and the male group has 266 individuals ($Mean_{age} = 50.88$, $SD_{age} = 12.61$). The average years of diabetes in female group and male group are 7.94 and 7.10, respectively. This research was examined and approved by the ethics committee of Bengbu Medical University (Reference number: No. 148 [2021]).

2.3 Data analysis

The current study used R (version 4.3.1) to analyse the data (36). In the beginning, we conducted a descriptive analysis to describe the basic information of the female group and the male group. Additionally, using the function *descrTable* of R package *compareGroups* (37), we also conducted a *t*-test to compare the age and scores of depression, anxiety, and self-efficacy between the female group and the male group. Secondly, to know the detection rates of anxiety and depression among the individuals with diabetes in the current sample, we calculated the prevalences of depression and anxiety according to the cut-off scores. Specifically, the cut-off scores of PHQ-9 and GAD-7 are 8 (33) and 7 (38), respectively.

To estimate the relations between different symptoms and construct the network model, the Gaussian Graphical Model (GGM) was conducted (39). However, to avoid the network being too complex to be understood, the GGM needed to be further regularized through the Extended Bayesian information criterion (EBIC) and graphical least absolute shrinkage and selection operator (LASSO) (40, 41). Then, we used the R package *qgraph* to achieve the visualization of the symptom network (42). In the present study, we constructed depression-anxiety symptom network models of males and females to examine the relations between symptoms of depression and anxiety. In the symptom network, each node represents a symptom of depression or anxiety. The edge represents the association between two symptoms and a thicker edge means a stronger association. Additionally, the green line and red line represent positive and negative relationships, respectively.

After constructing the symptom network models, we calculated the centrality indexes of each node to identify the significant symptoms of network models. First of all, we computed the Expected Influence (EI) of each symptom through the R package *qgraph* (42). This index is the sum of all positive and negative edge weights connected to a specific node, which is a reliable index to measure the significance of each node in the network model (43). Then, the R package *mgm* was used to calculate the predictability (i.e., R^2) of each node (44). R^2 measures the variance that a node can be explained by other neighbouring nodes in the network structure (45). Third, for the reason that the network models in the present study include depression and anxiety two disorders, to identify the important nodes that connected two disorders, we computed the bridge expected influence (bridge EI) of each node. Bridge EI is calculated in a similar way as EI. It is the sum of a node's edge weights, but only edges that connect nodes from one disorder with the other disorder are counted (46). Referring to previous studies, the symptoms with bridge EI higher than 1 were identified as bridge symptoms in the network (47).

To examine the accuracy and stability of the network models, we applied the R package *bootnet* (40). To test the accuracy, we evaluate the bootstrapped confidence intervals (95% CIs) by using a nonparametric bootstrap. A narrower CI means a more reliable network model. Additionally, to test if there is a significant difference between the edge weights or the centrality indexes (i.e., EI and bridge

EI) of two symptoms, we also conducted a bootstrapped difference test. To examine the stability of the network model, we computed the correlation stability – coefficients (CS-C) of EI. The CS-C represents the maximum proportion of the sample size that can be excluded while maintaining a correlation coefficient between the centrality index of the original sample and the after-dropped sample at least 0.7, with 95% probability. According to the criterion of previous research, the CS-C should be higher than 0.25 and it is preferable to be higher than 0.5 (48).

We also performed a Network Comparison Test (NCT) through the R package *NetworkComparisonTest* to evaluate the difference in the depression-anxiety network models between females and males (49). Using NCT, we can compare whether there are differences in global connectivity and local connectivity between two groups.

Aiming at identifying the significant symptoms of depression and anxiety that are directly connected with the self-efficacy of diabetes, we employed the function *flow* to construct the flow diagram containing self-efficacy of diabetes and symptoms of depression and anxiety. The flow diagram places self-efficacy of diabetes on the left side and shows us how symptoms of depression and anxiety are directly or indirectly connected to self-efficacy of diabetes.

3 Results

The descriptive information of the current sample and the *t*-test results between the female group and the male group are shown in Table 1. Specifically, according to the results of Table 1, we can find that the total scores of depression and anxiety have significant differences between two groups. The female group has higher total scores of depression and anxiety. The prevalences of depression and anxiety in the present sample are 43.82 and 31.72%. The prevalences of depression and anxiety in the female group are 52.38 and 38.10%. In the male group, the prevalences of depression and anxiety are 39.10 and 28.20%.

3.1 Network structure

The depression-anxiety symptom network models of the female and male groups are depicted in Figure 1. Figure 1A is the network of the female group. This network has 16 nodes, with 75 non-zero edges (62.5%). Among these edges, the edges between "GAD3" (Excessive worry) and "GAD4" (Trouble relaxing), "PHQ1" (Anhedonia) and "PHQ2" (Sad Mood), and "PHQ1" (Anhedonia) and "PHQ4" (Energy) have the strongest correlation (refer to Supplementary Table S1) and they are significantly higher than other edges among the network (see Supplementary Figure S1A). Figure 1B shows the network of the male group. In this network, there are 16 nodes and 67 non-zero edges (55.83%). Among all non-zero edges, the top three strongest edges are the edges of "PHQ1" (Anhedonia) and "PHQ4" (Energy), "PHQ3" (Sleep) and "PHQ4" (Energy), and "PHQ7" (Concentration) and "PHQ8" (Motor) (see Supplementary Table S2), which are significantly higher than other edges in the network model (see Supplementary Figure S1B).

Figure 2 shows the EI and bridge EI of the female group and the male group. Figure 2A is the EI of each symptom of the female group and male group. Among the female group, "GAD3" (Excessive worry), "GAD7" (Feeling afraid), and "GAD4" (Trouble relaxing) are the symptoms with the highest standardized EI. The EI of "GAD3" (Excessive worry) is significantly higher than 6 nodes in the network (see Supplementary Figure S2A). Differently, among the male group, the standardized EI of "GAD2" (Uncontrollable worry), "PHQ4" (Energy) and "GAD5" (Restlessness) ranked in the top three. The EI of "GAD2" (Uncontrollable worry) is significantly higher than the other 10 nodes in the male network (see Supplementary Figure S2B). The standardized bridge EI of symptoms is shown in Figure 2B. According to Figure 2B, "GAD1" (Nervousness) and "GAD5" (Restlessness) are the bridge symptoms of both the female group and male group, with standardized bridge EI higher than 1. Additionally, "PHQ8" (Motor) are the unique bridge symptom of the female group.

3.2 Network comparison

Figure 3 depicts the results of network comparison between the female group and the male group. There are no significant differences in the distribution of edge weights ($M = 0.233$, $p = 0.71$) and global strength ($S = 0.328$, $p = 0.139$) between two groups.

TABLE 1 The descriptive information of female group and male group and the results of *t*-test between two groups.

Variables	Labels	Female group (*n* = 147)	Male group (*n* = 266)	*p*
		Mean (SD)	Mean (SD)	
age		50.32 (14.54)	50.88 (12.61)	0.697
PHQ1	Anhedonia	1.11 (0.94)	1.06 (0.90)	0.610
PHQ2	Sad Mood	0.97 (0.94)	0.71 (0.84)	0.005
PHQ3	Sleep	1.28 (0.98)	1.05 (0.98)	0.025
PHQ4	Energy	1.29 (1.03)	1.21 (0.92)	0.485
PHQ5	Appetite	1.16 (0.95)	1.00 (0.90)	0.083
PHQ6	Guilt	0.79 (0.99)	0.66 (0.90)	0.183
PHQ7	Concentration	0.78 (0.96)	0.68 (0.95)	0.302
PHQ8	Motor	0.66 (0.84)	0.55 (0.81)	0.195
PHQ9	Suicidal ideation	0.43 (0.73)	0.25 (0.62)	0.014
GAD1	Nervousness	0.85 (0.89)	0.76 (0.88)	0.298
GAD2	Uncontrollable worry	0.82 (0.99)	0.60 (0.82)	0.020
GAD3	Excessive worry	1.02 (1.05)	0.78 (0.89)	0.019
GAD4	Trouble relaxing	0.88 (1.00)	0.68 (0.89)	0.040
GAD5	Restlessness	0.56 (0.84)	0.54 (0.86)	0.788
GAD6	Irritability	0.97 (0.96)	0.86 (0.90)	0.260
GAD7	Feeling afraid	0.73 (0.97)	0.50 (0.81)	0.012
Depression		8.47 (5.96)	7.17 (5.71)	0.033
Anxiety		5.84 (5.90)	4.71 (5.14)	0.051
SED		27.35 (7.19)	27.95 (7.68)	0.434

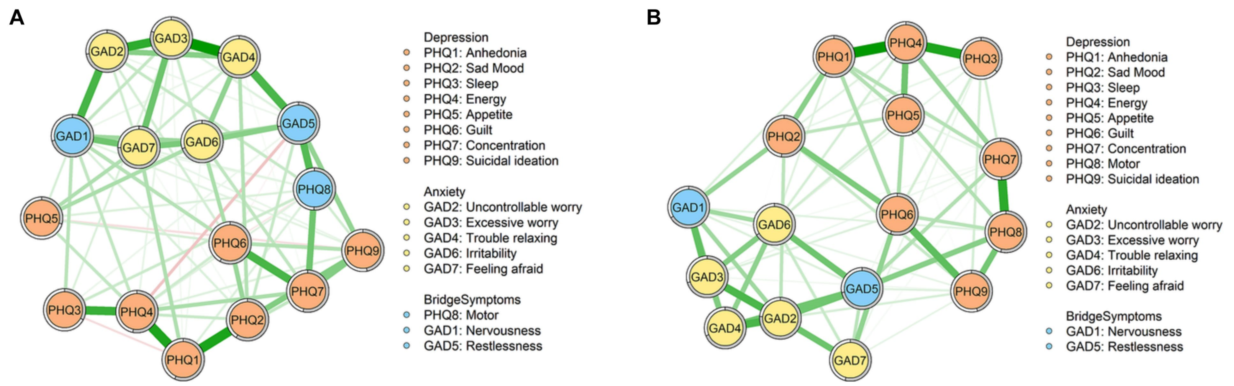

FIGURE 1
Network structures. **(A)** Depression-anxiety symptom network of the female group. **(B)** Depression-anxiety symptom network of the male group.

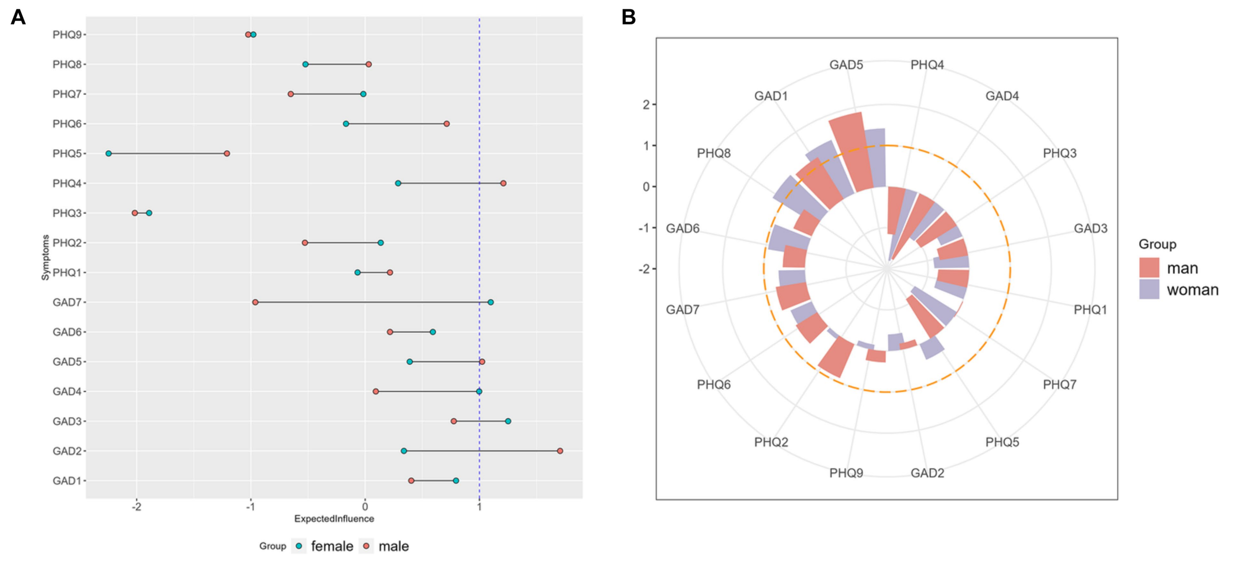

FIGURE 2
Standardized EI and bridge EI. **(A)** Standardized EI of each symptom in female and male groups. **(B)** Standardized bridge EI of each symptom in female and male groups.

3.3 Network stability and accuracy

The results of the bootstrapped analysis are depicted in Supplementary Figure S3. Additionally, Supplementary Figures S4, S5 show the results of case-dropping analysis. The CS-Cs of EI of the female group and male group are 0.592 and 0.594, respectively. In terms of the CS-Cs of bridge EI of two groups, the CS-C of the female group is 0.204 and the CS-C of the male group is 0.282.

3.4 Flow network

The flow diagrams of the female group and the male group are shown in Figure 4. According to Figure 4, we can find that compared with the male group, the female group has more symptoms that are directly connected with self-efficacy. Among the symptoms that are directly linked with self-efficacy, "PHQ6" (Guilt) is the symptom with the strongest connection in the female group. In the male group, "PHQ5" (Appetite) is the symptom that has the strongest negative association with self-efficacy.

4 Discussion

The present study focuses on individuals with diabetes, examining the symptom-level relation between depression, anxiety, and self-efficacy. Several striking findings needed to be further explained.

According to the results of the *t*-test, we discovered that, compared to males, females have higher prevalences of depression and anxiety. This is consistent with the other research considering the sex difference, suggesting that, among people with diabetes, females have higher risks of developing depression and anxiety (27, 50). Additionally, similar to other studies, we also found that the mean level of self-efficacy of females with diabetes is lower (29). Previous

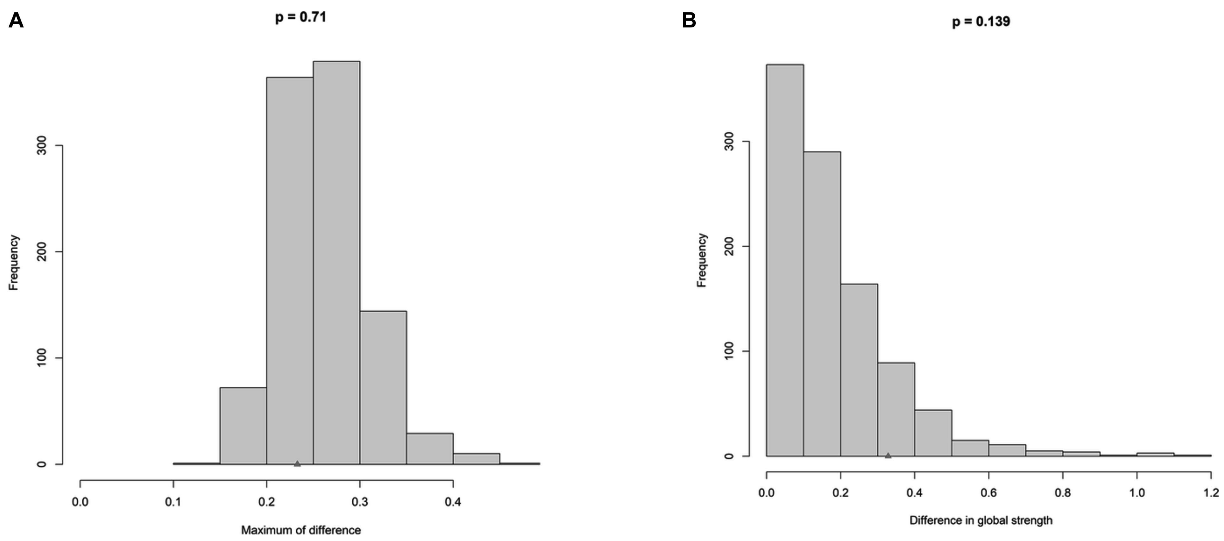

FIGURE 3
Comparison of network between trauma group and no-trauma group. **(A)** Differences in edge weights for the networks. **(B)** Differences in global strength for the networks.

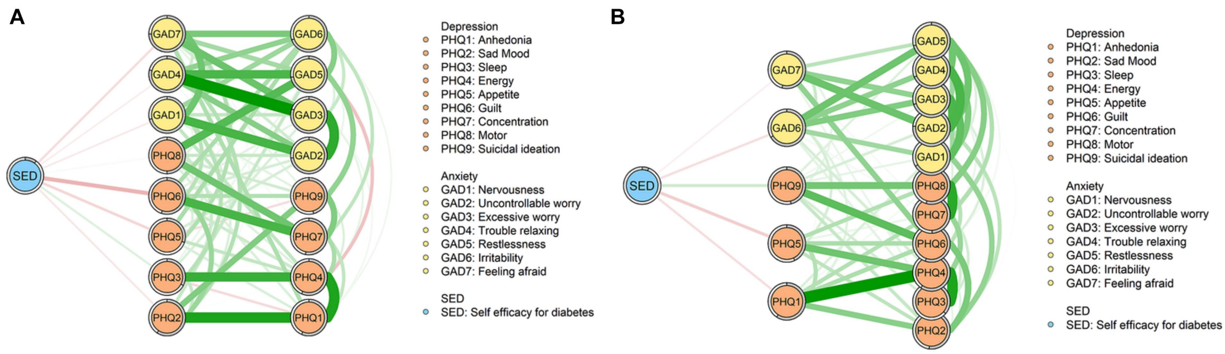

FIGURE 4
Flow network models. **(A)** Flow network of female group. **(B)** Flow network of male group.

research also identified that females seem to experience a greater impact of diabetes (51) and factors such as hormones, genes, and social roles may play a role (52). In other words, females facing diabetes may be more vulnerable to psychological problems, which need extra concern.

In terms of the results of depression-anxiety network, our analysis showed that the edge between "GAD3" (Excessive worry) and "GAD4" (Trouble relaxing) and the edge between "PHQ1" (Anhedonia) and "PHQ4" (Energy) are the strongest edges in the female and male group, respectively. The variation of the strongest edges may be related to the traditional social roles of different sexes. Traditionally, females usually need to be the caregiver and are expected to take care of household chores (53). This traditional perception of gender roles may be more typical in older individuals (54). Thus, females with diabetes in the current study may not only need to worry about their own physical and mental health but also need to take responsibility for other household chores and matters within the family. What's more, the study also suggests that females are more anxious about the disease (55). These may contribute to the strongest edge between "GAD3" (Excessive worry) and "GAD4" (Trouble relaxing) among the female network. Differently, the traditional social role of males is that males usually take more outdoor and social activities. Additionally, males seem to have a higher level of sensation seeking than females (56). Pleasurable activities will inevitably be restricted due to diabetes, which may make males feel a lack of enjoyment. This may be the possible explanation for the strongest edge between "PHQ1" (Anhedonia) and "PHQ4" (Energy) in the male group.

With respect to the results of EI and bridge EI of each node, our study found that, in both the female group and male group, symptoms with the highest EI and two bridge symptoms are related to worry and nervousness. Stuckey et al. (57) explored the psychosocial experiences of diabetes and found two main negative psychosocial themes. One of them is the anxiety and fear about hypoglycemia and complications of diabetes. Apart from this, a review of literature about qualitative studies on the lived experience of individuals with diabetes also pointed out that individuals with diabetes have uncertainty about the future and are afraid of losing functions (58). These findings, together with the results of our analysis, suggest that the uncertainty and worry about illness and life among people with diabetes is a key point that needs to be solved.

Out of our expectation, the analysis of NCT did not yield significant results, which showed that the global strength between two groups did not have a significant difference. On one hand, this finding shows that the connectivity between the nodes of two groups did not have a difference. This indicates that the increased susceptibility to developing depression and anxiety among females with diabetes (as evidenced by higher mean levels and prevalence rates of depression and anxiety) is not solely due to a closer association between anxiety and depression symptoms, which are more likely to trigger and perpetuate each other (59). Instead, there may be other factors that put females with diabetes in a situation where they are more likely to have anxiety and depression. Factors like culture, gender roles, and genes may contribute to this (52, 60). On the other hand, the limitations of sample size may be associated with this not non-significant result. Thus, future studies with larger sample sizes are needed.

A striking difference existed in flow diagrams of female and male groups including symptoms of depression and anxiety, and self-efficacy, which shows the outstanding relation between "PHQ6" (Guilt) and self-efficacy in the female group but not male group. In the male group, "PHQ5" (Appetite) and self-efficacy have the strongest association. "PHQ6" (Guilt) represents the extent to which an individual feels bad about themselves and feels that they are letting their family down (61). Our finding is similar to the results of previous research, which observed that females with diabetes experienced more interpersonal distress and males with diabetes experienced more regimen-related distress (62). Additionally, research also documented that females with diabetes reported more weight stigma (63) and lower self-esteem (64) compared to males. Thus, we can infer that females with diabetes may suffer from more interpersonal distress and may have low self-esteem. This may have an association with self-efficacy (62), as the results in the present study. Differently, regimen-related distress, such as problems of appetite, has a high association with self-efficacy. According to this, the intervention targeting to relieve the feeling of guilt and self-blame may be helpful for females with diabetes to improve their self-efficacy. For males with diabetes, it may be necessary to increase their self-efficacy by reducing regimen-related distress.

5 Limitations

Although the current study shows fresh insights about the symptom-level relation between depression, anxiety, and self-efficacy among people with diabetes and examines the sex differences, several limitations need to be noted. First, the current study used self-report questionnaires and it was undoubtedly affected by subjectivity. Thus, future studies can try to use some objective indicators or combine the other-report questionnaire, which can provide more comprehensive and objective information. Second, most of the participants in this study were middle-aged individuals. Considering the psychological and physical characteristics of middle-aged individuals, the results derived from this study may not be generalisable to individuals of other ages. Third, the results of bootstrapped analysis and case-dropping analysis showed that the accuracy and stability are less satisfactory, which may be due to the limited sample of the study. Thus, future studies can further examine and validate the results of this study.

6 Conclusion

This research, recruiting participants with diabetes, aims to explore the symptom-level relations between depression, anxiety, and self-efficacy through network analysis. Additionally, the current study also examined whether there are sex differences. Our analysis showed that females with diabetes had higher prevalences of depression and anxiety, and scored lower in self-efficacy. As to the depression-anxiety symptom network of females, the edge between "GAD3" (Excessive worry) and "GAD4" (Trouble relaxing) is the strongest edge. In the male group, the edge between "PHQ1" (Anhedonia) and "PHQ4" (Energy) is the strongest. In terms of the key symptoms in the network models, symptoms with the highest EI and two bridge symptoms relate to worry and nervousness across two groups. Last, our research found that the relations between depression and anxiety symptoms and self-efficacy differ in female and male groups. "PHQ6" (Guilt) played a significant role in the flow network of females.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by this research was examined and approved by the ethics committee of Bengbu Medical University (Reference number: No. 148 [2021]). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DW: Investigation, Methodology, Writing – original draft. ZS: Writing – review & editing. CW: Writing – review & editing. WS: Writing – review & editing. GJ: Conceptualization, Data curation, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1368752/full#supplementary-material

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Effects of exercise therapy on anxiety and depression in patients with COVID-19: a systematic review and meta-analysis

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Objective: With increasing rates of anxiety and depression during COVID-19, exercise treatment has drawn attention for its effects on COVID-19 patients with anxiety and depression. This study set out to assess the impact of exercise therapy on COVID-19 patients' anxiety and depression.

Methods: PubMed, EMBASE, Web of Science and Cochrane Library were used to search articles about exercise therapy as a means of treating anxiety and depression in COVID-19 patients from inception to April 30, 2023. The risk of bias was assessed by the Cochrane Collaboration bias risk tool. Data were pooled with the random effects model. RevMan version 5.4 was used for the statistical analyses. This work was registered in the PROSPERO database (registration number: CRD42023406439).

Selection criteria: Randomized clinical trials (RCTs) of COVID-19 patients with anxiety and depression were included to assess the impact of physical exercise on COVID-19 patients with anxiety and depression.

Results: 6 studies including a total of 461 COVID-19 patients were analyzed in this meta-analysis. Overall, the meta-analysis showed that compared with the control group, exercise could significantly improve anxiety (SMD = −0.76; 95%CI: −0.96, −0.55; $p < 0.00001$), depression level (SMD = −0.39; 95%CI: −0.70, −0.09; $p = 0.01$), the PHQ-9 score (MD = −1.82; 95%CI: −2.93, −0.71; $p = 0.001$) and the sleep quality (SMD = −0.73; 95%CI: −1.32, −0.14; $p = 0.01$) in COVID-19 patients.

Conclusion: The research provided evidence that exercise therapy is able to help COVID-19 patients experience less anxiety and depression and have better-quality sleep.

Systematic review registration: CRD42023406439.

KEYWORDS

exercise therapy, COVID-19, anxiety, depression, meta-analysis

Introduction

The novel coronavirus SARS-CoV-2 caused a febrile respiratory sickness outbreak, which swiftly led to a global outbreak known as coronavirus disease 2019 (COVID-19) (1, 2). The WHO estimates that there are currently over 760 million infected COVID-19 and over 6 million fatalities worldwide (3). To date, there is no specific therapy established to treat

COVID-19 and only symptomatic treatment can alleviate the symptoms, but it is unable to keep up with the rate of mutation (4). In particular, the appearance of the Omicron variant BA.1 has presented a rigorous challenge in the fight against COVID-19 (5). COVID-19 in addition to seriously jeopardizing the physical and mental health of COVID-19 patients, it caused severe morbidity, mortality, and financial stress for families and society (6).

Both depression and anxiety are severe neurological illnesses that may lead to suicidal thoughts and self-inflicted injury, as well as impairing memory and sleep. Globally, the COVID-19 epidemic has a profound psychological impact. Studies have shown that patients with COVID-19 had a markedly elevated chance of acquiring mental health issues, especially anxiety and depression. The total prevalence of anxiety and the total prevalence of depression were over 40% (7–9). Despite the fact that there are currently effective medications for depression or anxiety, many individuals do not benefit from them, find them intolerable, or get withdrawal symptoms when the medication is stopped (10). In recent years, many people who suffer from depression or anxiety turn to unconventional and non-pharmacological therapies (11). A randomized controlled trial showed that young people hospitalized to mental hospitals for anxiety and depression benefit both physically and psychologically from physical exercise (12). Exercise may offer individuals with COVID-19 and anxiety and depression a flexible, easy-to-use, and promising therapeutic option. The clinical evidence hierarchy is headed by a systematic review and meta-analysis (13). For the purpose of providing a reference for treating health crises brought on by post-COVID-19 anxiety and depression, this study will carry out a meta-analysis and systematic review to look into the impacts of exercise therapy in treating anxiety and depression produced by COVID-19.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria were followed in the conduct of this meta-analysis (14). And the PRISMA-Checklist is added in the Supplement.

Search strategy

This study searched articles about RCTs that the impacts of exercise therapy on COVID-19 patients with anxiety and depression in the online databases of PubMed, EMBASE, Web of Science and Cochrane Library from inception to April 30, 2023. We devised search techniques that blended free-text phrases containing people with COVID-19, depression, anxiety, exercise treatment, and randomized clinical trials (RCTs) with medical subject categories. The search strategy used in each database is shown in Supplementary File S1.

Abbreviations: RCTs, Randomized controlled trials; SMD, Standard mean difference; MD, Mean difference; COVID-19, Coronavirus disease 2019; SAS, Self-Rating Anxiety Scale; HAM-A, Hamilton Anxiety Rating Scale; SAI, State Anxiety Inventory; GAD-7, Generalized Anxiety Disorder Scale-7 Item; HADS, Hospital Anxiety and Depression Scale; SDS, Self-Rating Depression Scale; BDI, Beck Depression Inventory; PHQ-9, Patient Health Questionnaire-9; LPS, Lipopolysaccharide.

Inclusion criteria and exclusion criteria

Inclusion criteria
- Study population: COVID-19 patients who have symptoms of anxiety and depression
- Study type: RCTs
- Primary outcome indicators: the degree of anxiety and depression
- Secondary outcome indicators: Patient Health Questionnaire-9 (PHQ-9) and Quality of sleep
- Published from inception to April 30, 2023
Exclusion criteria
- Overview, review, protocol
- Meta-analysis
- Non-RCTs
- RCTs without published outcome indicators
- Non-COVID-19 patients, non-anxiety or non-depression
- Non-exercise therapy
- Letter, comment, abstract, chapter, erratum, dissertation or editorial journal

Interventions

Patients in the experimental group were treated by exercise therapy. The comparison groups involve other treatments except exercise therapy.

Outcome

The main results were the degree of anxiety and depression, with scores changing during treatment. Anxiety was assessed by the Self-Rating Anxiety Scale (SAS), the Hamilton Anxiety Rating Scale (HAM-A), State Anxiety Inventory (SAI), Generalized Anxiety Disorder Scale-7 Item (GAD-7), Hospital Anxiety and Depression Scale (HADS). Depression was assessed by the HADS, Self-Rating Depression Scale (SDS), Beck Depression Inventory (BDI). Secondary outcomes were Patient Health Questionnaire-9 (PHQ-9) and Quality of sleep.

Study selection

The studies are independently reviewed and screened by two reviewers (JT and HZ) in accordance with the review's inclusion and exclusion criteria. To exclude duplicate articles, the reviewers used EndNote X9 software. They then study the article titles and abstracts to weed out any plainly irrelevant material. They next read the complete contents of the remaining publications, filter them, and justify the exclusion of the researches that were not qualified. Disputes were resolved through discussing with the third reviewer (L-LC).

Data collection and analysis

Independently, after reading the literature, two reviewers (PW and L-LC) took the data out of the studies that were included. Each study's details, such as the publication year, first author, sample size, participant age, intervention, control, treatment plan, and primary outcome, were among the data that were gathered. In cases where there was a disagreement between the two reviewers throughout the screening process, the judgment was ultimately made after consulting a third reviewer (FM).

Risk of bias analysis of included studies

Two researchers (PW and L-LC) used the seven-item Cochrane Collaboration Risk of Bias assessment to independently assess the methodological quality of the literature (15). Each component's bias risk was evaluated, and the findings were divided into three risk categories: low risk of bias, unclear risk of bias and high risk of bias and then the risk of bias assessment was plotted by Review Manager 5.4 software.

Data analysis

RevMan version 5.4 was used to analyze the statistical. Continuous outcomes were analyzed using MD or SMD with a 95% CI, and the SMD statistic was selected when the outcome was assessed using different scales. Data were pooled with the random effects model. The assessment of study heterogeneity was conducted using I^2 statistic measurements. If $I^2 < 25\%$, will be considered as no significant heterogeneity. I^2 is between 25 and 50%, will be considered as moderate heterogeneity. $I^2 > 50\%$ will be considered as significant heterogeneity. When $I^2 \geq 25\%$, subgroup analysis was performed to identify the source of any clinical heterogeneity seen in the pooled findings.

Results

Study selection and basic characteristics

4 electronic databases were searched, yielding a total of 416 documents. 104 duplicate articles were eliminated. The titles and abstracts of these papers led to the exclusion of 294 citations. 12 researches were eliminated due to their failure to meet the qualifying requirements, leaving 18 papers that passed the full-text examination. Figure 1 illustrates how the remaining 6 RCTs, which had 461 individuals, fulfilled the eligibility requirements. Table 1 provides a summary of the baseline characteristics of the six trials.

Risk of bias assessment

All studies (16–21) mentioned randomly divided, due to Jung et al. (18) divided groups according to their bed number and

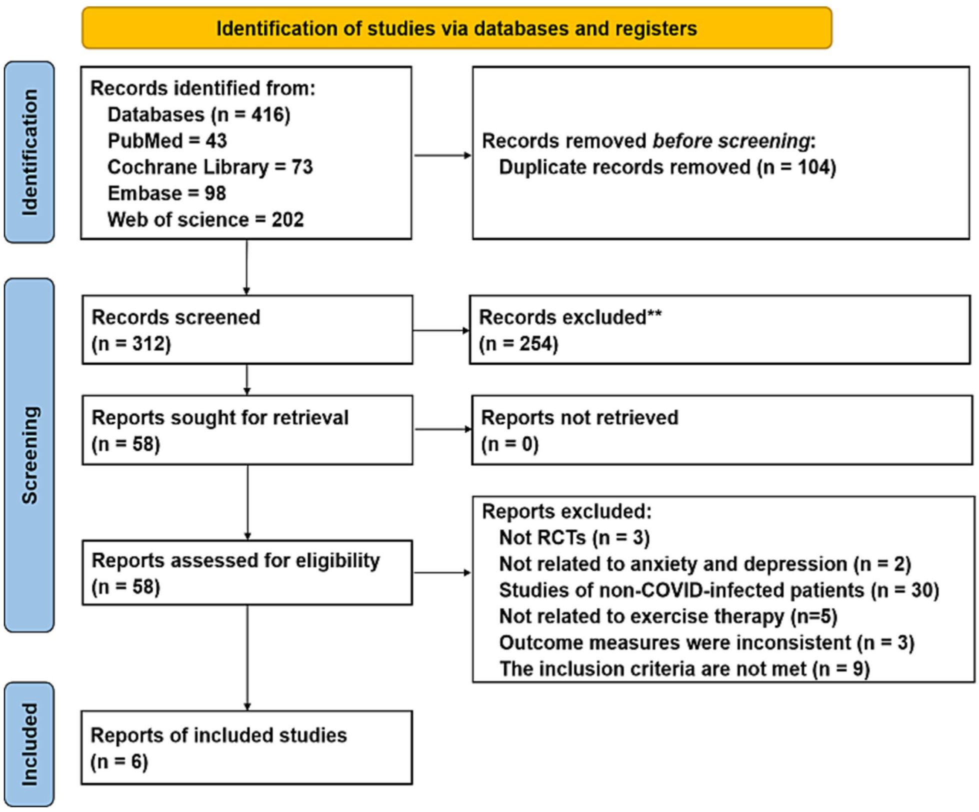

FIGURE 1
Literature screening process.

TABLE 1 Basic characteristics of the included literature.

Study	Country	Design	Sample size	Age (mean ± SD)		Intervention time	Outcome
				Experiment	Control		
Liu et al. (16)	China	RCT	72	69.4 ± 8.0	68.9 ± 7.6	6 weeks	DLCO 6-min walk distance test QoL (SF-36) ADL SAS SDS
Bhanda-ri et al. (17)	India	RCT	38	Male: 29.7 ± 6.2 Female: 34.1 ± 15.1	Male: 34.4 ± 11 Female: 28.6 ± 12	1 month	BDI HAM-A WHO-QoL-BREF DTS
Jung et al. (18)	Korea	RCT	109	51.06 ± 16.42	45.96 ± 17.20	7 days	SAS SDS PHQ-9 VAS ISI-K
Liu et al. (19)	China	RCT	140	NA	NA	1 month	SAI PSQI
Sharma et al. (20)	India	RCT	62	49.41 ± 12.51	53.64 ± 11.55	5–18 days	HADS GAD-7 PHQ-9 PSS-10
Zhang et al. (21)	China	RCT	40	41.30 ± 7.73	42.10 ± 8.47	3 month	SAS SDS PSQI

Sharma's study was a quasi-randomized study were assessed high risk of bias. None of the studies had sufficient information to judge whether to perform allocation scheme concealment and blinding of outcome evaluators were unclear risk of bias. Included studies were treated for exercise therapy, and for RCTs, the outcome indicators were not affected by allocation concealment, so all studies were low risk of bias. The outcome data for all study were complete were low risk. None of all studies had sufficient information to assess the risk of selective reporting were unclear risk of bias. No other potential sources of bias in all studies were low risk of bias (show in Figures 2, 3).

Primary outcomes

Anxiety level

Six studies (16–21) involving 461 participants examined how exercise therapy affected COVID-19 patients' anxiety. Anxiety was measured using the SAS, HAM-A, SAI, HADS, and GAD-7. Due to the wide range of dimensions, the study employed SMD to aggregate the data on anxiety symptoms. The meta-analysis shows that, in comparison to the control group, the intervention group significantly improved the anxiety levels of COVID-19 patients overall ($SMD = -0.76$; 95%CI: -0.96, -0.55; $p < 0.00001$), the difference was statistically significant (show in Figure 4).

Depression level

321 participants in five studies (16–18, 20, 21) assessed how exercise therapy affected COVID-19 patients' depression. The investigation employed SMD to compile the data on depression symptoms using assessment techniques such as SDS, BDI, and HADS. The comprehensive data showed that, overall, the treatment group outperformed the control group in improving COVID-19 patient depression symptoms ($SMD = -0.39$; 95%CI: -0.70, -0.09; $p = 0.01$), the difference was statistically significant (show in Figure 5).

Subgroup analysis

The treatment time is split into two categories: less than 1 month and more than 1 month, depending on how long the intervention is. The treatment group and the control group differ from one another, as seen by the results from different intervention durations. Subgroup distinctions exist, and in contrast to the control group, individuals with COVID-19 can experience improved depression with more than a month of exercise therapy (show in Figure 6).

One on respiratory motion study reached no conclusions. Four exercise-focused studies suggesting that there are subgroup differences, and exercise-focused exercise therapy can help COVID-19 patients who are depressed compared with the control group. Comprehensive outcomes of various intervention types demonstrate

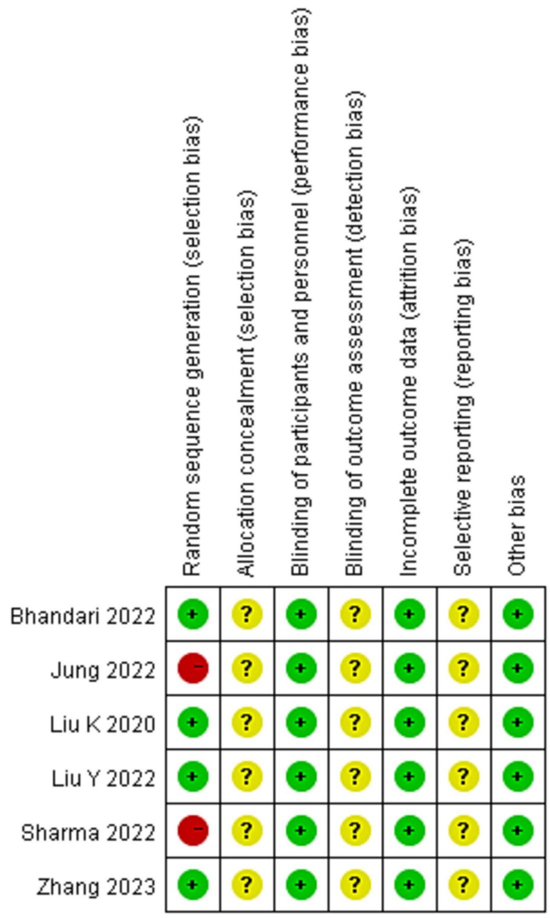

FIGURE 2
Risk of bias summary about each risk of bias item for each included study.

that the experimental group and the control group differ from one another (show in Figure 7).

Secondary outcomes

PHQ-9

According to DSM-IV criteria, the PHQ-9 is a standard screening tool used to identify depression. It is an accurate and reliable indicator of the severity of depression (22). The intended outcome, PHQ-9, was reported in two studies (18, 20). The intervention group significantly outperformed the control group in terms of improving PHQ-9 score (MD = −1.82; 95%CI: −2.93, −0.71; $p = 0.001$), a statistically significant difference was present (show in Figure 8).

Quality of sleep

There were 4 studies that reported on the patients' sleep quality, and since the data from 1 study was insufficient, 3 studies (18, 19, 21) were included. Quality of sleep was assessed by the PSQI and ISI-K. The data on depressive symptoms were combined by the study using SMD. The findings indicate a noteworthy distinction in the improvement of sleep quality between the intervention group and the control group (SMD = −0.73; 95%CI: −1.32, −0.14; $p = 0.01$), the difference was statistically significant (show in Figure 9).

Conclusion

For this study, the effects of exercise therapy on depression and anxiety were evaluated in six trials with a total of 461 COVID-19 participants. When compared to the control group, the intervention group significantly improved COVID-19 patients' anxiety overall. When compared to the control group, the intervention group showed improvements in the depressed symptoms of COVID-19 patients. This study conducted subgroup analysis because the total results were quite statistically diverse. The findings indicated that depression could be improved with more than a month of exercise therapy, and that depression could be improved with activity-focused exercise therapy when compared to the control group in COVID-19 patients. Patients with COVID-19 may have improvements in their PHQ-9 and sleep quality with exercise therapy. In conclusion, our study discovered evidence to suggest that exercise therapy significantly improves anxiety and depression in COVID-19 patients.

The form of exercise in this study had an impact on exercise therapy to treat depression in patients, and Table 2 lists the various strategies used in each study. The impact of breathing-based exercise on depression in COVID-19 patients did not differ statistically; all other exercise modalities effectively reduced depressive symptoms in these individuals. Among other things, the genre of literature and the sample size of the included literature may have an impact on this finding. Second, the set of changes achieved was not necessarily entirely due to exercise because five of the six included trials were multimodal therapies with an emphasis on exercise therapy. In certain research, secondary outcome indicators for anxiety and depression may have affected the results.

Discussion

Currently, there are no existing licensed anti-viral therapies, so non-pharmaceutical therapies continue to be essential for COVID-19 management (23). Increased rates of mental illness, depression, anxiety, self-harm, and suicide have been linked to the COVID-19 pandemic (24, 25). Depression and anxiety are serious public health problems. It is estimated that around 20–40% of patients who experience depressive episodes do not respond clinically to the antidepressant treatments now being used, furthermore, around half of the patients who get symptom amelioration still have persistent symptoms that impair their functioning and raise the risk of relapse (26). Furthermore, 76–85% of those suffering from mental illnesses get no therapy at all, which has a detrimental effect on the individuals, their families, and society (27). Studies have shown that mental illnesses make about 2% of all diseases worldwide. Study show that from 2010 to 2030, the estimated $2.5 trillion in treatment costs are predicted to have increased to $6 trillion (28). The prevalence of anxiety and depression has increased significantly, and new treatments are urgently needed because there is still a high failure rate in the treatment of these conditions, which poses a serious threat to people's mental health, particularly in the context of the long-term COVID-19

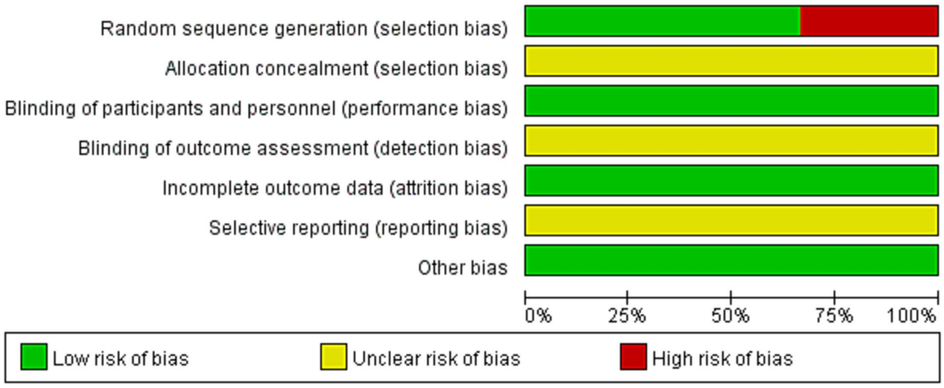

FIGURE 3
Demonstrate the risk of bias in the included studies.

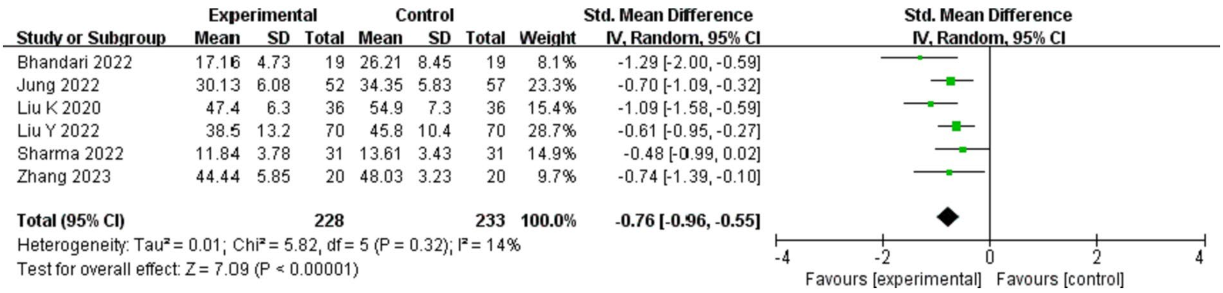

FIGURE 4
Effect of exercise therapy on anxiety in patients with COVID-19.

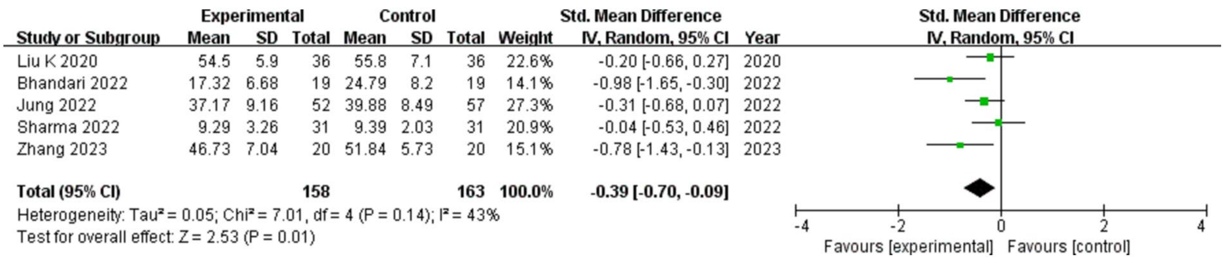

FIGURE 5
Effect of exercise therapy on depression in patients with COVID-19.

(29, 30). Research on anxiety and depression in COVID-19 patients has gained international attention since these conditions have a serious negative impact on patients' and their families' physical and emotional well-being throughout the pandemic. Furthermore, studies have shown that the COVID-19 pandemic may promote depression, anxiety symptoms, including children and adolescents (31, 32). And all types of physical activity among children and adolescents had a precipitous decline during the COVID-19 pandemic (33).

According to this study, exercise therapy could reduce anxiety and depressive symptoms in patients with COVID-19. It is well known that physical activity is good for both physical and mental health (34). When compared to psychotherapy and medicine, exercise therapy offers numerous advantages in terms of cost, side effects, and additional health benefits. It may produce results that are similar to those of psychotherapy and pharmacology (35). A study demonstrates that engaging in sport-based activities, whether solo or in a group setting, can reduce anxiety. Moreover, a higher frequency of physical activity is linked to reduced levels of melancholy and anxiety (36).

Exercise can reduce the symptoms of anxiety and depression through a variety of mechanisms. Increased oxidative stress and inflammation have been associated with depression and anxiety disorders (37–39), glucocorticoid release, overload of immune, anabolic and cardiovascular functions and hypothalamic–pituitary–adrenal (HPA) axis dysfunction, (40, 41) imbalance of intestinal flora

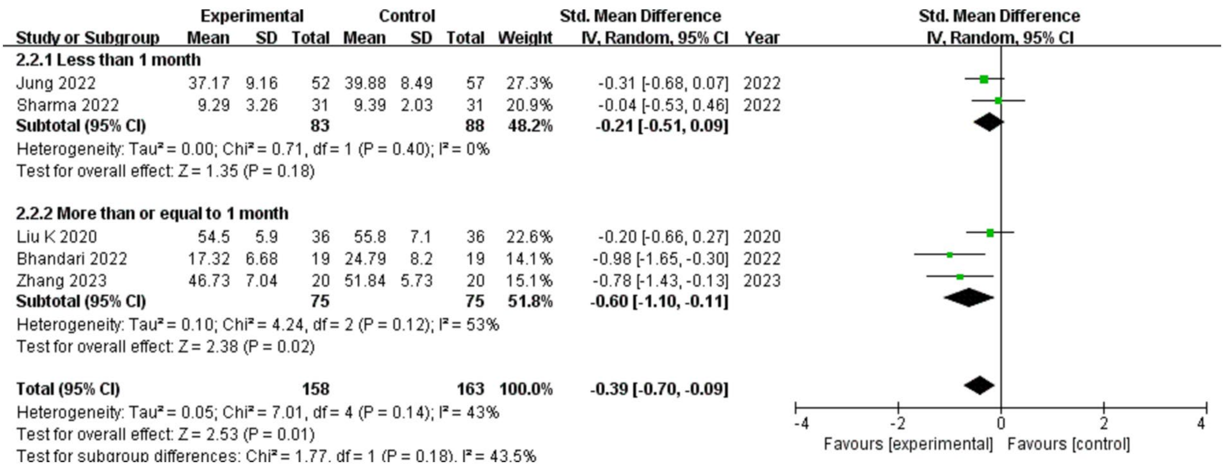

FIGURE 6
The effect of different of the length of intervention on depression in patients with COVID-19.

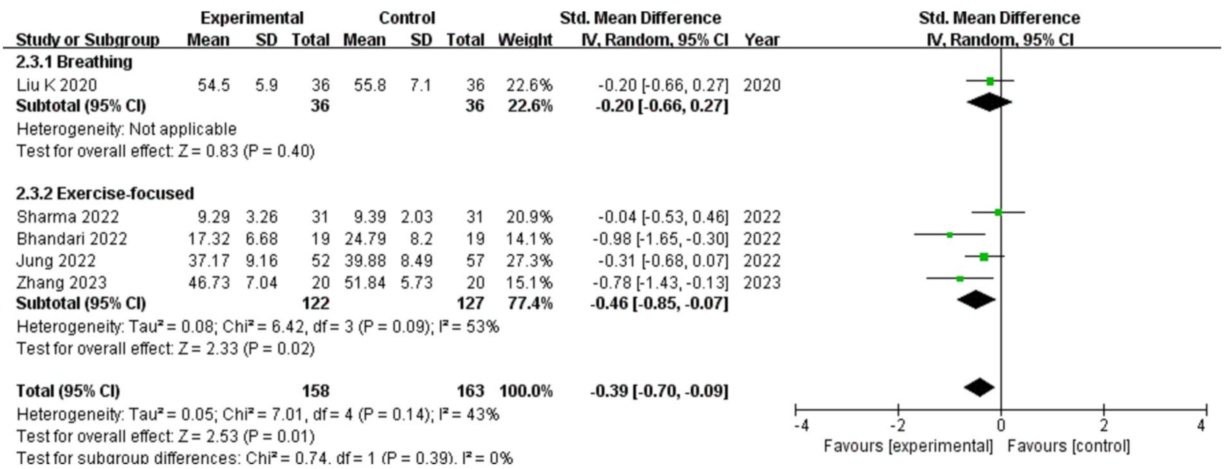

FIGURE 7
The effect of different exercise types on depression in patients with COVID-19.

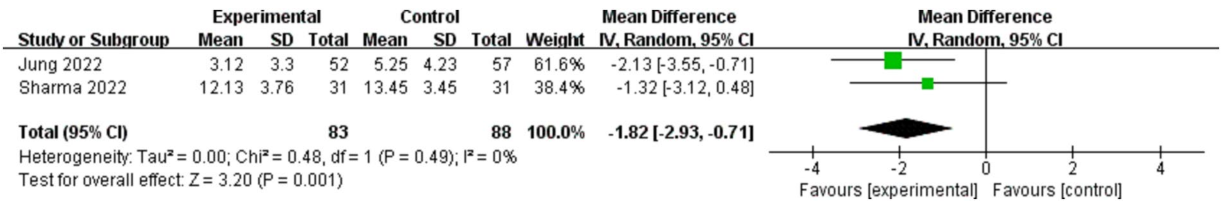

FIGURE 8
Effect of exercise therapy on PHQ-9 in patients with COVID-19.

(42) and so on in several studies and meta-analyses. Beheshti et al. found that Lipopolysaccharide (LPS)-induced depression- and anxiety-like behaviors were linked to the oxidative damage and neuroinflammation status of braintissues and the anti-LPS effects of amino guanidine included a decrease in inflammatory cytokines, a decrease in oxidative stress and a rise in anti-inflammatory mediators (43). Angulo et al. mentioned that exercise lowers oxidative damage and chronic inflammation, boosts autophagy, and enhances mitochondrial function (44). Wang et al. study found that aerobic exercise could decrease malondialdehyde (MDA), myeloperoxidase (MPO) levels and levels of IL-1β, TNF-α, and TGF-β in mice, supported that aerobic exercise was more effective in reducing cell

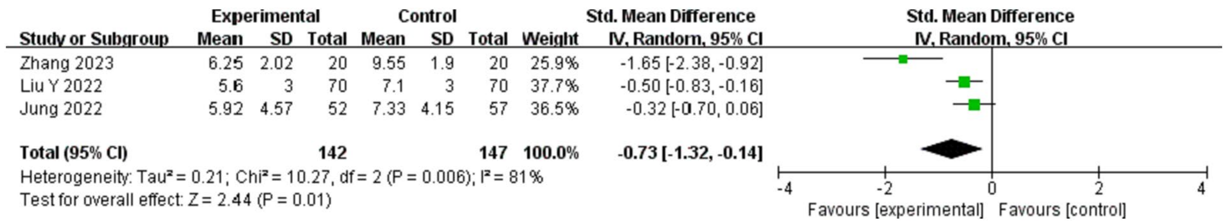

FIGURE 9
Effect of exercise therapy on the quality of sleep in patients with COVID-19.

TABLE 2 Characteristics of different exercise modality interventions.

Study	Interventions		Frequency	Anxiety assessment	Depression assessment
	Experiment	Control			
Liu et al. (16)	1. Respiratory muscle training; 2. Cough exercise; 3. Diaphragmatic training; 4. Stretching exercise; 5. Home exercise	Without any rehabilitation intervention	2 sessions per week for 6 weeks, once a day for 10 min	SAS	SDS
Bhanda-ri et al. (17)	1. Yoga exercises 2. Meditation	Routine care	Timing: 7:00 to 8:30 AM, 5 days a week	HAM-A	BDI
Jung et al. (18)	1. Physical activity 2. Education 3. Craft	Symptomatic treatment	20 min each day	SAS	SDS
Liu et al. (19)	1. Droup psychological intervention 2. Pulmonary rehabilitation exercises(Five-tone breathing exercises and Baduanjin exercises)	Routine care	Once a day, one day will last for about 30 min	SAI	NA
Sharma et al. (20)	Yoga exercises	Routine care	Once a day, 50 min yoga sessions	GAD-7	HADS
Zhang et al. (21)	Five-elements music therapy Baduanjin Qigong	Routine care	Twice a day repeatedly in sessions of about 30 min. One concentrated exercise per week	SAS	SDS

apoptosis, oxidative stress damage, and the inflammatory response (45). Research indicates that exercise treatment can impact the HPA axis, which is crucial for mood and cognition, and can lower levels of inflammatory cytokines (46). According to Ghannoum et al., an imbalance in the gut flora had a number of detrimental outcomes, such as imbalance of neurotransmitter levels and neuronal circuits, excessive production of proinflammatory cytokines in the immunological system, disruption of the intestinal barrier, and hyper activation of the HPA axis (47). Exercise has been demonstrated by Xia et al. to modify gut microbiota and improve malfunctioning gut-brain axis (48). Exercise increases the diversity of intestinal microorganisms, enriches good bacteria, and increases the number of butyrate-producing intestinal microbes, according to research by Du et al. These benefits are linked to improved health status (49). Overall, the effects of exercise on microbiota have been reported, mostly to improve colon health by increasing microbiota diversity and balancing the populations of harmful and helpful bacteria.

Exercise therapy can be effectively implemented in clinical practice because, according to this study, it can reduce the symptoms of anxiety and depression following COVID-19. It is also more acceptable than oral medication and aids patients' recovery with better compliance. In addition to the COVID-19, there are many epidemics such as HIV, tuberculosis (TB) and so on, which can also promote depression, anxiety symptoms (50–52). Exercise therapy can be used in future pandemics which promote depression and anxiety symptoms.

Limitations of the study

The limited number of publications included in this analysis is the first of its many shortcomings. Second, SMD was used in the analysis of the results due to the large number of various anxiety-depression-related rating scales that were used in the collected literature. The age in the third included study was primarily concentrated over 40 years, which may restrict the generalizability of the findings. Extensive high-quality randomized controlled trials are necessary to ascertain whether exercise therapy is beneficial in treating anxiety and depression in COVID-19 patients, especially those with varying age ranges. There is not enough information to determine how exercise treatment alone affects anxiety and depression in COVID-19 patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

JT: Writing – original draft. L-LC: Writing – review & editing. HZ: Writing – review & editing. PW: Writing – review & editing. FM: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1330521/full#supplementary-material

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Comparing multimodal physiological responses to social and physical pain in healthy participants

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Background: Previous physiology-driven pain studies focused on examining the presence or intensity of physical pain. However, people experience various types of pain, including social pain, which induces negative mood; emotional distress; and neural activities associated with physical pain. In particular, comparison of autonomic nervous system (ANS) responses between social and physical pain in healthy adults has not been well demonstrated.

Methods: We explored the ANS responses induced by two types of pain—social pain, associated with a loss of social ties; and physical pain, caused by a pressure cuff—based on multimodal physiological signals. Seventy-three healthy individuals (46 women; mean age = 20.67 ± 3.27 years) participated. Behavioral responses were assessed to determine their sensitivity to pain stimuli. Electrocardiogram, electrodermal activity, photoplethysmogram, respiration, and finger temperature (FT) were measured, and 12 features were extracted from these signals.

Results: Social pain induced increased heart rate (HR) and skin conductance (SC) and decreased blood volume pulse (BVP), pulse transit time (PTT), respiration rate (RR), and FT, suggesting a heterogeneous pattern of sympathetic–parasympathetic coactivation. Moreover, physical pain induced increased heart rate variability (HRV) and SC, decreased BVP and PTT, and resulted in no change in FT, indicating sympathetic-adrenal-medullary activation and peripheral vasoconstriction.

Conclusion: These results suggest that changes in HR, HRV indices, RR, and FT can serve as markers for differentiating physiological responses to social and physical pain stimuli.

KEYWORDS

social pain, physical pain, physiological signals, multimodal, autonomic nervous system

1 Introduction

Pain is not only a distressing experience in itself, but it can also have adverse effects on every aspect of life, including mood and the ability to perform daily roles (1). When pain persists and is not effectively managed, thus becoming chronic, it can cause emotional distress, impeding daily activities and affecting long-term health (2). In addition, pain is closely related to the quality of life (QOL) assessment, which reflects how satisfied and happy an individual's life is (1, 3). Pain encompasses cognitive, motivational, emotional, behavioral, and physical components, with the emotional aspect having the most significant impact on the QOL (4). Therefore, pain needs to be appropriately addressed to avoid detrimental outcomes in physical and mental health conditions. To achieve this, quantitative pain assessment can play an important role in obtaining accurate information about the pain, such as intensity, duration, and type (5).

The quantitative evaluation of pain based on physiological signals has attracted attention because of its potential to address health problems related to pain (5). For example, it is vital to quantify pain in hospitalized patients who cannot talk, and an accurate assessment of pain can assist healthcare providers understand the severity of a patient's condition and develop suitable treatments (6). Physiological signals are advantageous because signal acquisition by non-invasive sensors is comparatively straightforward, and physiological reactions to emotional stimuli exhibit considerable similarity across diverse societies and cultures (7). Previous physiologically-driven pain studies have demonstrated significant associations between several physiological signals and the presence of pain (5). Recently, automated methods for recognizing and analyzing pain have been demonstrated using machine-learning algorithms (8, 9).

Previous pain studies mainly focused on physical pain and estimated its intensity levels using various physiological signals, including electroencephalogram, electromyogram (EMG), electrodermal activity (EDA), electrocardiogram (ECG), and photoplethysmogram (PPG) (8–12). However, people experience various forms of pain including the termination of a social relationship as well as noxious bodily stimuli. Pain, by definition, is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (13). Pain is not only limited to physical pain but also includes a variety of negative emotional responses related to social injuries or perceptions of interpersonal rejection or loss (14).

Unlike physical pain—defined as "an unpleasant experience associated with actual or potential tissue damage or noxious physical stimuli"—social pain is "an unpleasant experience associated with actual or potential damage to one's sense of social connection or value owing to social rejection, exclusion, negative social evaluation, or loss" (15). In personality psychology, social pain refers to "the activation of pain affect in response to threats to, or losses of, social connection" (16). Hurt feelings are a subtype of social pain (16). Panksepp (14) explained that hurt feelings derived from these experiences are key emotional markers of social pain. From a clinical perspective, both physical and social pain are important. When pain is prolonged without adequate intervention or therapy, it can evoke a sense of helplessness (17). In severe cases, psychological distress that results from social loss can precipitate depressive episodes and even evoke suicidal thoughts (18).

On the surface, the two types of pain seem quite distinct. However, most pain studies have noted that the pain associated with a relationship break-up or the loss of a loved one is similar to the pain experienced upon physical injury, and researchers endeavored to tackle this issue by investigating the neural overlap between the two types of pain (19). Physiological results suggest that social and physical pain function through overlapping mechanisms involving the anterior cingulate cortex (ACC), periaqueductal gray brain structures, and the opioid and oxytocin neuroendocrine systems (20). The ACC—an area associated with the negative feelings of physical pain—responds to social exclusion tests (21). Endogenous brain opioid systems—known to regulate distress caused by physical pain—are neurochemical regulators of distress associated with social pain (15). Consistently, studies that investigated diverse scenarios capable of inducing social pain, such as social exclusion or bereavement, found activity in multiple neural regions that are linked to physical pain (15, 19). However, the distinctions between alterations of physiological signals induced by social and physical pain have not been thoroughly examined.

Previous studies on social pain have evaluated physiological responses but have mostly used negative evaluation tasks to induce pain (15). Although social pain also includes experiences in which a relationship is lost (15), physiological responses to social pain owing to the loss of a relationship require elucidation. Further, heart rate (HR) and blood pressure were primarily measured in previous studies on social pain (21, 22). Although these two features can represent changes in physiological responses, relying on these two measurements may not be sufficient to discriminate the activation patterns of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), which is important for understanding the dysregulation of physiological systems caused by social pain.

In recent research on physiological sensing to evaluate acute pain, some studies have utilized a combination of multiple physiological signals as potential indicators for pain recognition, most commonly evaluated through EDA, ECG, and PPG (23). Additionally, skin temperature and respiratory features have been used as metrics to evaluate pain. For example, local skin temperature (e.g., fingertip) decreases after experiencing painful stimuli (12, 24); a decrease in respiration rate (RR), which measures the number of breaths per minute, has been reported in response to pain (24, 25). Since each of these physiological measures has its constraints and advantages, integrating them can improve pain assessment.

Our aim was to explore the changes in autonomic nervous system (ANS) responses induced by two types of pain—social pain associated with a loss of social ties and physical pain caused by a pressure cuff—using multimodal physiological signals. We obtained ECG, EDA, PPG, respiration (RESP), and finger temperature (FT) data and then extracted the physiological features that evaluate the ANS response from the measured signals. These features were compared between social and physical pain to investigate whether there were differences in the ANS responses between pain types. We hypothesized that social and physical pain stimuli induce ANS responses reflected by multimodal signals, owing to the critical role of the ANS in response to mental and physical stress (26). In addition, we hypothesized that the SNS and PNS activity induced by the two pain types would show distinct patterns. The main contribution of this study is that we compared social and physical pain based on multimodal signals instead of focusing on the presence or absence of pain or pain intensity using fewer features, which provides new insights for understanding the difference in physiological responses to social and physical pain.

2 Materials and methods

2.1 Participants

Seventy-three healthy individuals (46 women; mean age = 20.67 ± 3.27 years) participated. No one reported a history of medical illness; use of neurological or psychiatric medication; or use of medication that could affect the cardiovascular, respiratory, or central nervous systems. All participants were introduced to the experimental procedure and signed informed consent forms before study commencement. This study was approved by the Institutional Review Board of Chungnam National University (no. 201309-SB-041-01). All participants received $30 USD.

2.2 Emotion-provoking stimuli

We specified social pain as the loss of a loved one to death, which could cause tremendous pain owing to the loss of access to a particular relational partner (27) and physical pain as a physical sensation that causes discomfort. To induce social pain, we used a 60-s long film clip showing a son grieving over his father's death, which was excerpted from a Korean drama entitled *Ruler of Your Own World* (28). We selected an audiovisual film clip as the emotion-provoking stimulus because film stimuli are readily standardized, dynamic rather than static, involve no deception, and demonstrate a considerable level of ecological validity (29). A 60-s long neutral film clip was excerpted from the same drama depicting a son talking to his father. To induce physical pain, a conventional blood pressure cuff was placed on the participant's non-dominant arm and progressively inflated to a peak pressure of 250 mmHg. Cuff inflation took 60 s, including maintaining the maximum pressure for 5 s. Simultaneously, during cuff inflation, participants were required to look at a plus sign (+) presented on the monitor. The plus sign was displayed in black on a white background to minimize the impact of color perception on the subject's response to the stimulus. As a neutral physical stimulus, the cuff was applied to the arm for 60 s without any inflation, and participants looked at the plus sign on the monitor. The stimuli were counterbalanced to minimize the effects of order and intensity. The pain-inducing stimuli are shown in Figure 1.

2.3 Procedure

Prior to the experiment, participants had a period of adaptation to feel comfortable in the laboratory setting. Electrodes for acquiring physiological signals were attached to the wrists, fingers, ankles, and chest. The following steps were applied to both social and physical pain: during the 60-s long baseline measurement of physiological signals, participants were asked to rest. Neutral and pain-inducing stimuli were then presented to the participants as described above, both of which lasted for 60 s. After the stimuli presentation, participants were asked to select the specific emotions they experienced during exposure (i.e., social pain, physical pain), and rate their dimensions (i.e., intensity, valence, and arousal) (Figure 1). Valence and arousal were rated on a scale ranging from −4 (negative valence and low arousal, respectively) to 4 (positive valence and high arousal, respectively). Intensity was rated on a seven-point Likert scale: 1 ("least") to 7 ("most"). The rating duration was 30 s. After the ratings, they were given 2 min to be debriefed and recover from their emotional states.

2.4 Physiological signal recordings

ECG, EDA, FT, RESP, and PPG signals were measured and analyzed using MP100WS and AcqKnowledge software (version 3.7.1) from Biopac Systems Inc. (Goleta, CA, United States). For all channels, the sampling frequency was set to 250 Hz. Amplification and bandpass filtering were applied to the collected signals. The ECG electrodes were attached to both wrists and the left ankle based on the lead-I configuration. The EDA signal was acquired using AgCl electrodes of 8-mm diameter attached to the volar surface of the distal phalanges of the index and middle fingers of the non-dominant hand. The electrodes were filled with a 0.05 molar isotonic NaCl paste to ensure a stable connection between the electrodes and the skin. The PPG sensor was placed on the first joint of the non-dominant thumb. The FT electrode was attached to the first joint of the non-dominant ring finger. The RESP sensor was wrapped around the chest using a Velcro strap to measure the expansion and contraction of the chest cavity based on the Hall effect. We chose ECG, EDA, FT, RESP, and PPG signals because they have been widely studied as important physiological signals that reflect ANS activity. Although these signals can be affected by motion or other environmental factors, their measurement using non-invasive sensors is simple and allows for real-time recording of a user's state. These physiological signals are less influenced by social and cultural differences and are resilient against social masking or factitious emotional expressions because they can be captured through spontaneous emotional responses (30).

2.5 Feature extraction

Data from the last 30 s of the baseline and the first 30 s of the neutral and pain-inducing states were used in the analysis (Figure 1). Twelve features were extracted from each experimental state: baseline, neutral, and pain-induced states (Table 1). Therefore, 36 features were extracted for each emotion type. HR, standard deviation of NN intervals (SDNN), root mean square of successive differences between adjacent NNs (RMSSD), and percentage of successive NNs that differed by more than 50 ms (pNN50) were extracted as the time-domain features of HR variability (HRV) from the ECG signals. Normalized powers in low frequency band (LFnu, 0.04–0.15 Hz) and high frequency band (HFnu, 0.15–0.4 Hz), and the LF/HF ratio were evaluated from HRV frequency spectral analysis (31). HFnu is the ratio of HF power to the sum of HF and LF power. LFnu is the ratio of LF power to the sum of HF and LF power. Therefore, LFnu and HFnu always add up to 1. LF/HF ratio is the ratio of LFnu to HFnu. Since LFnu and HFnu were exchangeable with a perfect linear association, we only used HFnu and LF/HF ratio in this study (32). Skin conductance level (SCL) and response (SCR) amplitude were analyzed as EDA indicators as they

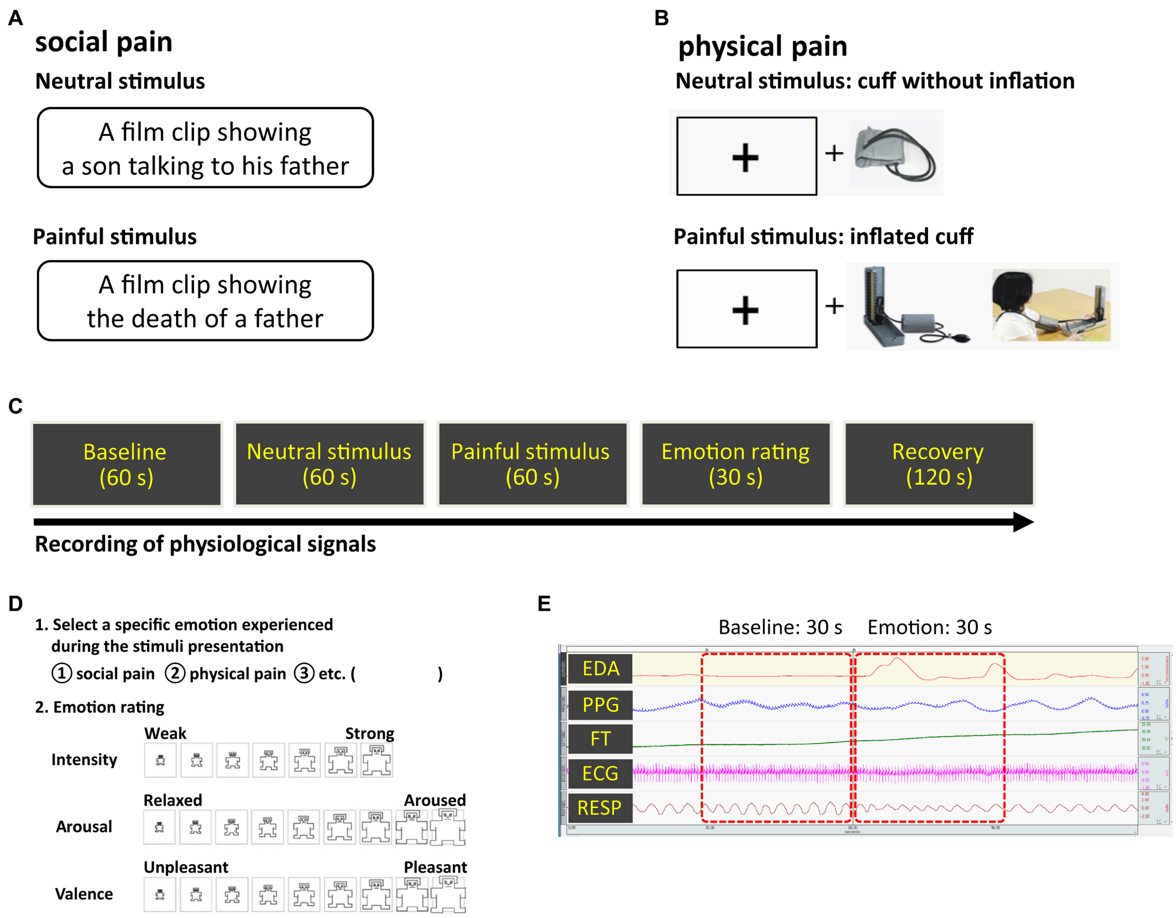

FIGURE 1
Experimental methods **(A)** social pain stimulus **(B)** physical pain stimulus **(C)** overall procedure **(D)** emotion rating scale **(E)** physiological signals observed during the experiment. Pain-inducing sessions were presented in random order.

represent changes in the electrical properties of the skin that are attributable to the functioning of sweat glands and are interpreted as conductance (33). SCL was the average of the tonic component of EDA. SCRs represent the phasic waves of the EDA signal. In the current study, SCR was calculated by averaging the SCR amplitude (0.05 µs or greater) of all the specific SCR events for a 30-s interval (34). The blood volume pulse (BVP) was calculated by averaging the BVP range, which refers to the difference between the highest and lowest values of each pulse wave, over a 30-s interval (35). Pulse transit time (PTT) was extracted from the ECG and PPG signals as it is a measure of the elapsed time between the R-peak of the ECG and the arrival of the pulse wave at the finger. RR was calculated by counting the number of breaths, defined as the number of times the chest increased during the baseline and emotional states. The FT was calculated by averaging the FT values for the 30-s interval.

In this study, we utilized the predominant method for measuring and analyzing emotion-specific ANS responses. Specifically, most previous studies averaged over 30- or 60-s intervals, while others frequently used interval durations of 0.5, 10, 120, 180, or 300 s (7). However, it has been observed that the average duration does not significantly influence the reported pattern of physiological responses (7), suggesting that a 30-s interval can be considered an appropriate ANS response measurement.

2.6 Statistical analysis

A paired t-test was used to compare the intensity ratings between two pain stimuli and to test differences in baseline feature values between two pain types. A two-way repeated-measures analysis of variance (ANOVA) was used to test the effects of the type of pain stimulus (social and physical) and experimental state (baseline, neutral, and painful) on physiological features. As a post-hoc analysis, between-pain type and between-state estimated marginal means were compared with confidence interval adjustments using the least significant difference method. The Bonferroni correction was used for multiple pairwise comparisons among experimental states for each pain type ($p < 0.0167$). All statistical analyses were performed using SPSS (version 21.0; IBM, Armonk, NY, United States).

3 Results

3.1 Participants' rating on the dimensions of emotion

Participants' ratings of the physical-and social pain-inducing stimuli on the dimensions of emotion (arousal and valence) showed

TABLE 1 Description of the physiological features used in the current study.

Signals	Features	Definition
ECG	HR (beat/min)	Average of HR
	SDNN (ms)	Standard deviation of NN intervals
	RMSSD (ms)	Root mean square of successive differences between adjacent NNs
	pNN50 (%)	Percentage of successive NNs that differed by more than 50 ms
	HFnu	HFnu = HF power / (LF power + HF power), where LF power and HF power are the absolute powers in the LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) bands, respectively.
	LF/HF	Ratio of LFnu to HFnu
RESP	RR (breath/min)	Number of breaths per minute
PPG	BVP (V)	Average of BVP range
ECG, PPG	PTT (ms)	Elapsed time between the R-peak of the ECG and the arrival of the pulse wave at the finger
EDA	SCL (μS)	Tonic level of electrical conductivity of skin
	SCR (μS)	Average of the SCR amplitude (0.05 μS or greater) of all the specific SCR events
Temperature	FT (°C)	Average of FT

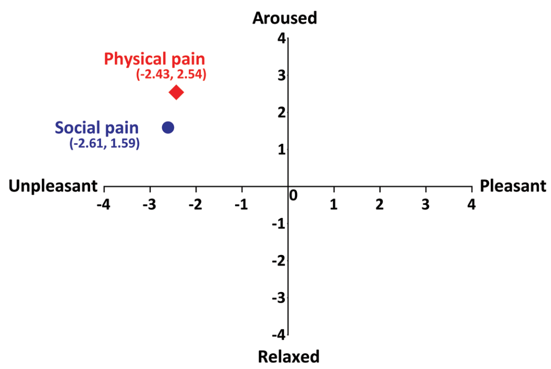

FIGURE 2
Participants' ratings of social and physical pain on the dimension of emotion. Vertical axis represents the arousal and horizontal axis represents the valence.

that both stimuli were located in the same quadrant (Figure 2). The mean intensities of social and physical pain-inducing stimuli were 5.74 ± 0.71 and 5.63 ± 0.72, respectively. No significant differences were found in the intensity ratings between two pain stimuli ($t(72) = 0.599$, $p = 0.551$).

3.2 Physiological responses induced by social and physical pain

Table 2 shows the mean values of the physiological features representing the ANS responses during the three experimental states (baseline, neutral, and painful) for both types of pain stimuli. No significant differences were observed in the baseline feature values between two pain types.

3.2.1 Physiological features

Table 3 shows the results of the two-way repeated-measures ANOVA, which was conducted to analyze the effects of the type of pain stimulus and experimental state on each physiological feature, using a 2 (pain type: social and physical) × 3 (experimental state: baseline, neutral, and painful) within-participant model.

3.2.1.1 HR

There were significant main effects of pain type ($F(1, 72) = 12.580$, $p < 0.001$, partial $\eta^2 = 0.149$) and experimental state ($F(2, 144) = 5.343$, $p = 0.006$, partial $\eta^2 = 0.069$) on HR. There was no interaction between the pain type and experimental state ($F(2, 144) = 2.304$, $p = 0.104$, partial $\eta^2 = 0.031$). HR in social pain (80.71 ± 1.00) was higher than in physical pain (78.80 ± 0.89, corrected $p = 0.001$). Post-hoc analysis revealed that HR in painful state (81.05 ± 1.14) was significantly higher than in baseline (79.62 ± 0.90, corrected $p = 0.040$) and neutral states (78.59 ± 0.97, corrected $p = 0.007$).

3.2.1.2 SDNN

The main effect of pain type was non-significant ($F(1, 72) = 1.466$, $p = 0.230$, partial $\eta^2 = 0.020$); however, the experimental state showed a significant main effect on SDNN ($F(2, 144) = 8.961$, $p < 0.001$, partial $\eta^2 = 0.111$). There was no significant interaction between the pain type and experimental state ($F(2, 144) = 1.076$, $p = 0.344$, partial $\eta^2 = 0.015$). Post-hoc analysis indicated that SDNN in painful state (39.00 ± 1.79) was significantly higher than in baseline (34.59 ± 1.29, corrected $p = 0.009$) and neutral states (33.24 ± 1.44, corrected $p < 0.001$).

3.2.1.3 RMSSD

There were main effects of pain type ($F(1, 72) = 14.934$, $p < 0.001$, partial $\eta^2 = 0.172$) and experimental state ($F(2, 144) = 7.051$, $p = 0.001$, partial $\eta^2 = 0.089$) on RMSSD. There was an interaction between the pain type and experimental state ($F(2, 144) = 3.119$, $p = 0.047$, partial $\eta^2 = 0.042$). RMSSD in social pain (28.58 ± 1.31) was lower than in physical pain (30.81 ± 1.35, corrected $p < 0.001$). Post-hoc analysis indicated that RMSSD in painful state (31.30 ± 1.47) was higher than in baseline (28.63 ± 1.30, corrected $p = 0.003$) and neutral states (29.15 ± 1.35, corrected $p = 0.011$).

3.2.1.4 pNN50

There were main effects of pain type ($F(1, 72) = 7.350$, $p = 0.008$, partial $\eta^2 = 0.093$) and experimental state ($F(2, 144) = 3.961$, $p = 0.021$, partial $\eta^2 = 0.052$) on pNN50. There was an interaction between pain

TABLE 2 Mean values (± SD) of physiological features measured during three experimental states in social and physical pain stimuli.

Feature	Social pain			Physical pain			t (p-value)[a]
	Baseline	Neutral	Painful	Baseline	Neutral	Painful	
HR (beat/min)	79.64 ± 3.94	80.11 ± 4.18	82.37 ± 6.08	79.60 ± 4.06	77.07 ± 5.91	79.74 ± 6.33	0.083 (0.934)
SDNN (ms)	34.88 ± 6.58	31.99 ± 6.29	37.68 ± 8.65	34.30 ± 6.66	34.49 ± 7.60	40.32 ± 9.66	0.337 (0.737)
RMSSD (ms)	28.67 ± 6.09	27.67 ± 5.50	29.40 ± 6.78	28.59 ± 5.75	30.63 ± 6.84	33.20 ± 6.78	0.076 (0.939)
pNN50 (%)	11.48 ± 7.45	9.56 ± 6.15	11.55 ± 7.04	10.14 ± 6.26	12.97 ± 8.04	14.57 ± 6.69	1.071 (0.288)
HFnu	0.59 ± 0.07	0.62 ± 0.07	0.62 ± 0.06	0.57 ± 0.08	0.58 ± 0.07	0.54 ± 0.06	1.202 (0.233)
LF/HF	0.82 ± 0.27	0.72 ± 0.25	0.67 ± 0.17	0.97 ± 0.36	0.87 ± 0.32	0.99 ± 0.26	−1.797 (0.077)
RR (breath/min)	3.83 ± 0.59	3.55 ± 0.38	3.45 ± 0.45	3.82 ± 0.57	3.66 ± 0.43	3.69 ± 0.51	0.100 (0.920)
BVP (V)	0.16 ± 0.05	0.14 ± 0.05	0.09 ± 0.03	0.17 ± 0.05	0.17 ± 0.05	0.08 ± 0.03	−0.408 (0.685)
PTT (ms)	275.45 ± 10.55	273.30 ± 10.21	266.62 ± 13.57	274.64 ± 9.79	276.53 ± 12.80	268.57 ± 12.84	0.593 (0.555)
SCL (μS)	0.22 ± 0.07	0.24 ± 0.76	0.30 ± 0.09	0.22 ± 0.07	0.23 ± 0.07	0.32 ± 0.08	0.890 (0.376)
SCR (μS)	0.07 ± 0.16	0.20 ± 0.25	0.62 ± 0.36	0.08 ± 0.10	0.08 ± 0.09	0.91 ± 0.35	−0.338 (0.736)
FT (°C)	32.24 ± 1.15	32.15 ± 1.20	32.01 ± 1.08	32.07 ± 1.24	31.90 ± 1.29	31.91 ± 1.28	1.154 (0.262)

[a]Differences in baseline values between two pain types.

type and experimental state ($F(2, 144) = 3.968$, $p = 0.021$, partial $\eta^2 = 0.052$). pNN50 in social pain (10.86 ± 1.44) was significantly lower than in physical pain (12.56 ± 1.48, corrected $p = 0.008$). Post-hoc analysis indicated that pNN50 in painful state (13.06 ± 1.50) was significantly higher than in baseline (10.81 ± 1.49, corrected $p = 0.020$).

3.2.1.5 HFnu

There was a main effect of pain type on HFnu ($F(1, 72) = 18.962$, $p < 0.001$, partial $\eta^2 = 0.208$) but not in experimental state ($F(2, 144) = 2.029$, $p = 0.135$, partial $\eta^2 = 0.027$). There was no interaction between pain type and experimental state ($F(2, 144) = 2.847$, $p = 0.061$, partial $\eta^2 = 0.038$).

3.2.1.6 LF/HF

There was a main effect of pain type on LF/HF ($F(1, 72) = 24.171$, $p < 0.001$, partial $\eta^2 = 0.251$) but not in experimental state ($F(2, 144) = 1.597$, $p = 0.206$, partial $\eta^2 = 0.022$). There was no interaction between pain type and experimental state ($F(2, 144) = 1.949$, $p = 0.146$, partial $\eta^2 = 0.026$).

3.2.1.7 RR

The main effect of pain type was non-significant ($F(1, 72) = 3.379$, $p = 0.070$, partial $\eta^2 = 0.045$). Experimental state had a main effect on RR ($F(2, 144) = 3.354$, $p = 0.038$, partial $\eta^2 = 0.045$). There was no significant interaction between pain type and experimental state ($F(2, 144) = 1.345$, $p = 0.264$, partial $\eta^2 = 0.018$). Post-hoc analysis indicated that RR in baseline (3.83 ± 0.13) was higher than in neutral (3.61 ± 0.09, corrected $p = 0.015$) or painful (3.57 ± 0.09, corrected $p = 0.046$) states.

3.2.1.8 BVP

The main effect of pain type was non-significant ($F(1, 72) = 0.919$, $p = 0.341$, partial $\eta^2 = 0.013$). There was a main effect of experimental state on BVP ($F(2, 144) = 55.884$, $p < 0.001$, partial $\eta^2 = 0.437$). There was no interaction between pain type and experimental state ($F(2, 144) = 2.851$, $p = 0.061$, partial $\eta^2 = 0.038$). Post-hoc analysis showed that BVP in painful state (0.09 ± 0.00) was lower than in baseline (0.17 ± 0.01, corrected $p < 0.001$) or neutral (0.16 ± 0.01, corrected $p < 0.001$) states.

3.2.1.9 PTT

The main effect of pain type was non-significant ($F(1, 72) = 2.606$, $p = 0.111$, partial $\eta^2 = 0.035$). There was a main effect of experimental state on PTT ($F(2, 144) = 23.035$, $p < 0.001$, partial $\eta^2 = 0.242$). There was no interaction between pain type and experimental state ($F(2, 144) = 1.873$, $p = 0.157$, partial $\eta^2 = 0.025$). Post-hoc analysis showed that the PTT in the painful state (267.60 ± 2.96) was lower than that in baseline (275.05 ± 2.29, corrected $p < 0.001$) or neutral (274.92 ± 2.49, corrected $p < 0.001$) states.

3.2.1.10 SCL

The main effect of pain type was non-significant ($F(1, 72) = 0.049$, $p = 0.826$, partial $\eta^2 = 0.001$). There was a main effect of experimental state on SCL ($F(2, 144) = 61.671$, $p < 0.001$, partial $\eta^2 = 0.461$) but no interaction between the pain type and experimental state ($F(2, 144) = 1.400$, $p = 0.250$, partial $\eta^2 = 0.019$). Post-hoc analysis indicated that SCL in painful state (0.31 ± 0.02) was higher than in baseline (0.22 ± 0.02, corrected $p < 0.001$) or neutral (0.23 ± 0.02, corrected $p < 0.001$) states.

3.2.1.11 SCR

The main effect of pain type was non-significant ($F(1, 72) = 2.752$, $p = 0.101$, partial $\eta^2 = 0.037$). There was a main effect of experimental state on SCR ($F(2, 144) = 91.438$, $p < 0.001$, partial $\eta^2 = 0.559$). There was an interaction between pain type and experimental state ($F(2, 144) = 9.305$, $p < 0.001$, partial $\eta^2 = 0.114$). Post-hoc analysis revealed that SCR in painful state (0.77 ± 0.07) was higher than in baseline (0.07 ± 0.02, corrected $p < 0.001$) or neutral (0.14 ± 0.04, corrected $p < 0.001$) states.

3.2.1.12 FT

There were main effects of pain type ($F(1, 72) = 5.899$, $p = 0.018$, partial $\eta^2 = 0.076$) and experimental state ($F(2, 144) = 3.599$, $p = 0.030$,

TABLE 3 Results from a two-way repeated-measures analysis of variance on the effects of the pain type and the experimental state on individual physiological features.

		SS	df	MS	*F*	*p*	η^2
HR	Pain type	397.09	1	397.09	12.58	**0.001**	0.149
	State	445.78	2	222.89	5.34	**0.006**	0.069
	Interaction	193.22	2	96.61	2.30	0.104	0.031
SDNN	Pain type	252.88	1	252.88	1.47	0.230	0.020
	State	269.29	2	1324.65	8.96	**< 0.001**	0.111
	Interaction	240.34	2	120.17	1.08	0.344	0.015
RMSSD	Pain type	543.38	1	543.38	14.93	**< 0.001**	0.172
	State	584.32	2	292.16	7.05	**0.001**	0.089
	Interaction	303.27	2	151.63	3.12	**0.047**	0.042
pNN50	Pain type	314.23	1	314.23	7.35	**0.008**	0.093
	State	413.99	2	206.99	3.96	**0.021**	0.052
	Interaction	506.86	2	253.43	3.97	**0.021**	0.052
HFnu	Pain type	0.28	1	0.28	18.96	**< 0.001**	0.208
	State	0.06	2	0.03	2.03	0.135	0.027
	Interaction	0.08	2	0.04	2.85	0.061	0.038
LF/HF	Pain type	4.72	1	4.72	24.17	**< 0.001**	0.251
	State	0.76	2	0.38	1.59	0.206	0.022
	Interaction	0.79	2	0.39	1.95	0.146	0.026
RR	Pain type	1.43	1	1.43	3.38	0.070	0.045
	State	5.54	2	2.77	3.35	**0.038**	0.045
	Interaction	1.20	2	0.60	1.35	0.264	0.018
BVP	Pain type	0.00	1	0.00	0.92	0.341	0.013
	State	0.57	2	0.28	55.88	**< 0.001**	0.437
	Interaction	0.02	2	0.01	2.85	0.061	0.038
PTT	Pain type	233.14	1	233.14	2.61	0.111	0.035
	State	5309.85	2	5309.85	23.04	**< 0.001**	0.242
	Interaction	311.18	2	155.59	1.87	0.157	0.025
SCL	Pain type	0.00	1	0.00	0.05	0.826	0.001
	State	0.66	2	0.33	61.67	**< 0.001**	0.461
	Interaction	0.02	2	0.01	1.40	0.250	0.019
SCR	Pain type	0.40	1	0.40	2.75	0.101	0.037
	State	43.15	2	21.57	91.44	**< 0.001**	0.559
	Interaction	3.24	2	1.62	9.31	**< 0.001**	0.114
FT	Pain type	3.94	1	3.94	5.89	**0.018**	0.076
	State	2.29	2	1.15	3.59	**0.030**	0.048
	Interaction	0.18	2	0.09	0.16	0.855	0.002

Bold = significant results.

partial $\eta^2 = 0.048$) on FT; however, there was no interaction between pain type and experimental state ($F(2, 144) = 0.157$, $p = 0.855$, partial $\eta^2 = 0.002$). FT in social pain (32.15 ± 0.26) was significantly higher than in physical pain (31.96 ± 0.29, corrected $p = 0.018$). Post-hoc analysis revealed that FT in baseline (32.16 ± 0.27) was higher than in neutral (32.03 ± 0.29, corrected $p = 0.027$) and painful (31.99 ± 0.27, corrected $p = 0.013$) states.

3.2.2 Pairwise comparisons

Figure 3 shows the physiological responses observed during the experimental states and indicates significantly different pairwise comparisons among the experimental states for each pain type, which were evaluated using post-hoc analyses. Table 4 lists the significantly different pairwise comparisons. HR showed significant differences between the painful state and baseline only in social pain. In the

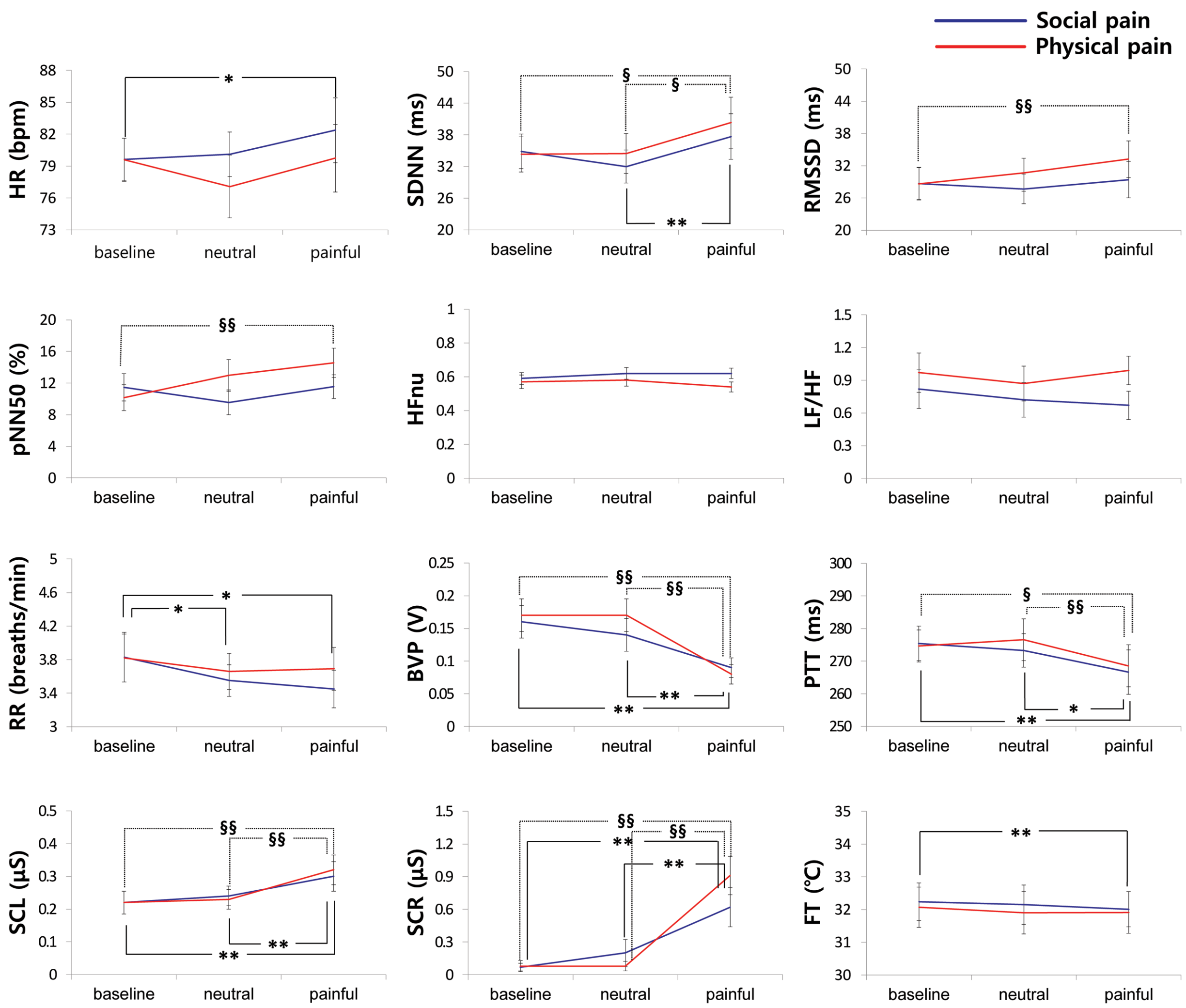

FIGURE 3
Physiological responses observed during the experimental states for each pain type. Significantly different pairwise comparisons among experimental states are indicated by asterisks for social pain (*$p < 0.0167$, **$p < 0.001$) and section signs for physical pain (§$p < 0.0167$, §§$p < 0.001$).

SDNN, there were significant differences between the neutral and painful states in both pain types. The RMSSD and pNN50 showed significant differences between the baseline and painful states in physical pain. The RR in the painful state was significantly lower than that in baseline for social pain. BVP and PTT in the painful state were significantly lower than those in the baseline and neutral states for both types of pain. There were significant increases in SCL and SCR during painful states compared with the baseline and neutral states for both types of pain. The FT in the painful state was significantly lower than that in baseline for social pain.

4 Discussion

We identified changes in ANS responses induced by social and physical pain stimuli and compared the differences in their responses between the two pain types. Figure 4 shows the physiological features that significantly responded to social or physical pain stimuli. The following features showed similar ANS responses to both social and physical pain stimuli: increased SDNN, SCL, and SCR but decreased BVP and PTT during the painful state. Because the SDNN reflects the total variability in the NN intervals during the recording period, it increases when the HRV is large and irregular (36). Mikuckas et al. (37) showed that the SDNN is increased by mental stress caused by irritating music. SC activity measures the psychogalvanic reflex response, in which the SNS activation stimulates the palmar and plantar eccrine sweat glands in reaction to emotional arousal, such as stress and fear (38). With sympathetic activation, sweat is secreted onto the skin surface, resulting in increased EDA; that is, a measurable increase in SC (38). Therefore, increased SCR indicates sweat secretion owing to the activated SNS. SCR is related to SAM activation, which indicates pain progression (12). BVP is a metric that indicates the volume of blood flowing through vessels such as those in the finger. It also serves as an indicator of changes in the vascular bed that are caused by vasoconstriction or vasodilation and changes in the elasticity of the vascular walls, which indicate changes in blood pressure (39). A reduction in BVP from baseline in response to a stimulus suggests peripheral vasoconstriction in the finger and is linked to arousal caused by social pain (16). PTT is the duration from the occurrence of the R-peak in the ECG to the moment the pulse

TABLE 4 Significantly different pairwise comparisons among experimental states for each pain type (Bonferroni correction for multiple comparisons, $p < 0.0167$).

	Social pain	Physical pain
HR	Pain > Baseline ($p = 0.012$)	N/A
SDNN	Pain > Neutral ($p < 0.001$)	Pain > Neutral ($p = 0.015$) Pain > Baseline ($p = 0.011$)
RMSSD	N/A	Pain > Baseline ($p < 0.001$)
pNN50	N/A	Pain > Baseline ($p < 0.001$)
HFnu	N/A	N/A
LF/HF	N/A	N/A
RR	Pain < Baseline ($p = 0.008$) Neutral < Baseline ($p = 0.015$)	N/A
BVP	Pain < Neutral ($p < 0.001$) Pain < Baseline ($p < 0.001$)	Pain < Neutral ($p < 0.001$) Pain < Baseline ($p < 0.001$)
PTT	Pain < Neutral ($p = 0.001$) Pain < Baseline ($p < 0.001$)	Pain < Neutral ($p < 0.001$) Pain < Baseline ($p = 0.001$)
SCL	Pain > Neutral ($p < 0.001$) Pain > Baseline ($p < 0.001$)	Pain > Neutral ($p < 0.001$) Pain > Baseline ($p < 0.001$)
SCR	Pain > Neutral ($p < 0.001$) Pain > Baseline ($p < 0.001$)	Pain > Neutral ($p < 0.001$) Pain > Baseline ($p < 0.001$)
FT	Pain < Baseline ($p < 0.001$)	N/A

N/A, not applicable.

wave reaches the finger (40). It is influenced by changes in the heart's contractile strength and the average arterial blood pressure. An increased PTT indicates suppression of SNS activation; thus, a significant decrease in PTT during the pain stimulus suggests sympathetic activation. In sum, pain-specific ANS responses to both pain stimuli are associated with the SAM and sympathetic activation of peripheral vasoconstrictions.

Contrastingly, the HR, RMSSD, pNN50, RR, and FT groups exhibited different responses to the pain stimuli. Social pain led to a significant increase in HR and a significant decrease in RR, and FT. It did non-significantly change the RMSSD or pNN50. However, physical pain induced a significant increase in RMSSD and pNN50, but did not affect HR, RR, or FT. HR is under the joint control of the SNS and PNS, and ample studies explored how the brain regulates the ANS in this process (41). The two branches of the ANS have opposite effects on the HR, with different response latencies. The SNS increases HR and blood pressure by enhancing adrenergic activity, whereas the PNS decreases HR through cholinergic activity, primarily targeting the sinoatrial node (26). It takes several seconds for the sympathetic system to increase the HR, but the PNS can affect the immediate subsequent heartbeat. Relative increases in SNS and PNS activities are associated with increases and decreases in HR, respectively (42). Thus, the increased HR caused by social pain suggests that activation of SNS mediated by adrenergic activity.

HRV features represent the autonomic regulation of the HR and can serve as an objective index of emotionality (43). RMSSD represents short-term variations in HR and is mostly affected by parasympathetic activity (44). It is correlated with HF power and indicates self-regulatory capacity (39). Similar to the RMSSD, pNN50 mostly reflects the effect of parasympathetic activity. Thus, RMSSD and pNN50 can monitor vagally mediated changes in HRV (29). Prior studies demonstrated an increase in the RMSSD using acute thermal pain, such as in the cold-pressor task (45) and hot immersion tests (46). Konstantinou et al. (47) showed that pNN50 was increased by a cold-pressor task when measured with a wearable device.

In this study, HFnu and LF/HF were not significantly affected by the pain stimuli; however, some previous studies demonstrated that pain induced significant changes in the HRV frequency domain features. LF/HF is calculated as a ratio between low frequency (LF, 0.04–0.15 Hz) power—influenced by both parasympathetic and sympathetic activities and high frequency (HF, 0.15–0.4 Hz) power—which reflects dominantly parasympathetic (vagal) activity (48). Stress, pain, and mental frustration are associated with an elevated LF/HF caused by either a relatively higher LF or lower HF (49). For example, an elevated LF reflects an increase in sympathetic baroreflex activity, which can be induced by painful stimuli, such as heat pain caused by contact thermodes (50). A decrease in the HF induced by painful stimulation has been reported, reflecting reduced vagal-parasympathetic activity (42). Physical pain induced by pressure leads to a significant increase in LF and LF/HF and a decrease in HF, indicating increased sympathetic activity (51). Contrastingly, a decrease in the LF/HF during periods of mental stress may be associated with improved modulation of emotional expression (52) and defensive reactions (53). However, HFnu and LF/HF were not as relevant as the other HRV features for differentiating between social and physical pain in our results.

RR is one of the most widely used respiratory indices, along with the respiratory period, respiratory depth, tidal volume, duty cycle, and respiratory variability (7). Physical pain induces an increase in respiratory frequency, flow, and volume (54). For example, RR was increased in healthy participants by tourniquet pain in the calf (55) and by saline infusion into the masseter muscle (56). In clinical studies, patients experiencing pain exhibited increased RR (57, 58),

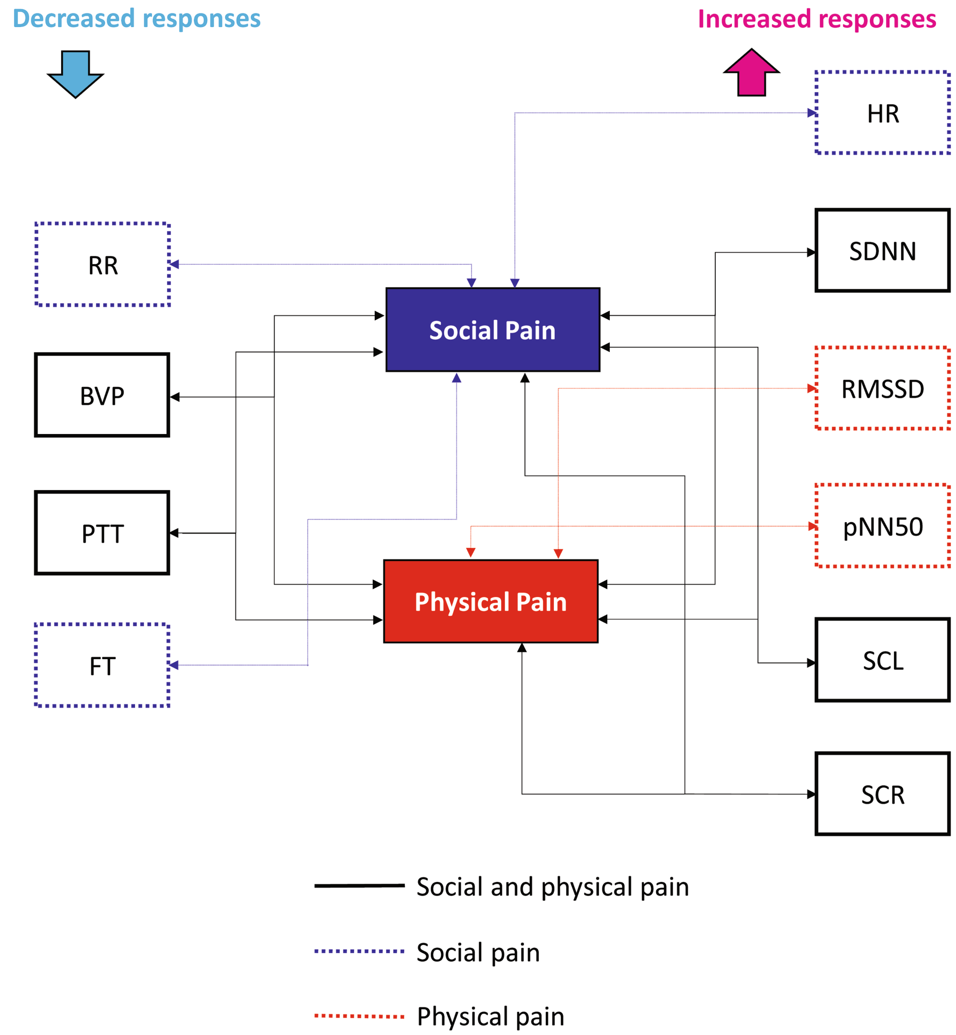

FIGURE 4
Physiological features that significantly responded to social or physical pain stimuli.

suggesting the potential of RR as an indicator of pain in severely ill adults and intensive care patients. These findings support the idea that hyperventilation acts as a respiratory stress response in situations involving uncontrollable stress, fear, and pain (59, 60). However, we did not observe a significant change in RR with a physical pain stimulus. In addition, RR can be significantly affected by emotional changes. For example, the arousal caused by negative emotions induces shallower and more rapid breathing (61, 62), which could result in decreased blood carbon dioxide (7). Our results showed a significant decrease in RR during social pain, which may be related to deactivation of the sadness response—characterized by sympathetic withdrawal (7). Deactivation of the sadness response induced by films, music excerpts, and standardized imagery was associated with decreased respiratory activity, as indicated by a decrease in RR (63, 64). The change in RR can be affected by individual differences. Masaoka and Homma (62) showed that the respiratory response to mental stress and physical load is related to personality anxiety.

The FT serves as an indicator of the changes in blood flow due to vascular reactivity, reflecting the ANS response (12). It is primarily affected by sympathetic adrenergic vasoconstrictor nerves, and the activation of the sympathetic system results in vasoconstriction in the extremities, leading to lower extremity temperatures (65). The temperature showed a significant change under emotional stress. As the muscles become more tense, the blood vessels contract and the extremity temperature decreases. FT is decreased by stress and fear and increased by relaxation, boredom, and sleep (12). FT did not change during physical pain but significantly decreased during social pain, indicating that a sufficient amount of emotional stress is induced by social pain but not physical pain.

5 Limitations

In this study, we used a clip from a Korean drama to elicit social pain. It is possible that some participants have already watched the drama, thus being familiar with the content of the film clip, which could have influenced the study results. However, this study did not explore the effects of this familiarity on the participants' responses. In future studies, we plan to gather information about participants' prior knowledge of the stimulus to assess whether familiarity significantly impacts their responses. Additionally, while we chose a black-and-white color scheme (a black plus sign on a white background), it is important to acknowledge that color perception can affect an individual's stress levels. Therefore, we must consider the potential impact of color perception on participants' responses to stimuli.

The ANS responses to social pain were similar to those to sadness. According to Kriebig's (7) review, previous studies that used films for sadness induction reported increased HR (64) and EDA (64, 66, 67) and decreased BVP, PTT, RR, and FT (64). For participants who cry in response to a sadness-inducing film clip, previous studies unanimously reported an increased HR, which was also associated with increased SCL and decreased BVP and FT (68). Contrastingly, sadness participants who did not cry while watching the film clip showed decreased HRV, represented by spectral respiratory sinus arrhythmia (66, 67) and decreased FT (68). In this study, social pain induced increased HR and SC features and decreased BVP and FT, similar to those observed in participants who crying in response to a sadness-inducing film clip. Simultaneously, the social pain used in this study led to decreased FT values, similar to those of sad participants who did not cry while watching a film clip. Because our stimulus was designed to induce social pain through the imminence of loss or loss of relationships, such as the death of the father, participants were likely to feel sadness. However, additional emotional assessment is needed to determine whether the stimulus used for social pain induces sadness. Social pain induced by the loss of relationships could also include threats, fear, or social distress owing to social rejection. Prior studies indicated that social pain such as social rejection evokes increases in HR and SCL (69, 70). Thus, diverse stimuli for inducing social pain are needed to examine social pain-specific ANS responses.

This study differentiated pain into two types—social and physical—and assumed that these two types were distinct. However, a wide range of factors related to pain stimuli and their responses are required. We identified ANS responses related to social pain using loss of relationship as psychological pain; however, psychological or emotional pain can arise from various causes when psychological needs (e.g., affiliation or achievement) are frustrated or the need to avoid harm, shame, or embarrassment occurs (71). Pain can be evoked by mixing different emotions, such as fear and sadness (72) and may be accompanied by other emotions [e.g., fear, sadness, anger, anxiety, and shame (27, 73)]. Owing to the diverse definitions of psychological pain and the various methods employed to induce pain, the evaluation of responses to such pain is complex. Physical pain could lead to different responses depending on the properties of the stimuli, such as heat, cold, pressure, and pricking. Further research is necessary to determine the specific types of pain stimuli that should be administered.

6 Conclusion

This study did not consider the participants' familiarity with the stimulus content, the possibility of inducing emotions through the stimulus, and the various types of pain stimuli to verify pain-specific ANS responses. Nonetheless, we identified changes in ANS responses to social and physical pain stimuli and differences in ANS responses between the two pain types. Social pain induced increased HR and SC features, and decreased BVP, PTT, RR, and FT, suggesting a heterogeneous pattern of sympathetic–parasympathetic coactivation. Moreover, physical pain induced increased HRV features and SC features, decreased BVP and PTT, and resulted in no change in FT, indicating SAM activation and peripheral vasoconstriction, which is consistent with our previous study (12). These results suggest that changes in HR, HRV indices, RR, and FT can serve as significant markers for differentiating physiological responses to social and physical pain stimuli.

Data availability statement

The datasets presented in this article are not readily available because of privacy restrictions. Requests to access the datasets should be directed to swbyun@inu.ac.kr.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of Chungnam National University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

E-HJ: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. Y-JE: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Methodology, Visualization. DY: Funding acquisition, Writing – review & editing. J-HS: Writing – review & editing, Supervision. SB: Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Peace through health: traditional medicine meditation in the prevention of collective stress, violence, and war

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In the midst of global armed conflicts, notably the Israel-Hamas and Ukraine-Russia wars, there is an urgent need for innovative public health strategies in peacebuilding. The devastating impact of wars, including mortality, injury, disease, and the diversion of healthcare resources, necessitates effective and durable interventions. This perspective aligns with WHO recommendations and examines the role of evidence-based meditation from Ayurveda and Yoga in public health to mitigate collective stress and prevent collective violence and war. It highlights the Transcendental Meditation program, recognized for reducing stress, with contemporary evidence supporting its effectiveness in mental health, mind–body disorders, cardiovascular disease, and public health. Empirical studies with cross-cultural replications indicate that these Traditional Medicine meditation practices can reduce collective stress and prevent collective violence and war activity while improving quality of life. The mechanisms of group meditation in mitigating collective violence are explored through public health models, cognitive neuroscience, population neuroscience, quantum physics principles, and systems medicine. This perspective suggests that Transcendental Meditation and the advanced TM-Sidhi program, as a component of Traditional Medicine, can provide a valuable platform for enhancing societal well-being and peace by addressing brain-based factors fundamental to collective stress and violence.

KEYWORDS

war, population health, meditation, Transcendental Meditation, collective stress, collective violence, armed conflict, traditional medicine 2

Introduction

War and armed conflicts cause severe damage to public health through widespread injuries, diseases, disabilities, premature deaths, displaced populations, environmental contamination, and often violations of human rights and international humanitarian law. Moreover, it redirects crucial resources from health and social services to conflict-related activities, potentially perpetuating further violence (1).

The current Israel-Hamas war is part of an "intractable conflict" that has lasted at least 75 years (2). The persistent and ongoing collective violence in the Middle East bears a significant portion of the worldwide burden of immediate, long-term, and inter-generational impacts on health. Other major ongoing wars include Russia-Ukraine, Sudan, Myanmar, and Maghreb (3). Such intractable conflicts, without apparent end demand innovative approaches to peacebuilding beyond conventional diplomacy, military interventions, and public health (2, 4).

Preventing collective violence

Amidst escalating tensions that threaten to reverberate beyond regional borders, the imperative for healthcare professionals to engage in public health strategies to mitigate and prevent collective violence is underscored by a growing body of evidence and public outcry from international leaders in medicine (5).

The *Lancet* Commission declared that these and related crises *have exposed the inadequacy of national and global leadership and governance structures* (6). Levy and others emphasize the relationship between peace and health. Peace is vital for nations and their populations to achieve their utmost health potential. Conversely, health is a determinant of peace, as expressed in the *peace through health* approach proposed by Arya and others (7).

Traditional medicine for prevention of collective violence

The World Health Organization (WHO) upholds that preventing collective violence and war is a critical public health mandate (8, 9). WHO initiatives are rooted in recognizing that societal health and prosperity are fundamentally intertwined with the state of peace (6, 10). Further, recent declarations of WHO and G20 Leaders recognize Traditional, Complementary, and Integrative Medicine (TCIM) for its vital role in preventive medicine and public health (11, 12).

Bridging the seemingly disparate themes of prevention of collective violence and Traditional Medicine aligns with the contemporary vision for public health of peace through health (7). This convergence underscores a paradigm where healthcare is not merely reactive but proactively contributes to peacebuilding and society-building (6, 10).

Using the host-agent-environment triad model of public health, Levy proposes that strategies can be developed to prevent armed conflicts. In this context, we present a model to prevent collective violence based on strategies for improving the health and well-being of the people or host element of the triad rather than the agent/military or environment/external factors (10).

A traditional medicine meditation program for reduction of individual and collective stress and prevention of collective violence

WHO endorses the incorporation of TCIM, notably Ayurveda and Yoga, from the traditional Vedic medicine of India, acknowledging their contributions not just to individual health concerns but also as crucial resources for preventive medicine and public health (11, 12). In Ayurveda, public health is described in the section on *Janapadodhvansa* (13, 14). This traditional discipline addresses the causes of war and outlines preventive strategies. Ayurveda recommends reducing stress by settling the mind and body and experiencing the innermost self to promote mental, physical, and behavioral health with a meditative practice. These descriptions can be found in *Satvavajaya* (mental health), *Sadvritta* (behavior recommendations for social harmony) and *Achar Rasayana* (behavioral recommendations for health and long life) (13, 15).

One technology from Ayurveda and Yoga, that has been revived and extensively investigated in contemporary settings for individual and collective stress reduction is the Transcendental Meditation technique (16, 17). Transcendental Meditation is described as a simple, natural technique for allowing mental activity to spontaneously settle down and experience a state of inner silence or transcendental consciousness (16, 17). Practitioners report experiences of peace, unity, and transcendence during and after the practice (17). Studies conducted across several continents and cultures indicate that it may be easily learned, practiced, and clinically effective regardless of education, culture, language, religion, or philosophy (17) (See below.)

The literature of Ayurveda and Yoga describes how regular practice of this type of traditional meditation can reduce stress and violent behaviors in society and the individual (1, 11, 12, 15). Over the past 50 years, individual and collective stress reduction hypotheses have been empirically tested for individual health and public health effects, including prevention of collective violence (18).

On the neuroscience of meditation

There are many kinds of meditation methods, with different goals and varying techniques, concluded Nash and Newberg in their updated classification and taxonomy of meditation methods (19). While meditation methods have unique goals and procedural techniques, a shared principle among them is the intention to cultivate a targeted, enhanced mental state (19).

Cognitive neuroscience reviews emphasize that since meditation procedures and goals differ, it is not surprising that empirical studies demonstrate contrasting neurophysiological changes associated with the types of meditation methods (19, 20). Neuroimaging research shows distinct cortical and subcortical activation and deactivation patterns in different types of meditation (19, 20). Based on electroencephalographic (EEG) patterns, Travis and Shear proposed three categories of meditation, providing a neuroscience-based taxonomy that corresponds with phenomenology (20, 21).

The first category involves *focused attention* or concentration on an object of attention. Examples are from Buddhist-derived practices, e.g., Vipassana and Zen. Empirically, these are characterized by the gamma frequency in EEG studies, which is associated with effortful thinking and mental control.

The second category, called *open monitoring* type meditation, prescribes observation of thoughts, emotions, breath or body sensations, observed without judgment. The practice is also described as nonreactive monitoring of the momentary content of experience. Examples are Mindfulness meditations and Zazen, characterized by prominent theta and posterior alpha EEG patterns. These records are associated with attention to internal mental processing.

The third category of meditation is called *automatic self-transcending*. This method involves transcending or "going beyond" usual mental activity, i.e., thoughts, emotions, and bodily awareness. The practice allows the practitioners' attention to move from active thinking to inner silence without effort. The most commonly studied example is Transcendental Meditation from the Vedic system of Traditional Medicine. The process of transcending is characterized by frontal alpha EEG in the alpha-1 range, which is associated with reduced frontal executive processing. Another characteristic of this category is activating the default mode neural network corresponding to the experience of "relaxed wakefulness" (20).

Further, neuroscientific study of spiritual and religious practices (sometimes called neurotheology) indicates that prayer and meditation practices differ in their methods and neurophysiological correlates (19, 22). Prayer is typically a form of communication involving expressions of gratitude, seeking guidance, or asking for assistance. Meditation, particularly Transcendental Meditation, allows the active thinking mind to settle to a silent inner state or transcendence. Thus, while prayer is typically outwardly directed and communicative, meditation is inwardly focused on experiencing a state of inner silence or relaxed wakefulness (23).

Meta-analyses suggest that during the practice of Transcendental Meditation, the individual experiences a unique neurophysiological state of restful alertness characterized by relatively higher galvanic skin response (GSR) resistance, lower respiration rate, and lower plasma lactate in addition to the neurophysiological changes mentioned above (17, 18).

Mental and physical health effects of Transcendental Meditation

Individual levels of anxiety and other mental health disorders contribute to public health patterns of mental health. Meta-analyses of controlled clinical studies report that Transcendental Meditation appears distinctively effective in reducing anxiety, especially in participants with high levels of anxiety at baseline and has shown clinical effectiveness in treating posttraumatic stress disorder, burnout, and related symptoms of depression and exhaustion cross-culturally (24–27).

Despite advances in modern medicine and public health, cardiovascular disease (CVD) persists as the leading cause of death and disease globally (28). Moreover, psychosocial and environmental stress increases the risk for CVD (29). These may be considered social determinants of health or public health risk factors. By contrast, a series of randomized controlled trials reported that Transcendental Meditation practice, in conjunction with usual medical care, reduces CVD risk factors, morbidity and mortality (27, 30, 31).

Specifically, meta-analyses and clinical trials show lower rates of hypertension, metabolic syndrome, smoking, and substance abuse; reductions in surrogate markers of atherosclerotic CVD, including carotid artery atherosclerosis and myocardial ischemia; decreased relative risk for mortality, myocardial infarction, and stroke; and reductions in healthcare utilization and costs (27, 30, 31).

Public health applications

Based on the literature of traditional Vedic medicine (13, 14, 32), Maharishi Mahesh Yogi proposed a theory of collective health which predicted that the practice of traditional meditation techniques could not only reduce stress in the individual but would reduce stress in society at large and favorably impact trends of collective violence (18).

A critical meditation technique in this peace-creating program is the TM-Sidhi program, which is described as an advanced meditation technique to train the individual to sustain thought and activity from the silent state of awareness (transcendental consciousness), thus integrating the experience of pure consciousness with activity and amplifying the effects of meditation in individual and collective functioning. The advanced program is practiced in conjunction with the core Transcendental Meditation technique (17, 18).

It was further predicted that objectively measurable societal effects would occur when the size of a group practicing the Transcendental Meditation and TM-Sidhi program together in one place exceeds the square root of 1 % of the target population (18). This hypothesis has been tested in more than 30 peer-reviewed and published controlled studies (18).

Several of these studies tested the group meditation for peace hypothesis in the Middle East, particularly Israel and Lebanon, in addition to studies in Asia and a recent multi-year time series analysis in the US, as reviewed below.

Israel and Lebanon

In a prospective, quasi-experimental research project conducted in Israel, a group of Transcendental Meditation and TM-Sidhi program participants came together in Jerusalem for two months in 1983 (33). The group varied in size throughout this period, depending on individual availability. Improvements were found for measures of war intensity and war deaths in the Israel-Lebanese armed conflict derived by standardized methods of content analysis from daily news sources. Time series cross-correlation analyses indicated that the participant numbers had a leading effect in time on the dependent variables. The study also found significant improvements in indices of quality of life at the city and national levels (33). In response to critiques indicating possible confounding factors, the authors published several re-analyses of the data, which supported their initial findings (34).

A study of group meditation effects in the Lebanon civil war examined seven occasions when there were short-term groups of Transcendental Meditation and TM-Sidhi program participants over a 2.25-year period from 1983 to 1985 in Lebanon, which were large enough for the hypothesized effect on the ongoing conflict. Using a daily database created from nine international and regional news sources by an independent Lebanese rater blind to these hypotheses, Box-Tiao impact analysis indicated reduced conflict intensity, conflict fatalities, and increased cooperation by factions during the seven assemblies of Transcendental Meditation and TM-Sidhi program participants in contrast to all other days. The analysis controlled for seasonality and trends in the data, temperature, holidays, and weekends (35).

India, Philippines, Puerto Rico

Box-Tiao ARIMA impact-assessment studies at the state, or province, level examined the impact of groups of TM-Sidhi program participants that came together temporarily on special courses. These studies reported crime reductions in the Union Territory of Delhi, India, a reduction of daily Indian Penal Code totals, in Metro Manila, a reduction of weekly crime index totals, equivalent to the FBI Uniform Crime Index in the U.S. and in Puerto Rico a reduction of monthly Type 1 crimes, comparable to the FBI uniform crime index (36).

United States

A recent study on the effects of group practice of the Transcendental Meditation and TM-Sidhi programs on collective violence over 17 years in the United States stands out for its methodological rigor. It employed interrupted time-series analysis and used multiple control variables and statistical tests to ensure the robustness of the results (18). The study found that when a group practicing Transcendental Meditation and the TM-Sidhi program reached the predefined threshold of the square root 1% of the US population, there were significant reductions in indicators of national violence, including homicides, rape, aggravated assault, robbery, drug-related deaths, motor vehicle fatalities and injury fatalities alone and in a composite index. After the group numbers substantially decreased, the public health indicators reverted to their baseline state (18).

This collection of studies accounted for alternative explanations for the observed effects, such as changes in economic conditions, shifts in political leadership, and other secular trends (18).

Comparison with other methods

While considering meditation methods for reducing collective stress and preventing collective violence and war, it is relevant to compare with intercessory prayer practices and outcomes (37, 38). Above, we outlined fundamental differences in practice between meditation and prayer. Meditation, particularly the transcending types, aims to automatically reduce mental activity and gain a unique neurophysiological state of restful alertness. In contrast, prayer typically involves outward communication, seeking guidance, or requesting assistance, which engages more active neurocognitive pathways (22).

These distinctions have practical implications for efficacy in public health interventions. The empirical evidence for meditation, especially in group settings, suggests a capacity to mitigate collective stress and violence in the population (reviewed above). Conversely, the effectiveness of intercessory prayer in similar contexts is undetermined. A Cochrane systematic review analyzed health outcomes of intercessory prayer for specific individuals with health disorders. The results showed neither significantly beneficial nor harmful results (37). A current literature review indicates no published studies on the effects of intercessory prayer on the prevention of collective violence or war. Similarly, to our knowledge, there are no published controlled studies on the effect of other types of meditation methods on public health outcomes.

Mechanisms of group meditation in preventing collective violence

Population health

Drawing on the public health model of the host-agent-environment framework, Levy translated these terms for preventing collective violence to people, weapons/military, and conditions in which people live (10). Using this framework, we suggest that a traditional group meditation practice addresses the people or host component by reducing stress and increasing neurophysiological coherence and associated health conditions that may reduce collective stress and violence.

Population neuroscience

Population neuroscience also known as collective neuroscience, examines how cognitive processes, brain functions, and behavior interact with and mutually influence larger social environmental factors (39). In the words of Falk and colleagues, it is where *neuroscience meets population science* (40). Within this framework, group meditation programs may be viewed as a collective cognitive neuroscience stabilizing activity. These programs may synchronize individual cognitive and neurophysiological states, leading to a shared, enhanced cognitive experience in the community.

Distributed cognition model

As proposed by Sloman and colleagues, cognitive neuroscience processes are not confined to individual brains but are distributed across a community or potentially large group of people, thereby influencing collective behavior of the population (39).

Impact of group meditation on collective behavior

The coherence and peace experienced individually in meditation may be projected outward, influencing the collective cognitive neuroscience of the population. This could lead to observable changes, such as a decrease in collective violence. In the case of group meditation according to the principles described above, this shared cognitive neuroscience state may contribute to societal changes, such as a reduction in collective behavioral violence.

Physics principles

The principles of interconnectedness and nonlocality from quantum physics provide a theoretical basis for understanding these phenomena. In this context, actions or states in one part of a system (individual mind or consciousness) may affect distant parts of the system (collective consciousness) (41, 42).

Unified field of consciousness

Expanding on these concepts, Nader hypothesizes that through Traditional Medicine practices of Transcendental Meditation and the TM-Sidhi program, individuals can access a unified field of consciousness that transcends individual awareness and contributes to a collective harmonized state of neuroscience and behavior (43).

The approach presented in this perspective, rooted in cognitive and population neuroscience and models from quantum physics, offers a novel perspective on how individual cognitive practices, notably a traditional Vedic medicine meditation program, can have far-reaching impacts on public health and societal well-being.

Systems medicine and public health

A model of whole health that connects individual and environmental health based on advances in mind–body medicine and population health has been proposed that demonstrates the interrelationships of these domains and the reciprocal influence between individual health and collective health (27). This paradigm is derived from traditional Vedic medicine and modern scientific evidence in a systems science, medicine and public health framework. The model is called the *Connectome of Health* (27).

A new paradigm

Despite progress in modern public health and preventive medicine, widespread collective violence and armed conflicts continue, illustrated by the current Israel-Hamas war and other "intractable" wars. A range of measures have been recommended to prevent war but without adequate success to date (44).

The incorporation of group meditation in public health strategies for mitigating collective stress and violence, despite robust scientific validation and neuroscientific explanations, represents a paradigmatic shift as delineated by Kuhn in *The Structure of Scientific Revolutions* (45). The transition from a conventional biomedical paradigm to a biopsychosocial systems model, which incorporates the burgeoning field of population neuroscience, could disrupt prevailing perspectives. The practice of group meditation for peace represents a paradigm shift from an external locus of change to an internal one, where cultivating inner peace within individuals can lead to positive outcomes on a societal scale.

However, as Ho observes in his critique of the history of science, medicine, and public health, the relationship between evidence and theory largely depends on individual and collective worldviews for their interpretation and acceptance of new scientific findings and technologies (46).

Conclusion

To address the critical public health need for prevention of collective stress, violence, and war, we present a framework that integrates Traditional Medicine with current scientific understanding and evidence. In this perspective, we propose that group meditation practices can effectively diminish collective stress and violence, a hypothesis supported by over 30 peer-reviewed and published field studies. This strategy is in line with population salutogenesis, which focuses on the societal factors contributing to mental distress and the escalation of collective stress and violence (47).

The evidence supporting the group practice of a traditional medicine meditation program, the Transcendental Meditation and TM-Sidhi program, suggests that this method offers more than individual benefits; it could be a vital part of a broad, evidence-based strategy for societal well-being, public health, and global peace.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

RS: Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. MD: Conceptualization, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. GY: Investigation, Writing – original draft, Writing – review & editing. TN: Conceptualization, Resources, Writing – review & editing.

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Conflict of interest

TN is chairman and CEO of Maharishi Foundation International, a nonprofit organization where the position is unpaid.

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Publisher's note

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Evaluating qigong as integrative support for COVID-19 and Long-COVID-19 rehabilitation: a systematic review

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Introduction: Amidst the ongoing global impact of COVID-19 on public health, there is an increasing focus on holistic strategies encompassing integrative therapies and rehabilitation techniques, particularly in addressing the challenges posed by Long-COVID-19. This review investigates the potential of Qigong, an ancient Chinese practice characterized by gentle movements, controlled breathing, and meditative elements, within the context of COVID-19.

Methods: A systematic search of PubMed, EMBASE, Web of Science, Scopus, and Google Scholar was conducted to identify pertinent clinical studies.

Results: Following thorough database scrutiny, nine studies were identified as meeting the eligibility criteria. Across the spectrum of COVID-19 severity, individuals engaging in qigong practice exhibited notable enhancements in both physical and psychological wellbeing, evidenced by ameliorated respiratory symptoms, reduced anxiety levels, enhanced sleep quality, bolstered mental wellbeing, and augmented health-related quality of life. Moreover, qigong training, whether employed independently or in conjunction with other therapies, demonstrated beneficial effects on Long-COVID-19 symptoms, encompassing persistent respiratory issues, dizziness, sleep disturbances, and compromised health-related quality of life.

Discussion: This review underscores the necessity for further investigation to quantify and standardize the contribution of Qigong to COVID-19 recovery and rehabilitation. Such endeavors aim to integrate this accessible and low-impact practice into public health strategies and comprehensive treatment regimens.

Systematic review registration: The review protocol was registered in the Open Science Framework under the following doi: 10.17605/OSF.IO/7K5X6 (URL: https://osf.io/7k5x6).

KEYWORDS

qigong, mind-body therapy, COVID-19, coronavirus, health

1 Introduction

1.1 Long-COVID-19

COVID-19, caused by the SARS-CoV-2 virus, emerged as a pandemic from early 2020, with significant global consequences not only on health but also on socio-economic aspects (Ciotti et al., 2020; Mishra et al., 2020). While the disease typically manifests with fever, cough, and predominantly respiratory symptoms, it can result in severe interstitial pneumonia characterized by an abnormal systemic inflammatory response, sometimes leading to fatal outcomes despite hospital care, especially in individuals with pre-existing comorbidities (Çalica Utku et al., 2020). Research conducted on recovered patients has revealed that COVID-19, even in its non-severe manifestations, can result in persistent symptoms that endure or emerge over a span of 3 months following the acute phase of the disease, aligning with the current definition of Long-COVID-19 (Crook et al., 2021). These symptoms encompass a spectrum of manifestations, including chronic fatigue, headache, cardiac or respiratory alterations, arthralgia, muscle pain, taste or olfactory dysfunctions, sleep disorders, cognitive impairment, post-traumatic stress disorder, and mood disturbances, which may persist for weeks or even months following the initial illness episode (Sykes et al., 2021; Yong, 2021). In particular, Long-COVID-19 is defined by the WHO-led Delphi study as symptoms persisting for at least 3 months from the onset of the acute disease, with manifestations lasting at least 2 months, often presenting in an episodic nature, while clinicians lack standardized guidelines for diagnosis, relying on symptom evaluation and exclusion of other health conditions (Srikanth et al., 2023). Elderly age, female gender, pre-existing comorbidities, severe COVID-19 requiring hospitalization, and supplemental oxygen are all risk factors associated with the development of Long-COVID-19 (Srikanth et al., 2023). The distinction between the acute phase and Long-COVID-19 highlights the evolving trajectory of the disease's effects on individuals, emphasizing the need for tailored therapeutic strategies. In the results section of this review, studies investigating the effects of qigong specifically for COVID-19 and those focusing on Long-COVID-19 will be differentiated, reflecting the specific considerations required for managing the diverse manifestations of the disease over time.

Despite the fact that vaccines have proven effective in decreasing the occurrence of COVID-19 and mitigating its prolonged symptoms (Català et al., 2024), evidence-based rehabilitation strategies designed to expedite recovery from the disease are still useful, along with proper treatment management, addressing comorbidities, and compensating for socio-economic disparities in access to healthcare. Additionally, proper treatment management and efforts to bridge socio-economic gaps in healthcare access are essential components in this endeavor (Hossain et al., 2023). Among various approaches, mind-body techniques stand out for their dual benefit, as they simultaneously alleviate physical and mental symptoms by engaging both aspects of the human experience (Astin et al., 2003). In fact, the potential utility of mind-body interventions in post-COVID recovery is underscored by their holistic approach to health, which does not isolate physical symptoms from mental wellbeing (Maric et al., 2021; Alschuler et al., 2022; Brough et al., 2022).

1.2 Qigong and its benefits

Qigong is an oriental system of mind-body practices aimed at promoting health which involves the execution of well-coordinated movements, adopting specific positions, and engaging in breathing exercises and meditation (Dorcas and Yung, 2003). The term "qigong," literally translated as "cultivating Qi" or "mastering Qi," refers to the use of this activity in the context of Traditional Chinese Medicine to improve psychophysical wellbeing and the body's vital energy ("Qi") (Liu and Chen, 2010). Qigong's history dates back thousands of years, possibly originating with the legendary Huangdi, the Yellow Emperor, and the medical books attributed to him (Ng, 1999). While its exact origins remain uncertain, this practice stands as one of the oldest roots of Chinese culture: even today, qigong remains widely practiced in the general population and it is not uncommon to see individuals doing qigong exercises in public parks of major Chinese cities (Palmer, 2003).

The various forms of qigong, influenced by Eastern religious traditions (Taoism, Buddhism, Confucianism) and martial arts, are sometimes grouped into two major categories: active qigong, which is more dynamic, and passive qigong, characterized by a predominant meditative component (Klich and Milert, 2018). Active forms involve more movement, dynamism, and higher physical engagement, whereas passive qigong forms are more static, focusing on maintaining specific postures, breath control exercises, and meditative practices. Nevertheless, in qigong sessions, there is a common practice of incorporating a harmonious blend of both active and passive forms, with the choice between the two being guided by the individual's intentions and current physical fitness level (this practice is accessible to individuals of all ages, even suffering from chronic conditions) (Tsang et al., 2002).

Modern science, based on studies conducted in recent years, attributes the following benefits to qigong practice:

- Promotion of psychophysical relaxation with better stress and emotion management (particularly useful for the working-age population) (Wang et al., 2014; van Dam, 2020).
- Improvement of respiratory kinetics, strengthening the diaphragm, and thoracic muscles (Xu et al., 2022).
- Reduction of falls and increase in skeletal mineral density, enhancing overall quality of life and functionality related to daily needs (significant for the elderly) (Rogers et al., 2009; Song et al., 2017).
- Potential contribution to reducing blood pressure in hypertensive subjects and improving pain control in individuals with painful symptoms related to various chronic pathologies (Bai et al., 2015; Ching et al., 2021).
- Possible improvement in inflammatory indices and immune system functionality, likely indirectly attributed to the anti-stress effect (Półrola et al., 2018; Oh et al., 2020).

Overall, qigong practice implies a holistic approach that targets both the physical and mental aspects of health (Kurt et al., 2022), offering potential benefits for mitigating specific symptoms like chronic fatigue, cognitive impairment, and mood disturbances in Long-COVID-19 recovery. Three elements merit specific attention:

- Movement: qigong involves gentle, flowing movements that promote flexibility, balance, and circulation throughout the body. These movements can help alleviate chronic fatigue by boosting overall vitality (McGregor et al., 2024). Moreover, the rhythmic nature of qigong movements induces a relaxation response in the body, reducing tension and promoting a sense of calmness that may contribute to improved mood and cognitive function (Zhang Q. et al., 2023).
- Breath control: qigong emphasizes deep, diaphragmatic breathing techniques that synchronize breath with movement. Controlled breathing exercises can help regulate the autonomic nervous system, promoting relaxation and

reducing stress levels (Zaccaro et al., 2018). By enhancing oxygenation of tissues and improving respiratory function, qigong may alleviate symptoms of fatigue and enhance cognitive clarity. Additionally, mindful breathing practices in qigong can cultivate present-moment awareness and mindfulness, which are associated with improved mood and cognitive function (Johnson et al., 2015).

- Meditation: qigong incorporates meditation techniques that cultivate mental focus, clarity, and emotional balance. Through meditation, practitioners learn to observe their thoughts and emotions without judgment, promoting a sense of inner peace and emotional resilience (Wang et al., 2016). This can help alleviate mood disturbances such as anxiety and depression (Saeed et al., 2010) commonly associated with Long-COVID-19. Additionally, meditation practices in qigong may enhance cognitive function by improving attention, concentration, and memory recall.

In light of these considerations and the recognized benefits of physical therapies in accelerating the recovery of patients afflicted by COVID-19 or experiencing persistent manifestations of the disease (Pollini et al., 2024), qigong has been integrated into strategies aimed at enhancing individual health during the pandemic (Feng et al., 2020; Yang et al., 2022; Zhong et al., 2023). However, to date, there is a lack of a systematic overview of the evidence on the subject, capable of defining the efficacy of the treatment in this type of patient. Notably, recent research underscores that qigong constitutes an ideal form of exercise (Feng et al., 2020), particularly pertinent within confined spaces, and feasible for individuals to perform independently with a high degree of safety (Jahnke et al., 2010); furthermore, it requires minimal equipment, thereby promoting cost-effectiveness, and remains accessible to individuals of all genders and age groups (Phansuea et al., 2020). Therefore, conducting a systematic review can be useful to inform future research efforts and optimize the role of qigong in the management and rehabilitation of COVID-19 patients.

1.3 Research aim

This review aims at investigating the efficacy of qigong training for COVID-19 integrative support and Long-COVID-19 rehabilitation.

2 Materials and methods

This systematic review adhered to the guidelines reported in the PRISMA statement (Liberati et al., 2009). The review protocol, registered in the Open Science Framework (OSF) under the following doi: 10.17605/OSF.IO/7K5X6, was devised in January 2024 and subsequently published online in March 2024 (URL: https://osf.io/7k5x6), following the literature search but preceding the data extraction process.

Incorporated into our analysis were relevant clinical investigations assessing the impact of practicing qigong on recovery from COVID-19 and long-COVID-19 symptoms, with no limitations on publication dates. To ensure robust selection criteria, studies had to be available in the English language or, at the very least, include an English abstract or summary. Furthermore, selected studies had to be formally published in peer-reviewed journals as original research articles.

The subsequent PICOS criteria were applied for article inclusion in this review:

- P (population): patients diagnosed with COVID-19 or Long-COVID-19 syndrome (utilizing qigong for integrative treatment or rehabilitative purposes).
- I (intervention): qigong practiced for any number of sessions, either alone or in combination with other treatments (standard care, drug therapy, nutritional supplements, dietary advice, other types of physical activity, massage, etc.).
- C (comparison): the comparison category encompassed any type, including studies with no control.
- O (outcomes): significant enhancements in symptoms associated with COVID-19 and Long-COVID-19 over the course of time, including improvements in both physical and psychological wellbeing.
- S (study design): clinical investigations comprising controlled trials, observational studies, and case reports. Laboratory experiments conducted *in vitro* or *in vivo* with animal or cell models were intentionally excluded from the primary search.

A systematic screening of PubMed, EMBASE, Web of Science, Scopus, and Google Scholar was carried out to identify relevant studies. The search covered data from the inception of these databases up until February 2024. The search strategies used for each scientific database were the following:

- PubMed: ("qi gong"[Title/Abstract] OR "qi kung"[Title/Abstract] OR "chi gong"[Title/Abstract] OR "chi kung"[Title/Abstract] OR "qigong"[Title/Abstract] OR "chigong"[Title/Abstract]) AND ("COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR coronavirus[Title/Abstract]).
- EMBASE: ('qi gong':ab OR 'qi kung':ab OR 'chi gong':ab OR 'chi kung':ab OR 'qigong':ab OR 'chigong':ab) AND ('covid-19':ab OR 'covid19':ab OR coronavirus:ab).
- Web of Science: (AB=('qi gong') OR AB=('qi kung') OR AB=('chi gong') OR AB=('chi kung') OR AB=('qigong') OR AB=('chigong')) AND (AB=('covid-19') OR AB=('covid19') OR AB=(coronavirus)).
- Scopus: (TITLE-ABS-KEY ('qi AND gong') OR TITLE-ABS-KEY ('qi AND kung') OR TITLE-ABS-KEY ('chi AND gong') OR TITLE-ABS-KEY ('chi AND kung') OR TITLE-ABS-KEY ('qigong') OR TITLE-ABS-KEY ('chigong')) AND (TITLE-ABS-KEY ('covid19') OR TITLE-ABS-KEY ('covid19') OR TITLE-ABS-KEY (coronavirus)).
- Google Scholar (limited to the first 100 results): "Qigong" AND "COVID-19."

One researcher (M.A.) initially evaluated all materials obtained through the database search, concentrating on titles and abstracts. Subsequently, a second investigator (D.D.) reviewed articles that met the aforementioned inclusion criteria. This two-tiered assessment process was structured to ensure a proper selection of relevant studies for subsequent analysis. Disagreements between the two researchers were resolved through thorough discussion until a consensus was reached, ensuring the accuracy of the final selection. Inter-rater reliability scores were calculated to evaluate agreement between the two researchers: out of the 170 articles screened after duplicates were removed, they concurred on including 10 articles for subsequent full-text analysis, agreed on excluding 155 studies, and for five studies, there were some discussions. This led to an overall agreement of 97%, with a Cohen's κ value of 0.78, indicating substantial agreement. Following the article selection process, one investigator (M.A.) manually compiled information from studies meeting the inclusion criteria using an Excel spreadsheet. Simultaneously, the second researcher (D.D.) conducted a random verification process to validate the accuracy and completeness of the collected data.

The essential data components extracted from the studies included in the review comprised participant demographics, specific research methodologies, relevant details about the intervention and its comparison, as well as the documented outcomes. The key findings from the literature review were summarized and then discussed to generate a qualitative synthesis. Additionally, *p*-values indicating statistically significant differences favoring qigong practice for disease recovery were provided, along with the intervention effect size. In cases where effect size data were unavailable but essential information was present in the original text of the articles, effect sizes were computed using suitable statistical tools tailored for each study design, as outlined here: https://www.psychometrica.de/effect_size.html.

Each eligible Randomized Controlled Trials (RCTs) underwent evaluation utilizing the Jadad scale (Jadad et al., 1996). Each study underwent an assessment resulting in an overall rating between −1 and 5, indicating its methodological quality. Studies scoring 3 or higher were deemed to be of high quality, while those scoring lower were categorized as low quality. Despite the Jadad score criteria stipulating double-blinded trials for high quality, a single-blind design was deemed acceptable due to the inherent difficulty in fully concealing a physical intervention like qigong practice. Non-RCT studies were assessed to ensure compliance with specific guidelines recommended by the EQUATOR network (Simera et al., 2009), including STROBE for observational studies and CARE for case reports. Furthermore, the quality assessment of pre-post studies and case reports was conducted using the NIH - National Institutes of Health (URL: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) and JBI - The Joanna Briggs Institute (URL: https://jbi.global/critical-appraisal-tools) tools, respectively. The risk-of-bias assessment was used to inform the review discussion.

3 Results

After screening all databases, nine studies were eventually deemed eligible for inclusion (Chen et al., 2020; Liu et al., 2021; Tang et al., 2021; Brough et al., 2022; Mekky et al., 2022; Patel et al., 2023; Wang et al., 2023; Xing et al., 2023; Zhang H. et al., 2023). Among them, four were RCTs (Liu et al., 2021; Wang et al., 2023; Xing et al., 2023; Zhang H. et al., 2023), one was a controlled trial with no randomization of the participants (Mekky et al., 2022), while the remaining were three pre-post studies without any control group and a case report (see Table 1 for further details). One study was presented as a conference abstract (Mekky et al., 2022), whereas full-text versions were accessible for the remaining studies.

The article selection process is summarized in a dedicated flowchart (Figure 1), as requested by the PRISMA recommendations. A total of 285 research items were screened, comprising 41 from PubMed, 41 from EMBASE, 33 from Web of Science, 70 from Scopus, and 100 from Google Scholar. Following an initial screening, 115 duplicates were eliminated, and subsequently, 155 records were excluded based on title and abstract. Fifteen studies underwent full-text analysis, of which six were excluded either due to the absence of patients with COVID-19 or Long-COVID-19 symptoms (Li et al., 2022; Yang et al., 2022; Gonçalves et al., 2023; Seiça et al., 2023) or because they were not original research articles but rather narrative literature reviews (Feng et al., 2020; Mendo et al., 2022). Ultimately, nine studies met the criteria for inclusion in this review.

Five of the included trials examined the integrative use of qigong in COVID-19 treatment (Chen et al., 2020; Liu et al., 2021; Wang et al., 2023; Xing et al., 2023; Zhang H. et al., 2023), while four studies delved into its efficacy in enhancing the recovery of Long-COVID-19 patients (Tang et al., 2021; Brough et al., 2022; Mekky et al., 2022; Patel et al., 2023). Within the former group of trials, patient numbers varied from a minimum of 10 to a maximum of 177 (median: 128), with all but one study (Chen et al., 2020) adopting a randomized controlled design. Qigong training, practiced for 20–60 min daily throughout the COVID-19 duration, was complemented by standard medical care and other integrative therapies such as acupressure, music therapy, and health education (see Table 1 for additional information). Conversely, controlled groups, if included, solely received standard treatment as per current medical guidelines. Regardless of the severity of COVID-19, individuals undergoing qigong practice demonstrated superior physical and psychological outcomes, including improvements in respiratory symptoms, anxiety levels, sleep quality, mental wellbeing, and health-related quality of life (see Table 2 for further details). Additionally, four studies explored the effects of qigong training (Tang et al., 2021; Brough et al., 2022; Mekky et al., 2022; Patel et al., 2023), either independently or in conjunction with other treatments, on Long-COVID-19 symptoms, encompassing persistent respiratory dysfunction, dizziness, sleep disturbances, and compromised health-related quality of life. Across these studies, which comprised sample sizes ranging from 1 to 357 (median: 29), improvements in the measured outcomes were consistently observed, with some instances demonstrating additional benefits related to weight management. Among the qigong exercises and forms, the most commonly practiced by the study participants were Liu Zi Jue (Six Healing Sounds) and Baduanjin (Eight Pieces of Brocade).

Overall, this review encompassed four RCTs (Liu et al., 2021; Wang et al., 2023; Xing et al., 2023; Zhang H. et al., 2023), which primarily investigated the efficacy of qigong in COVID-19 integrative care, emphasizing its advantageous effects on psychological wellbeing. Conversely, non-RCT studies (Chen et al., 2020; Tang et al., 2021; Brough et al., 2022; Mekky et al., 2022) included in this review primarily focused on qigong practice

TABLE 1 Summary of the included studies.

Main health condition	Population (n)	Intervention		Comparison (n)	Mental wellbeing/ QoL†	Sleep quality†	Respiratory symptoms†	Study design	References
		Details	Qigong exercises						
COVID-19	177 patients with asymptomatic COVID-19 Age (range): 18–60 yo Gender: 111 M/66 F	Standard care + Music therapy + Qigong training (60 min/day) for the entire quarantine period (6–7 days on average) ($n = 96$)	Baduanjin (Eight Pieces of Brocade)	Standard care ($n = 81$)	✓	✓	-	Randomized controlled trial	Wang et al., 2023
	154 patients with asymptomatic COVID-19 Age (range): 18–65 yo Gender: 64 M/90 F	Standard care + Health education + Qigong training (20 min/day) for 12 days ($n = 74$)	11 exercises from the Yi Jin Jing method	Standard care + Health education ($n = 80$)	✓	-	-	Randomized controlled trial	Xing et al., 2023
	128 patients hospitalized for severe COVID-19 Age (range): 20–80 yo Gender: 55 M/73 F	Standard care + Acupressure + Qigong training (40 min/day) for the entire hospitalization period (18–21 days on average) ($n = 64$)	Liu Zi Jue (Six Healing Sounds)	Standard care ($n = 64$)	-	-	✓	Randomized controlled trial	Liu et al., 2021
	40 patients with COVID-19 Age (mean ± SD): 41.30 ± 7.73 yo - intervention group, 42.10 ± 8.47 yo - control group Gender: 24 M/16 F	Standard care + Music therapy + Qigong training (60 min/day) for the entire quarantine period (?) ($n = 20$)	Baduanjin (Eight Pieces of Brocade)	Standard care ($n = 20$)	✓	✓	-	Randomized controlled trial	Zhang H. et al., 2023
	10 patients hospitalized for non-severe COVID-19 Age (mean ± SD): 50.20 ± 12.04 yo Gender: 6 M/4 F	Standard care + Qigong training (30 min/day) for 2 weeks ($n = 10$)	Eight-segment pulmonary rehabilitation exercises	None	✓	-	✓	Pre-post study with no control group	Chen et al., 2020
Long-COVID-19	357 patients with insomnia after COVID-19 Age: 18 + yo Gender: M/F?	Qigong training (? min/day) for 2 weeks + Z-drugs/sleep medications ($n = 106$)	?	Z-drugs/sleep medications ($n = 251$)	-	✓	-	Controlled study with no randomization	Mekky et al., 2022

(Continued)

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TABLE 1 (Continued)

Main health condition	Population (n)	Intervention		Comparison (n)	Mental wellbeing/ QoL†	Sleep quality†	Respiratory symptoms†	Study design	References
		Details	Qigong exercises						
	33 patients discharged from hospital after COVID-19 with persistent respiratory symptoms Age (mean ± SD): 43.2 ± 10.4 yo Gender: 17 M/16 F	Qigong training (20 min/day) for 4 weeks ($n = 33$)	Liu Zi Jue (Six Healing Sounds)	None	-	-	✓	Pre-post study with no control group	Tang et al., 2021
	25 patients with Long-COVID-19 Age: 15 + yo (most of the participants (20/25) had an age comprised between 25 and 65 yo) Gender: 7 M/15 F/3 ?	A program including Qigong training, nutritional support, meditation exercises, group discussions, and aromatherapy for 4 weeks ($n = 25$)	?	None	✓	-	-	Pre-post study with no control group	Brough et al., 2022
	1 patient with Long-COVID-19 respiratory, gastrointestinal, and systemic symptoms Age: 62 yo Gender: 1 F	Taichi exercises for 2 months after the acute phase of COVID-19, then Qigong (10 min/day) + Taichi (35 min/day) training every day for as long as the symptoms persisted ($n = 1$)	Gentle exercises with a focus on controlled breathing	None	-	-	✓	Case report	Patel et al., 2023

F, Females; M, Males; yo, years old. †Significant improvements (✓) in mental wellbeing/QoL (Quality of Life), sleep quality, and/or respiratory symptoms associated with the intervention. ? stands for unavailable/undisclosed information.

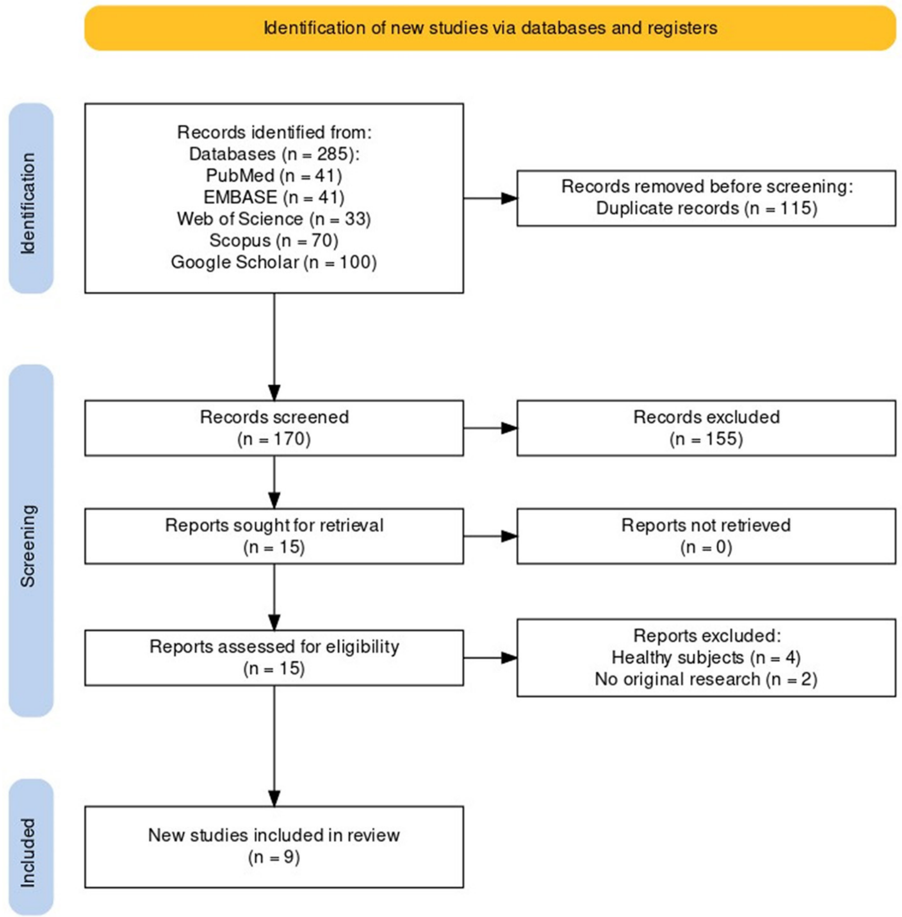

FIGURE 1
PRISMA flowchart describing the article selection process (Haddaway et al., 2022).

for Long-COVID-19 management, assessing benefits across both physical and psychological domains. Another distinction between RCTs and non-RCTs lies in the administration of qigong: in RCTs, qigong was predominantly administered alongside other therapies, whereas in non-RCTs, it was often administered alone and occasionally compared with no treatment. Furthermore, insights from the sole case report incorporated in this review indicate that qigong may offer benefits beyond respiratory enhancements, extending to weight management during the recovery phase from Long-COVID-19 (Patel et al., 2023).

The RCTs included in the review (Liu et al., 2021; Wang et al., 2023; Xing et al., 2023; Zhang H. et al., 2023) consistently demonstrated high quality. However, some methodological weaknesses were identified, particularly in terms of inadequate blinding of study investigators and notable dropout rates in one instance (further details in the Supplementary material). In contrast, non-RCTs lacked clear adherence to internationally recognized methodological guidelines in all cases. One study could not be evaluated due to its reporting as a conference abstract (Mekky et al., 2022). Pre-post studies examined in this review exhibited an average-to-low quality, characterized by limited sample sizes and, in some cases, insufficient information on statistical analysis or study design (see the Supplementary material for further specifics). However, the sole case report included in this review achieved a high score in the NIH quality assessment.

4 Discussion

4.1 Critical overview of the available evidence and mechanisms of action

The review included both trials investigating the use of qigong in COVID-19 integrative treatment and studies examining its effectiveness in Long-COVID-19 recovery (see Table 1). Qigong, practiced daily for 20–60 min alongside standard medical care, not only led to superior psychological and physical outcomes in COVID-19 patients but also contributed to shortening the duration of the disease (Liu et al., 2021). Similarly, qigong showed promising results in alleviating Long-COVID-19 symptoms, with improvements observed across various health indicators. In general, psychological benefits were supported by stronger evidence. All the same, the intervention primarily yielded effect sizes ranging from 0.25 to 0.75, indicative of a moderate impact on the outcomes measured: this suggests that qigong had a noticeable impact on the outcomes measured in the studies, with effects falling somewhere between small and large (see Table 2 for additional details). Such a medium effect size underscores the meaningfulness of the intervention's impact on the variables under consideration, further supporting its efficacy in producing tangible results. The most commonly practiced qigong exercises were Liu Zi Jue and Baduanjin.

TABLE 2 Main outcomes and results of the studies eligible for inclusion.

Main health condition	Outcomes	Statistical significance (*p* value)	Effect size	Study design	References
COVID-19	↑ Mental wellbeing and health-related QoL: GAD-7 (mean difference, 95% CI): 2.9 [2.2; 3.6]*; PHQ-9 (mean difference, 95% CI): 3.6 [2.9; 4.4]*; PHCS (mean difference, 95% CI): −5.0 [−6.1; −3.9]* ↑ Sleep quality: JSS (mean difference, 95% CI): 2.7 [2.0; 3.3]*	GAD-7: $p < 0.001$ PHQ-9: $p < 0.001$ PHCS: $p < 0.001$ JSS: $p < 0.001$	d (GAD-7) = 0.70 d (PHQ-9) = 0.35 d (PHCS) = 0.28 d (JSS) = 0.32	RCT	Wang et al., 2023
	↓ Anxiety: HAMA total score (mean ± SD): 2.50 ± 5.05 vs. 4.71 ± 7.07* Significant changes were also reported for the HAMA mental and somatic scores	HAMA total score: $p = 0.028$	d (HAMA) = 0.36	RCT	Xing et al., 2023
	↓ Dyspnea: mMRC (mean difference, 95% CI): −0.3 [−0.6; 0.1]*; MBS (mean difference, 95% CI): −0.7 [−1.3; 0.0]* ↓ Days of hospitalization: 18.5 vs. 20.8* ↓ Cough (days of symptom duration): 14.3 vs. 17.0*	mMRC: $p = 0.018$ MBS: $p = 0.045$ Days of hospitalization: $p = 0.042$ Cough duration: $p = 0.046$	d (mMRC) = 0.19 d (MBS) = 0.52 d (days of hospitalization) = 0.37 d (cough duration) = 0.35	RCT	Liu et al., 2021
	↓ Anxiety: SAS (mean ± SD): 44.44 ± 5.85 vs. 48.03 ± 3.23* ↑ Mood: SDS (mean ± SD): 46.73 ± 7.04 vs. 51.84 ± 5.73* ↑ Sleep quality: PSQI (mean ± SD): 1.10 ± 0.71 vs. 1.65 ± 0.81*	SAS: $p = 0.023$ SDS: $p = 0.016$ PSQI (sleep quality): $p = 0.029$	d (SAS) = 0.76 d (SDS) = 0.80 d (PSQI) = 0.72	RCT	Zhang H. et al., 2023
	↑ Physical activity, perception of dyspnea, and QoL (no numerical findings)	/	/	Pre-post study	Chen et al., 2020
Long-Covid-19	↑ Sleep quality: improvement among cases (%): 68.18% vs. controls: 64.20%	Not reported	RR = 0.89	CS	Mekky et al., 2022
	↑ Functional capacity (MIP, PIF, DM-DB) and QoL (HAMA and SF-36) MIF (mean increase ± SD): 13.46 ± 20.06 cmH2O* PIF (mean increase ± SD): 0.74 ± 0.58 L/sec* DM-DB (mean increase ± SD): 0.57 ± 1.18*	MIF: $p < 0.001$ PIF: $p < 0.001$ DM-DB: $p = 0.009$	Pre- and post-test data graphically reported	Pre-post study	Tang et al., 2021
	↑ Health-related QoL: WHHQ-18 (mean ± SD): from 33.7 ± 12.5 at baseline to 39.5 ± 10.8 at the end of the treatment	Not reported	d (QoL) = 0.50	Pre-post study	Brough et al., 2022
	↓ Dyspnea and improvement in SpO2 levels from 83% to 93% ↓ Dizziness ↑ Balance ↑ Weight control	/	/	Case report	Patel et al., 2023

CS, Controlled Study with no randomization of the participants; d, Cohen's d (measure of effect size); DM-DB, Diaphragm Movement in Deep Breathing; GAD-7, General Anxiety Disorder (7 items); HAMA, Hamilton Anxiety Rating Scale; JSS, Jenkins Sleep Scale; MBS, Modified Borg Dyspnea Scale; MIP, Maximal Inspiratory Pressure; mMRC, Modified British Medical Research Council Questionnaire (Dyspnea Scale); PHCS, Perceived Health Competence Scale; PHQ-9, Patient Health Questionnaire (9 items); PIF, Peak Inspiratory Flow; PSQI, Pittsburgh Sleep Quality Index; QoL, Quality of Life; RCT, Randomized Controlled Trial; RR, Risk Ratio; SAS, Self-rating Anxiety Scale; SD, Standard Deviation; SDS, Self-rating Depression Scale; SF-36, Short Form Health Survey (36 items); SpO2, Oxygen Saturation; WHHQ-18, Warwick Holistic Health Questionnaire (18 items). *$p < 0.05$ (significant change in favor of the intervention).

Interpreting the effects of qigong in light of neuroscientific theories such as the polyvagal theory suggests that the benefits of this practice on psychophysical relaxation result from stimulation induced by exercise on the autonomic nervous system's regulatory centers, particularly the vagal tone, promoting ventral vagal complex activity (Seppala et al., 2017). This could lead to increased control and resilience of the autonomic nervous system responses to external stressors, enhancing cardiovascular and respiratory activity, mood tone, as well as a general effect of increased concentration and psychophysical relaxation (Donelli et al., 2023). Thus, the traditional concept of qigong as a practice restoring "Qi" balance can be interpreted neuroscientifically as the potential to contribute, through exercises, to "harmonizing" the activity of both the ventral and dorsal vagal complexes, whose physiological actions are mutually antagonistic, ultimately promoting individual psychophysical wellbeing. Qigong, as a training to achieve a state of "inner silence," is a discipline that requires simultaneous focus and relaxation during movement: this implies a simultaneous presence of high vagal tone and orthosympathetic tone, which is maximally beneficial because it enhances control over heart rate, breathing, and phonation, and also induces beneficial eustress for immune and biohumoral reasons (Donelli et al., 2023). Indeed, this interpretative paradigm has been applied with interest and scientific credibility to other meditative disciplines, such as Yoga, originating from the Ayurvedic tradition (Sullivan et al., 2018), and mindfulness-based techniques (Lucas et al., 2018; Poli et al., 2021).

The potential effectiveness of qigong in enhancing respiratory function and improving psychological outcomes, as evidenced in the included studies (refer to Table 2 for further details), can be attributed to several underlying mechanisms. Firstly, the controlled breathing exercises inherent in qigong practice can promote respiratory muscle strength and endurance, thereby improving lung capacity and efficiency (Ding et al., 2014). Additionally, the rhythmic breathing patterns facilitate relaxation and stress reduction, which can alleviate anxiety and improve overall psychological wellbeing (Ng and Tsang, 2009). Moreover, the gentle movements involved in qigong promote circulation and oxygenation of tissues, which may aid in tissue repair and enhance overall respiratory health (Lee et al., 2003). Furthermore, the meditative aspect of qigong fosters mindfulness and emotional regulation, helping individuals cope with stress, anxiety, and depression (Chow et al., 2012; Yeung et al., 2018). These combined physiological and psychological benefits make qigong a promising adjunctive therapy for improving both respiratory function and mental health outcomes.

From a scientific perspective, evidence-based rehabilitative protocols must include effective strategies addressing four fundamental points (Osadnik et al., 2015; Pt and Ccc-A/slp, 2015; Stott and Quinn, 2017; Nicolau et al., 2022):

- Exercise, including any motor activity stimulating the patient's functional reserve following an acute illness.
- Practice, involving the repetition of exercises for a sufficient time to achieve the maximum possible degree of functional recovery.
- Psychological support, beneficial for the individual's mental wellbeing.
- Patient education, facilitating proper self-management of health conditions and attentive long-term monitoring.

In general, qigong aligns well with the four fundamental points of evidence-based rehabilitative protocols. It involves a series of slow, controlled movements and postures, providing a form of motor activity that stimulates the body's functional reserve following illness, promoting physical rehabilitation after an acute illness. By emphasizing the repetition of exercises over time, qigong supports maximum functional recovery and enhances neuroplasticity, proprioceptive re-education, cardio-respiratory kinetics, and muscle tone. This aspect assumes particular significance given the respiratory manifestations and sequelae often associated with COVID-19 (Boutou et al., 2021): in fact, by incorporating techniques aimed at enhancing lung capacity, improving oxygenation, and promoting respiratory muscle strength, qigong breathing exercises can mitigate the respiratory challenges posed by COVID-19 and its long-term complications. Moreover, qigong incorporates mindfulness techniques and focused breathing, which can have a profound impact on mental wellbeing, offering valuable psychological support during the recovery process and promoting reintegration into the social context. This holds significance, particularly concerning the cognitive impairment associated with Long-COVID-19, commonly referred to as "brain fog" (Nouraeinejad, 2023): cognitive exercises have shown efficacy in addressing this condition (Rabaiotti et al., 2023), and research indicates that qigong can enhance cognitive functions, particularly in elderly populations (Qi et al., 2021). Through qigong practice, individuals can learn self-management strategies for their health conditions, including proper breathing techniques, body awareness, and stress management, empowering them to take an active role in their recovery and long-term health journey. Additionally, qigong instructors can offer educational resources and support to help patients navigate their rehabilitation effectively. Qigong is optimal for the elderly as it constitutes a gentle yet comprehensive exercise, engaging aspects such as respiration, cardiac function, resistance training, balance, and coordination. However, for younger age groups, it may be more beneficial for neuro-autonomic aspects, albeit less effective in achieving cardiovascular prevention goals due to its insufficient intensity to count toward the recommended amount of weekly aerobic activity (at least 150 min/week) (Pelliccia et al., 2021).

Qigong is a cost-effective and accessible health-promoting practice, demonstrating versatility in its application across various demographics, even during the COVID-19 pandemic (Jahnke et al., 2010; Klich and Milert, 2018; Mendo et al., 2022). Its simplicity makes it attainable for individuals with severe illnesses, chronic conditions, or disabilities, ensuring inclusivity in its practice (Ng and Tsang, 2009; Guo et al., 2018). Furthermore, its adaptability allows for indoor sessions, making it feasible even within the confines of small living spaces like apartments and quarantine rooms, while its compatibility with outdoor environments encourages practitioners to engage with nature in parks or forests (Feng et al., 2020; Hung et al., 2021). Additionally, the digital age has facilitated the dissemination of qigong teachings through online platforms, enabling individuals to participate in live or recorded training sessions from the comfort of their homes (Oh et al., 2021; Akinci et al., 2022). This multifaceted accessibility underscores the potential of qigong as a widely accessible and sustainable means of promoting physical and mental wellbeing among patients with COVID-19 symptoms or long-term sequelae.

Furthermore, qigong's compatibility with various treatment modalities and practices makes it a versatile addition to integrated therapeutic regimens, enhancing its efficacy in addressing diverse health needs and complementing medical interventions. Qigong's potential to promote relaxation and reduce stress may offer additional benefits, potentially leading to a reduction in the intake of anxiolytic drugs or sleep inducers (Wang et al., 2013; Mekky et al., 2022; Xing et al., 2023; Zhang H. et al., 2023). Moreover, regular engagement in qigong can cultivate a deeper appreciation for an active lifestyle among practitioners, encouraging them to embrace physical activity as an integral part of their daily routine (Horowitz, 2009). Indeed, in a case report, the overweight individual with Long-COVID-19 symptoms who commenced qigong training successfully achieved better long-term weight management (Patel et al., 2023).

Finally, research suggests that regular practice of qigong can effectively reduce stress, anxiety, and depressive symptoms by promoting relaxation, enhancing emotional regulation, and fostering a sense of inner calm (Wang et al., 2013). Its emphasis on mindful breathing and slow, deliberate movements helps individuals to connect with their bodies, quiet the mind, and cultivate resilience in the face of adversity. Particularly in professions like healthcare, where workers are often exposed to high levels of stress and emotional strain, integrating qigong into daily routines can offer a valuable means of self-care and support mental wellbeing (Gutierrez et al., 2023; Seiça et al., 2023). Similarly, students facing academic pressure and uncertainty can benefit from incorporating qigong practices into their study breaks or daily routines to alleviate stress and improve focus (Li et al., 2022; Gonçalves et al., 2023). In fact, research shows that physical activity (along with socio-economic status) significantly influenced psychological wellbeing and sleep quality in college students during the COVID-19 pandemic (Rassolnia and Nobari, 2024). By providing a holistic approach to mental wellness, qigong offers a valuable resource for individuals navigating challenging circumstances and seeking to enhance their psychological resilience.

4.2 Study limitations

One limitation of this review is the potential confounding effect of combining qigong with other therapies in several of the included trials. The co-administration of qigong with additional interventions, such as music therapy or acupressure, makes it challenging to isolate the specific efficacy of qigong alone. Consequently, the observed effects may be influenced by the concurrent treatments, complicating the interpretation of results and making it difficult to attribute improvements solely to qigong practice. Moreover, variations in the duration, frequency, and intensity of qigong sessions across studies could introduce heterogeneity into the results, impacting the ability to draw definitive conclusions about its efficacy. Additionally, the quality of some included studies may be limited, potentially affecting the reliability and generalizability of the findings. Finally, publication bias could influence the results if studies with negative or neutral findings are underrepresented in the literature. These limitations emphasize the need for future well-designed controlled trials with rigorous methodologies to provide more conclusive evidence regarding the isolated efficacy of qigong in COVID-19 and Long-COVID-19 recovery.

As highlighted in a particular trial (Liu et al., 2021), achieving an optimal sample size is crucial for detecting significant physiological effects, if any, of qigong in COVID-19 recovery: in particular, the study suggests that a sample size of approximately 65 participants per trial arm would be necessary to effectively discern any physiological benefits of qigong practice in individuals recovering from COVID-19. Similarly, this sample size would also be applicable in evaluating the effects of qigong on psychological wellbeing.

5 Conclusions

In conclusion, while this review highlights the potential benefits of qigong in promoting health and aiding in the recovery of COVID-19 patients, there is a clear need for future studies to further elucidate its therapeutic effects. Rigorous study designs, such as randomized controlled trials with sufficient sample sizes, are necessary to accurately quantify the efficacy of qigong training. Moreover, future research endeavors should prioritize clarity and relevance in research questions, focusing on precision in study design and objectives rather than solely on sample size magnitude. Additionally, investigating the impact of qigong as a standalone intervention, independent of other complementary therapies, can provide insights into its unique contributions to specific health outcomes. By adhering to stringent methodological standards and exploring the effects of qigong in isolation, researchers can advance our understanding of its therapeutic potential and explore its broader integration into clinical practice.

Overall, the available evidence indicates that qigong practice is beneficial for both COVID-19 and Long-COVID-19 recovery, with recommended durations ranging from several days to weeks. A minimum of 20 min per day, up to a maximum of 60 min, is deemed necessary for optimal therapeutic effects. For COVID-19 recovery, even a week of regular practice may yield noticeable benefits, while for Long-COVID-19, it is recommended to continue for at least 1 month to experience more substantial improvements. Key qigong forms such as Liu Zi Jue and Baduanjin, or any gentle total body activity combined with breathing exercises, are particularly effective in promoting physical and psychological wellbeing during recovery from both acute and prolonged phases of the disease.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. DD: Data curation, Methodology, Supervision, Validation, Writing—original draft, Writing—review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Yoga as a therapeutic approach to mental health in university students: a randomized controlled trial

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Objectives: The purpose of this study has been to analyze the efficacy of a yoga-based intervention on stress, emotional wellbeing, state anxiety and trait anxiety in university students.

Methods: This study was a randomized controlled trial. The sample consisted of 129 university students, of which 65 underwent a yoga training for 12 weeks and a control group that did not carry out any type of intervention. The primary outcome was stress, which was collected through The Perceived Stress Scale (PSS). The secondary outcomes were emotional wellbeing which was measured through the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), and anxiety through State–Trait Anxiety Inventory (STAI). All variables were measured before and after the intervention.

Results: Participants in the experimental group showed statistically significant improvements in the primary outcome perceived stress (Cohen's $d = 0.44$) and the secondary outcomes emotional wellbeing (Cohen's $d = 0.47$), and both state anxiety (Cohen's $d = 0.38$) and trait anxiety (Cohen's $d = 0.80$) compared to the control group that did not carry out any type of physical training.

Conclusion: This study demonstrated that a 12-week yoga intervention can significantly reduce perceived stress and anxiety, and improve emotional wellbeing in university students. Initially, the experimental group (EG) reported higher levels of stress and anxiety than the control group (CG), but after the intervention, the EG experienced significant improvements compared to the CG.

KEYWORDS
yoga, perceived stress, emotional wellbeing, anxiety, university students

1 Introduction

In recent years, there has been a notable increase in interest toward the mental health of university students (1, 2), in response to the observed increase in the prevalence of psychological disorders in this population (3). Prior studies (4–6) have shown that many students encounter elevated levels of stress and anxiety throughout their university experience. While universities provide avenues for personal and academic development, they also present challenges that can impact mental wellbeing negatively (7). Stress, anxiety, and shifts in emotional health are increasingly recognized issues in this setting, affecting not only academic achievements but also the overall quality of life among young university students.

Perceived stress among university students can originate from various sources, such as academic workload, social expectations, financial pressures, and the transition to independent living at university (8). This constant tension can manifest in physical, emotional, and cognitive symptoms, affecting concentration, decision-making, and interpersonal relationships (9). Anxiety is also a common condition among university students (10) and manifests in two main forms: as a temporary state and as a persistent trait. The temporary state of anxiety is commonly experienced in moments of academic stress, such as during exams or presentations. However, these episodes are transient and tend to disappear once the stressful situation has passed. On the other hand, anxiety as a trait involves a predisposition to experience anxiety in various situations, without depending on a specific stressful stimulus (11). Students with this characteristic may show chronic worry, persistent muscle tension, excessive self-demand, and anticipatory fear about their academic and professional future (12), which can have a significant impact on their academic performance and on their quality of life both physically and mentally (13, 14).

Given this context, it is crucial to investigate effective interventions that can mitigate stress, reduce anxiety, and promote emotional wellbeing among the student population. Yoga, an ancient discipline that merges physical movements to strengthen and flexibilize the body, breathing exercises to control respiratory rhythm, deep relaxation methods to alleviate physical and mental tension, meditation to increase awareness of the body and mind, and mindfulness techniques to enhance emotional regulation through the practice of yama and niyama (15), has gained popularity as a potential strategy for improving mental health and overall wellbeing (16). From a scientific perspective, studies support the benefits of yoga in reducing mental pathologies (17–19). Yoga practices, which include mind–body interaction through physical exercise combined with breathing techniques and meditation, have shown an increase in noradrenaline levels and a reduction in plasma adrenaline levels (20), a decrease in cortisol levels and an improvement in the response of the autonomic nervous system (21), which translates into a reduction of perceived stress. Additionally, it has been observed that the practice of yoga increases the production of neurotransmitters like serotonin (22) and dopamine (23), associated with emotional wellbeing.

These findings suggest that yoga has proven effective in regulating various biological systems, including the autonomic nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, and heart rate variability, which supports its beneficial effects on mental and emotional health (15). This makes it a valuable tool to incorporate into intervention programs aimed at helping university students manage stress, anxiety, and improve their quality of life. The present study seeks to analyze the effectiveness of a yoga-based intervention on stress, emotional wellbeing, state anxiety and trait anxiety in university students.

2 Materials and methods

2.1 Research design and participants

Randomized controlled trial aimed at analyzing the effectiveness of a 12-week yoga-based intervention on perceived stress, emotional wellbeing, state anxiety and trait anxiety in university students. This study was registered prior to its commencement (NCT06304662) and was approved by the Ethics Committee of the Mid-Atlantic University (CEI/05–006).

The recruitment of participants was carried out from November to February of 2024, taking advantage of placing advertisements at key points within the university campus, dissemination through social networks linked to the university, and direct contact with students via emails sent from the educational entity's database. Those who showed interest in participating in the study completed an informed consent form in accordance with the Declaration of Helsinki, Good Clinical Practice, and all applicable laws and regulations, which clearly explained the study's goals, the methods to be followed, potential risks and benefits, and the confidential handling of the obtained data. Included in the study were students who: (i) were university students who had participated in a yoga training program in the previous 12 months; (ii) have adequate physical capacity to carry out the activities demanded in the study; and (iii) that they have the ability to interpret the project instructions, programs and protocols. The exclusion criteria were: (i) that they did not meet the minimum number of sessions required to complete the study; and (ii) that they had extensive experience and experience in the practice of yoga.

2.2 Randomization

The distribution of participants was carried out using a sequence of random numbers generated by computer, placing individuals equally in an experimental group (EG) and a Control group (CG) following a 1:1 ratio. The group assignments were kept hidden from both the participants and the researchers, and the physiotherapist responsible for carrying out the intervention. This process was carried out using sealed, opaque envelopes that were sequentially numbered, which were kept locked and were only opened by a person not directly involved in the study. At the conclusion of this procedure, 65 individuals were assigned to the experimental group and another 65 to the Control group.

2.3 Intervention

Participants in the experimental group (EG) underwent a yoga program twice a week (Tuesdays and Thursdays) for 12 weeks in person, totaling 24 sessions with duration of 60 min each. Each of these sessions during this period consisted of a total of 4 distinct parts: (i) 5 min dedicated to breathing techniques through Pranayama postures; (ii) 10 min of warm-up based on joint movement exercises; (iii) 35 min allocated to the central part of the intervention where postures based on Hatha yoga were performed, one of the most traditional and widely practiced forms of yoga that focuses on physical postures (asanas), breathing techniques (pranayama) and meditation (dhyana); and (iv) 10 min for relaxation techniques based on flexibility and stretching exercises. In the core part of the intervention, different postures were carried out distributed according to position: (a) standing postures: Utkatasana (Chair Pose), Uttanasana (Standing Forward Bend), Vrksasana (Tree Pose), Garudasana (Eagle Pose), Naṭarajasana (Dancer Pose), Virabhadrasana I (Warrior I), Virabhadrasana II (Warrior II), Virabhadrasana III (Warrior III), Utthita Trikonasana (Triangle Pose), and Parivrtta Baddha Parsvakonasana (Revolved Side Angle Pose); (b) seated postures: Dasana (Staff Pose), Janu Sirsasana (Head-to-Knee Pose), Parivrtta Janu Sirsasana (Revolved Head-to-Knee Pose), Baddha Konasana (Bound Angle Pose), Gomukhasana (Cow Face Pose), Navasana (Boat Pose), and Ardha Matsyendrasana (Half Lord of the Fishes Pose); (c) knee postures: Balasana (Child's Pose), Supta Virasana (Reclining Hero or Heroine Pose), Ustrasana (Camel Pose), Eka Pada Rajakapotasana (One-Legged King Pigeon Pose), Parighasana (Gate Pose), and Simha asana (Lion Pose); (d) prone postures: Savasana (Corpse Pose), Apanasana (Knees-to-Chest), Setu Bandha Sarvangasana (Bridge Pose), Sarvangasana (Shoulder Stand), Viparita Karani (Legs-Up-the-Wall Pose), Halasana (Plow Pose), and Jathara Parivrtti Asana (Belly Twist); and lastly, (e) supine postures: Bhujangasana (Cobra Pose), Dhanurasana (Bow Pose), and Salabhasana (Locust Pose).

All sessions were under the supervision of a professional trained in Physiotherapy with more than 5 years of experience in various styles of yoga. A criterion for analysis was set as participation in at least 80% of the scheduled sessions. Participants in the control group were recommended to continue with their daily lives without significant changes; especially they were instructed not to enroll in any training program or structured physical activity during the study period. The current levels of physical activity of the participants were controlled in both the intervention group and the control group through regular telephone calls. These calls were made periodically throughout the study period and served to collect detailed information about any physical activity in which the participants were engaged outside of the scheduled study sessions.

2.4 Outcomes

The general procedure for data collection included administration of questionnaires in a controlled environment, usually within the university campus, to ensure accuracy and consistency in responses. Participants completed these questionnaires under supervision to resolve any questions in real time and ensure complete understanding of each question. Regarding the schedule of evaluations, they were carried out the week before the start of the yoga intervention, thus establishing the baseline for the measurements. Subsequently, once the intervention was completed, the participants were evaluated again the following week. This scheduling of evaluations allowed immediate and effective monitoring of the effects of the intervention. Before assignment, descriptive characteristics such as age, sex, employment, physical activity, weight, height, and BMI were collected in the presence of experienced interviewers. The Body Mass Index (BMI) was calculated as weight (kg)/height (m^2) (24).

Primary outcome:

Perceived stress was measured through The Perceived Stress Scale (PSS) (25) in its Spanish version (26), a 14-item questionnaire that assesses the level of stress perceived over the last month. It consists of 14 items with a response format on a five-point scale (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = very often). The total PSS score is obtained by reversing the scores of items 4, 5, 6, 7, 9, 10, and 13 (in the following way: 0 = 4, 1 = 3, 2 = 2, 3 = 1, and 4 = 0) and then adding up the 14 items. The direct score obtained ranges from 0 to 56 points and indicates that a higher score corresponds to a higher level of perceived stress.

Secondary outcomes:

Emotional wellbeing was measured through the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) (27), a 14-item questionnaire on mental wellbeing that includes subjective wellbeing and psychological functioning. All items on a 5-point Likert scale are phrased positively and address aspects of positive mental health, measuring the frequency of the subject's attitudes from "never" to "always." Higher scores indicate better mental wellbeing. The Spanish version of WEMWBS showed good psychometric properties similar to the original scale from the United Kingdom (28).

The anxiety of the participants was measured by the State–Trait Anxiety Inventory (STAI) (29), a self-report composed of 40 items designed to assess two independent concepts of anxiety: state anxiety (a transient emotional condition) and trait anxiety (a relatively stable anxious propensity). The temporal frame of reference for state anxiety is "right now, at this moment" (20 items) and for trait anxiety is "in general, on most occasions" (20 items). Each subscale is made up of a total of 20 items in a 4-point Likert response system according to intensity (0 = almost never/none; 1 = somewhat/sometimes; 2 = moderately/often; 3 = very much/almost always). The total score on each of the subscales ranges from 0 to 60 points. Both the original questionnaire and its Spanish version have good psychometric properties, with levels of internal consistency ranging, for both the total score and each of the subscales, between 0.84 and 0.93 (30).

2.5 Sample size calculation

The sample size was determined using the freely available statistical software Epidat 4.2 (Xunta de Galicia. Consellería de Sanidade-Servizo Galego de Saúde) with the following parameters referring to the level of stress perceived as a primary outcome: it was proposed to evaluate an expected mean difference of 2.4 units between the two groups (31) or a reduction of 0.6 in each group (32). With a significance level of 5% (corresponding to a z-value of 1.96) and a power of 90% (corresponding to a z-value of 1.28). A loss percentage of 15% was also considered, which allowed adjusting the sample size to 122 participants to compensate for possible dropouts or missing data during the study.

2.6 Statistical analysis

For population characterization, categorical variables were presented in terms of frequency and percentage. An exploratory analysis was conducted to validate the normal distribution of quantitative variables, ensuring adherence to the requisite assumptions for each analysis (Kolmogorov–Smirnov >0.05). Subsequently, mean values and standard deviations were computed for each variable of interest. The Student's *t*-test for independent samples was employed to assess inter-group differences.

Moreover, an effective treatment analysis was executed. This entailed the utilization of a mixed analysis of variance, with the intervention (YGE vs. CG) acting as the between-groups factor and the measurement time (pre-treatment versus post-treatment) serving as the within-subject variable. Dependent variables, such as perceived stress, emotional wellbeing, and anxiety, underwent separate analyses. An exploration of potential interactions between treatment group and measurement time was conducted.

Additionally, Cohen's d was utilized to determine intergroup effect sizes, with values of ≤0.2, 0.5, and 0.8 indicating small, medium, and large effects, respectively. A significance level of $p < 0.05$ was established for all analyses. Bonferroni correction was used to adjust the *p*-values for independent samples t-tests and for multiple comparisons in the case of the mixed analysis of variance. Statistical computations were performed using SPSS statistical software, version 17.0 (SPSS, Inc., Chicago, IL, United States).

3 Results

At the start of the study, a total of 142 university students from various universities were contacted, of which 130 met the inclusion criteria and participated in the study (Figure 1). This study consists of 48.8% male participants and 51.2% female participants (Table 1).

3.1 Perceived stress

Before the intervention, participants in the Experimental Group (EG) reported higher values in the primary variable of perceived stress (25.82 ± 7.24) compared to those in the Control Group (CG) (24.83 ± 6.25). However, post-measurement revealed higher stress levels in the CG (25.09 ± 6.41) compared to the EG (22.77 ± 6.45). Significant differences were found in Group × Time: $F(1, 127) = 16.853$, $p = 0.001$, $\eta^2 = 0.117$, and in Time: $F(1, 127) = 11.880$, $p = 0.001$, $\eta^2 = 0.086$, but not in Group: $F(1, 127) = 0.376$, $p = 0.541$, $\eta^2 = 0.003$ (Figure 2). The comprehensive analysis showed statistically significant differences between groups in the post-intervention measurement, $t(127) = 2.053$, $p = 0.042$, with a small effect size ($d = 0.36$). Additionally, significant differences were observed in pre and post-measurements for the group undergoing yoga treatment/training, $t(64) = 3.921$, $p = 0.001$, with a

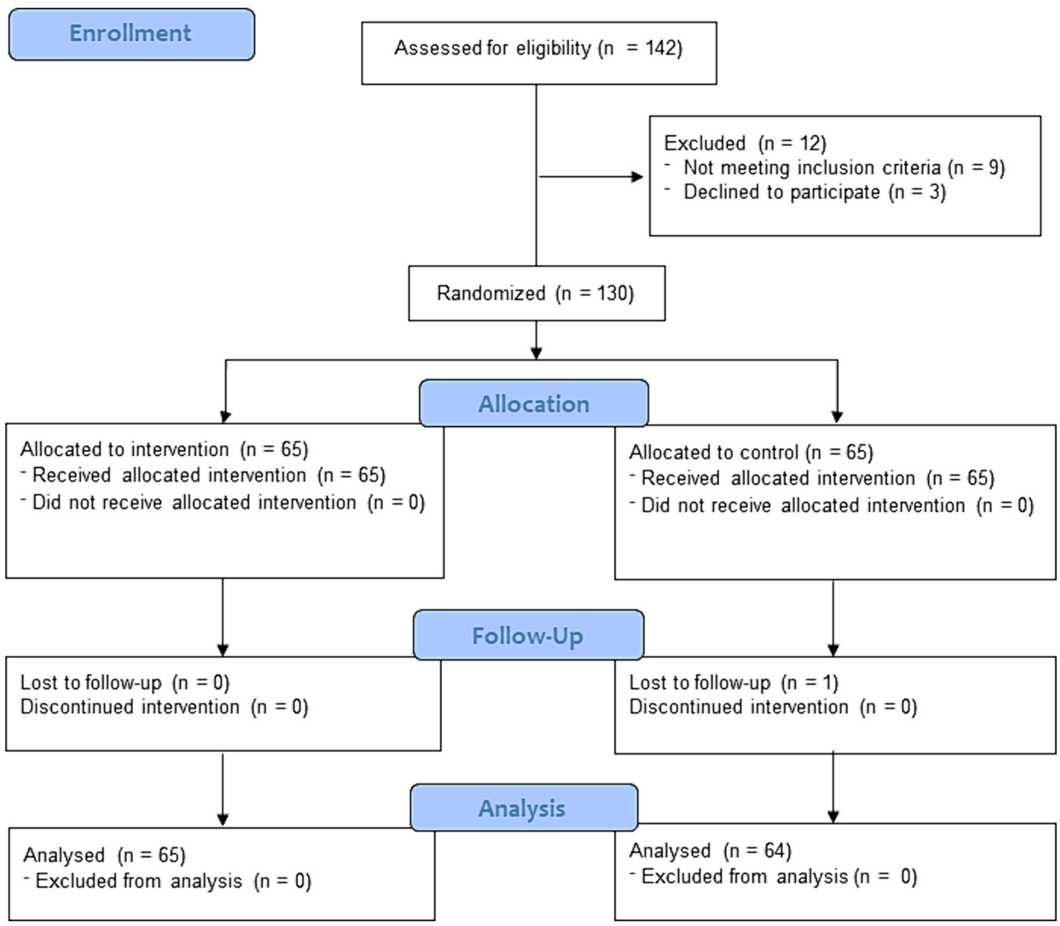

FIGURE 1
Flow diagram of the study.

TABLE 1 Initial characteristics of study participants.

		Total (n = 129)	Experimental group (n = 65)	Control group (n = 64)	p-value
Age		20.29 ± 1.77	20.29 ± 1.78	20.30 ± 1.76	0.487
Sex	Male	63 (48.8)	33 (52.4)	30 (47.6)	0.649
	Female	66 (51.2)	32 (48.5)	34 (51.5)	
Occupational status	With job	61 (47.3)	32 (47.1)	36 (52.9)	0.327
	Without job	68 (52.7)	33 (54.1)	28 (45.9)	
Physical activity	Less than once a week	38 (29.5)	20 (52.6)	18 (47.4)	0.432
	Once a week	47 (36.4)	25 (53.2)	22 (46.8)	
	More than once a week	44 (34.1)	20 (45.5)	24 (54.5)	
Weight		71.33 ± 12.29	73.05 ± 12.23	69.59 ± 12.19	0.870
Height		1.73 ± 0.11	1.74 ± 0.11	1.72 ± 0.12	0.082
BMI		23.73 ± 2.59	24.13 ± 2.60	23.32 ± 2.53	0.120
Perceived stress (PSS)		25.33 ± 6.76	25.82 ± 7.24	24.83 ± 6.25	0.391
Emotional wellbeing (WEMWBS)		43.83 ± 7.82	43.42 ± 8.20	44.25 ± 7.46	0.408
State anxiety (STAI)		35.02 ± 12.52	32.69 ± 12.12	37.39 ± 12.56	0.472
Trait anxiety (STAI)		39.05 ± 11.49	40.74 ± 12.37	37.34 ± 10.33	0.069

Quantitative variables are presented as mean and standard deviation. Qualitative variables are presented as frequency and percentage. PSS, The Perceived Stress Scale; WEMWBS, Warwick-Edinburgh Mental Wellbeing Scale; STAI, State Anxiety Inventory.

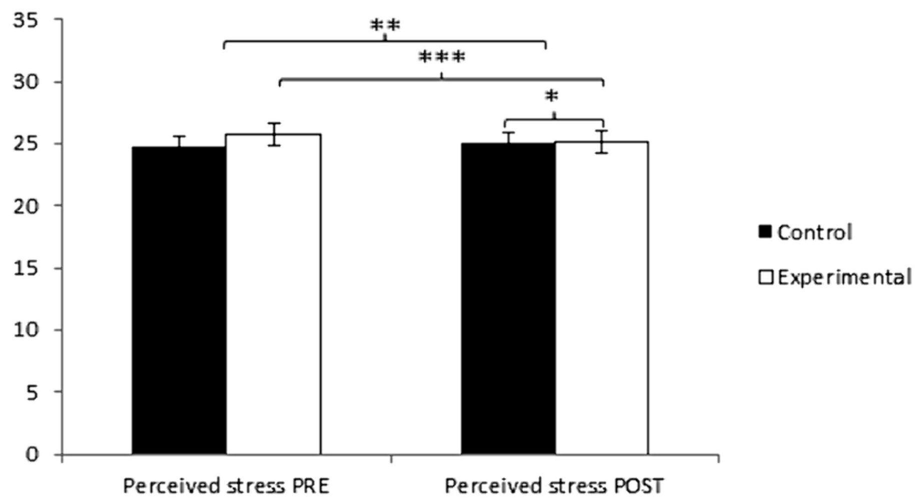

FIGURE 2
Inter- and intra-group comparisons regarding perceived stress. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

small effect size ($d = 0.44$). After Bonferroni correction, the differences remained significant: $t(127) = 2.053$, $p = 0.042$* (adjusted), $d = 0.36$ (small effect size) for group comparison, and $t(64) = 3.921$, $p = 0.001$* (adjusted), $d = 0.44$ (small effect size) for pre-post comparisons. (*Significant after Bonferroni correction, $p < 0.05/3 = 0.017$) (Table 2).

3.2 Emotional wellbeing

In emotional wellbeing, participants in the Control Group (CG) initially reported higher values (44.25 ± 7.46) compared to those in the Experimental Group (EG) (43.42 ± 8.20). However, conversely, the EG participants (47.00 ± 7.10) achieved higher values than the CG (44.06 ± 7.55). Significant differences were observed in Group × Time: $F(1, 127) = 11.383$, $p = 0.001$, $\eta^2 = 0.082$, and in Time: $F(1, 127) = 9.232$, $p = 0.003$, $\eta^2 = 0.068$, but not in Group: $F(1, 127) = 0.751$, $p = 0.388$, $\eta^2 = 0.006$ (Figure 3). After Bonferroni correction, the comprehensive analysis revealed statistically significant differences between both groups in the post-intervention measurement, $t(127) = -2.277$, $p = 0.024$, with a small effect size ($d = 0.08$). Additionally, statistically significant differences were observed between the pre and post-measurements in the group that received treatment/training in yoga, $t(64) = -3.405$, $p = 0.001$, with a small effect size ($d = 0.47$) (Table 2).

TABLE 2 Effects of yoga program on perceived stress, emotional wellbeing, state anxiety and trait anxiety.

	Pre-intervention			Post-intervention			Group				Time				Group × Time			
	EG	CG	Valor p	EG	CG	Valor p	F(1.127)	P-value	η^2	Cohen's d (Group)	F (1.127)	P-value	η^2	Cohen's d (Time)	F(1.127)	P-value	η^2	Cohen's d (Group × Time)
Perceived stress (PSS)	25.82 ± 7.24	24.83 ± 6.25	0.58	22.77 ± 6.45	25.09 ± 6.41	0.042	0.376	0.541	0.003	0.36	11.880	0.001	0.086	0.61	16.853	0.001	0.117	0.73
Emotional wellbeing (WEMWBS)	43.42 ± 8.20	44.25 ± 7.46	0.62	47.00 ± 7.10	44.06 ± 7.55	0.14	0.751	0.388	0.006	0.08	9.232	0.003	0.068	0.47	11.383	0.001	0.082	0.598
State anxiety (STAI)	32.69 ± 12.12	37.39 ± 12.56	0.15	28.42 ± 10.26	37.05 ± 12.75	0.001	11.246	0.001	0.000	0.75	11.053	0.001	0.080	0.59	8.008	0.005	0.059	0.50
Trait anxiety (STAI)	40.74 ± 12.37	37.34 ± 10.33	0.30	31.95 ± 9.56	36.19 ± 10.38	0.066	0.066	0.798	0.001	0.42	24.248	0.000	0.182	0.94	16.634	0.001	0.116	0.72

Quantitative variables are presented as mean and standard deviation. Qualitative variables are presented as frequency and percentage. PSS, The Perceived Stress Scale; WEMWBS, Warwick-Edinburgh Mental Wellbeing Scale; STAI, State Anxiety Inventory.

3.3 Anxiety

Regarding state anxiety, participants in the Control Group (CG) reported higher values (37.39 ± 12.56) than those in the Experimental Group (EG) (32.69 ± 12.12) before the start of the intervention, as well as in the post-intervention measurement (37.05 ± 12.75 vs. 28.42 ± 10.26), and significant differences appeared in Group × Time: $F(1, 127) = 8.008$, $p = 0.005$, $\eta^2 = 0.059$, in Time: $F(1, 127) = 11.053$, $p = 0.001$, $\eta^2 = 0.080$, and in Group: $F(1,127) = 11.246$, $p = 0.001$, $\eta^2 = 0.000$ (Figure 4). The comprehensive analysis of the interaction demonstrates the existence of statistically significant differences between both groups in the post-intervention measurement, $t(127) = 4.240$, $p = 0.001$* (adjusted with Bonferroni correction), with a small effect size ($d = 0.75$). Additionally, the existence of statistically significant differences between the pre and post-measurement in the group that received the treatment/training in yoga was observed, $t(64) = 3.148$, $p = 0.002$* (adjusted with Bonferroni correction), with a medium effect size ($d = 0.38$).

Regarding trait anxiety, participants in the Experimental Group (EG) reported higher values (40.74 ± 12.37) than those in the Control Group (CG) (37.34 ± 10.33) before the start of the intervention. Conversely, in the post-measurement, the CG obtained higher values (36.19 ± 10.38) than the EG (31.95 ± 9.56), and significant differences appeared in Group × Time: $F(1.27) = 16.634$, $p = 0.001$, $\eta^2 = 0.116$ and in Time: $F(1,127) = 24.248$, $p = 0.000$, $\eta^2 = 0.182$, but not in Group: $F(1, 127) = 0.066$, $p = 0.798$, $\eta^2 = 0.001$ (Figure 4). The comprehensive analysis of the interaction demonstrates the existence of statistically significant differences between both groups in the post-intervention measurement, $t(102) = 2.410$, $p = 0.017$* (adjusted with Bonferroni correction), with a small effect size ($d = 0.42$). Additionally, the existence of statistically significant differences between the pre and post-measurement in the group that received the treatment/training in yoga was observed, $t(51) = 6.406$, $p = 0.001$* (adjusted with Bonferroni correction), with a medium effect size ($d = 0.80$) (Table 2; Figure 5).

4 Discussion

The aim of this study was to analyze the effects of a yoga-based intervention on stress, emotional wellbeing, state anxiety, and trait anxiety in university students. The results of this study provide significant insight into the impact of a 12-week yoga-based intervention on university students. Firstly, regarding perceived stress (primary outcome), a significant decrease was observed in the experimental group (EG) compared to the control group (CG) after the intervention. This aligns with previous studies (33–35), reaffirming the effectiveness of yoga in reducing perceived stress. This is based on physiological processes that include the regulation of the autonomic nervous system (ANS), the peripheral nervous system, the activity of the limbic system, endocrine functions, and inflammatory responses (16); Similarly, it is proposed that yoga has immediate and positive effects on baroreflex sensitivity and heart rate variability (HRV), which results in the reduction of vagus nerve stimulation that in turn leads to a decrease in sympathetic system activation, implying a reduction in the release of stress hormones (36–38).

In terms of emotional wellbeing, a similar trend was observed. Although at the beginning of the study the participants in the

FIGURE 3
Inter- and intra-group comparisons regarding emotional wellbeing. *$p < 0.05$. **$p < 0.001$.

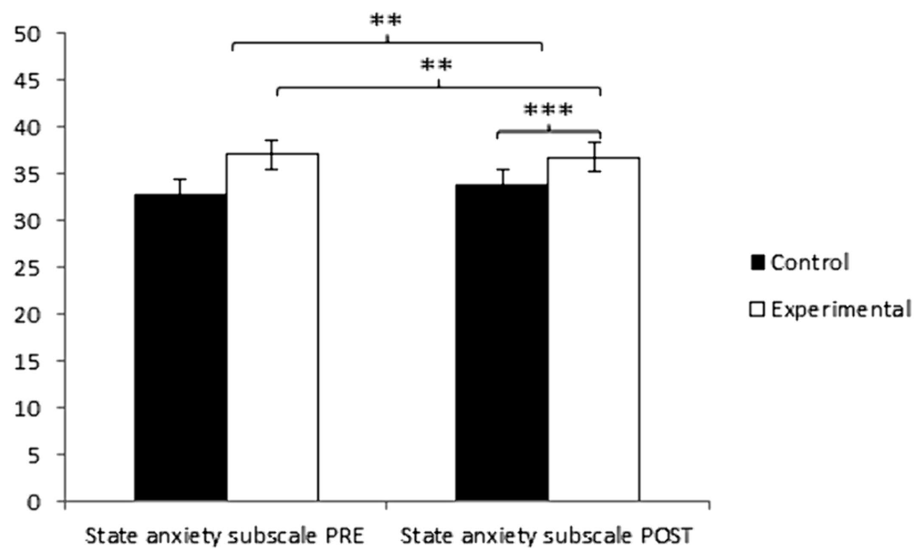

FIGURE 4
Inter- and intra-group comparisons regarding state anxiety. **$p < 0.01$. ***$p < 0.001$.

control group reported slightly higher levels, those in the experimental group experienced a significant improvement after the intervention. This finding coincides with previous research that has found similar results in populations with comparable characteristics (39, 40). This suggests that the improvement could be related to an increased release of dopamine, which translates into an improved mood, a feeling of happiness and emotional satisfaction, as well as enhanced attention, concentration, and a sense of connection and fullness (41). Furthermore, a decrease in the readiness to take actions is observed, suggesting that practicing mindful meditation could inhibit nervous communication through the glutamate neurotransmitter between the cerebral cortex and the striatum (42).

The results of the present study exhibit notable consistency with previous literature, as evidenced by references (43–45), which underpin the biological basis of anxiety in γ-aminobutyric acid (GABAergic) activity (46). Specifically, a significant reduction in anxiety levels was observed within the experimental group following the implementation of the intervention, in contrast to the stability observed in the control group. These findings underscore the efficacy of the intervention in anxiety reduction, thereby contributing to the understanding and management of this clinical condition.

The implementation of this study within the existing research context reveals fundamental insights into the pathophysiology of anxiety, emphasizing the importance of further exploration in this field. However, it is crucial to acknowledge the methodological

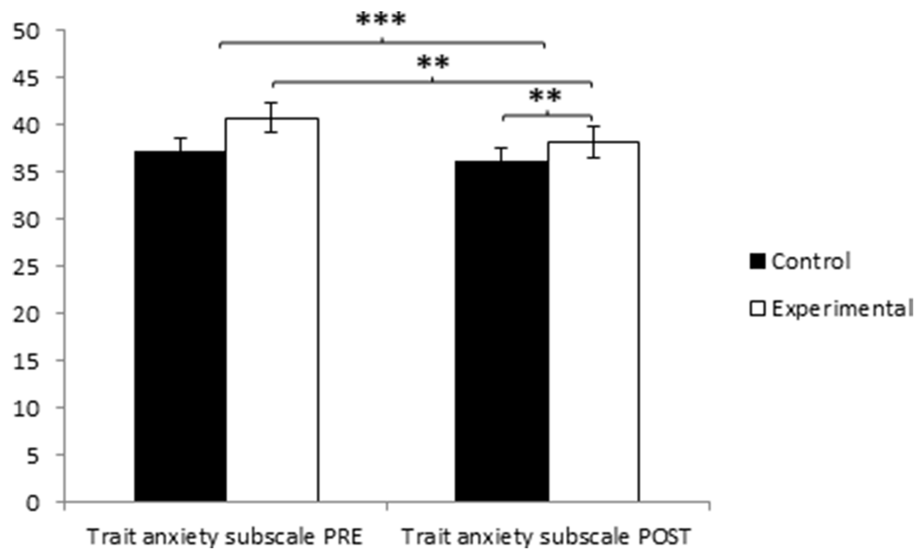

FIGURE 5
Inter- and intra-group comparisons regarding trait anxiety. *$p < 0.05$. ***$p < 0.001$.

limitations inherent in the study design, such as the potential presence of biases or the need for greater sample diversity to generalize the results more broadly. The results of this research underline the importance of considering yoga-based interventions as a viable and effective strategy to promote wellbeing in university students. By offering practical and accessible tools for managing stress and anxiety, these interventions have the potential to significantly improve the university experience and the academic performance of students. Given the nature of the intervention, along with its selection criteria and structural support, no clinically relevant adverse situations were presented. Continuous follow-up of participants allowed for constant communication and timely response to any concerns, as well as the ability to provide additional support when necessary.

The yoga intervention was carried out by a single physiotherapist, which strengthens the internal validity of our results. Variables were measured through validated and self-reported questionnaires, which decreases information bias; likewise, blinding of researchers, assessors, and data analysts prevented the results from being influenced by expectations. Even though the sample size was computed to ensure statistical representativeness, the distinct attributes of the population might constrain the broad applicability of the results. Therefore, it would be beneficial to conduct population-level research linked to educational public policies, as it responds to a problem needing attention worldwide. Future research is needed to determine the optimal dose required to achieve an effective reduction in stress and anxiety, as well as to improve emotional wellbeing. It is also crucial to assess how these results vary at different stages of university life (beginning or end) or during phases of the same academic period (exams, thesis defenses, among others).

Given that preliminary clinical evidence suggests that the effects might not differ from other meditation interventions (47, 48), future research is needed to compare the results between different body–mind activity strategies, as well as to conduct long-term follow-up of these outcomes. This study not only represents a significant step in research on interventions to improve the mental health of university students but also offers valuable information for the development of intervention programs in academic settings. The results obtained can have important implications in promoting wellbeing and reducing stress in the student community, thus contributing to a healthier and more productive university environment. Additionally, it is important to note that in this study, several additional parameters were identified that were initially planned for inclusion in the analysis, but were not presented in this publication. These parameters include D2, MAAS, PAAS and Handgrip Strength. The omission of these parameters represents a deviation from the study protocol. Future research is encouraged to consider including these parameters in subsequent analyzes for a more complete understanding of the observed effects.

5 Conclusion

This study highlights the effectiveness of a 12-week yoga-based intervention in reducing perceived stress and anxiety, as well as improving emotional wellbeing among university students, demonstrating the benefits of yoga for stress regulation and mental health. These findings have significant clinical implications, suggesting that yoga can be a valuable complementary therapeutic strategy in managing stress and anxiety in young populations. Furthermore, this research underscores the importance of including yoga programs in academic settings to promote a healthier and more productive university environment. Future research should focus on comparing the efficacy of yoga with other forms of intervention for anxiety and stress and assessing the long-term effects of regular yoga practice. This will not only expand our understanding of yoga-based interventions but also inform the development of policies and programs aimed at improving the mental and physical wellbeing of university students.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Ethics Committee of the Mid-Atlantic University (CEI/05–006). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YC-C: Conceptualization, Writing – original draft. MC-F: Supervision, Writing – review & editing. AA-A: Methodology, Writing – original draft. YR-C: Formal analysis, Writing – original draft. AG-M: Conceptualization, Writing – review & editing.

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Conflict of interest

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The role of a mindful movement-based program (Movimento Biologico) in health promotion: results of a pre-post intervention study

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Introduction: Mindful movement is a comprehensive approach that integrates various bodily, emotional and cognitive aspects into physical activity, promoting overall well-being. This study assessed the impact of a mindful movement program, known as Movimento Biologico (MB), on participants psychological well-being (PWB), positive mental health (PMH), sense of coherence (SOC), and interoceptive awareness.

Methods: MB program was conducted for students attending the bachelor's degree in Kinesiology and Sport Sciences of University of Perugia over 8 weeks (from October 16 to November 27, 2022). Participants were requested to fill in four questionnaires before and after the MB program: (1) 18-item PWB scale; (2) 9-item PMH scale; (3) 13-item SOC scale; (4) 32-item scale for Multidimensional Assessment of Interoceptive Awareness (MAIA). Wilcoxon signed-rank tests were used to assess changes, with significance set at $p < 0.05$.

Results: Thirty-eight students (mean age 21.2, 60.5% male) participated. Several MAIA subscales, including noticing ($p = 0.003$), attention management ($p = 0.002$), emotional awareness ($p = 0.007$), self-regulation ($p < 0.001$), body listening ($p = 0.001$), and trusting ($p = 0.001$), showed significant improvements. PMH increased significantly ($p = 0.015$), and there was a significant enhancement in the autonomy subscale of PWB ($p = 0.036$). SOC and overall PWB also improved, though not significantly.

Conclusion: The MB program significantly improved participants' positive mental health and interoceptive awareness. This likely resulted from better recognition and management of positive physiological sensations, a stronger link between physical sensations and emotions, enhanced confidence in one's body, and increased autonomy.

KEYWORDS

mindful movement, psychological well-being, mental health, sense of coherence, interoceptive awareness, young adults, Movimento Biologico

Introduction

Young adults, also known as emerging adults, are people between the late teens and twenties (1) who experience a critical period for their individual's development, with lasting implications for their health, well-being, and economic stability. Contrary to popular belief, they can be surprisingly unhealthy, exhibiting an even worse health profile than thirty-year-olds (2). Therefore, it is crucial to support them in successfully transitioning from adolescence to adulthood (2, 3) addressing their mental health needs, and promoting both mental and physical health and well-being.

Mental health refers to a state of emotional, psychological, and social well-being in which individuals can effectively cope with the demands of everyday life (4).

It encompasses various dimensions, including cognitive functioning, emotional regulation, a sense of connection to others and interpersonal relationships, and the ability to cope with adversity (5).

Mental health and psychological well-being are fundamental to individuals' overall functioning, quality of life, and ability to adapt to the challenges they encounter. The World Health Organization (WHO) recognizes the essential role of psychological well-being and mental health promotion, describing it as "a key function for ensuring healthy lives and promoting well-being at all ages." This highlights the need for greater attention from public health in promoting mental health from a salutogenic perspective (6).

There is international evidence (7, 8) regarding feasible and effective interventions to promote mental health.

Psychoeducational and cognitive-behavioral interventions, relaxation programs, mindfulness and meditative/mindful movement (MM) practices are among the interventions found to be effective in improving mental well-being in the young adult population (9). Mindfulness is defined as intentionally directing attention to present-moment experiences in a non-judgmental way (10), with an orientation to curiosity, openness, acceptance and non-reactivity (11, 12). Mindfulness-based interventions have evolved over time and currently also include programs centered on MM (13, 14).

MM interventions (15) are practices of mindful movement that aim to dissolve the mind–body separation promoting instead their integration. They rely on theories (16, 17) that emphasize how the experience of oneself in the world as conscious being involves a complex interaction of the brain, body, and environment, and the seamless integration of interoceptive, proprioceptive (including vestibular), kinesthetic, tactile, and spatial information (18–20). These practices are indeed animated by the desire to overcome the historical Cartesian dualism of mind and body separation (21) in search of the ontological unit of an articulated multiplicity, as human being is (22).

Mind–body dualism is actually not biologically plausible (23) because the mind is not to be regarded either a disembodied internal representation of the external world, nor as a system of brain modules, neural symbols, and algorithms. On the contrary, an embodied mind manifests and integrates the current state of the entire organism as it interacts with its environment (24).

Furthermore, movement of the body can reveal effects on the structure and function of the brain (25–28). Interactions between brain, mind, body and behavior can be used to promote health, enhancing well-being, mood, sleep, cognition (29), attention, learning, emotion regulation (30) and positively impacting stress reduction and self-regulation (31). MM practices, such as yoga, qigong, and tai chi, incorporate the purposeful regulation of movement and coordination between the breath, mind, and body (32) and are based on mental presence and a meditative attitude. Movimento Biologico® (MB) is a MM intervention characterized by the integration of formal meditation techniques (body awareness, breathing awareness, walking meditation, loving-kindness meditation) and informal meditation (during daily activities). It encompasses psycho-education on stress and emotional management, dialogic practices, breathing practices, free expressive movements, motor games, experiential anatomy practices, motor problem solving exercises, self-knowledge diaries, vocal practices and many other forms of teaching-learning mediated by movement (33, 34) harmonized with each other through the filter of body pedagogics and embodied learning. (35, 36).

MM interventions have already been shown to alleviate symptoms of various clinical conditions (37, 38) and induce measurable changes in physiological markers of stress (39, 40), cognitive functions (41, 42), and sensory motor acuity (43). Changes in several psycological outcomes were also assessed in the general adult or older adult population with positive results shown in respect to quality of life (44), depressive symptoms (44, 45), anxiety (45), and sleep quality (44, 46). Recent studies have also examined such practices in adolescents (47, 48) to investigate their impact on cognitive functions and young adults (49–51). The latter evaluated specific aspects, such as depression, stress, quality of life and affective state without considering the broad concept behind psychological well-being.

It emerges from the above that research on MM is relatively less developed in respect to that on conventional meditation and exercise and physical activity (52) and this could be due to the multifaceted nature of MM interventions, which typically involve sequences of specific movements, the particular use of breathing and the modulation of attention (53). Furthermore, despite the current interest in "mind–body medicine," the Cartesian paradigm persists, as does the continuing gap between MM and traditional medical and psychiatric theory (54).

Considering MM characteristics, it is reasonable to expect that MM can positively impact psychological, emotional, and social well-being (55, 56), namely the "Positive Mental Health" (PMH). From a salutogenic perspective, better PMH can positively impact the capacity to utilize resources, i.e., the sense of coherence (SOC), a cornerstone of the salutogenic model that relates to individuals' ability to manage life events (57). The connection between PMH, SOC, and salutogenesis is implicit in the definition of PMH as expressed by the WHO (58), which states that PMH represents the foundation of individuals' well-being and effective functioning. On the other hand, SOC expresses individuals' ability to manage and give meaning to internal and external stimuli from their environment over the course of life, valuing their capacity to use resources to cope with difficulties and maintain better physical and mental health (59, 60). Indeed, both salutogenesis (61) and PMH focus on the construction of those "positive qualities" that embody the positive vision of health on one hand and positive psychology on the other (62, 63).

Based on this foundation, the present study aims to evaluate the short-term impact of a MM program known as Movimento Biologico® (MB) on these domains in a young adult population.

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Materials and methods

Study design and population

We conducted an experimental pilot study without a control group. The study population included subjects aged 18 to 26 years old, attending the 2nd and 3rd year of the bachelor's degree in Kinesiology and Sport Sciences at the University of Perugia. Individuals with pre-existing psychological disorders or those currently involved in competitive sports, mindfulness activities, or MM practices were excluded. The number of participants was set at 40 for logistical issues and the enrollment was voluntary, with applications collected during the second half of September 2022 through the project's designated contact person. Applications were considered on a first-come, first-served basis. Students were informed of the possibility to enroll in the program through the website of the Degree in Kinesiology and Sport Sciences, as well as students mailing list and WhatsApp group. The training program was advertised after the project received the approval from the Local Ethics Committee.

Intervention: the mindful movement program Movimento Biologico® (MB)

The MB program was led by an expert with a background in Kinesiology and Sports Sciences with 17 years of experience in the field of MM, neuroscience and meditation. The program lasted 8 weeks (from October 16th to November 27th, 2022) and consisted of 8 intensive sessions of 4 or 8 h, carried out in groups associated with activities to be carried out individually as homework.

It was based on a set of activities that allowed for a more meaningful and evolutionary contact with the substantial dimension of the person, namely corporeality, and through it, with the unique, creative, and spiritual depth of the personality. The program included theoretical and practical sessions, as well as self-managed activities to be carried out at home. The sessions were conducted with the whole group while the "homework" practices were carried out independently by each participant and without direct supervision.

The group sessions included moments of psycho-education, meditation and contemplation practices (such as body scan, breathing awareness, walking meditation, loving-kindness meditation), individual motor practices (such as kinesphere, floorwork, juggling, and experiential anatomy), motor games in partnering, dialogic mindfulness practices, vocal practices, creation of drawings, diaries for self-knowledge, motor problem solving exercises and other teaching-learning tools. The group activities took place in the gyms of the Degree Course in Kinesiology and Sports Sciences.

The homework practices were facilitated using supporting audio or video files and paper materials (such as diaries) that were provided to participants during the group sessions. It was not possible to systematically monitor the homework, therefore, we relied on the participants' ethics and adherence to the program. The total duration of the program was 48 h, with a maximum of 8 h of allowed absence that was set to minimize the risk of not being able to reliably assess the impact of the program for a loss of potential achievable benefits.

Table 1 provides a summary of the intervention while the detailed program is included in Supplementary material.

Study procedures and data management

During the enrollment, a structured interview was conducted by the research staff to collect socio-demographic data (date and month of birth, gender, residential address, citizenship, educational qualification) and clinical-anamnestic data (self-perceived health, pre-existing medical conditions, depressed mood in the last 2 weeks, medication intake, lifestyle habits such as smoking, alcohol consumption and physical activity, sports involvement). Body mass index (BMI) was calculated considering self-reported weight and height.

The questions regarding smoking habits addressed three main aspects: the current smoking status of the person, the quantity of cigarettes smoked and the duration of smoking habit, and the length of time since they quit smoking for former smokers. The questions about alcohol habits focused on the total number of alcoholic units consumed within a 30-day period, and on consumption of 6 or more alcoholic units on a single occasion (binge drinking). An alcoholic unit is made up of a can of beer (330 mL) or a glass of wine (125 mL) or a shot of liquor (40 mL).

The questions regarding physical activity included inquiries about whether the individual had moderate/intense physical activity in the last 30 days and its weekly duration. Furthermore, in order to identify physical active people responders were requested to say if they had at least 30 min of moderate physical activity on at least 5 days a week and/or 20 min of intense physical activity on at least 3 days a week.

Measures

Additionally, participants were requested to complete four questionnaires before and after the MB program:

1 An 18-item questionnaire, validated in Italian, to assess the Psychological Well-Being (PWB) in terms of six dimensions, namely self-acceptance, positive relationships with others, autonomy, environmental mastery, purpose in life, personal growth. Each item of this questionnaire is rated on a 6-point Likert scale ranging from 1 to 6, where 1 represents "Completely disagree" and 6 represents "Completely agree." Higher scores indicate higher levels of well-being. The Cronbach's alpha (α) of the questionnaire is 0.52 for self-acceptance, 0.56 for positive relationships with others, 0.37 for autonomy, 0.49 for environmental mastery, 0.33 for purpose in life, and 0.40 for personal growth (64).

2 A 9-item questionnaire, validated in Italian, to measure Positive Mental Health (PMH). Each item of this questionnaire is rated on a 4-point Likert scale ranging from 0 (strongly disagree) to 3 (strongly agree). Higher scores indicate higher PMH. The Cronbach's alpha is 0.93 (65).

3 A 13-item questionnaire, validated in Italian, to evaluate the Sense of Coherence (SOC) and its three underpinning dimensions, namely the cognitive (Comprehensibility), the instrumental or behavioral (Manageability) and the motivational dimension (Meaningfulness). Each item of this questionnaire is rated on a 7-point Likert scale ranging from 1 (never) to 7 (always). Higher scores indicate greater levels of SOC. The Cronbach's alpha is 0.83 (66).

TABLE 1 MB program sessions and activities.

Session	Duration	Theoretical contents of education in conscious embodiment	Body–mind practices	Homework
1.	8 H	Reflection on expectations, anticipation, and motivations | Exploration of conceptual horizons: awareness, embodiment, self-care, attention, transformative "technologies," pillars of practice	An Mo & Do In (self-massage movements) | Self-analysis and breath re-education | Kinesphere [use of an imaginary sphere for movement stimulation] (KS) | Body Scan	Body Scan + KS
2.	4 H	\	Sitting Meditation [breath awareness (BA)] | Guided experiential anatomy | Statue, Snail, Jellyfish | Free exploration in floorwork (floor movements) (FEF) | Dialogic practice	BA + FEF
3.	4 H	Obstacles to practice and "antidotes"	Dialogic practice | Review of practices from the previous session (BA, FEF, KS)	BA + FEF + KS
4.	8 H	Modes of "doing" vs. "being" | Relationship between body, emotions, and thoughts ABC model (antecedents, beliefs, consequences) | Autopilot and living in the head | Decentralization	Sitting Meditation (personal analysis and motivation) | Body-thoughts-emotions exercise based on mindfulness | Breathing Space	BA + Pleasant Events Diary + Breathing Space
5.	4 H	Stressors and stress | Reaction vs. response	Dialogic practice | Balance games with a partner | Juggling	BA + Problem Solving Foot Block + Unpleasant Events Diary + Breathing Space
6.	4 H	Salutogenesis (promotion of health) | General resources of resilience | Sense of coherence	Sitting Meditation (personal resources practice) | Walking Meditation	BA + Walking Meditation
7. + 8.	16 H	Opening to experience: relationship, problem-solving, expressiveness, vocalization, empathy	Sitting Meditation (Open Monitoring) (Loving Kindness, Compassion) (Equanimity) - Trust Practice | Dialogic Practice | Auditory and Vocal Practices | Floorball | Matrix Practice | Steals the handkerchief | Juggling | Balance Practice | Orchestra Conductor | Guiding the other's body with your touch | Mimesis | Moving the Body at a Distance | Dancing each other's dance | Pass the cup of water as a group	Self-Management with Personalized Biographical Practices

A 32-item questionnaire, validated in Italian, known as the Multidimensional Assessment of Interoceptive Awareness (MAIA), to assess the perception and interoceptive awareness of the body and its dimensions (noticing, not distracting, not worrying, attention regulation, emotional awareness, self-regulation, body listening, and trusting). Each item of this questionnaire is rated on a 6-point Likert scale from 0 to 5 with '0' indicating 'Never' and '5' indicating 'Always'. Higher scores equate to more awareness of bodily sensation. Cronbach's alpha vary among the subscales: noticing ($\alpha=0.69$), Not-Distracting ($\alpha=0.66$), Not-Worrying ($\alpha=0.67$), Attention Regulation ($\alpha=0.87$), Emotional Awareness ($\alpha=0.82$), Self-Regulation ($\alpha=0.83$), Body Listening ($\alpha=0.82$) and Trusting ($\alpha=0.79$) (67). The total score as well subscales scores were calculated pre- and post-intervention.

Statistical analysis

A descriptive analysis was performed through absolute and relative frequencies and means (± standard deviation) as opportune.

The Wilcoxon signed-rank test was executed to determine whether MB program produced a significant difference in post-intervention scores. The choice of a non-parametric test was led by the small sample size. A p-value of less than 0.05 was considered statistically significant.

Effect sizes (ES) were calculated dividing the mean difference between post and pre intervention by the standard deviation of the difference. ES were categorized as small (ES = 0.2), medium (ES = 0.5), and large (ES ≥ 0.8), according to the benchmarks proposed by Cohen (68).

A secondary analysis was also performed excluding participants who exceeded the 8-h absence limit.

All analyses were conducted using STATA 14.0 (Stata Corp ltd, TX).

Results

Thirty-eight students (mean age 21.2 years; range 20–25; SD 1.2; 60.5% males) attended the MB program. Sociodemographic and clinical anamnestic data are presented in Table 2.

Six students (15.8%) did not reach the expected amount of attendance hours (hours of absence: min 8h30min, max 16h, mean 10h52min).

In Table 3, pre- and post-intervention scores are shown.

The majority of the MAIA subscales, including noticing ($p = 0.003$), attention regulation ($p = 0.002$), emotional awareness ($p = 0.007$), self-regulation ($p < 0.001$), body listening ($p = 0.001$), and trusting ($p = 0.001$), improved significantly after the MB program. A significant increase also occurred in PMH score ($p = 0.015$).

On the other hand, except for the autonomy subscale of PWB ($p = 0.036$), neither PWB nor SOC scores improved significantly.

Medium ESs were observed for all the scores that showed significant changes with higher values for MAIA subscales. The secondary analysis conducted excluding participants who exceeded the absence limit did not show any notable difference in the results (Table 4).

TABLE 2 Population's sociodemographic and clinical anamnestic data.

Variable		N.
Sex	Male	23 (60.5%)
	Female	15 (39.5%)
Age	Mean (±SD)	21.2 (± 1.2)
BMI	- Underweight (16–18.49)	3 (7.9%)
	- Healthy weight (18.5–24.99)	27 (71%)
	- Overweight (25–29.99)	6 (15.8%)
	- Obesity class 1 (30–34.99)	2 (5.3%)
Self-perceived health	- Very good	10 (26.3%)
	- Good	20 (52.6%)
	- Average	5 (13.2%)
	- Fragile	3 (7.9%)
	- Very fragile	0 (0%)
Depression mood	- Yes	10 (26.3%)
	Mean of days with depression mood	*5.2 (SD 2.7)*
	- No	28 (73.7%)
Smoke	- Smoker	17 (44.7%)
	Mean N° of cigarettes smoked weekly (±SD)	*38.9 (±43.9)*
	Months of smoking, mean (±SD)	*44.5 (±25.7)*
	Ex- smoker	9 (23.7%)
	≥ Six months	*6 (66.7%)*
	< Six months	*2 (22.2%)*
	Unknown	*1 (11.1%)*
	Non- smoker	12 (31.6%)
Alcohol (at least 1 alcohol unit) during the past 30 days	- Yes	27 (71.1%)
	Mean N° of alcohol unit during the past 30 days (± SD)	*1.1 (±0.7)*
	Binge drinking	*3 (11.1%)*
	- No	11 (28.9%)
Physical activity (Moderate-intense physical activity during the past 30 days)	- Yes	32 (84.2%)
	Mean moderate-intense physical activity (min/week) (±SD)	*337.7 (±270.2)*
	- No	6 (15.8%)
Physical active	- Yes	29 (76.3%)
	- No	9 (23.7%)

Discussion

The findings of our study provide evidence that the MB program had positive effects on interoceptive awareness and psychological mental health among young adults.

We observed significant changes in the most of MAIA subscales. Participants demonstrated improved abilities to recognize body sensations, manage attention, become more emotionally aware, engage in self-regulation, listen to their bodies, and establish trust in their bodily experiences. These findings are consistent with previous research that has found that MM practices, such as yoga and tai chi, improve interoceptive awareness (69–71) and could be interesting in the light of the known relationship between interoceptive awareness and emotional regulation (72, 73).

Furthermore, the MB program resulted in a significant increase in psychological mental health, as assessed by the PMH scale. This finding suggests that the training could have enhanced the participants' general well-being and mental functioning. In this respect MM activities have already been shown to reduce stress, anxiety, and depressive symptoms, while also fostering positive emotions and psychological resilience (74–76). The participants' engagement in MB program exercises might have provided opportunities for self-expression, stress reduction, and emotional regulation, leading to improved PMH.

As far as psychological well-being is concerned, only the PWB autonomy subscale showed significant changes. The autonomy subscale measures an individual's perception of having control over their own actions, choices, and behaviors. It reflects the extent to which a person feels independent, self-directed, and able to make decisions aligned with their own values and interests (77). Autonomy is a central aspect in the developmental process of emerging adults who face evolutionary challenges such as starting work, leaving the parental home, and engaging in stable and lasting relational experiences. Higher levels of autonomy during this phase of life are viewed as "being self-determined and independent; being able to resist social pressures in thinking and acting; being capable of self-regulating one's behavior; and evaluating oneself based on personal standards" (78). Therefore, the results shown by our study could be interesting as autonomy can have a positive impact on health and well-being (78, 79).

Regarding the SOC, the results of our study did not show significant improvements. The SOC refers to an individual's perception of the world as comprehensible, manageable, and meaningful, and it has been associated with better mental health and well-being (80). The lack of significant improvements in SOC may be attributed to several factors. One possibility is that the relatively short duration of the program was not enough to impact the SOC. It is possible that a longer intervention period may have

TABLE 3 Pre and post MB program scores.

		PRE			POST				
		Median	Interquartile range	SD	Median	Interquartile range	SD	*p*	ES
MAIA	**Noticing**	3.75	3–4	0.84	4.25	3.75–4.50	0.63	**0.003**	0.53
	Not-distracting	2	1.67–2.67	0.81	2.33	1.67–2.67	0.70	0.689	0.07
	Not worrying (37)	2.67	2–3.33	1.02	2.67	2–3.67	1.06	0.934	0.02
	Attention regulation	2.86	2.29–3.29	0.79	3.57	2.86–3.86	0.78	**0.002**	0.60
	Emotional awareness	4	3.2–4.4	0.93	4.1	3.8–4.6	0.49	**0.007**	0.50
	Self-regulation	2.75	2.25–3.25	1.00	3.5	2.75–4.25	1.01	**<0.001**	0.74
	Body-listening	2.67	1.67–3.33	1.01	3.67	2.67–4	1.07	**0.001**	0.67
	Trusting	3.67	2.67–4	1.18	4	3.33–5	0.82	**0.001**	0.60
PWB	**Self-acceptance (37)**	12	10–13	2.46	12	11–14	2.11	0.286	0.24
	Positive relations with others	15	12–17	3.02	14.5	12–17	2.56	0.796	0.05
	Autonomy	14	10–15	3.17	14.5	13–15	2.66	**0.036**	0.43
	Environmental mastery (36)	12	11–14	2.36	13	10–14	2.49	0.769	0.08
	Purpose in life (36)	12	11–13	2.14	13	10–13	1.76	0.223	0.18
	Personal growth	16	15–18	2.16	16	14–17	2.02	0.491	−0.11
	Total (34)	84.5	73.5–88.5	11.97	84	75.5–90	9.18	0.387	0.18
PMH	**Total (37)**	18.0	15–21	4.87	19	16–22	4.06	**0.015**	0.46
SOC	**Comprehensibility (36)**	20.5	17–22.5	5.28	21.5	19–25	4.52	0.161	0.25
	Manageability	17	13–20	4.83	15.5	12–18	4.22	0.153	−0.25
	Meaningfulness	20.5	16–23	4.62	21	17–24	3.73	0.271	0.21

Significant *p*-values are reported in bold.

allowed for a more comprehensive exploration and cultivation of participants' sense of comprehensibility, manageability, and meaningfulness but this needs to be addressed in further studies.

Additionally, it should be noted that the activities included in the intervention program were mostly directed to target the dimensions of the PWB and interoceptive awareness. Nonetheless the program also included a specific activity on salutogenesis and was expected to potentially improved SOC because it enhanced "internal" resistance resources, namely physical, psychic, relational, emotional, mental, cognitive, intellectual and spiritual potential of the individual.

To the best of our knowledge our study is rather unique in terms of type of intervention proposed and broadness of outcomes assessed. In fact, other studies on the same target population, namely young adults, have mostly investigated mindfulness-based interventions that gave priority to the mindfulness practices. Systematic reviews of studies evaluating mindfulness-based interventions in university students have shown improvements in respect to stress and mindfulness (81–83), mental health and well-being (81–83) but also coping capacities (82).

The unprecedented integration that MB proposes among the multiple dimensions of motor skills (sensory, perceptive, expressive, symbolic, communicative, relational, playful, creative, cognitive, spiritual) is meant to constitute a pragmatic "bridge" of interaction between body, mind, and emotions in line with the emerging mind–body medicine. In this context, the body, mind, and emotions are regarded as working in unity (84). Furthermore, MB is characterized as a tool for enriching "body awareness," a term frequently used (67, 85–87) to define a mental function characterized by a keen sensitivity to bodily signals, which leads to conscious identification of states deriving from subtle bodily reactions to internal and external conditions (88). In this respect MB focuses on the quality of movement, on "how" movements are experienced in relation to space, time and energy (89). The "embodiment" of experience constitutes a potential pillar for a deeper and more fruitful bodily awareness and could be a tool for improving the functional quality of specific neural processes, allowing the cultivation of an attentional ability that may be transferred to multiple contexts and areas (90, 91).

This is a rather "new" approach since the evaluations done by clinicians and researchers is still driven by anatomical, biomechanical and physiological parameters, despite the large spectrum of psychological, social and humanistic dimensions that the movement contains (92).

It is important to note some limitations of this research. Firstly, a control group was not foreseen, and the study population was relatively small and selected from a specific university context. These limits prevent to assess the efficacy of the program in a robust way and to generalize the results, but it should be observed that the purpose of this study was exploratory.

Another limit is due to the fact that the impact of the program was evaluated just in a short-term horizon and only in healthy

TABLE 4 Pre and post MB program scores in subjects who had not exceeded the limit of hours of absence.

		PRE			POST				
		Median	Interquartile range	SD	Median	Interquartile range	SD	*p*	ES
MAIA	**Noticing**	3.88	3.13–4.25	0.73	4.25	3.75–4.50	0.50	**0.009**	0.51
	Not-distracting	2	1.67–2.83	0.82	2.33	1.67–2.67	0.74	0.881	0.04
	Not worrying (31)	2.67	1.67.3.33	1.02	2.67	1.83–3.33	1.06	0.617	0.09
	Attention regulation	2.86	2.29–3.21	0.76	3.57	2.86–3.93	0.72	**0.001**	0.70
	Emotional awareness	4	3.3–4.4	0.87	4.1	3.8–4.6	0.46	**0.008**	0.51
	Self-regulation	2.75	2.25–3.13	0.96	3.5	2.75–4.25	0.98	**<0.001**	0.84
	Body-listening	2.83	2.17–3.5	0.97	3.67	2.5–4	1.08	**0.004**	0.61
	Trusting	3.67	2.5–4	1.26	4	3.33–5	0.83	**0.002**	0.63
PWB	**Self-acceptance**	11.5	10–14	2.61	12	11–14	2.18	0.552	0.20
	Positive relations with others	14.5	12–16	3.07	15	12–17	2.66	0.247	0.28
	Autonomy	14	10.5–15.5	3.30	15	13–16	2.43	**0.017**	0.54
	Environmental mastery (30)	12	10–14	2.50	13	10–15	2.45	0.498	0.22
	Purpose in life (31)	11	10–13	2.13	12.5	10–13	1.80	0.135	0.28
	Personal growth	16	14.5–18	2.29	16	14–17.5	2.06	0.663	0.06
	Total (29)	84	72–88	12.69	84	75–91	9.60	0.108	0.31
PMH	**Total (31)**	18	14–21	4.81	19	16–23	4.22	**0.013**	0.51
SOC	**Comprehensibility (30)**	21	16–23	5.37	21.5	19–25.5	4.75	0.108	0.31
	Manageability	16	13–19.5	4.96	15	11.5–18.5	4.40	0.167	−0.24
	Meaningfulness	20	16–23	4.58	21	18–24	3.80	0.110	0.31

Significant *p*-values are reported in bold.

students not affected by any psychological disorder. In particular, the exclusion of students with pre-existing psychological disorders was reasoned by the evidence (93) that psychological disorders might influence sensory perception and subjective evaluation of environmental stimuli and physical activities and, subsequently, the impact of the intervention. It should also be considered that, because of the small sample size, stratified analyses were inconclusive (results not shown). Nevertheless, in future studies it would be important to address if socio-demographic variables, such as sex, as well as personal lifestyles could influence the impact of the program. Finally, we need to consider that the low Cronbach's alpha value of the domains of the PWB questionnaire could impair results in terms of their reproducibility but it should be also considered that the 18-item questionnaire is widely used in research because of its validity.

Our study has also some strengths, including the use of validated tools for evaluating the program impact and the good level of engagement of participants that was demonstrated by the absence of dropouts and by the high level of questionnaire completion. Furthermore, the positive results issued by our pilot study provide the basis for planning further studies also including a control group and a longer follow up.

Our results provide preliminary evidence of the potential of MB as a mean to promote well-being and physical and mental health during the critical period of young emerging adulthood. The positive preliminary results showed could be attributed to a positive physiological sensation recognition and management, a deeper connection between physical sensations and emotional states, and a greater perception of one's own body. Further research with different study designs and larger and diverse study populations are envisaged to confirm and expand upon these preliminary findings and to explore the mechanisms underlying the observed effects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Comitato Etico Regionale dell'Umbria. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SSP: Writing – review & editing. MC: Writing – review & editing. FI: Writing – review & editing. LB: Writing – review &

editing. GP: Writing – review & editing. RC: Writing – original draft. CG: Writing – original draft. CL: Writing – original draft. AC: Writing – review & editing. GS: Writing – review & editing. CM: Writing – review & editing. AB: Writing – review & editing. CdW: Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1372660/full#supplementary-material

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The mediating effect of personal mastery and perceived social support between emotional intelligence and social alienation among patients receiving peritoneal dialysis

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Aim: This study aims to assess the extent of social alienation in patients undergoing peritoneal dialysis and examine how personal mastery and perceived social support mediate the association between emotional intelligence and social alienation in this patient population.

Methods: This study adopts a cross-sectional survey design. A total of 192 patients were recruited from a tertiary hospital located in Henan Province, China, using a convenience sampling method. We have developed a structural equation model to investigate the mediating influence of personal mastery and perceived social support on the emotional intelligence and social alienation of patients undergoing Peritoneal dialysis.

Results: Peritoneal patients exhibited an social alienation score of 42.01 ± 3.15. Elevated EI levels (coefficient = −0.616, $p < 0.001$) were significantly correlated with reduced social alienation. The mediation model demonstrated that personal mastery and perceived social support fully mediated the impact of emotional intelligence on social alienation.

Conclusion: The social alienation of peritoneal dialysis patients is serious, and healthcare professionals should pay attention to patients' social alienation, improve patients' emotional intelligence through relevant interventions, increase personal mastery and perceived social support, and finally reduce social alienation.

KEYWORDS

peritoneal dialysis, emotional intelligence, personal mastery, perceived social support, social alienation

Introduction

Chronic kidney disease (CKD) is a worldwide public health concern, affecting approximately 13.4% of the global population (1). Patients with chronic kidney disease face a threefold higher risk of heart failure and an increased susceptibility to urinary tract infections, gastrointestinal bleeding, hip fractures, and other related comorbidities (2). These complications significantly diminish patients' quality of life. Progressive deterioration of kidney function ultimately leads to the development of end-stage renal disease (ESRD), necessitating renal replacement therapy for survival. Research indicates a projected increase in the number of patients requiring renal replacement therapy, expected to rise from 2,455,000 in 2016 to 5,439,000 by 2030 (3).

Peritoneal dialysis, as a modality of renal replacement therapy, has gained acceptance among patients and is utilized in various countries and regions due to its attributes, including the preservation of residual renal function, the option for home-based administration, and cost-effectiveness (4). Globally, 10–20% of patients are currently undergoing peritoneal dialysis treatment (5). Continuous Ambulatory Peritoneal Dialysis (CAPD) refers to patients exchanging dialysate 3–5 times per day, with each exchange volume of 1.5–2 L. Dialysate is left in the peritoneal cavity for 4–6 h/time during the daytime, and 10–12 h during the night. CAPD is the most dominant peritoneal dialysis modality, accounting for 90% of PD patients (6).

Regrettably, Dialysis fluid exchange at specific times and places restricts patients' travel and the irreversible aggravation of their psychological burden by their kidneys, leading to the prominence of the phenomenon of "social alienation" (SA), such as peritoneal dialysis patients' active avoidance of social interaction and the feeling of being alienated by others (7). SA is an objective phenomenon in which an individual is detached from social relationships, accompanied by emotional experiences such as loneliness and indifference, as well as avoidance and rejection of social activities (8). Qing-Er et al. (9) conducted a questionnaire survey involving 300 peritoneal dialysis patients, revealing that 70% of them exhibited deficits in social functioning. Tao Weiwei et al. (10) discovered that, following dialysis, 36.3% of patients experienced reduced interaction with family and community members, rarely engaging in group activities. Moreover, 14.6% of patients remained entirely homebound, with this figure escalating to 84.93% in rural regions. Cuevas-Budhart et al. (11) conducted in-depth interviews with 29 peritoneal dialysis patients across 13 hospitals in Mexico. Their findings indicated that patients' experiences of family isolation and socioeconomic difficulties led to somatization of emotions, resulting in manifestations of sadness, anxiety, loneliness, and social abandonment.

The SA threatens peritoneal dialysis patients' physical and mental health. Research has demonstrated that SA induces hypofunction of the hypothalamic–pituitary–adrenal (HPA) axis, subjecting patients to a pro-inflammatory milieu, thus exacerbating the inflammatory aspects of diseases like atherosclerosis, thereby becoming a significant risk factor for cardiovascular disease (11, 12). Furthermore, severe SA exhibits a substantial association with rapid renal failure in patients, serving as a prognostic indicator for the deterioration of renal function and the acceleration of disease progression (13).

Emotional intelligence (EI) is the ability of an individual to recognize and control his or her own emotions and those of others, and to be able to use emotions correctly to deal with and solve problems (14). Previous studies have found a correlation between EI and SA (15), enhancing emotional intelligence and promoting positive emotional expression in patients can help expand social networks and restore social functioning (16). However, how EI affects SA remains a black box that needs to be explored in further research. Understanding the mechanisms of influence will help healthcare professionals to develop targeted interventions to alleviate social alienation in peritoneal dialysis patients.

According to the Cascading Model, the association between EI and behavioral performance is not straightforward; instead, it is influenced by intervening variables (17). Consequently, it is reasonable to hypothesize the presence of mediating variables rather than direct mediators linking EI to SA. The Neurocognitive Processing Model of Emotional Intelligence suggests that emotional intelligence affects social relationships in a way that requires individuals to re-identify and increase their confidence, and that the effectiveness of emotional intelligence relies heavily on reliable feedback from the surrounding environment (18).

Personal mastery is the degree to which an individual perceives control over his or her life and surroundings, and reflects the patient's self-confidence in life and disease management (19). Furthermore, mentioning the level of EI has been shown to enhance patient self-confidence and elevate self-efficacy, a pivotal factor influencing the personal master (20, 21). It was found that patients with a high personal mastery were more inclined to respond to changes in things with an open and inclusive mindset, actively engage in social interactions, and feel less SA during stressful situations (22, 23). Therefore, this study proposes the hypothesis that EI may improve SA by enhancing patients' personal mastery.

Perceived social support is an individual perceives or appreciates material or emotional support from the outside world, which reflects the emotional response of the surrounding environment to the patient.

Emotional intelligence was positively correlated with perceived social support, with individuals with high EI subjectively perceiving more social support and utilizing it (24). According to the WHITE heuristic cognitive model of the cognitive theory of emotion, patients in a state of somatic vulnerability tend to actively detach themselves from social activities and persist in negative emotions if the perceived level of social support is low (25). Above all, this study again hypothesizes that EI influences the SA process in which perceived social support plays an important role.

To date, despite some studies examining the connections among EI, personal mastery, perceived social support, and SA, the precise nature of their interrelationships remains ambiguous. Consequently, this study seeks to explore the mediating functions of personal mastery and perceived social support in the relationship between EI and SA among peritoneal dialysis patients.

This endeavor aims to establish a theoretical foundation for intervention strategies aimed at mitigating social alienation within this patient population. Therefore, we developed a mediation model (see Figure 1) to explore the effects and mediating mechanisms of EI

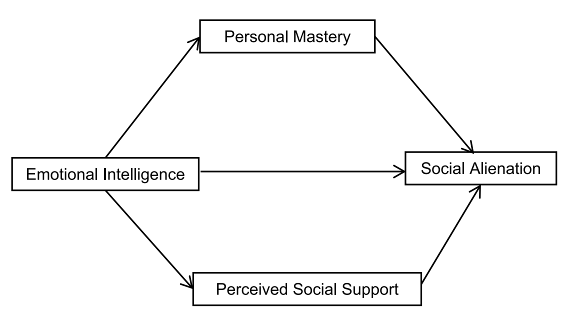

FIGURE 1
Mediation model.

on SA in peritoneal dialysis patients, which outlines the hypotheses that (1) EI may affect SA in peritoneal dialysis patients (2) personal mastery and perceived social support mediate EI and SA in peritoneal dialysis patients.

Methods

Participants

This study was approved by the author's university ethics review board and adhered to the principles outlined in the Declaration of Helsinki. This study employed a cross-sectional survey design, and it included peritoneal dialysis patients who met the predetermined inclusion and exclusion criteria. These patients were recruited from the Department of Nephrology at the First Affiliated Hospital of Zhengzhou University between December 2022 and March 2023, utilizing a convenience sampling approach. Inclusion criteria encompassed (a) undergoing peritoneal dialysis more than 1 month; (b) aged ≥18 years; (c) exhibiting stable vital signs; (d) ability to read and understand Chinese language; (e) willing to provide informed consent for active participation in the study.

Exclusion criteria comprised participants who underwent a change in their renal replacement therapy, including transitioning to hemodialysis or receiving a renal transplantation. A total of 202 questionnaires were distributed between December 2022 and March 2023. After eliminating invalid questionnaires, 192 responses were deemed eligible for inclusion.

Sample size

To ascertain the appropriate sample size, the researcher considered the guideline that the sample size for multiple linear regression analysis should be at least 5–10 times the number of study variables (26). Given the presence of 26 study variables, the sample size was calculated as 7 times this number, resulting in a preliminary sample size of 182. Additionally, to account for potential invalid questionnaires (estimated at 10%), the final sample size was determined to be 202. The study encompassed 202 participants, from whom 192 valid questionnaires were collected, resulting in an effective recovery rate of 95.0%. This high participation rate bolstered the study's statistical power and ensured the accuracy of its findings.

Measures

General information about the patient

We employed a self-administered general information questionnaire to gather pertinent demographic data from the participants. This questionnaire comprised 13 items, encompassing gender, age, marital status, education, occupation, monthly family income (yuan), methods of medical expense payment, living arrangements, time of disease diagnosis (year), duration on dialysis (year), underlying disease etiology, comorbidity count, and biochemical values for calcium, phosphorus, urea nitrogen, and blood creatinine (to be filled out by the researcher after reviewing medical records).

Wong Law Emotional Intelligence Scale Chinese version (WLEIS-C)

The Wong Law Emotional Intelligence Scale (WLEIS) was developed by Wong and Kenneth in 2002 based on Gross's theoretical model of emotion regulation (27). Later, Chinese scholars Yifei (28) revised the scale into a Chinese version. The scale comprises four dimensions: self-emotional assessment, emotional assessment of others, emotional control, and emotional use, featuring 16 items. This scale employs a 7-point Likert scale, with responses ranging from "Strongly Disagree" to "Strongly Agree," yielding a total score between 0 and 96. A higher score indicates a higher level of EI. The WLEIS-C has been validated in a Chinese adult population, and the Cronbach's alpha coefficient for this scale is 0.89, which is highly reliable.

General Alienation Scale Chinese version (GAS-C)

The General Alienation Scale (GAS) was developed by Safipour et al. (29) in 1977, and translated and revised into Chinese by Wu Shuang et al. (30). The GAS assesses feelings of alienation concerning personal roles, uncertainty regarding the significance of engagement in activities, and perceived alienation from others. It comprises 15 items organized into four dimensions: alienation from others, skepticism, self-alienation, and meaninglessness. Responses are recorded on a 4-point Likert scale, with each item ranging from 1 to 4, anchored by "strongly disagree" and "strongly agree." Items 2, 5, and 13 are reverse-scored. The total score ranges from 15 to 60 points, with higher scores indicating a greater severity of SA. The Cronbach's coefficient for GAS-C applied to peritoneal dialysis patients was 0.902, indicating acceptable reliability (31).

Personal Mastery Scale Chinese version (PMS-C)

Personal Mastery Scale was developed by Pearlin and Schooler (32), and translated into Chinese by Yu Yibing (33). The PMS assesses an individual's sense of control over life events' outcomes. This scale comprises seven items and employs a 5-point Likert scale, with each item scored from 1 ("not at all") to 5 ("very much"). The total score ranges from 7 to 35 points, with higher scores denoting a stronger perception of individual control. PMS-C has been validated in Chinese peritoneal dialysis patients with reliable reliability (34).

Perceived Social Support Scale Chinese version (PSSS-C)

Perceived Social Support Scale was developed by Chinese scholars Qianjin (35). The PSSS assesses an individual's self-awareness and their perceived level of social support. This scale comprises three dimensions: family support, friend support, and support from others, totaling 12 items. Responses are collected on a 7-point Likert scale, with each item spanning from "Strongly Disagree" to "Strongly Agree." The total score ranges from 12 to 84 points, with higher scores signifying greater perceived social support. A higher score reflects an elevated level of social support comprehension. The scale exhibits strong reliability, as indicated by a Cronbach's alpha coefficient for this scale applied to Chinese peritoneal dialysis patients of 0.880 (36).

Statistical analyses

The SPSS 25.0 and Amos 24.0 software were used for data entry and analysis. Continuous variables following a normal distribution were summarized using mean (M) and standard deviation (SD), and differences between groups were assessed via independent samples *t*-tests. Categorical variables were described using counts and percentages, and group differences were evaluated using chi-square (χ^2) tests. Two independent samples t-tests and one-way ANOVA were employed to compare the SA scores of peritoneal dialysis patients with differing characteristics. Multiple stepwise regression analyses were conducted to identify significant predictors of social alienation in peritoneal dialysis patients. Additionally, Pearson correlation analysis was used to examine the relationships between patients' demographic information, EI, personal mastery, perceived social support, and SA. Multiple linear regression analyses were performed to identify significant predictors of SA in peritoneal dialysis patients. Finally, structural equation models were developed using Amos 24.0, and mediation model testing was carried out utilizing the Bootstrap method, with 2,000 resampling iterations and a two-sided significance level of $\alpha = 0.05$.

The researchers checked the collected data one by one, and entries with more than 20% missing items were deleted. Two researchers entered the data separately and then exchanged the results to ensure that the data were correct.

Results

Comparison of SA scores in peritoneal dialysis patients with different characteristics

Among the 192 patients, 98 were male and 94 were female. The mean age of the patients was (42.93 ± 12.64) years, calcium was (2.30 ± 0.39) mmol/L, phosphorus was (2.05 ± 0.52) mmol/L, urea nitrogen was (26.23 ± 6.67) mmol/L, and blood creatinine was (763.66 ± 345.05) μmol/L. Other specific data are shown in Table 1.

Correlation analysis of EI, personal mastery, perceived social support and SA in peritoneal dialysis patients

As shown in Table 2, the total SA score of peritoneal dialysis patients was negatively correlated with the total EI score ($r = -0.616$, $p < 0.001$), with the total Personal Mastery score ($r = -0.661$, $p < 0.001$), and also with the Perceived Social Support score ($r = -0.696$, $p < 0.001$).

Multiple linear regression analyses of SA

The SA score was used as the dependent variable. Age, marital status, monthly family income (yuan), living arrangements, time of diagnosis of disease (year), and duration on dialysis (year), EI, personal mastery, and perceived social support were used as the independent variables, and the values assigned to the independent variables are shown in Table 3. The results showed that age, duration on dialysis (year), EI, personal mastery, and perceived social support were influential factors leading to SA in peritoneal dialysis patients (all $p < 0.05$), explaining a total of 66.1% of the total variance, as detailed in Table 4.

A model test of the relationship between EI, personal mastery, perceived social support and SA in peritoneal dialysis patients

A structural equation model was constructed to test the relationship between EI, Personal Mastery, Perceived Social Support and SA in peritoneal dialysis patients. The model fit indices were calculated using great likelihood estimation: $\chi^2/df = 1.973(<3)$, $CFI = 0.931(>0.9)$, $GFI = 0.\ 902(>0.9)$, $IFI = 0.933(>0.9)$, $TLI = 0.909(>0.9)$, and $RMSEA = 0.060(<0.08)$. The peritoneal dialysis patients' structural equation models for EI, Personal Mastery, Perceived Social Support and SA are shown in Figure 2.

The results showed that the indirect effect of EI on SA was −0.876, with 95% confidence interval excluding 0, so the indirect effect of EI on SA was established, and since the direct effect of EI on SA was not significant and was not included in the model, the personal mastery and the perceives social support played a fully mediating role in EI and SA at this time. The mediating effect value of personal mastery was −0.423, accounting for 48.29% of the total mediating effect, and the mediating effect value of perceived social support was −0.453, accounting for 51.71% of the total mediating effect. The analysis of effects is shown in Table 5.

Discussion

Social alienation (SA) represents an inescapable challenge faced by peritoneal dialysis patients, profoundly impacting their mental well-being. Consequently, it is imperative to scrutinize the determinants of SA and to formulate tailored intervention strategies. In this investigation, the SA score among peritoneal dialysis patients averaged 42.01 ± 3.15, indicating a notably elevated level compared to the scale's median total score of 37.50. These findings align closely with the scores reported by Xiaofang et al. (37) for lung cancer patients, though they slightly surpass scores observed in stroke patients (38). Several factors contribute to this discrepancy. Firstly, Zhao Cuicui (38) study encompassed a substantial proportion of older adult patients, the cognitive and physical functions of the older adult population are in a stage of decline, which, with increasing age, causes them to be socially inactive and thus aggravates SA. While this study predominantly enrolled young and middle-aged individuals who shoulder diverse family and occupational responsibilities, thus experiencing heightened demands for social

TABLE 1 Comparison of social alienation scores in peritoneal dialysis patients with different characteristics ($n = 192$, $\bar{x} \pm S$).

Item	Categories	N	%	SA score	t/F	p-value
Age	18-	103	53.6%	43.25 ± 2.74	20.939	<0.001
	45-	76	39.6%	40.51 ± 3.04		
	≥60	13	6.8%	40.92 ± 2.87		
Gender	Male	98	51.0%	41.88 ± 3.32	0.354	0.553
	Female	94	49.0%	42.15 ± 2.98		
Marital status	Unmarried	34	17.7%	43.94 ± 3.23	16.293	<0.001
	Married	118	61.5%	41.08 ± 2.98		
	Widowed or divorced	40	20.8%	43.13 ± 2.47		
Education	Primary school and below	16	8.3%	43.25 ± 2.46	1.688	0.171
	Middle school	68	35.4%	42.28 ± 3.44		
	High school	79	41.1%	41.81 ± 2.71		
	College and above	29	15.1%	41.24 ± 3.75		
Occupation	Unemployed	55	28.6%	42.53 ± 2.43	0.877	0.454
	Full-time work	66	34.4%	41.82 ± 3.67		
	Part-time work	59	30.7%	41.97 ± 3.26		
	Retired	12	6.3%	41.17 ± 2.44		
Monthly family income (yuan)	<1,000	51	26.6%	43.55 ± 2.97	14.481	<0.001
	1,000-	48	25.0%	42.69 ± 2.40		
	3,000-	51	26.6%	41.67 ± 2.78		
	≥5,000	42	21.9%	39.79 ± 3.31		
Living arrangements	Living with spouse	108	56.3%	41.19 ± 2.98	7.963	<0.001
	Living with children	16	8.3%	41.94 ± 2.82		
	Living with parents	29	15.1%	42.62 ± 3.31		
	Living alone	39	20.3%	43.85 ± 2.85		
Time of diagnosis of disease (year)	≤1	25	13.0%	43.92 ± 3.24	6.814	0.001
	1–3	46	24.0%	42.33 ± 3.27		
	>3	121	63.0%	41.50 ± 2.94		
Duration on dialysis (year)	≤1	56	29.2%	44.57 ± 2.54	42.773	<0.001
	1–3	78	40.6%	41.59 ± 2.47		
	>3	58	30.2%	40.10 ± 2.91		
Underlying disease etiology	Glomerular diseases	86	44.8%	41.91 ± 3.34	0.349	0.845
	Diabetic nephropathy	37	19.3%	42.30 ± 2.94		
	Hypertensive nephropathy	32	16.7%	41.75 ± 3.09		
	lupus nephropathy	13	6.8%	42.77 ± 3.44		
	Others	24	12.5%	41.88 ± 2.86		
Comorbidity count	0	62	32.3%	41.77 ± 2.94	0.776	0.509
	1	85	44.3%	42.06 ± 3.37		
	2	27	14.1%	41.74 ± 2.36		
	≥3	18	9.4%	43.00 ± 3.99		

SA, social alienation. The results showed that the SA scores of peritoneal dialysis patients of different age, marital status, monthly family income (yuan), living arrangements, time of diagnosis of disease (year), and duration on dialysis (year) were compared, and the differences were statistically significant ($p < 0.05$).

engagement (39). Furthermore, the social role of supporting the older adult and caring for children compounds the burdens borne by these patients. Additionally, influenced by traditional Chinese cultural norms, individuals frequently refrain from sharing the impact of their illness with others, believing that such vulnerability does not align with societal expectations. This restraint fosters heightened anxiety, feelings of powerlessness, and a sense of detachment.

TABLE 2 Correlation analysis of EI, personal mastery, perceived social support and SA in peritoneal dialysis patients.

Item	SA total score	Self-alienation	Alienation from others	Skepticism	Meaninglessness
EI total score	−0.616**	−0.174*	−0.483**	−0.422**	−0.382**
self-emotional assessment	−0.459**	−0.117	−0.364**	−0.344**	−0.256**
emotional assessment of others	−0.542**	−0.205**	−0.425**	−0.345**	−0.316**
emotional control	−0.570**	−0.150*	−0.427**	−0.354**	−0.429**
emotional use	−0.568**	−0.132	−0.459**	−0.422**	−0.323**
Personal mastery total score	−0.661**	−0.222**	−0.465**	−0.397**	−0.507**
Perceived social support total score	−0.696**	−0.214**	−0.522**	−0.451**	−0.474**
Family support	−0.546**	−0.275**	−0.378**	−0.265**	−0.412**
Friend support	−0.590**	−0.149*	−0.369**	−0.499**	−0.392**
Other people's support	−0.519**	−0.080	−0.480**	−0.330**	−0.322**

*$p < 0.05$, **$p < 0.001$. EI, emotional intelligence; SA, social alienation.

TABLE 3 Assignment of values to independent variables.

Independent variables	Mode of assignment
Age	18–44 = 1, 45–59 = 2,60- = 3
Marital status	Unmarried = 1, Married = 2, Widowed or divorced = 3
Monthly family income (yuan)	<1,000 = 1,1,000- = 2,3,000- = 3, ≥5,000 = 4
Living arrangements	Living with spouse = 1, Living with children = 2, Living with parents = 3, Living alone = 4
Time of diagnosis of disease (year)	≤1 = 1, 1–3 = 2, >3 = 3
Duration on dialysis (year)	≤1 = 1, 1–3 = 2, >3 = 3
EI	Actual scale score
Personal mastery	Actual scale score
Perceived social support	Actual scale score

EI, emotional intelligence; SA, social alienation.

Simultaneously, our findings underscore the significance of age and duration on dialysis as pivotal determinants of SA in peritoneal dialysis patients. Surprisingly, our study revealed elevated SA scores among younger patients, a trend contrary to the findings of several previous investigations (40, 41). Notably, dialysis-related complications manifest as discernible alterations in patients' physical appearance, encompassing generalized edema (42), melanosis (43) and characteristic hyperparathyroidism (44), etc. These conspicuous disease-related attributes are prone to create unfavorable impressions on others, further exacerbated by societal misconceptions and potential instances of social discrimination, thereby inducing psychological distress among patients (44, 45). Younger patients, in particular, grapple with the pronounced impact of these appearance-related changes, which can lead to challenges in pursuing marriage, forming new social connections, and realizing their socialization aspirations (46). Moreover, younger patients often exhibit reticence in sharing their emotions and experiences, ultimately isolating themselves from active engagement in social activities, thus fostering SA (47).

Furthermore, the study results indicate that peritoneal dialysis patients with a dialysis vintage of less than 1 year exhibited higher scores on social alienation, aligning with the findings of Xiaofang et al. (37). Peritoneal dialysis necessitates multiple daily fluid exchanges, meticulous monitoring of fluid balance, and the endurance of complications like pruritus and sleep disturbances (48, 49). For patients with a short dialysis history, striking a swift equilibrium between demanding self-care regimens and their pre-existing work commitments poses a formidable challenge. For patients who have been on peritoneal dialysis for a longer period of time, they have had a rich experience with nephrological care, better adapted to dialysis treatments, and have found the right place in their lives for dialysis, and therefore are less concerned about feeling alienated (50). Consequently, confronted with the stressors of dialysis, these patients often struggle to adapt to and redefine their roles, harboring numerous anxieties and reservations about their treatment. The amplification of psychological symptoms exacerbates their inclination toward social avoidance and SA (51). As a result, healthcare practitioners should direct their attention toward younger patients with shorter dialysis histories, proactively monitoring their emotional shifts. Collaborative interventions, such as patient support associations, can be instrumental in fostering positive emotional experiences, thereby establishing stable social bonds and mitigating their degree of social alienation.

The study's findings reveal a negative association between higher levels of EI and lower levels of SA among peritoneal dialysis patients. These results align with previous research and contribute to a deeper understanding of the underlying mechanisms (52). Individuals with elevated EI exhibit a propensity to mitigate the impact of stress within their social environment through positive coping strategies, such as cognitive reappraisal. This serves as a protective factor against SA, in

TABLE 4 Multiple linear regression analysis of factors influencing social alienation in peritoneal dialysis patients ($n = 192$).

Independent variable	Regression coefficient	Standard error	Standardized regression coefficient	t	P-value	VIF
Constant	66.085	1.944		33.997	<0.001	
Age	−0.704	0.241	−0.139	−2.926	0.004	1.286
Marital status	0.161	0.225	0.032	0.718	0.474	1.122
Monthly family income (yuan/month)	−0.107	0.143	−0.038	−0.747	0.456	1.444
Living arrangements	0.021	0.118	0.008	0.181	0.856	1.228
Time of diagnosis of disease (year)	0.282	0.236	0.064	1.194	0.234	1.650
Duration on dialysis (year)	−1.117	0.238	−0.274	−4.702	<0.001	1.939
EI	−0.085	0.019	−0.243	−4.373	<0.001	1.770
Personal mastery	−0.224	0.063	−0.212	−3.553	<0.001	2.041
Perceived social support	−0.161	0.038	−0.272	−4.295	<0.001	2.296

$R^2 = 0.682$, adjusted $R^2 = 0.666$, $F = 44.372$, $p < 0.001$. EI, emotional intelligence; SA, social alienation.

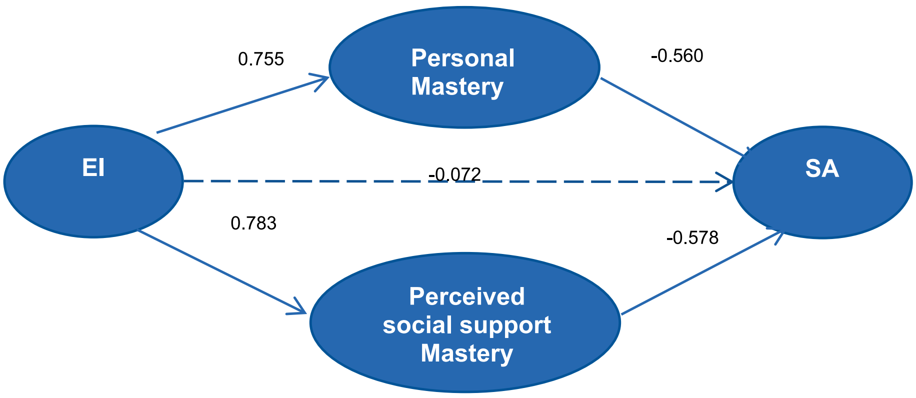

FIGURE 2
Structural equation modeling of peritoneal dialysis patients' EI, personal mastery, perceived social support and SA. EI, emotional intelligence; SA, social alienation.

TABLE 5 Effect analysis of factors influencing SA in peritoneal dialysis patients.

Effect type	Impact pathways	Estimated value of an effect	LLCL	ULCI	p
Direct effect	EI-SA	−0.072	−0.524	0.782	0.736
Indirect effect	EI-personal mastery-SA	−0.423	−0.188	−0.617	<0.001
	EI-perceived social support-SA	−0.453	−0.167	−0.751	<0.001

EI, emotional intelligence; SA, social alienation.

accordance with the stress buffer model (53). During this process, individuals tend to refrain from negative emotional expressions (self-containment and avoidance), increase positive emotional experiences, bolster resource development when facing stressful circumstances, and fulfill the prerequisites for social participation. These dynamics align with the extended construction theory (54). It was found that one feature of EI - affective differentiation – neutralizes neural responses to social rejection (i.e., dACC and forebrain insulae) (55), and from this perspective, EI creates conditions for patients to initiate social interactions. These findings lay the groundwork for further exploration of the interplay between personal mastery, perceived social support, EI, and SA among peritoneal dialysis patients.

Our study reveals that personal mastery acts as a complete mediator between EI and SA in peritoneal dialysis patients. According to the theory of limited self-control, self-control resources are finite, allowing individuals only short-term exertion of self-control.

Externally stressful situations deplete these resources, diminishing self-control, and potentially resulting in emotional regulation failures (56). Peritoneal dialysis patients, grappling with the enduring burden of lifelong dialysis, job transitions, and life adjustments, often experience a significant erosion of self-worth, which profoundly affects their personal mastery. Moreover, personal mastery is cultivated through continuous social interactions. EI emerges from the amalgamation of self-cognitive processes and emotional management (57). In the realm of emotion regulation and control, patients employ self-beneficial coping strategies, facilitating the transformation of negative emotions into positive ones through cognitive reappraisal. The sustenance of positive emotions fosters self-management confidence, life optimism, and an ensuing personal mastery. Patients possessing high personal mastery exhibit superior disease-related stress coping mechanisms, and through positive outlooks, they confront adverse events related to their condition, thereby fostering improved societal engagement and lower levels of SA (23, 58).

Additionally, our study reveals that perceived social support fully mediates the relationship between EI and SA in peritoneal dialysis patients. Individuals with high EI excel at perceiving and effectively regulating emotions, fostering positive emotional states during social interactions. These positive emotions often extend to family members and friends, fostering positive social interactions, aligning with the concept of emotional contagion (59, 60). Moreover, high EI equips patients to harness valuable social resources effectively. Perceived social support enhances patients' sense of belonging and identity, compensating for social roles lost due to illness and encouraging proactive engagement in social interactions, ultimately reducing SA (61).

Our study further demonstrates that personal mastery and perceived social support partially mediate the relationship between EI and SA in peritoneal dialysis patients. Notably, navigational social support plays a more substantial mediating role than personal mastery, suggesting that perceived social support may be a stronger predictor of SA. However, additional research is required to validate this hypothesis. This study offers a mechanistic examination of the EI-SA relationship, addressing a gap in previous research. Nevertheless, relevant studies remain limited, and the precise mechanisms require further validation through additional research. Several limitations should be acknowledged. Firstly, this study is cross-sectional, precluding the establishment of causal relationships among variables. Subsequent longitudinal investigations are warranted to validate these findings. Secondly, the study sample was drawn from a single province in China, limiting its generalizability to all peritoneal dialysis patients.

To delve deeper into these intricate connections, future research could explore them through longitudinal surveys and mixed-method studies, incorporating qualitative research components.

Conclusion

In summary, our study has revealed a pronounced level of SA in peritoneal dialysis patients, with a robust association with EI. Personal mastery and perceived social support emerge as crucial mediators in this relationship. Specifically, implementing an emotional intelligence management program has the potential to enhance patients' personal mastery and perceived social support, resulting in a subsequent reduction in SA levels. These findings offer a substantive theoretical foundation for addressing SA among peritoneal dialysis patients, suggesting that future clinical practice should consider tailoring interventions, such as the development of an emotional intelligence management program, to augment patients' personal mastery and perceived social support, ultimately mitigating SA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Zhengzhou University Life Science Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KD: Conceptualization, Methodology, Writing – original draft. JW: Methodology, Writing – review & editing. YZ: Data curation, Methodology, Writing – original draft. YH: Data curation, Investigation, Writing – original draft. YS: Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Demographic and clinical profile of adolescents suicide attempters admitted to an emergency department during the COVID-19 pandemic – a retrospective cohort study using hospital information system

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Background: The prevalence of suicidal attempts among adolescents during COVID-19 significantly increased compared with pre-pandemic estimates. The aim of the study was to explore the demographic and clinical profile of adolescent suicide attempters admitted to the emergency department during the COVID-19 pandemic.

Material and method: The retrospective analysis included, on the basis of electronic medical records in the CliniNet system, sociodemographic and clinical data of patients aged 10–18 years with a diagnosis of suicide attempt. Follow-up period: from March 20, 2020 to May 16, 2023.

Results: During the COVID-19 pandemic, there were 425 emergency department visits among adolescents aged 11–17 due to a suicide attempt, with the largest number in the 15–17 (69%) age range. The percentage of emergency department visits was higher among females (80%) and urban residents (75.3%). Self-poisoning was the most common cause of suicide attempts (52.4%), followed by self-harm (41.4%), hanging (3.2%) and jumping from a height (2.1%). The most common toxic substances in self-poisonings were antidepressants and antipsychotics, followed by paracetamol. About 70% of visits were associated with adolescent mental disorders, of which depressive disorder was the most common. One death per 425 visits was recorded (0.2%).

Conclusions: Adolescents attempting suicide during COVID-19 were most likely female, aged 15–17, city dwellers, undergoing psychiatric treatment mainly for depressive disorders. The mental health consequences of the pandemic may be more long term, and further monitoring will be needed in the years to come.

KEYWORDS

suicide attempts, adolescents, COVID-19 pandemic, demographic emergency, emergency department

Introduction

The COVID-19 pandemic, announced by the World Health Organization (WHO) on March 11, 2020 (1) was perceived both by adult and minors as a very stressful period (1, 2). Multiple factors were found to be associated with pandemic-related stress such as worrying about infection with the SARS-CoV-2 virus, the deterioration of a household's economic status, social problems (e.g., difficult child-parent relationship, social isolation), school problems (e.g., experiencing difficulty completing schoolwork at home), or suboptimal physical environment (e.g., crowding at home) (3–5). Previous study has discovered a relationship between pandemic-related stressors and psychopathology—higher exposure to stressors was associated with increases in internalizing and externalizing psychopathology (3).

It was observed that the prevalence of mental health problems in adolescents during COVID-19 significantly increased compared with pre-pandemic estimates (4, 6). Racine et al. found, based on a meta-analysis of 29 studies involving 80,879 participants in the age 18 years or younger—from Europe, East Asia, North/Central/South America, and from the Middle East—that the incidence of depression and anxiety symptoms during the pandemic doubled compared to the pre-pandemic period (7).

The overall pattern of results, reported in previous study, also suggests that mental health problems—among them: depression, psychosis, anxiety/personality/eating disorders, trauma—are a general risk factors for suicide attempts (8). The method most frequently used by adolescents admitted to an emergency department due to a suicide attempt was exogenous intoxication, mainly by medication (9, 10). A systematic review and meta-analysis conducted by Madigan et al. provide good evidence of an increase in emergency department visits for attempted suicide during the COVID-19 pandemic. It is worth adding that analyzed sample included 11.1 million pediatric emergency department visits across 18 countries (11). Yard et al. noted that during the pandemic period, emergency department visits for suspected suicide attempts began to increase among adolescents aged 12–17 years (12).

Polish police data for the years 2012–2021 indicates a growing trend of suicidal behavior among people under 18 years of age. However, the sharp increase in the number of suicide attempts and suicide deaths in 2021 compared to 2020 (an increase of 77% in suicide attempts and 19% in suicidal deaths) or to the earlier period appears to be an adverse effect of the COVID-19 pandemic. It is also worth mentioning that in 2021 the number of girls who attempted suicide more than doubled compared to 2020 (1,086 vs. 538) (13). The results of other studies also suggest that the increase in suicidal attempts are more conclusive for girls than for boys (14–16).

The COVID-19 pandemic is associated with deterioration of young people's mental health, the consequences of which may be long-term and further monitoring of their health will be necessary in the coming years. Additionally, knowing the profile of adolescents admitted to the emergency department due to a suicide attempt may allow the ability to develop targeted, holistic suicide prevention strategies and strengthen the role of the emergency departments in identifying the special clinical needs of these patients. Thus, the aim of the study was to explore the demographic and clinical profile of adolescent suicide attempters admitted to the emergency department during the COVID-19 pandemic.

Materials and methods

Study design, setting, and ethical consideration

This was a retrospective cohort study. We analyzed 425 electronic health records of patients aged 10–18 years, admitted to the Emergency Department of the University Children's Hospital in Krakow due to suicide attempts between March 20, 2020 and May 16, 2023 (the state of epidemic announced by the Polish Minister of Health in connection with SARS-CoV-2 virus infections – in this study called 'the COVID-19 pandemic) (17). The study followed the guidelines of RECORD statement (The Reporting of studies Conducted using Observational Routinely collected health Data) (18). This study was conducted after obtaining the consent of the Bioethics Committee of the Andrzej Frycz Modrzewski Krakow University (opinion nr KBKA/53/O/2022). The obtaining data from the medical records were completely anonymous.

Participants

All patients diagnosed with suicidal attempts, both sexes, aged between 10–18 years, were included (Figure 1). Eligible records were

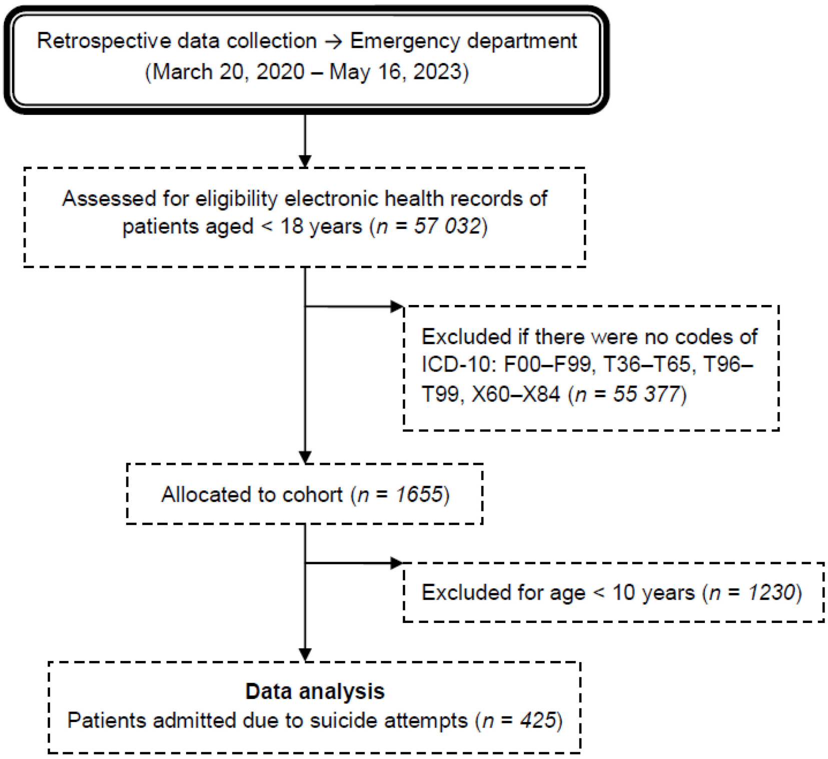

FIGURE 1
Flow chart of the medical record review process for patients admitted to the emergency department due to suicide attempts during the COVID-19 pandemic. ICD-10 → International Statistical Classification of Diseases and Related Health Problems 10th Revision. F00–F99 → Mental and behavioral disorders. T36–T50 → Poisoning by drugs, medicaments and biological substances. T51–T65 → Toxic effects of substances chiefly nonmedicinal as to source. T96 → Sequelae of poisoning by drugs, medicaments and biological substances. T97 → Sequelae of toxic effects of substances chiefly nonmedicinal as to source. T98 → Sequelae of other and unspecified effects of external causes.X60–X84 →Intentional self-harm. Incl.: purposely self-inflicted poisoning or injury suicide (attempted).

emergency department billing records with an ICD-10-CM code: F00–F99 (Mental and behavioral disorders), T36–T50 (Poisoning by drugs, medicaments and biological substances), T51–T65 (Toxic effects of substances chiefly nonmedicinal as to source), T96 (Sequelae of poisoning by drugs, medicaments and biological substances), T97 (Sequelae of toxic effects of substances chiefly nonmedicinal as to source), T98 (Sequelae of other and unspecified effects of external causes), and X60–X84 (Intentional self-harm. Incl.: purposely self-inflicted poisoning or injury suicide [attempted]) (19).

Duplicates of electronic health records and those whose data was not fully completed were excluded.

Variables

Data regarding people trying to commit suicide included: age, gender, place of residence and date of the suicide attempt, frequency, methods and type of toxic substance used during the suicide attempt, existing mental and behavioral disorders, psychiatric treatment, health condition of respondents after a suicide attempt, as well as the type of medical interventions undertaken. Data sources were: administrative billing records for emergency department visits and electronic medical records in the CliniNet system.

Statistical analysis

Data were analyzed using STATISTICA v.13 (TIBCO Software Inc., Kraków, Poland 2017). Qualitative data were presented as numbers and percentages. Continuous data are presented as median (percentiles 25–75). Relationships between qualitative variables determined using the chi-square test or Fisher's exact test. The Mann-Whitney test was used for quantitative comparison. The normality of distribution was tested using the Shapiro-Wilk test. A p value < 0.05 was considered significant.

Results

Frequency of suicide attempts depending on age, gender, and place of residence

During the study period, there were 425 emergency department visits due to suicide attempts among adolescents aged 10–18 years

(Table 1; Figure 2). The most suicide attempts occurred among girls (79.8%) and urban residents (75.3%). Suicide attempts remained more common among minors aged 15–17 (68.9%) than at the age 11–14 (31.1%). Gender distribution ($\chi2$ = 1.51; p = 0.22) and place of residence ($\chi2$ = 1.11; p = 0.73) in both age groups were similar. Every third visit concerned a patient who made more than one suicide attempt during the studied period. It was observed that the longer the pandemic lasted, the higher the number of suicide attempts (Figure 3).

TABLE 1 Characteristics of emergency department visits among adolescents due to suicide attempts during the COVID-19 according to sex, age and place of residence.

Variables	Number of emergency department visits (%)
Number of suicide attempts	
• One	284 (66.8)
• ≥ Two	141 (33.2)*
Sex	
• Female	339 (79.8)
• Male	86 (20.2)
Age (years)	
• 11–14	132 (31.1)
• 15–17	293 (68.9)
Residence	
• Urban	320 (75.3)
• Rural	105 (24.7)

*Urban residents were more likely to make at least two suicide attempts than rural residents (37.2% vs. 20.9%; $\chi2$ = 9.39; p = 0.002).

Suicide method

The suicide attempt methods chosen by teenagers are presented on Figure 4. Self-poisoning was most often attempted by teenagers, both in the age group over 14 and younger (n = 85; 64.8% vs. n = 190; 64.9%; $\chi2$ = 0.0001; p = 0.99) and in the group of girls and boys (n = 225; 66.6% vs. n = 50; 58.1%; $\chi2$ = 2.14; p = 0.14). These differences were not statistically significant. Self-poisoning, as a form of suicide, was more often chosen by teenagers living in the countryside than in the city (n = 77; 74% vs. n = 198; 61.9%; $\chi2$ = 5.09; p = 0.02). Self-harm was associated primarily with female gender (n = 181; 53.4% vs. n = 35; 40.7%; $\chi2$ = 4.42; p = 0.03), while hanging (n = 7; 8.1% vs. n = 10; 2.1%; $\chi2$ = 4.81; p = 0.028), and jump from height (n = 7; 8.1% vs. n = 4; 1.2%; $\chi2$ = 13.2%; p = 0.0003) with male gender.

Every fourth emergency department visit (n = 97; 22.9%) was the result of teenagers using two methods to kill themselves – the most common were self-poisoning and self-harm (n = 86; 20.2%). It should be mentioned that three suicide attempt methods were registered in the age group over 14 among two boys and one girl. The percentage of emergency department visits caused by the use of more than one suicide method was similar both in the age group over 14 and younger (n = 63; 21.5% vs. n = 34; 25.8%; $\chi2$ = 0.93; p = 0.33), in the group of girls and boys (n = 82; 24.2% vs. n = 15; 17.4%; $\chi2$ = 1.77; p = 0.18), and minors living in rural areas and cities (n = 29; 27.6% vs. n = 68; 21.2%; $\chi2$ = 1.82; p = 0.17).

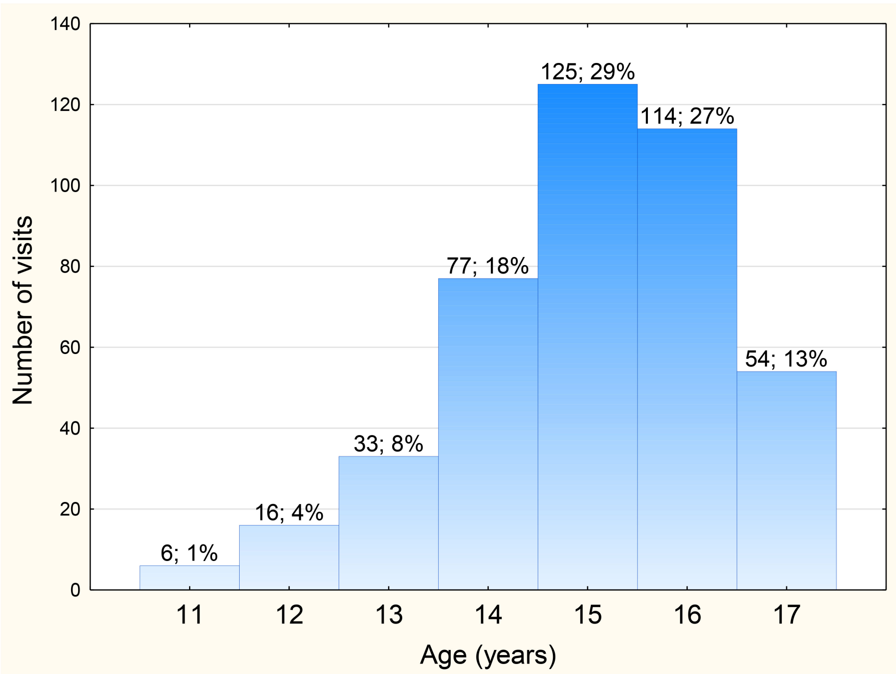

FIGURE 2
Distribution of the number of emergency department visits among adolescents due to suicide attempts during the COVID-19 pandemic depending on age.

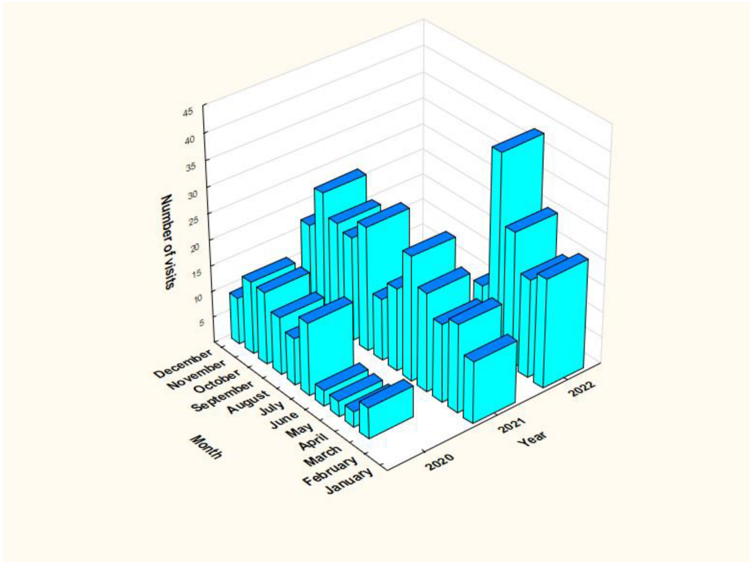

FIGURE 3
Distribution of the number of emergency department visits among adolescents due to suicide attempts during the COVID-19 pandemic depending on the month and year (from March 20, 2020 to May 16, 2022).

Type of toxic substance

Self-poisoning was the cause of 275 emergency department visits, mainly due to the consumption of drugs (n = 227; 82.5%). In this group, 8.3% (n = 23) of visits involved a combination of drugs and alcohol, while approximately 8% (n = 21) of visits were caused by the use of alcohol alone.

Girls chose drugs for suicide purposes more often than boys (n = 209; 61.6% vs. n = 41; 47.7%; $\chi2$ = 5.53; p = 0.02), and rural residents (n = 72; 68.6% vs. n = 178; 55.6%; $\chi2$ = 5.47; p = 0.02). Alcohol was consumed more often by boys than girls (n = 14; 16.3% vs. n = 39; 8.8%; $\chi2$ = 4.08; p = 0.04), and minors over 14 years of age consumed it more than twice as often as in the younger group (n = 37; 12.6% vs. n = 7; 5.3%; $\chi2$ = 5.26; p = 0.02). Among all drugs used for self-poisoning (Table 2), both in single-drug and multi-drug poisonings, the largest percentage were antidepressants and antipsychotics, followed by paracetamol. The percentage of emergency department visits due to self-poisoning with antidepressants and antipsychotics (n = 91; 31.3% vs. n = 22; 16.4%; $\chi2$ = 1037; p = 0.001) and hypnotics/sedatives/anticonvulsants (n = 28; 9.6% vs. n = 4; 3.0%; $\chi2$ = 5.80; p = 0.02) was higher among adolescents receiving psychiatric treatment than among those not treated. The opposite situation occurred in the case of the use of paracetamol (n = 32; 23.9% vs. n = 39; 13.4%; $\chi2$ = 7.23; p = 0.007) and other non-opioid analgesics (n = 24; 17.9% vs. n = 23; 7.9%; $\chi2$ = 9.34; p = 0.002). Moreover, paracetamol was more often used by girls (n = 63; 18.6% vs. n = 8; 9.3%; $\chi2$ = 4.25; p = 0.04) and rural residents (n = 27; 25.7% vs. n = 44; 13.7%; $\chi2$ = 8.13; p = 0.004).

Single-drug and multi-drug poisonings occurred with similar frequency among girls and boys ($\chi2$ = 0.27; p = 0.60), adolescents

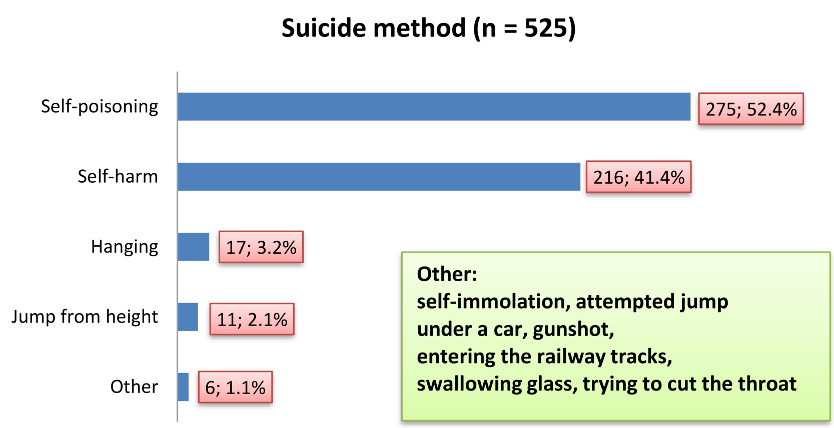

FIGURE 4
Characteristics of emergency department visits among adolescents during the COVID-19 according to suicide method.

TABLE 2 Drugs used in deliberate self-poisoning among adolescents admitted to the emergency department during the COVID-19 pandemic.

Drugs	Number (percentage)		
	Overall n = 330 (100)	Single-drug n = 185 (100)	Multiple-drug n = 145 (100)
Antidepressants and antipsychotics	113 (34.2)	81 (43.8)	32 (22.1)
Hypnotics and sedatives, anxiolytics, antiepileptics	32 (9.7)	12 (6.5)	20 (13.8)
Paracetamol	71 (21.5)	40 (21.6)	31 (21.4)
Other analgesics	47 (14.2)	18 (9.7)	29 (20)
Cardiovascular drugs	8 (2.4)	4 (4.3)	4 (2.7)

living in rural areas and cities ($\chi 2 = 0.30$; $p = 0.58$), and in the age group both over 14 and younger ($\chi 2 = 0.46$; $p = 0.50$).

A type of mental disorder

The study showed that suicide attempts were often associated with mental disorders. Depression was the most common cause of emergency department visits (n = 187; 44%), mainly among patients aged 15–16 years (n = 71). Girls diagnosed with depression have visited the emergency department more often than boys (n = 160; 47.2% vs. n = 27; 31.4%; $\chi 2 = 6.95$, $p = 0.008$). However, eating disorders were exclusively associated with the female gender (n = 16, 3.7%) – the youngest patient was 12 years old, and the most emergency department visits for this reason were among 16-year-old patients (n = 7). Emotion disorders (n = 18; 20.9% vs. n = 37; 10.9%; $\chi 2 = 6.12$, $p = 0.013$) and personality disorders (n = 7; 8.14% vs. 8; 2.4%; $\chi 2 = 6.73$; $p = 0.009$) were more predominated among boys.

Suicide attempts depending on the type of duty

55.5% (n = 236) of all emergency department visits due to suicide attempt occurred during night shifts. During this time, people with suicidal intentions after drinking alcohol were admitted more often than during the day duty (n = 36; 15.2% vs. n = 8; 4.2%; $\chi 2 = 13.73$; $p = 0.0002$). However, the day-time emergency department was more frequently visited by adolescents who had attempted suicide by hanging (n = 12; 6.3% vs. n = 5; 2.1%; $\chi 2 = 4.89$; $p = 0.026$), with adjustment disorders (n = 11; 5.8% vs. n = 4; 1.7%; $\chi 2 = 5.24$; $p = 0.02$), and nutrition disorders (n = 11; 5.8% vs. n = 5; 2.1%; $\chi 2 = 3.97$; $p = 0.046$).

A total of 215 medical services were provided in the emergency department in the form of dressing wounds after self-harm (50.6% of emergency department visits). Almost every sixth patient required gastric lavage and administration of activated charcoal via a gavage (n = 71; 16.7% of hospitalizations), and every tenth patient needed an antidote (n = 43; 10.1%). In 5.2% of cases (n = 22), patients required treatment in the pediatric intensive care unit. One fatal case per 425 emergency department visits was recorded (0.2%).

Discussion

The study showed that adolescents attempting suicide during COVID-19 pandemic are mostly female, aged 15–17, city dwellers, undergoing psychiatric treatment for depressive disorders. The most common method of suicide attempts were deliberate self-poisonings with prescription drugs followed by over-the-counter analgesics such as paracetamol.

This study revealed, that during the period of the COVID-19 pandemic, girls visited the emergency department for suicide attempts more often than boys (79.8% vs. 20.2%). These findings are consistent with the results of another Polish study conducted by Pilarska et al. in the age group of 8–17 years, where approximately 80% of this group were girls (10). Similar results were found by Kirič et al. (14) among the Slovak children and adolescents, who required emergency help with suicidality and attempted suicide. They assessed suicidal behavior more frequent among females than males (69.3% vs. 30.7). Gender disparity in suicide attempts in community adolescents and young adults aged 12–26 years was confirmed by Miranda-Mendizabal et al. (8) in their systematic review and meta-analysis of longitudinal studies. They found that females had an almost twice higher risk of suicide attempts than males. The female preponderance in a suicidal tendency may be partly explained by greater risk of developing depressive or eating disorders (8, 20). Other risk factors specific to the female gender, but not assessed in our study, include: post-traumatic stress disorder, being a victim of dating violence, interpersonal problems and a previous abortion (8).

Our findings showed, that suicide attempts were significantly more common among adolescents aged 15–17 years than younger, and those living in urban than rural areas. Similar observations were obtained in the study by Zygo et al. (21), who in pre-pandemic period determined that more Polish minors attending schools in Eastern Poland, aged 17–18 reported suicidal thoughts, plans and attempts than those aged 13–16 years; most of them were city residents. Goldman-Mellor et al. (22) found, that before the pandemic, rural U.S. youth were significantly less likely to report suicide attempts than their urban counterparts. Salt et al. (23) identified any change in the incidence of suicidal attempts within any demographic subgroup of U.S. pediatric sample in the 6 months post-SARS-CoV-2 when compared to the 6 months of the prior year, most likely due to group size limitations. However, they found an increase in incidence of suicidal ideation among adolescents aged 14–17, and those residing rural areas.

Both our studies and those conducted by others (24, 25) found an association between suicide attempt and depression. There is scientific evidence, that people who have experienced their first depressive episode (26) or depressive symptoms associated with the psychotic episode, in the early stages of the disorder, before the first admission or contact with health services (27), have received psychiatric treatment and have undergone psychotherapy in the past (28), are at high risk of attempting suicide. Furthermore, Ong et al. (25) showed, that depressive disorder among pediatric patients were associated with a higher likelihood of suicide attempt than attention deficit disorder, disruptive behavior disorder, bipolar disorder, or schizophrenia.

Based on the January 2020 and June 2021 date (n = 154) collected by Pilarska et al. (8), self-poisoning, followed by self-injury and jumping from height, emerged as the most common method of Polish pediatric patients who have attempted suicide. A similar order of occurrence of suicide methods was recorded in our own study. The main cause of self-poisoning, as in the study by Barbeito et al., was an overdose of prescribed drugs (27), such as antidepressants and antipsychotics, followed by paracetamol. Koppen et al. (29) found significant increase in deliberate self-poisonings during COVID-19 pandemic, with a preference for paracetamol, especially among 13-, 14-, and 15-year-old Dutch female adolescents. However, self-poisoning is less likely to result in death than hanging, shooting a firearm or jumping from a height (30).

Youth suicide rates increase with age, and females are less likely to die by suicide than males. This hypothesis was confirmed by Glenn et al. in a meta-analytic review of worldwide suicide rates among adolescents. They found that hanging/suffocation was the most common method of suicide across all countries and for both sexes (31). Pikala and Burzyńska who assessed mortality trends due to suicide in Poland in the years 2000–2019, reported higher percentage of suicide deaths in age 15–24 than 5–14 (10.2% vs. 0,27%). The percentage of fatal cases among girls in mentioned age groups was 8.4% and 0.6%, respectively (32).

In our study, we recorded one death per 425 emergency department visits (0.2%) – it was a 16-year-old girl who suffered sudden cardiac arrest as a result of hanging. In 5.2% of the cases, patients required treatment in the intensive care unit. Bruns et al. found that although among German adolescents serious suicide attempts requiring intensive care treatment dramatically increased during COVID-19 pandemic, fatal suicide rates remained stable (33).

To sum up, suicide attempts among adolescents are a serious and complex public health problem, that is constantly increasing and an exceptional time that may have aggravated this problem was the period of the COVID-19 pandemic. In Poland, the psychiatric and psychological care system does not meet the rapidly growing needs of children and adolescents in crisis. It should also be added, that in the last few years, Poland has taken the inglorious second place in the European Union in terms of suicide attempts among people under 18 years of age. This situation may be caused by many factors, including the fact that in Poland access to professional help, i.e. to psychologists and educators from whom young people could obtain professional help is still difficult. According to the Central Register of Doctors of the Republic of Poland kept by the Supreme Medical Council, as of March 31, 2024, there were 553 professionally active doctors with specialization in child and adolescent psychiatry registered in Poland. In accordance with the WHO recommendations, there should be 10 psychiatrists per 100,000 children. Although currently in Poland this ratio is 10.49, the waiting time for a visit is more than 30 days (34, 35) Currently, Poland is undergoing a reform of the psychiatric and psychological care system for children and adolescents. Within this framework, it is crucial to implement the first of three levels of reference, the task of which is to provide care in the patient's environment (i.e. at home - in the family, at school – among peers) by psychologists, psychotherapists and community therapists (36).

Limitation

Our study had several limitations. Firstly, the data was collected only in one of the available emergency departments for children and adolescents in the country, thus this data is not nationally representative. Secondly, because our study was a retrospective study, we were unable to assess and control many of the factors influencing suicidal behavior among adolescents. Thirdly, no pre-COVID-19 data had been collected for this specific population, which prevents the study from being able to assess whether and how the situation might have changed over the past year.

Conclusion

Adolescents attempting suicide during COVID-19 pandemic were most often females, aged 15–17, city dwellers, undergoing psychiatric treatment mainly for depressive disorders. This study highlights the need to improve suicide prevention strategies among adolescents.

Implications for clinical practice and future directions

Activities to create effective, comprehensive suicide prevention programs among young people, taking into account risk factors (e.g. females, aged 15–17) should be intensified. Among the preventive measures, early diagnosis of mental disorders (including depression), should be strengthened through appropriate public education and access to psychologists and psychiatric treatment. Such education and policies should also take into account the key role that social networks and community engagement play in promoting positive youth development, emotional support, help and access to resources in coping with such challenges (37). National information campaigns promoting ways to seek professional help in the event of a mental health crisis should also be more present. It is important that people after a suicide attempt receive continuous, individualized and coordinated psychiatric care. Future research should focus on longitudinal studies to monitor the long-term impact of the pandemic on mental health among adolescents, including suicidal behavior. Additionally, exploring protective factors and resilience-building strategies among adolescents could increase the effectiveness of preventive and intervention efforts (38).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study was conducted after obtaining the consent of the Bioethics Committee of the Andrzej Frycz Modrzewski Krakow University (opinion nr KBKA/53/O/2022). The obtaining data from the medical records were completely anonymous.

Author contributions

LT: Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization, Funding acquisition, Formal analysis, Visualization. PK: Writing – original draft, Data curation. ET: Writing – original draft, Methodology, Investigation. EB: Writing – review & editing, Data curation, Conceptualization, Investigation. IM: Writing – original draft, Investigation. WD-M: Writing – review & editing, Visualization, Supervision, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of mind–body therapies on depression among adolescents: a systematic review and network meta-analysis

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Background: Depression poses significant threats to adolescents' health globally. Research has shown the potential of mind–body therapies to alleviate depression, but limited studies have directly compared the therapeutic effects of different types of mind–body therapies on adolescent depression and the optimal therapy remain unclear. Therefore, we conducted a systematic review and network meta-analysis of randomized controlled trials that met the inclusion criteria to explore the effectiveness of different types of mind–body therapies as interventions to improve depression among adolescents, and to identify the most effective interventions.

Methods: A comprehensive search of databases including PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus up to January 2024 was conducted to assess the impact of mind–body therapies on depression among adolescents. The risk of bias of the included studies was evaluated using Cochrane Review Manager 5.4. STATA 18.0 was used for network meta-analysis. The node-splitting method was used to test the local inconsistency of the network meta-analysis. Funnel plots and the Egger's test were utilized to assess the potential impact of bias in this study.

Result: This network meta-analysis included 9 randomized controlled trials involving a total of 955 subjects. The results indicated that yoga, dance therapy and Tai Chi were more effective than other mind–body therapies in reducing symptoms of depression among adolescents. Specifically, according to the SUCRA ranking, yoga was rated to be the optimal intervention for adolescents with depression (SCURA: 82.2%), followed by dance therapy (SCURA: 77.5%) and Tai Chi (SCURA: 64.9%).

Conclusion: This study revealed that mind–body therapies have positive effects on improving depression among adolescents. Yoga may be the most effective intervention among the different types of mind–body therapies. However, due to the small sample size of patients included, the certainty of the results was limited to some extent. Therefore, further investigation is necessary to strengthen the evidence base when more relevant studies become available.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42024508774.

KEYWORDS

mind–body therapies, adolescents, depression, network meta-analysis, yoga, dance therapy, Tai Chi

1 Introduction

An estimated 3.8% of the population worldwide experience depression (1). Previous studies indicate that approximately 34% of adolescents worldwide are at risk of developing clinical depression, with the highest rates observed among adolescents living in the Middle East, Africa, and Asia (2). According to Report on National Mental Health Development in China (2021–2022), 24.1% adolescents were depressed, meaning that about one in four adolescents suffers from depression (3). Depression is a common, debilitating, burdensome, and chronic mental health problem that is prevalent during adolescence (4, 5). Stressors among adolescents, usually aged 10 to 19 (6), include physical and mental changes, academic pressure, and shifts in family and social relationships. At this time, due to the immature emotion regulation abilities of adolescents, long-term exposure to these stressors causes difficulty in coping with negative emotions, leading to malfunction of reward system (i.e., abnormal secretion of endorphins, dopamine, oxytocin, etc.) or the abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis, which may provide the environment for the emergence of depression (7, 8). This mood disorder is broadly characterized by persistent feelings of sadness, loss of interest in activities, and impairment of daily functioning (1, 9). The damaging effects of depression also extend to adolescents' social relationships to academic performance, and depression-induced suicide has become the second leading cause of death among adolescents (10–12). Moreover, adolescent depression has high comorbidity with other mental disorders such as anxiety, substance abuse, and conduct disorders, and is often associated with risky behaviors. Early onset of depression during adolescence presents a more severe depression in adulthood (i.e., longer episodes, higher recurrence rates, and more residual symptoms), and adverse psychosocial outcomes such as lower subsequent educational attainments, lower perceived social support (13–16). Rather than conceptualizing depression as qualitatively distinct "entities" (i.e., major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, etc.) (9), current research proposed the dimensional model, which conceptualizes depression as a continuously process starting from subthreshold depression (17), with all individuals falling somewhere on the depressive symptom spectrum, distress and impairment occurring at the extremes of the continuum where the individual lies (4, 18–20). Since dimensional models have been proven to be more valid than traditional categorical models in examining the etiology and treatment of adolescent depression (19), we will also use the term "depression" in the rest of this review to broadly refer to various collections of depressive disorders and symptoms.

Medication and psychotherapy are the primary clinical interventions for depression among adolescents. However, despite the fact that these therapeutic approaches have been adequately implemented, they can only reduce the disease burden of depression by 30% (21). A significant number of patients received insufficient relief of their symptoms, while 50% suffered at least one recurrence of a depressive episode after 6–12 months of treatment (22). Previous studies denoted that antidepressant medication carried potential side effects and might increase the risk of suicidality among adolescents (23–25). For instance, Selective Serotonin Reuptake Inhibitors (SSRIs) in clinical trials have increased the intensity of suicidal predictors in depressed patients, such as dysphoria, anxiety, impulsiveness, aggressivity, agitation, etc. (26). Besides, although psychotherapy can be effective, many patients may refuse it due to the stigma related to their symptoms, and for some adolescent patients, especially in low-and middle-income countries, it is very expensive and unaffordable (1, 27). In this context, there is a paramount necessity to find cost-effective, side-effect-free, and easily accessible forms of treatment for depression in addition to options that already exist (28).

Due to its low cost, simplicity of implementation, varied forms and enjoyable nature, exercise therapy has become a prevalent adjunctive treatment for adolescent depression in recent years (29, 30). Research has demonstrated that the physiological mechanisms underlying the positive effects of exercise on depression are related to cytokines, monoamine neurotransmitters, inflammatory factors, neural systems and other factors in the body (31). However, mind–body therapies (MBTs), combining various forms of exercise, have been developed as an effective intervention for the treatment of depression by strengthening the mind's capacity to interact dynamically with the body's functions and symptoms, and to establish a strong connection between the brain, mind, body and behavior, in order to achieve overall health (32). To date, MBTs may include, but are not limited to, yoga, mindfulness-based meditation practices, Tai Chi, dance therapy, Qigong, and Buduanjin etc., and effects varied with different forms of exercise. For instance, yoga reducing stress and psychiatric symptoms, can be an effective treatment option for depression (33, 34). As it helps regulate negative emotions and attention, mindfulness training is essential for both preventing and treating depression (35). Traditional Chinese MBTs like Tai Chi, Qigong, and Buduanjin were proven to enhance patients' neurocognition through mild movements combined with breathing relaxation techniques (36, 37). However, despite the growing variety of mind–body therapies from the East and West (32), there is a lack of evidence to support the efficacy of different MBTs for depression among adolescents, and the best non-pharmacological treatment strategy for depression in adolescents is unclear (38).

Therefore, the aim of this study is to assess the effects of different types of MBTs on depression among adolescents, and use a network meta-analysis to comprehensively compare and rank multiple different mind–body interventions, thus providing a basis for selecting the optimal treatment plan and informing clinicians when developing non-pharmacological treatment strategies.

2 Materials and methods

We have registered (CRD42024508774) this systematic review and network meta-analysis in the International Prospective Register of Systematic Reviews (PROSPERO), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Network Meta-Analysis (PRISMA -NMA) statement for reporting. Ethical approval is not required as it is a systematic review.

2.1 Search strategy

We performed a systematic search following in the five electronic databases (PubMed, Embase, Cochrane Library, Web of Science, and Scopus) and used a snowball strategy to find relevant articles from their references and subsequent citations. The search was limited to

English language literature and the period covered from the inception of each database until January 2024, and the search strategy followed the PICOS principle:

(P) population: adolescent patients with depression or depressive symptoms;

(I) intervention: mind–body therapies, including Yoga, Mindfulness, Tai Chi, Dance, etc.;

(C) control group: usual care including daily care, waitlist control conditions, routine exercise or other social activities;

(O) outcomes: The outcome measures included at least one of the following: the Patient Health Questionnaire (PHQ-9), the Beck Depression Inventory (BDI), the Symptom Checklist (SCL), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Hamilton Rating Scale for Depression (HAM-D);

(S) study type: randomized controlled trials (RCTs).

The search strategy is provided in the Supplementary material, as the PubMed interface.

2.2 Exclusion criteria

The current study excluded: (1) non- randomized controlled trials, such as quasi-randomized controlled trials, animal studies, protocols, conference abstracts, case reports, etc.; (2) studies with incomplete or unreported data; (3) purely descriptive studies.

2.3 Literature screening

We utilized Endnote X9 literature management software to detect and exclude the duplications. Subsequently, two authors (SLL and ZYM) independently evaluated the titles and abstracts of the retrieved articles to ensure their eligibility for inclusion in the study. No further review was conducted for studies that did not meet inclusion criteria. Then, the two authors reviewed the full texts of the remaining literature. During this process, any disagreements were discussed to reach a resolution, or addressed by consulting another author (SL).

2.4 Data extraction and quality assessment

Three authors (GSF, GGM, and XYZ) independently extracted the data from selected RCTs including (1) basic information such as the first author's name, year of publication, and country; (2) characteristics of the subjects, including mean age and gender; (3) experimental settings, including sample size, exercise type, cycle, frequency, and time; (4) primary outcome measures and measurement tools.

Risk of bias (ROB) assessment was conducted using Cochrane Review Manager 5.4 version, the assessment criteria included the following seven aspects: (1) Generation of the random sequence, (2) Hidden treatment allocation, (3) Blinding of study subjects or intervention personnel, (4) Blinding of result assessors, (5) Completeness of data results, (6) Selective reporting of results, and (7) Other bias. Each item was evaluated using "Low risk of bias," "High risk of bias" and "Unclear risk of bias." Trials were categorized into three levels of ROB by the number of components for which high ROB potentially existed: high risk (five or more), moderate risk (three or four) and low risk (two or less).

2.5 Statistical analysis

We utilized Stata 18.0 to perform a network meta-analysis and followed the PRISMA-NMA instruction manual. This method is particularly effective for data processing in multi-arm trials, providing comprehensive comparisons of multiple interventions while the statistical power and precision of the estimates are well-maintained (39). Considering that the outcome measures were continuous variables and the assessment scales were different across included articles, we used the standard mean difference (SMD) and 95% confidence interval (CI) as the effect size measure of the summarized results, with $p < 0.05$ indicating statistical significance. Statistical tests were used for evaluating heterogeneity, when $p > 0.10$ and $I^2 < 50\%$, indicating low heterogeneity, a common-effect model was used; while $p < 0.10$ and $I^2 > 50\%$ indicated high heterogeneity and a random-effects model was used (40). A global consistency test was conducted to assess potential inconsistency between direct and indirect evidence, and node splitting was employed to ascertain local consistency (41). If the analysis showed $p > 0.05$, indicating that the direct and indirect comparisons did not have a significant difference, the effect sizes of multiple treatment comparisons could be analyzed using a consistency model. If not, an inconsistency model was applied. When there were closed loops present in the comparative studies, a test for inconsistency in the loops was conducted, with a 95% CI containing 0 denoting no significant loop inconsistency.

By comparing the surface under the cumulative ranking curve (SUCRA), rankings of different MBTs were established. A higher SUCRA value implies a higher probability of ranking (42). Network funnel plots were generated and visually monitored using symmetry criteria to assess if a small-scale study could result in publication bias in the network meta-analysis. In summary, the above methods for investigating the geometry of the treatment network and potential biases contributed to a more valid and reliable network meta-analysis result.

3 Results

3.1 Literature selection

A total of 1869 articles were identified from five databases aforementioned. After excluding 743 duplicates, 10 non-English literature and 9 conference abstracts, we completed a preliminary review of titles and abstracts, excluding 910 irrelevant articles and meta-analyses. The remaining 197 articles were eligible for the full-text review, after a comprehensive and careful review, 188 articles were excluded for reasons such as being non-randomized controlled trials, containing incomplete data, being improper article types like meeting abstract, or inappropriate intervention type. Finally, we included 9 published randomized controlled trials in this systematic review and network meta-analysis. The whole selection process has been illustrated in Figure 1.

3.2 Quality assessment of the included studies

All 9 studies included in this review mentioned using methods like random number tables and computers to generate random

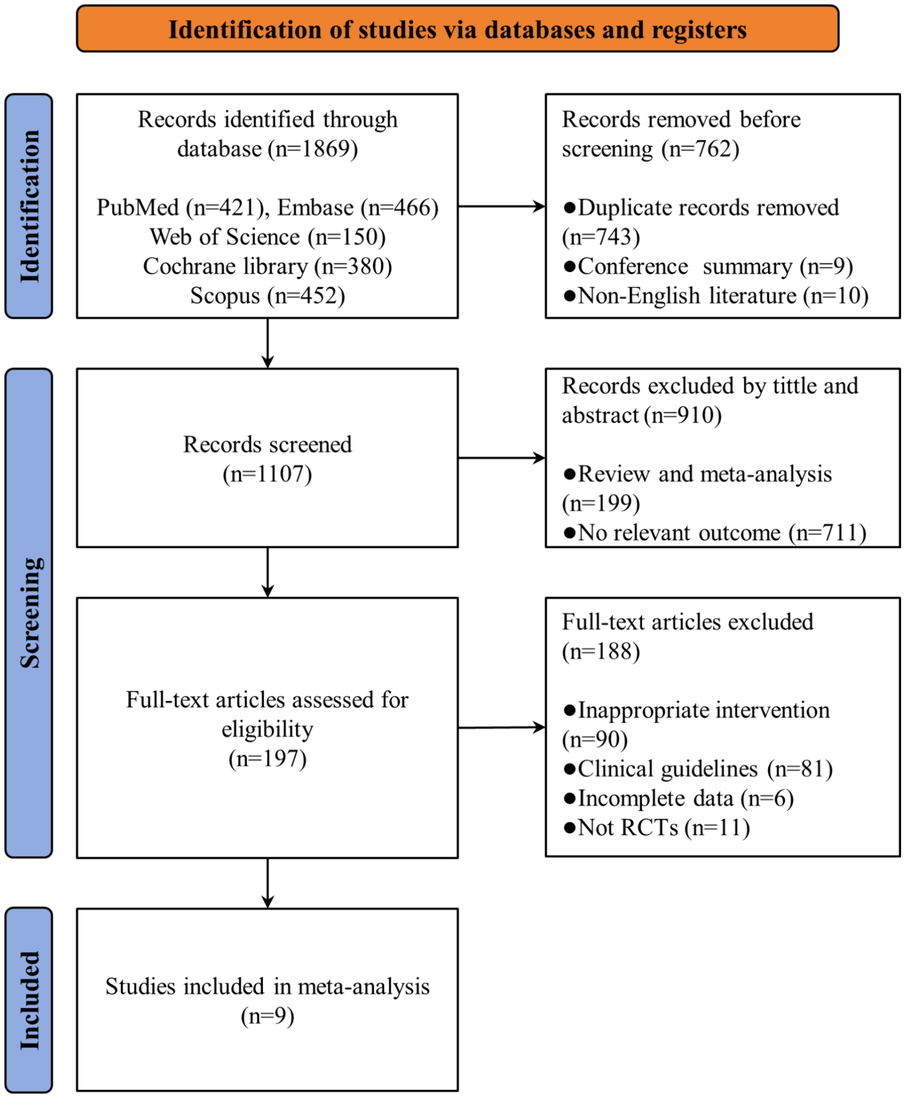

FIGURE 1
Flow diagram of literature selection.

sequences. Six studies allocation reported concealment methods such as opaque sealed envelopes. Five studies blinded patients, while only 3 blinded those who assessed the study results. The integrity of data in all 9 studies was generally good, and no signs of selective reporting were observed. Two studies showed no other biases, and for the remaining studies, other biases were unknown. The detailed quality assessment results are presented in Figure 2.

3.3 Basic characteristics of the selected studies

This study covers 9 randomized controlled trials, which involved a total of 955 adolescent patients with varying levels of depression. All participants were randomly assigned to the experimental group and control group. The experimental group was treated with a variety of interventions, including 4 involving mindfulness-based interventions, two involving yoga, two involving Tai Chi, and one involving dance therapy. Each intervention lasted 45 min–2 h, and the frequency varied from once a week to six times a week. The control group received interventions such as treatment as usual, physical exercises, and relaxation activities. The distribution of the included studies takes place in China (4), the United States (2), Spain (1), Finland (1), and Columbia (1), with the publication year mainly concentrated between 2015 and 2023. The outcome measurements varied across studies. Depression among adolescents were evaluated utilizing the Patient Health Questionnaire, Beck Depression Inventory, Revised Beck Depression Inventory, Symptom Checklist 90, and Strengths and Difficulties Questionnaire. The characteristics and details of the selected literature are summarized in Tables 1, 2.

3.4 Network meta-analysis

This study adheres to the principles of coherence, transferability, and consistency when conducting network meta-analysis. A network

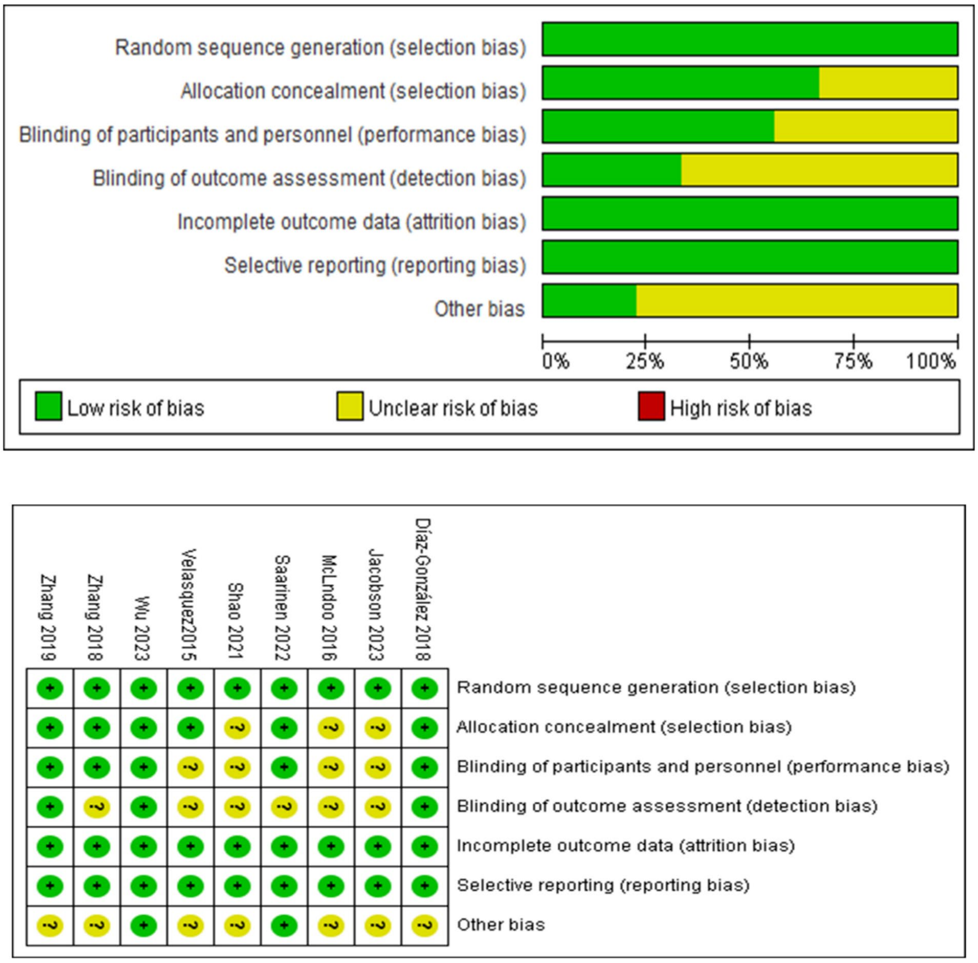

FIGURE 2
Quality assessment of included studies.

diagram (Figure 3) was established between different MBTs used to treat depression among participated adolescents. More specifically, the presence of the line between the two nodes in the diagram represents the direct comparison of studies, and vice versa. The thickness of the lines linking interventions reflects the number of studies comparing the two interventions. Figure 3 shows the comparisons among different interventions. Figure 4 demonstrates the rankings of interventions according to their potential to be the best choice for depression among adolescents (Table 3).

The *p*-values for indirect and direct comparisons between studies were examined for global inconsistency. The effect of consistency between studies was acceptable since all *p*-values were above 0.05. The network relationship was centered on treatment as usual and formed three closed loops (Figure 3) which were subjected to local inconsistency tests using the node-splitting method, and the results indicated no significant inconsistency in the closed loops.

The results of network meta-analysis showed that yoga and dance therapy were significantly effective in reducing depression when compared to treatment as usual received by the control group. In the SUCRA ranking table (Figure 4), yoga was rated to be the optimal intervention for adolescents with depression with a probability of 82.2%, followed by dance therapy (77.5%) and Tai Chi (64.9%). According to the results of ranking, the effects of decreasing adolescents' depression of different MBTs are as follow: yoga> dance therapy> Tai Chi> mindfulness-based Tai Chi> mindfulness-based stress reduction> mindfulness-based intervention> relaxation> control group.

3.5 Publication bias test

We generated funnel plot for outcomes using STATA software version 18 to asses potential publication bias. The results showed that the symmetrical distribution of all the studies in the funnel plot could not be well observed, so we further conducted the Egger's test for quantitative analysis of the publication bias test. The *p*-value in the Egger's test was 0.09, indicating that there was no significant publication bias for the outcome indicators. The funnel plot is shown in Figure 5.

3.6 Sensitivity analysis

We performed sensitivity analyses by excluding individual studies, and the results showed no significant change in the statistical

TABLE 1 Basic characteristics of the included studies.

Study	Country	Age	Population	Total/male/female	Intervention	Control
Wu et al. (51)	China	T: 19 C: 19	Subthreshold depression	T:49/15/34 C:54/18/36	Tai Chi training Length of Intervention: 12 weeks; Freq: 3 times a week; Duration: 1 h.	Waiting list
Jacobson (44)	United States	T:NA C:NA	Depression of all levels (Including subthreshold)	T:30/NA/NA C:32/NA/NA	Hatha yoga training Length of Intervention: 6 weeks; Freq: 3 times a week; Duration: 60–70 min.	Routine health program
Saarinen et al. (35)	Finland	T:NA C:NA C:NA	Subthreshold depression	T:166/57/109 C:157/47/110 C:46/9/37	Mindfulness-based Intervention Length of Intervention: 9 weeks; Freq: 5–6 times a week; Duration: 45 min.	Relaxation/No intervention
Shao (45)	China	T:NA C:NA	Subthreshold depression	T:32/15/17 C:30/15/15	Dance therapy Length of Intervention: 8 weeks; Freq: once a week; Duration: 2 h.	No intervention
Zhang et al. (46)	China	T: 19.1 C: 18.7	Subthreshold depression	T: 28/11/17 C: 28/13/15	Mindfulness-based stress reduction training Length of Intervention: 8 weeks; Freq: once a week; Duration: 1 h.	No intervention
Zhang et al. (47)	China	T:NA C:NA	Subthreshold depression	T: 32/NA/NA C:32/NA/NA	Mindfulness-based Tai Chi PE classes Length of Intervention: 8 weeks; Freq: Twice a week; Duration: 90 min.	No intervention
Díaz-González et al. (48)	Spain	T: 14.6: 14.5	Subthreshold depression	T: 41/18/23 C: 39/18/21	Mindfulness-based stress reduction training Length of Intervention: 8 weeks; Freq: once a week; Duration: 90 min	Treatment as usual
McIndoo et al. (49)	USA	T: 19.3 C: 19	Depression of all levels (Including subthreshold)	T: 20/8/12 C: 14/6/8	Mindfulness-Based intervention Length of Intervention: 4 weeks Freq: once a week; Duration: 1 h.	Waiting list
Velásquez et al. (50)	Colombia	T:NA C:NA	Subthreshold depression	T: 68/NA/NA C: 57/NA/NA	Yoga training Length of Intervention: 12 weeks; Freq: 2 times a week; Duration: 120 min.	Waiting list

significance of the outcomes in this study. This further validates the robustness of our results.

4 Discussion

This network meta-analysis aimed to evaluate the effectiveness of different mind–body interventions on depression among adolescents and compared it with the control group. The results showed that MBTs such as yoga, dance therapy, Tai Chi, significantly alleviated depression levels compared to the control group interventions. These findings are consistent with the previous reviews with respect to the effects of MBTs addressing the mental health issues among adolescents (32). Therefore, the current review findings may provide referenceable evidence to apply MBTs to the young population. Pairwise comparisons revealed that yoga and dance therapy showed stronger effects on depression than other interventions. Based on the size of the efficacy and the ranking probability of the SUCRA values, yoga proved to be the most effective for depression among adolescents (SUCRA: 82.2%), followed by dance therapy (SUCRA: 77.5%) and Tai Chi (SUCRA: 64.9%).

Yoga is an ancient spiritual discipline that includes physical postures, movement control, breathing exercises, and mindfulness meditation (52–54). These methods facilitate the integration of the body, breath, thought and affect, thereby relieving stress and psychiatric symptoms (34, 55). Our findings revealed that yoga ranks high in SUCRA values for addressing depression in adolescents, demonstrating its potential as an optimal complementary treatment option. The pathogenesis of depression has not been elucidated clearly and is currently thought to be related to biological, genetic, environmental

TABLE 2 Details of participation controls for included studies.

Study	Participation inclusions	Participation exclusions
Wu et al. (51)	(1) Age between 18 and 25 years; (2) Score ≥ 16 on the Centre for Epidemiological Studies Depression Scale (CES-D); (3) No clinical intervention for depressive symptoms in the past 6 months; (4) Did not practice regular mind–body exercise in the past 6 months; (5) No contraindication to MRI examination.	The presence of suicide tendency as measured by the suicidality scale (cutoff score ≥ 6) of the Mini International Neuropsychiatric Interview (MINI version 5.0). The withdrawal criteria were: (1) volunteering to withdraw; (2) developing serious diseases that would not allow continuation of the intervention; (3) suffering from serious adverse events related to the intervention; (4) receiving Tai Chi training during the waitlist period.
Jacobson (44)	(1) The Beck Depression Inventory II, (BDI-II) scoring between 14 and 63; (2) Between the ages of 13–17; (3) Be able to do basic exercise. (4) Not to change medications if they were on them for depression.	(1) Having other debilitating mental disorders with the exception of anxiety; (2) Had history of suicide attempts.
Saeed et al. (35)	Not specified; invited comprehensive school students of appropriate age for participation and used a modified version of the Beck Depression Inventory (RBDI) to assess symptoms of depression.	Not specified.
Shao (45)	(1) The Symptom Checklist 90 (SCL-90) criterion of depression factor greater than 3.; (2) Those who are healthy and without physical diseases; (3) Those who volunteer to participate in group psychological counseling; (4) Those who are willing to complete the questionnaire survey carefully.	(1) Those who have serious psychological problems or mental diseases and are accepting drug treatment; (2) Those who are receiving psychological consultation or continuous systematic psychological counseling; (3) Those who are unwilling to complete the questionnaire survey; (4) Those with serious physical diseases.
Zhang et al. (46)	The Beck Depression Inventory (BDI) score > 14 and the Self-rating Depression Scale (SDS) score > 53	(1) Had recently suffered from major stress events; (2) Had major depressive disorder, bipolar disorder or other types of mental illnesses; (3) Had participated in or were participating in similar interventions (such as yoga or meditation)
Zhang et al. (47)	(1) Aged 16–19 years; (2) Had subthreshold symptoms of depression defined by nine-item Patient Health Questionnaire depression scale, (PHQ-9) as 2–4 symptoms of depression experienced more than half of the days or nearly every day for 2 or more weeks, which have affected study, social life, or functioning.	(1) Had other major disabling medical or mental disorder; (2) Had or being participated in a similar intervention; (3) Having major depression or no depression.
Díaz González et al. (48)	(1) Presence of psychological symptoms assessed by the Symptom Checklist 90 (SCL-90); (2) Age between 13 and 16 years.	(1) Having a neurological or psychiatric disorder that might interfere with participation (for example severe brain injuries, significant cognitive impairment, mental retardation, autism spectrum disorders, psychotic disorders, current suicidal ideation); (2) Current drug or alcohol misuse or dependence.
McIndoo et al. (49)	(1) The Beck Depression Inventory (BDI-II) score > 14; (2) Refrain from mindfulness practices, such as yoga, progressive muscle relaxation, and meditation during the study.	(1) Current alcohol and substance dependence and psychosis; (2) Medicated or not stabilized (i.e., same dosage for a minimum of 8 weeks) on antidepressant and antianxiety medication; (3) Receiving any current psychotherapy or counseling.
Velásquez et al. (50)	Not specified; selected appropriate aged students from public schools for participation and assessed symptoms of depression using the strengths and difficulties questionnaire (SDQ).	Not specified.

and psychosocial factors. Initially, it was thought that depression was associated with abnormalities in monoamine neurotransmitters, with dopamine being one of them (43). Dopamine is related to emotion regulation and plays an important role in the reward circuitry (56). By affecting the neurochemicals released in the brain, yoga is considered one of the most beneficial coping strategies for reducing stress (57). Many studies have proven the effects of yoga on the regulation of the dopamine system. During yoga meditation, there was a 7.9% reduction in ^{11}C-raclopride binding in the ventral striatum, indicating a 65% increase in endogenous dopamine release (56). In addition, yoga induces complete relaxation of the body through simple to advanced breathing exercises that bring one into a meditative state, which can enhance inhibitory neuronal function (58–60), thereby helping to adjust the overreactive state of the dopamine system (61). However, recent theories suggest that depression is also related to more complex neuromodulator systems and neural circuits (43). Typical examples such as HPA axis dysfunction and inflammatory cytokines induced by psychosocial stressors may trigger depression (62–64). Specifically, yoga's mindfulness techniques assist in stress reduction, exert a positive influence on an individual's ability to self-regulate (65, 66), and inhibit the overactive HPA axis function (67). In addition, the yoga components of slow breathing, relaxation practices, mindfulness of sensations in the body can activate the vagal anti-inflammatory pathways (68, 69), which could be an essential mechanism whereby yoga practice reduces depression (70).

Dance therapy is the psychotherapeutic use of movements to promote emotional, social, cognitive, and physical integration in the individual, for the purpose of improving health and well-being (71).

Over the decades, dance therapy has become a typical MBTs intervention prevailing in many regions of the world and across all age groups (72). Our results indicated that dance therapy ranked second only to yoga. The antidepressant effect of dance therapy can be explained from an endocrine perspective. Firstly, endorphins are chemicals naturally produced by the nervous system to control pain or stress which are commonly labeled as "feel-good" chemicals (73). The movement, music and rhythm involved in dance therapy can affect endorphin release by significantly altering mood, stimulating intense feeling states and even strengthening prefrontal cortex function (74–79). Moreover, oxytocin is a hypothalamic neuropeptide associated with interpersonal functioning, stress coping, social memories formation and prosocial behavior in humans (80–83). Research previously found negative correlation between severity of depression and serum oxytocin concentrations in a clinical population (84). Deficits in oxytocin levels make it difficult for depressed people to cushion the negative emotions of loneliness, which is a significant predictor of depression, via the perception of social support (85, 86). Dance therapy augments the mirror neuron system when using mirroring techniques (87, 88) to produce synchronized movements, which affects oxytocin (89), thus helping to alleviate depression. Furthermore, contrary to yoga and Tai Chi, dance therapy movements may be more vigorous and rhythmic, making it more appealing to adolescents, especially young girls. Thus, the social potential of this intervention for antidepressant impact cannot be ignored. Depressed adolescents who gather to practice dance and get in touch with others struggling with similar symptoms can help them overcome loneliness and promote a positive antidepressant effect (90).

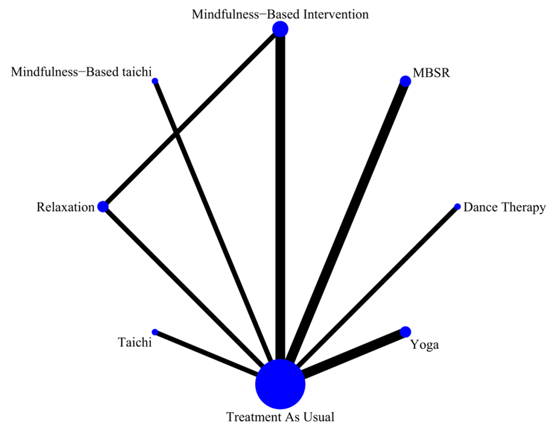

FIGURE 3
The network plot of the analyzed treatment comparisons for depression among adolescents.

Tai Chi is a traditional Chinese fitness practice well known for its slow, fluid movements, deep breathing and meditative elements. It is particularly favored by a large group of older people as being composed of a series of gentle movements. Many studies have

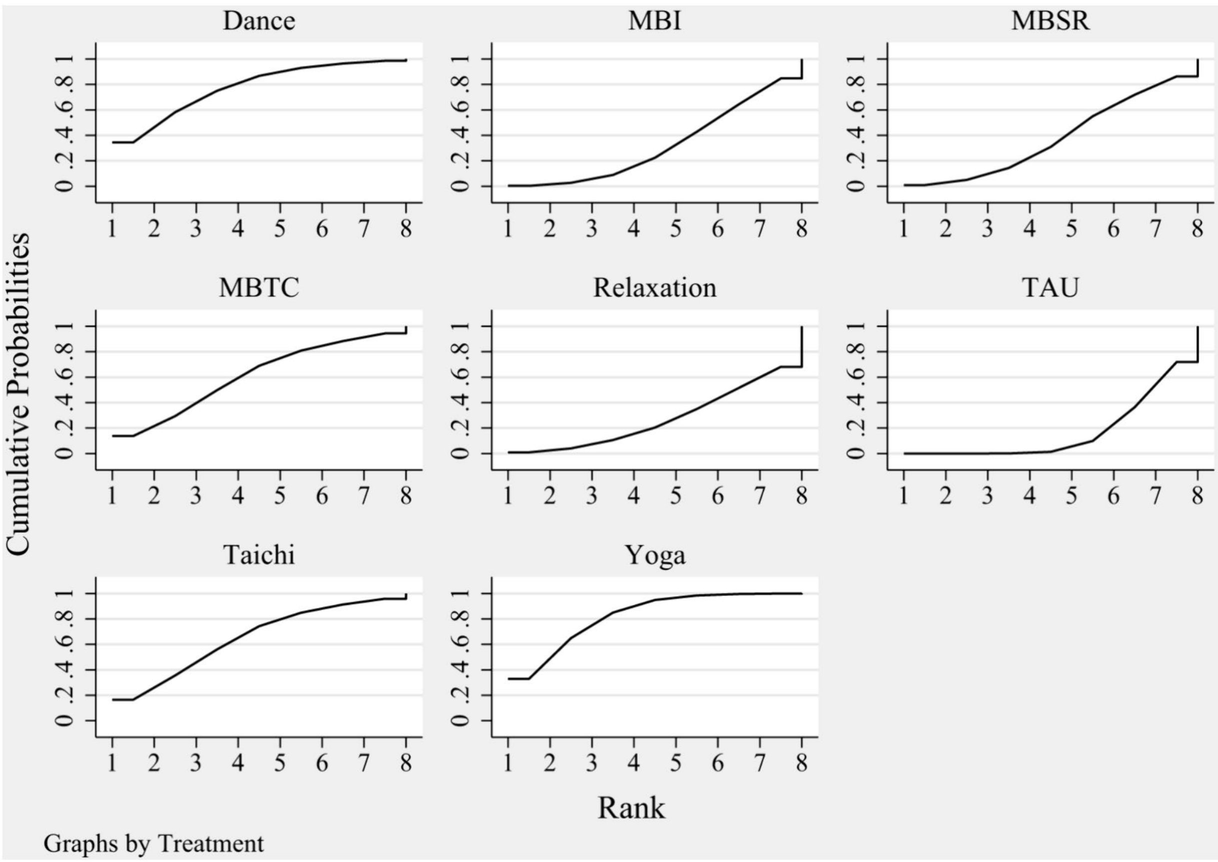

FIGURE 4
SUCRA score plot for depression among adolescents.

TABLE 3 League table for outcomes.

Yoga	−6.46 (−14.56, 1.63)	2.14 (−7.75, 12.03)	2.57 (−7.33, 12.48)	5.21 (−2.88, 13.30)	6.70 (−3.16, 16.57)	6.94 (−2.93, 16.80)	6.94 (1.18, 12.70)
6.46 (−1.63,14.56)	Dance	6.46 (−4.92,17.85)	6.23 (−5.16,17.61)	4.74 (−5.15,14.62)	−1.90 (−13.25,9.46)	2.10 (−9.32,13.52)	1.67 (−9.74,13.07)
−2.14 (−12.03,7.75)	−6.46 (−17.85,4.92)	Tai Chi	0.43 (−10.95,11.81)	3.07 (−6.77,12.91)	4.56 (−6.78,15.91)	4.80 (−6.55,16.14)	4.80 (−3.24,12.84)
−2.57 (−12.48,7.33)	−6.23 (−17.61,5.16)	−0.43 (−11.81,10.95)	MBTC	2.64 (−7.21,12.49)	4.13 (−7.23,15.49)	4.36 (−6.99,15.72)	4.37 (−3.69,12.42)
−5.21 (−13.30,2.88)	−4.74 (−14.62,5.15)	−3.07 (−12.91,6.77)	−2.64 (−12.49,7.21)	MBSR	1.49 (−8.32,11.30)	1.73 (−8.09,11.54)	1.73 (−3.94,7.40)
−6.70 (−16.57,3.16)	1.90 (−9.46,13.25)	−4.56 (−15.91,6.78)	−4.13 (−15.49,7.23)	−1.49 (−11.30,8.32)	MBI	0.24 (−7.77,8.24)	0.24 (−7.77,8.24)
−6.94 (−16.80,2.93)	−2.10 (−13.52,9.32)	−4.80 (−16.14,6.55)	−4.36 (−15.72,6.99)	−1.73 (−11.54,8.09)	−0.24 (−8.24,7.77)	Relaxation	0.00 (−8.01,8.01)
−6.94 (−12.70,-1.18)	−1.67 (−13.07,9.74)	−4.80 (−12.84,3.24)	−4.37 (−12.42,3.69)	−1.73 (−7.40,3.94)	−0.24 (−8.24,7.77)	−0.00 (−8.01,8.01)	TAU

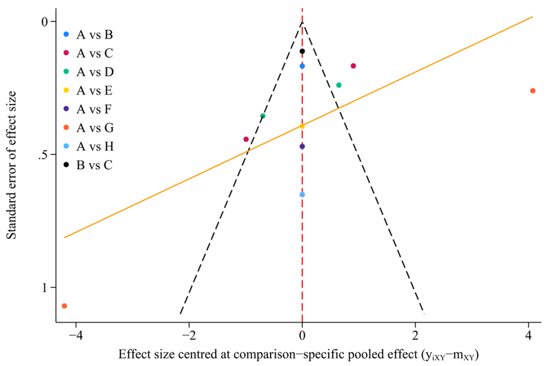

FIGURE 5
Funnel plot on publication bias.

investigated the effects of Tai Chi on the physical and mental health of older adults (91, 92). However, the high SUCRA rankings of Tai Chi in our findings support its applicability to the adolescent population. As mentioned previously, the difficulty in regulating negative emotions caused by various stressors is an important contributor to depression among adolescents (7). However, Tai Chi's emphasis on meditation and the connection between mind and body promotes superb emotional management (93). Besides, the deep breathing practices of Tai Chi enable individuals to cope with stressors in a more composed manner by stabilizing the autonomic nervous system, creating full relaxation of the body and mind, decreasing tension and anxiety (94). Additionally, when practicing Tai Chi, the focus on fluid body postures and combined with meditation can enhance concentration and self-harmony as well as reduce negative thoughts, which is a key factor in alleviating anxiety and depression and enables individuals to better cope with depressive emotions (37, 95).

Overall, this study bridges the research gap involving the adolescent population. The results of our network meta-analysis suggest that MBTs, particularly yoga, possess potential value in the treatment of depression among adolescents. However, it is worth noting that antidepressant medications remain the first-line therapies for the treatment of depression. Therefore, what needs to be clarified is that our findings should not be viewed as evidence that over-emphasizes such supplementary therapies. We would like to call for future research to devote more efforts to combining non-pharmacological treatments such as mind–body therapies with traditional medication and psychotherapeutic interventions, and to explore their interactions and strengths, so as to make up for the shortcomings of the existing treatment system.

5 Limitations and future directions

There are several limitations in this network meta-analysis. Firstly, we focused only on the overall effects of MBTs due to methodological limitations of the study without considering the influence of other exercise factors such as frequency, duration and intensity of exercise. Second, few studies have reported on the treatment of depression among adolescents after a longer follow-up period (no less than 6 months), even though one study showed that the intervention was still effective in reducing depression levels after 6 months, we do not suggest that it provides sufficient evidence of the long-term effectiveness for adolescent depression. Moreover, although the adoption of MBTs for the adolescent population is an emerging and promising practice, some MBTs remain underutilized, such as Qigong, Buduanjin, and Pilates, whose effects on adolescent depression have not been explored in depth. Consequently, the types of mind–body therapies covered in our current study are limited. Lastly, due to the limited number of eligible studies, we included a small sample size. The included studies were of relatively low quality and relied on self-reported outcomes measured by scales. There were a few studies that kept some depressed patients on stable medication for the duration of the trial to ensure stability due to patient health concerns, as well as a small number of studies that did not explicitly report participation exclusions, so there was a possibility that the effects of MBTs could have been slightly interfered with. Therefore, the results should be construed cautiously and might be reconsidered by researchers in the future when more quality studies are available.

In forthcoming research endeavors, it would be beneficial to discuss and investigate the dose effects related to MBTs, including the optimal frequency, duration, and intensity. Moreover, the long-term effects of MBTs on depression among adolescents deserve further investigation. Finally, it is absolutely imperative that more rigorous, standardized, high-quality randomized controlled trials be conducted to validate and enhance the reliability of the current findings. In particular, where feasible, a broader range of mind–body interventions, including but not limited to Qigong, Buduanjin, Pilates, etc., should be used to provide a more scientific and comprehensive exploration of the clinical outcomes of MBTs on adolescent depression.

6 Conclusion

Previous studies may have overlooked the application of MBTs in the adolescent population. This study is the first to explore the effectiveness of different types of MBTs for the treatment of depression among adolescents. Our findings revealed that yoga, dance therapy, and Tai Chi were effective in reducing depression level, with yoga producing the greatest effect. Considering the challenges of implementing effective interventions and the economic burden of treating adolescent depression, our findings are of significant value. However, the certainty of the evidence is limited by the small sample size of patients included and the low quality of the studies, and further investigation is necessary to strengthen the evidence base when more relevant studies become available.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

SUL: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. ZM: Supervision, Validation, Visualization, Writing – review & editing. GF: Data curation, Writing – review & editing. GM: Data curation, Writing – review & editing. XZ: Data curation, Writing – review & editing. SIL: Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1431062/full#supplementary-material

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Depression literacy, mental health literacy, and their relationship with psychological status and quality of life in patients with type 2 diabetes mellitus

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Background: This study was conducted to measure depression literacy (D-Lit) and mental health literacy (MHL) and to investigate their relationship with psychological status and quality of life among Iranian patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study was conducted in 2021 among 400 patients with T2DM in Iran. Samples were selected using proportional stratified sampling. Data collection tools comprised a demographic questionnaire, measures of MHL and D-Lit, the diabetes quality of life (DQOL) scale, and the DASS-21. After confirming the normality of the data using the Kolmogorov-Smirnov test, parametric statistical tests (such as one-way ANOVA, independent samples t-test, and Chi-Square) were used to investigate the relationship between the variables using SPSS v_{22} software. The results of continuous quantitative data are reported in the form of means and standard deviations, and qualitative data are reported in the form of absolute and relative frequencies.

Results: In this study, 10.25% of the participants ($n = 41$) had severe depression, while 36.75% ($n = 147$) experienced severe anxiety. The mean (standard deviation) of MHL was 80.92 (9.16) from 130 points. Of the participants, only 1.7% ($n = 7$) did not answer any questions correctly on the D-lit scale, and only 5.8% ($n = 23$) were able to answer 15 questions or more correctly on the D-lit. MHL had a significant negative correlation with depression ($r = -0.236$), anxiety ($r = -0.243$), and stress ($r = -0.155$) ($P < 0.001$). There was a positive and significant correlation between MHL and D-Lit ($r = 0.186$) ($P < 0.001$). D-Lit had a significant negative correlation with depression ($r = -0.192$), anxiety ($r = -0.238$), and stress ($r = -0.156$) ($P < 0.001$). There was a positive and significant correlation between the ability to recognize disorders ($r = 0.163$), knowledge of self-treatment ($r = 0.154$), and DQOL ($P < 0.001$). Depression ($r = -0.251$), anxiety ($r = -0.257$), and stress ($r = -0.203$) had a significant negative correlation with DQOL ($P < 0.001$).

Conclusion: MHL and D-Lit levels were found to be inadequate in patients with T2DM. These low levels of MHL and D-Lit among patients with T2DM were associated with higher levels of anxiety, depression, and stress, as well as a lower quality of life. Therefore, designing and implementing preventive programs to improve the mental health of patients with T2DM can help prevent mental disorders and ultimately improve their quality of life.

KEYWORDS

mental literacy, stress, psychological status, depression, anxiety

Background

Type 2 diabetes mellitus (T2DM) is a common chronic and serious disease that threatens life, causes complications and disabilities, increases the cost of living, and reduces life expectancy (1, 2). The prevalence of global diabetes in adults is approximately 10.5% (536.6 million) and is estimated to increase in 2045 to 12.2% (783.2 million) (1). In addition, according to the report of the IDF (International Diabetes Federation) in 2019, the areas of the Middle East and North Africa had the highest prevalence of diabetes (12.2%) (3, 4). In Iran, approximately five million adults developed diabetes in 2017, and it is estimated that by 2030, 9.2 million people will have the disease (3, 5).

Diabetes and psychiatric disorders have a bidirectional association that influences one another in multiple ways and in different patterns (6). Studies have shown that anxiety, depression, stress, and distress are key psychological factors affecting diabetes, which may directly affect the development of the disease and the effectiveness of treatment (7–11). Depression is the most common psychiatric disorder in individuals with diabetes, and it worsens glycemic control and increases the risk of developing secondary complications (12, 13). Along with depression, anxiety is also common among patients with diabetes, and many studies have reported it (14–16). During psychological stress, counter-regulatory hormones such as catecholamine, a neurotransmitter, glucocorticoids, growth hormones, and glucagon are activated, which may cause poor glycemic control and functional impairment (17). Psychological stress, as a chief causative factor for psychosomatic disorders, has important effects on the development of diabetes through different pathways via behavioral and physiological mechanisms. Stress is associated with unhealthy lifestyle behaviors, such as inadequate eating in terms of food quality and quantity, low exercise levels, smoking, and alcohol abuse (18).

Health literacy (HL), including mental health literacy (MHL), is an important health predictor (19). MHL refers to the ability to obtain and maintain mental health information, understand mental disorders, treat them, reduce the stigma associated with mental disorders, and increase efficiency (20). A type of MHL is depression literacy (D-Lit), which includes personal and general knowledge of depression and belief in its treatment (21). Studies have shown that most people have inadequate MHL (22, 23). Most people do not know about psychological disorders, and they have a negative attitude toward their treatment or the effectiveness of treatment (24). However, the mental health of individuals in the community requires increased knowledge regarding mental illnesses to facilitate early diagnosis and intervention programs for mental disorders (24).

MHL has a negative correlation with depression and anxiety (25). D-Lit is a variable that can lead to increased professional help-seeking and improved mental health (26). Results: a study showed that MHL played a mediating role between psychological distress and mental help-seeking intentions (27). A study in Portugal reported that with improved MHL, stigma was reduced (28). A previous study mentioned that D-Lit had a negative correlation with depression stigma (29). MHL and D-Lit had a positive correlation with quality of life, and improving MHL could improve quality of life (30).

T2DM has a major impact on QOL in various domains, such as social, physical, and psychological wellbeing (31, 32). In Iran, some studies have been conducted in the field of HL and QOL among patients with T2DM (33, 34). According to the findings of a previous study, the QOL of patients with T2DM was predictable based on HL and self-care behaviors, and improved HL and self-care behaviors increased the QOL of patients with T2DM (35). In another study, MHL for psychiatric disorders associated with T2DM improved compatibility, thereby improving the quality of life and lifestyle of people with T2DM (36). However, no study has been conducted that surveys the D-Lit and MHL with regard to psychological status and quality of life in patients with T2DM. Therefore, the purpose of this study was to determine the status of MHL and depression literacy and their relationship with psychological status and quality of life among Iranian patients with T2DM.

Method

This cross-sectional survey study was conducted in 2021 among 400 patients with T2DM in Gonabad city, Iran.

Abbreviations: MHL, Mental health literacy; HL, health literacy; D-Lit, depression literacy; DQOL, diabetes quality of life; T2DM, Type 2 diabetes mellitus; QOL, quality of life.

Sample size

According to a previous study (37) and based on the following formula (the test power of 80%, the confidence level of 0.95%, the accuracy/d = 0.09, and the standard deviation of QOL= 0.62), the sample size required was calculated as 372. In addition, with a 10% drop rate, the sample size increased to 413 participants.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2\ (s)^2}{(d)^2} \quad n = \frac{(7.84)\ (0.62)^2}{(0.09)^2} = 372$$

Sampling method

We used proportional stratified sampling to select the required sample. In the first stage, we considered Gonabad health centers to be strata. Then, from each center, patients with T2DM who met the inclusion criteria were selected via the simple random sampling method. After selecting the samples, we provided questionnaires to the eligible participants, who completed the questionnaires in a self-reporting manner. In this study, the researcher completed a questionnaire for illiterate people using an interview method. In this study, the inclusion criteria were as follows: patients had at least 1 year of residence in Gonabad city, had T2DM, had more than a year since the diagnosis of their diabetes, and were satisfied to participate in the study. People who did not answer more than 20% of the questions were excluded during the analysis phase.

Data collection instruments

Data were collected using a demographic questionnaire and four additional scales: the MHL scale, the D-Lit scale, the diabetes quality of life (DQOL) scale, and the DASS-21 scale (depression, anxiety, and stress).

1. ***Demographic questionnaire:*** In this section, we describe the demographic details of T2D patients (marital status, sex, age, inhabitant, education level, job status, age at the onset of diabetes, and duration of diabetes).
2. ***DASS-21:*** Lovibond designed the scale to measure depression, stress, and anxiety. This scale has 21 questions and three subscales of anxiety, depression, and stress, with seven questions (38). The questions were measured on a 4-point Likert scale (did not apply to me at all, applied to me to some degree or some of the time, applied to me to a considerable degree or a good part of the time, and applied to me very much or most of the time). A lower score in each subscale indicates better depression, stress, and anxiety. In the Iranian population, the validity and reliability of this scale were assessed by Samani and Joukar, and Cronbach's alpha coefficients of depression, stress, and anxiety were 0.85, 0.87, and 0.75, respectively (39). In addition, the r value of the depression subscale of the DASS was 0.74 compared with the Beck depression inventory, and the anxiety subscale was 0.81 compared with the Beck anxiety inventory (38).
3. ***MHL scale:*** O'Connor created and evaluated the MHL scale in 2015 (40). The validity and reliability of this questionnaire in the Iranian population were assessed by Nejatian et al. in 2021 (41). The questionnaire was confirmed with 29 questions and six subscales: the ability to recognize disorders with eight questions, knowledge of self-treatment with two questions, attitudes that promote recognition or appropriate help-seeking behavior with 10 questions, knowledge of the professional help available with three questions, knowledge of risk factors and causes with two questions, and knowledge of where to seek information with four questions. The questions are measured with 5-point Likert scale and 4-point Likert scale, with the scoring range of this questionnaire being 29–130, with a higher score indicating a better MHL status. In addition, the omega-McDonald's and Cronbach's alpha coefficients for the entire questionnaire were 0.797 and 0.789 (41). The results of the MHL test-retest in the O'Connor study showed good stability ($r = 0.797$) (40).
4. ***D-Lit scale:*** This scale was created and evaluated by Griffiths et al. (42, 43), and Cronbach's alpha calculated as 0.70 (42). The validity and reliability of the D-Lit were assessed by Tehrani et al. in the Iranian population, and the Cronbach's alpha coefficient of the D-Lit was 0.890 (44). This scale has 21 questions and five subscales of knowledge about the effectiveness of available treatment methods (four questions); knowledge of psychological symptoms (five questions); knowledge about taking medications and their side effects (four questions); knowledge about cognitive-behavioral symptoms (six questions); and knowledge of disease severity with two questions. The questions were measured using a 3-point Likert scale ranging from "I don't know," "True," and "False." Each correct answer received a score of 3, the incorrect answer received a score of 1, and I do not know if it received a score of 2. The questionnaire's scoring range is 21–63, with higher scores indicating better D-Lit status (44). The results of D-Lit's test-retest indicated good stability and reliability ($r = 071$) (42).
5. ***DQOL Brief Clinical Inventory scale:*** Burroughs and Partners designed this scale for people with T2DM (45). The questionnaire contains 15 questions and evaluates the QOL of patients with type 2 diabetes. The eight questions were measured using a 5-point Likert scale (completely unhappy to completely satisfied), and seven questions were measured by a 5-point Likert scale (never to always). The questionnaire's scoring range is 15–75, and a higher score indicates an appropriate DQOL status. The validity and reliability of this tool were evaluated by Mirfeizi in Iran, and the Persian version had a CVR >0.99, a CVI >0.75, and acceptable Cronbach's alpha coefficient (a = 0.75) and test-retest reliability (intraclass correlation coefficient = 0.81) (46).

Statistical analysis

SPSS v_{22} software was used for data analysis. Before the data analysis, the normality of the data was verified using the Kolmogorov–Smirnov test, which was found to be normal. Therefore, parametric statistical tests consisting of one-way ANOVA (relationship between a quantitative variable and a qualitative variable with three or more states), an independent *t*-test (relationship between a quantitative variable and a qualitative

TABLE 1 Characteristics of the demographic variables.

Variables		(n = 400)	
		n	%
Sex	Male	225	56.7
	Female	172	43.3
Age group	<30	20	5
	30–50	229	57.25
	>50	151	37.75
Marital status	Married	306	80.1
	Single	76	19.9
Education level	Illiterate	13	3.3
	Elementary	32	8.2
	Middle school	22	5.7
	High school	26	6.7
	Diploma	114	29.3
	Academic degree	182	46.8
Job	Housewife	89	22.94
	Employed	100	25.8
	Retired	56	14.43
	Self-employed	108	27.83
	labor	35	9
Inhabitant	Urban	307	79.9
	Rural	77	20.1
Age at the onset of diabetes	≤ 40	202	55.5
	> 40	162	44.5
Duration of diabetes mellitus	≤ 5	163	45.3
	6-10	101	28
	> 10	96	26.7
Methods of obtaining health information	Physician/health care providers	80	20.15
	Internet	137	34.5
	Newspapers/magazines	17	4.3
	Friends and acquaintances	53	13.3
	Book	15	3.8
	Radio, television, and satellite	80	20.15
	I do not know	15	3.8
Obtain information related to mental illness	Yes	300	78.8
	No	96	24.2
Methods of obtaining information related to mental illness	Physician/healthcare providers	75	24.3
	Psychologist/psychiatrist	19	6.15
	Friends and acquaintances	35	11.3
	Book	9	2.9
	Internet	129	41.75
	Radio, television, and satellite	42	13.6

variable with two states), and a chi-square test (relationship between qualitative variables) were used to investigate the relationship between variables. Pearson's correlation coefficient was used to evaluate the correlation between quantitative variables. Continuous parametric data are presented as mean and standard deviation, while dichotomous data are presented as absolute and relative frequencies. All tests were analyzed at a significance level of 0.05.

Results

In this study, the response rate was 96.85%. Table 1 presents the demographic information about the participants. The mean (standard deviation) age of the patients, the age at the onset of diabetes, and the duration of the disease were 48.18 (11.69), 40.79 (9.60), and 8.38 (6.80), respectively. Most participants were men (n = 225) and married (n = 306). Other information is provided in Table 1.

Education level had a significant relationship with anxiety, and the level of anxiety was higher among those with elementary education, whereas those with academic education had a lower level of anxiety ($P = 0.002$). There was a significant relationship between receiving mental health information and depression levels, with those who received mental health information having lower depression levels ($P = 0.014$). There was a significant relationship between methods of obtaining information about mental health and anxiety, and those who received information from their friends and acquaintances had lower anxiety levels ($P = 0.001$). There was a significant relationship between the method of obtaining information about mental health and stress, and those who received their information from physicians/health care providers had lower stress levels ($P = 0.042$).

Age had a significant relationship with depression ($P = 0.046$), stress ($P = 0.001$), and anxiety ($P < 0.001$), whereas people younger than 30 years had lower levels of depression, stress, and anxiety. Job status had a significant relationship with anxiety, and self-employed individuals had low levels of anxiety ($P = 0.023$). Job status had a significant relationship with stress, and individuals with employed jobs experienced low levels of stress ($P = 0.021$). The age at the onset of diabetes had a significant relationship with stress ($P = 0.009$) and anxiety ($P = 0.026$), and people who had diabetes at the age of 40 years or less experienced low levels of stress and anxiety. The duration of diabetes had a significant relationship with depression, stress, and anxiety, and individuals with a duration of

TABLE 2 Relationship between demographic variables and psychological status (depression, anxiety, and stress).

Variables		DASS-21; *Mean (SD)*					
		Depression	*P*-value	Anxiety	*P*-value	Stress	*P*-value
Sex*	Male	15.29 (3.83)	0.194	13.01 (3.45)	0.704	16.35 (4.01)	0.087
	Female	15.80 (3.90)		13.23 (3.38)		17.04 (3.79)	
Age group**	<30	14.25 (4.20)	0.046	11.40 (3.28)	< 0.001	15.50 (4.47)	0.001
	30–50	15.27 (3.82)		12.68 (3.17)		16.13 (3.62)	
	>50	16.07 (3.92)		14.13 (3.52)		17.62 (4.26)	
Marital status*	Married	15.66 (3.75)	0.574	13.25 (3.28)	3.13	16.76 (3.84)	0.737
	Single	15.38 (4.27)		12.81 (3.67)		16.59 (4.24)	
Education level**	Illiterate	14.46 (3.57)	0.193	13.76 (3.87)	0.002	16.76 (4.63)	0.062
	Elementary	15.81 (3.60)		14.93 (3.52)		18.40 (3.09)	
	Secondary	16.09 (3.51)		14.09 (3)		17.40 (4.14)	
	High school	14.23 (3.78)		12.69 (3.42)		15.92 (3.89)	
	Diploma	16 (3.94)		13.24 (3.44)		16.71 (3.94)	
	Academic	15.20 (3.87)		12.50 (3.13)		16.18 (3.97)	
Job**	Housewife	15.95 (4.10)	0.253	13.19 (3.38)	0.023	17.01 (3.74)	0.021
	Employed	15.78 (4.21)		12.94 (3.63)		15.92 (4.06)	
	Retired	15.91 (3.65)		14.53 (3.12)		17.87 (4.35)	
	Self-employed	14.87 (3.76)		12.81 (3.26)		16.24 (3.83)	
	labor	15.17 (3.16)		12.85 (2.65)		17 (3.26)	
Inhabitant *	Rural	15.85 (3.67)	0.491	13.09 (2.96)	0.876	16.75 (3.55)	0.842
	Urban	15.51 (3.99)		13.15 (3.55)		16.75 (4.11)	
Age at the onset of diabetes *	≤40	15.58 (3.93)	0.960	12.95 (3.17)	0.026	13.74 (3.61)	0.009
	>40	15.60 (3.98)		13.74 (3.61)		16.21 (3.73)	
Duration of diabetes **	≤ 5	15.15 (4.18)	0.036	12.79 (3.38)	< 0.001	16.28 (3.84)	0.004
	6–10	15.56 (3.89)		12.89 (3.22)		16.32 (4.06)	
	>10	16.46 (3.50)		14.69 (3.23)		17.86 (3.82)	
Obtain information related to mental illness*	Yes	15.24 (3.83)	0.014	13.01 (3.43)	0.160	16.60 (4.04)	0.830
	No	16.35 (3.89)		13.57 (3.32)		16.76 (3.79)	
Methods of obtaining health information**	Physician/healthcare providers	15.38 (3.45)	0.131	13.63 (3.27)	< 0.001	16.43 (3.97)	0.025
	Internet	14.97 (3.87)		12.15 (3.31)		16 (3.96)	
	Newspapers/magazines	17.41 (2.37)		15 (2.87)		18.29 (2.86)	
	Friends and acquaintances	15.92 (4.14)		13.26 (3.17)		16.69 (3.90)	
	Book	15.80 (4.12)		12.93 (3.80)		18.40 (4.48)	
	Radio, television, and satellite	16.10 (4.07)		14.12 (3.30)		17.56 (3.67)	
	I do not know	14.80 (4.63)		12.33 (4.08)		16 (5.05)	
Methods of obtaining information related to mental illness**	Physician/healthcare providers	14.96 (3.16)	0.195	13.78 (3.37)	0.001	16.48 (4.03)	0.042
	Psychologist/psychiatrist	16.10 (3.01)		13.84 (2.96)		17.05 (3.20)	

(Continued)

TABLE 2 (Continued)

Variables		DASS-21; *Mean (SD)*					
		Depression	*P*-value	Anxiety	*P*-value	Stress	*P*-value
	Friends and acquaintances	15.42 (4.62)		12.11 (3.19)		16.57 (4.90)	
	Book	16.66 (4.41)		13.11 (3.62)		18 (3.27)	
	Internet	15.35 (4.04)		12.55 (3.51)		16.58 (3.96)	
	Radio, television, and satellite	16.76 (3.86)		14.76 (3.08)		18.73 (3.26)	

*Independent sample t-test, **one-way ANOVA.

diabetes of 5 years had low levels of depression ($P = 0.036$), stress ($P = 0.004$), and anxiety ($P < 0.001$) (Table 2).

The mean (standard deviation) of MHL was 80.92 (9.16). Marital status had a significant relationship with MHL, and single individuals had a higher MHL ($P = 0.009$). The level of education had a significant relationship with knowledge of where to seek information, and those with higher education levels had a higher HL on this subscale ($P < 0.001$). The economic situation had a significant relationship with MHL, and patients with better economic conditions had higher MHL ($P < 0.001$). The economic situation had a significant relationship with knowledge of where to seek information, and those with better economic conditions had higher HL scores in this subscale ($P < 0.001$) (Table 3).

There was a significant relationship between receiving mental health information and the level of MHL, with those who received mental health information having higher levels of MHL ($P = 0.001$). There was a significant relationship between receiving mental health information and the ability to recognize disorders ($P = 0.001$), knowledge of self-treatment ($P = 0.001$), and knowledge of the professional help available ($P = 0.015$), and those who received mental health information in these subscales had higher levels of MHL. Similarly, patients who received health information online had a higher MHL ($P < 0.001$). Patients who received mental health information from a psychologist/psychiatrist had higher levels of MHL ($P = 0.014$) (Table 3).

Age was significantly associated with MHL, and patients younger than 30 years had higher levels of MHL ($P < 0.001$). Job status had a significant relationship with MHL, and self-employed individuals had higher levels of MHL ($P = 0.010$). Age at the onset of diabetes had a significant relationship with MHL, and patients who had diabetes at the age of 40 years or less had higher levels of MHL ($P = 0.040$). The duration of diabetes was significantly associated with MHL, and patients with a duration of diabetes of $\leq$5 years had higher levels of MHL ($P = 0.026$) (Table 3).

Age had a significant relationship with D-Lit, and people younger than 30 years had a higher D-Lit ($P = 0.002$). Job status had a significant relationship with D-Lit, and self-employed individuals had higher levels of D-Lit ($P = 0.029$). Age at the onset of diabetes had a significant relationship with D-Lit, and individuals who had a disease at the age of $\leq$40 years had higher levels of D-Lit ($P = 0.044$). There was a significant relationship between receiving mental health information and D-Lit levels, with those who received mental health information having higher levels of D-Lit ($P = 0.001$). Patients who received health information from the book had higher levels of D-Lit ($P < 0.001$). Patients who received mental health information from the book had higher D-Lit scores ($P = 0.002$) (Table 4).

In response to the D-Lit questions, only 1.7% ($n = 7$) of the participants failed to answer any questions correctly, and 5.8% ($n = 23$) were able to answer 15 questions or more correctly (Table 4). The participants' responses to the questions and subscales of the D-Lit are listed in Table 5. The mean (SD) D-Lit of the participants was 44.69 (4.28). The mean (SD) of the subscales of the D-Lit are presented in Table 5.

Regarding the subscales of the D-Lit questionnaire, the responses revealed varied levels of knowledge among the participants. Specifically, only 21.5% ($n = 86$) could correctly answer all items related to knowledge of psychological symptoms. Only 2% ($n = 8$) correctly answered all questions about the effectiveness of available treatment methods. A slightly higher percentage, 4.5% ($n = 18$), correctly answered all questions pertaining to cognitive-behavioral symptoms. The participants' knowledge about taking medications and their side effects was accurately known by 13% ($n = 52$). Furthermore, 19.3% ($n = 77$) were able to correctly answer all questions regarding knowledge about disease severity.

There was a significant relationship between the sources of mental health information and the DQOL. Specifically, those who received information from their friends and acquaintances reported a higher DQOL ($P = 0.042$) (Table 6). Additionally, the results of Tukey's *post hoc* tests exploring the relationships between demographic factors and variables such as depression, anxiety, stress, MHL, D-Lit, and DQOL are presented in Supplementary Files S1–S6.

As can be observed from Table 7, only 10.3% ($n = 41$) had severe depression, 36.8% ($n = 147$) had severe anxiety and extremely severe anxiety, and 31% ($n = 124$) had moderate stress. Depression ($P = 0.010$), anxiety ($P < 0.001$), and stress ($P = 0.008$) were significantly associated with D-Lit, whereas patients with severe depression, extremely severe anxiety, and moderate stress had lower levels of D-Lit. Depression ($P < 0.001$), anxiety ($P < 0.001$), and stress ($P = 0.001$) were significantly associated with MHL, and patients with severe depression, extremely severe anxiety, and moderate stress had lower levels of MHL. In addition, depression ($P < 0.001$), anxiety ($P < 0.001$), and stress ($P = 0.002$) were significantly associated with DQOL, and patients with severe depression, extremely severe anxiety, and moderate stress had lower levels of DQOL (Table 7).

TABLE 3 Relationship between demographic variables and mental health literacy.

Variables		Mental health literacy (MHL) Mean (SD)													
		Ability to recognize disorders	*P*-value	Knowledge of risk factors and causes	*P*-value	Knowledge of self-treatment	*P*-value	Knowledge of the professional help available	*P*-value	Knowledge of where to seek information	*P*-value	Attitudes that promote recognition or appropriate help-seeking behavior	*P*-value	Total MHL	*P*-value
Sex*	Male	22.99 (4.04)	0.727	5.55 (1.53)	0.167	5.68 (1.21)	0.943	9.28 (1.47)	0.143	12.71 (3.60)	0.057	24.61 (5.88)	0.868	80.85 (6.14)	0.820
	Female	22.85 (3.77)		5.33 (1.69)		5.69 (1.23)		9.06 (1.43)		13.40 (3.46)		24.71 (6.14)		81.06 (8.75)	
Age group**	<30	24.50 (3.20)	0.002	5.55 (1.73)	0.878	6.15 (1.34)	0.012	9.65 (1.03)	0.354	14.35 (4.22)	< 0.001	23.60 (6.65)	0.541	83.80 (10.16)	< 0.001
	30-50	23.31 (3.56)		5.41 (1.66)		5.78 (1.28)		9.17 (1.45)		14.02 (3.10)		24.57 (5.79)		82.29 (8.84)	
	>50	22.09 (4.37)		5.48 (1.53)		5.47 (1.09)		9.16 (1.50)		11.23 (3.41)		25.03 (6.25)		78.48 (9.04)	
Marital status*	Married	22.63 (3.90)	0.040	5.44 (1.58)	0.697	5.59 (1.16)	0.053	9.10 (1.45)	0.278	12.76 (3.49)	0.077	24.39 (5.71)	0.490	79.93 (8.74)	0.009
	Single	23.64 (3.68)		5.52 (1.73)		5.89 (1.33)		9.30 (1.41)		13.56 (3.66)		24.95 (6.51)		82.90 (9)	
Education level**	Illiterate	22 (5.79)	0.176	5.53 (2.25)	0.871	5.92 (1.32)	0.032	9.38 (2.53)	0.106	10.30 (2.46)	< 0.001	25.84 (6.25)	0.761	79 (7.04)	0.429
	Elementary	23.77 (5.31)		5.25 (1.74)		5.83 (1.13)		9.69 (1.42)		9.46 (3.34)		24.29 (6.86)		78.32 (11.88)	
	Secondary	22.04 (4.02)		5.50 (2.04)		5.22 (1.06)		9.36 (1.59)		12.45 (3.69)		26.45 (6.78)		81.04 (9.26)	
	High school	24.34 (3.88)		5.50 (1.67)		6.07 (1.46)		9.23 (1.14)		13.11 (4.02)		24.33 (5.95)		82.60 (10.47)	
	Diploma	22.60 (3.42)		5.61 (1.50)		5.47 (1.07)		8.91 (1.40)		13.98 (3.03)		24.56 (5.70)		81.16 (8.76)	
	Academic	23.05 (3.77)		5.40 (1.56)		5.82 (1.27)		9.27 (1.39)		13.29 (3.46)		24.73 (5.95)		81.60 (8.70)	
Job**	Housewife	22.94 (3.73)	0.738	5.50 (3.88)	0.887	5.69 (1.19)	0.518	8.94 (1.44)	0.252	13.50 (3.35)	< 0.001	23.77 (6.05)	0.214	80.36 (8.87)	0.010
	Employed	22.80 (3.50)		5.52 (1.65)		5.72 (1.27)		9.08 (1.53)		13.93 (3.22)		24.36 (6.42)		81.43 (9.33)	
	Retired	22.79 (4.85)		5.49 (1.79)		5.50 (1.17)		9.42 (1.52)		10.46 (3.49)		24.19 (6.09)		77.88 (8.81)	
	Self-employed	23.15 (3.76)		5.31 (1.59)		5.76 (1.28)		9.31 (1.41)		13.44 (3.40)		25.65 (5.34)		82.65 (8.93)	
	labor	22.11 (4.07)		5.40 (1.35)		5.42 (1.03)		9.25 (1.37)		11.28 (3.18)		25.17 (5.88)		78.65 (8.813)	
Inhabitant *	Rural	22.93 (3.74)	0.872	5.46 (1.61)	0.952	5.68 (1.07)	0.848	9.06 (1.47)	0.548	12.50 (3.43)	0.224	0.509	0.515	80.57 (7.55)	0.949
	Urban	22.84 (3.84)		5.47 (1.59)		5.65 (1.23)		9.17 (1.43)		13.06 (3.59)		24.42 (5.94)		80.64 (9.37)	

(Continued)

TABLE 3 (Continued)

Variables		Mental health literacy (MHL) *Mean (SD)*													
		Ability to recognize disorders	*P*-value	Knowledge of risk factors and causes	*P*-value	Knowledge of self-treatment	*P*-value	Knowledge of the professional help available	*P*-value	Knowledge of where to seek information	*P*-value	Attitudes that promote recognition or appropriate help-seeking behavior	*P*-value	Total MHL	*P*-value
Age at the onset of diabetes *	≤40	23.11 (3.61)	0.086	5.44 (1.58)	0.593	5.64 (1.26)	0.607	9.09 (1.45)	0.569	13.71 (3.17)	< 0.001	24.43 (5.86)	0.372	81.45 (9.16)	0.040
	>40	22.41 (4.14)		5.53 (1.59)		5.57 (1.14)		9.18 (1.47)		11.77 (3.69)		24.99 (6.09)		79.48 (9.01)	
Duration of diabetes **	≤ 5	23.14 (3.68)	0.235	5.37 (1.48)	0.558	5.72 (1.23)	0.360	9.10 (1.40)	0.743	13.67 (3.37)	< 0.001	24.86 (5.42)	0.864	81.88 (8.87)	0.026
	6–10	22.32 (3.640		5.57 (1.70)		5.51 (1.25)		9.08 (1.43)		13.15 (3.05)		24.51 (6.04)		80.16 (8.87)	
	>10	22.68 (4.35)		5.53 (1.62)		5.56 (1.13)		9.23 (1.61)		11.21 (3.81)		24.53 (6.65)		78.77 (9.61)	
Economic status**	Good	23.13 (3.50)	0.526	5.31 (1.82)	0.372	5.83 (1.28)	0.278	9.20 (1.61)	0.609	14.26 (3.68)	< 0.001	26.40 (5.95)	0.007	84.15 (9.42)	< 0.001
	Medium	22.6 (4.07)		5.53 (1.49)		5.59 (1.20)		9.10 (1.32)		12.88 (3.35)		24.11 (5.70)		79.87 (8.89)	
	Weak	22.49 (4.09)		5.28 (1.47)		5.69 (1.06)		9.30 (1.54)		11.24 (3.04)		24.22 (5.92)		78.25 (8.19)	
Obtain information related to mental illness**	Yes	23.36 (3.84)	0.001	5.43 (1.71)	0.713	5.79 (1.31)	0.001	9.29 (1.47)	0.015	13.13 (3.60)	0.177	24.81 (6.18)	0.419	81.83 (9.27)	0.001
	No	21.66 (3.89)		5.49 (1.28)		5.38 (0.87)		8.88 (1.37)		12.57 (3.42)		24.23 (5.51)		78.25 (8.36)	
Methods of obtaining health information**	Physician/ health care providers	23.91 (3.65)	< 0.001	5.56 (1.83)	0.399	5.54 (1.19)	< 0.001	9.18 (1.78)	0.949	13.07 (3.45)	< 0.001	25.30 (6.60)	0.001	82.58 (8.62)	< 0.001
	Internet	23.68 (3.64)		5.59 (1.67)		6.09 (1.28)		9.27 (13.1)		14.01 (3.35)		24.47 (6.26)		83.14 (9.63)	
	Newspapers/ magazines	20.05 (2.68)		5.76 (1.52)		5.64 (1.05)		9.23 (1.82)		11.05 (2.65)		27.45 (5.68)		79.22 (6.80)	
	Friends and acquaintances	23.18 (3.50)		5.45 (1.59)		5.32 (1.05)		9 (1.41)		12.69 (3.52)		24.09 (5.04)		79.74 (7.36)	

(Continued)

TABLE 3 (Continued)

Variables		Mental health literacy (MHL) Mean (SD)													
		Ability to recognize disorders	*P*-value	Knowledge of risk factors and causes	*P*-value	Knowledge of self-treatment	*P*-value	Knowledge of the professional help available	*P*-value	Knowledge of where to seek information	*P*-value	Attitudes that promote recognition or appropriate help-seeking behavior	*P*-value	Total MHL	*P*-value
	Book	19.66 (3.67)		5 (1.51)		5.73 (0.59)		9.13 (1.50)		8.86 (2.77)		29.98 (4.42)		78.38 (4.93)	
	Radio, television, and satellite	22.33 (4.45)		5.17 (1.43)		5.44 (1.27)		9.26 (1.29)		13.13 (3.48)		23.26 (5.05)		78.62 (9.86)	
	I do not know	20.12 (2.84)		5.13 (0.91)		5.40 (0.98)		9.06 (1.43)		10.13 (2.97)		24.13 (6.83)		73.99 (8.60)	
Methods of obtaining information related to mental illness**	Physician/ health care providers	24.34 (4.17)	0.009	5.97 (1.78)	0.005	5.94 (1.44)	0.069	9.50 (1.71)	0.121	12.67 (3.96)	0.334	25.22 (6.41)	0.486	83.67 (9.17)	0.014
	Psychologist/ Psychiatrist	24.05 (3.30)		5.57 (1.67)		5.42 (0.83)		8.78 (1.47)		13.57 (3.54)		26.48 (5.46)		83.90 (10.38)	
	Friends and acquaintances	22.79 (3.07)		5.62 (1.86)		5.54 (1.19)		8.97 (1.40)		12.60 (3.27)		24.42 (6.09)		79.96 (6.80)	
	Book	21.93 (2.35)		4.44 (1.81)		5.33 (1)		10 (0.86)		13 (3.93)		27.97 (6.37)		82.69 (7.63)	
	Internet	23.09 (3.67)		5.15 (1.59)		5.94 (1.32)		9.24 (1.38)		13.43 (3.47)		24.79 (6.09)		81.66 (9.16)	
	Radio, television, and satellite	21.71 (4.49)		5.09 (1.33)		5.40 (1.25)		9.02 (1.38)		12.14 (3.58)		24.21 (6.06)		77.59 (9.84)	

*Independent sample t-test, ** One-way ANOVA.

TABLE 4 Frequency distribution of demographic factors and depression literacy (D-lit) status.

Variables		D-lit status; *n* (%)					D-Lit	
		Incorrect response/ don't know	The correct response to 1–7 questions	The correct response to 8–14 questions	The correct response to 15 questions or more	P-value[c]	Mean (SD)	*P*-value
Sex	Male	3 (1.35)	64 (28.4)	146 (64.9)	12 (5.35)	0.599	44.63 (4.26)	0.837[a]
	Female	4 (2.3)	56 (32.6)	101 (58.7)	11 (6.4)		44.72 (4.32)	
Age group	<30	0	5 (25)	14 (70)	1 (5)	0.235	46.40 (4.84)	0.002[b]
	30-50	2 (0.9)	62 (27.1)	149 (65)	16 (7)		45.13 (4.08)	
	>50	5 (3.3)	53 (35.1)	87 (57.6)	6 (4)		43.80 (4.36)	
Job	Housewife	2 (2.25)	36 (40.45)	47 (52.8)	4 (4.5)	0.289	44.17 (4.23)	0.029[b]
	Employed	2 (2)	26 (26)	65 (65)	7 (7)		45.16 (4.22)	
	Retired	0	20 (35.7)	33 (58.9)	3 (5.4)		43.55 (4.95)	
	Self-employed	3 (2.8)	24 (22.2)	73 (67.6)	8 (7.4)		45.48 (4.19)	
	labor	0	11 (31.4)	24 (68.6)	0		44.05 (3.62)	
Marital status	Married	5 (1.6)	97 (31.7)	188 (61.45)	16 (5.25)	0.261	44.30 (4.30)	0.661[a]
	Single	2 (2.6)	16 (21.1)	55 (72.4)	3 (3.9)		44.89 (3.90)	
Education level	Illiteracy	0	4 (30.8)	8 (61.5)	1 (7.7)	0.108	43 (4.12)	0.001[b]
	Elementary	1 (3.1)	16 (50)	14 (43.8)	1 (3.1)		42.34 (4.17)	
	middle school	0	8 (36.4)	14 (63.6)	0		44 (5.15)	
	High school	1 (3.85)	9 (34.6)	15 (57.7)	1 (3.85)		44.92 (3.77)	
	Diploma	1 (0.8)	41 (36)	66 (57.9)	6 (5.3)		44.34 (4.25)	
	Academic	4 (2.2)	36 (19.8)	128 (70.3)	14 (7.7)		45.56 (4.07)	
Age at the onset of diabetes	≤40	3 (1.5)	60 (29.7)	124 (61.4)	15 (7.4)	0.437	44.95 (4.29)	0.044 [a]
	>40	4 (2.5)	51 (31.5)	101 (62.3)	6 (3.7)		44.05 (4.08)	
Duration of diabetes mellitus	≤ 5	4 (2.4)	41 (25.2)	110 (67.5)	8 (4.9)	0.301	44.95 (3.94)	0.064 [b]
	6-10	1 (1)	32 (31.7)	60 (59.4)	8 (7.9)		44.57 (4.13)	
	>10	2 (2.1)	37 (38.5)	52 (54.2)	5 (5.2)		43.68 (4.66)	
Economic status	Good	2 (2.2)	23 (25.6)	57 (63.3)	8 (8.9)	0.840	45.22 (4.09)	0.080[b]
	Medium	4 (2)	63 (30.7)	128 (62.4)	10 (4.9)		44.60 (4.16)	
	Weak	1 (1.5)	22 (33.3)	39 (59.1)	4 (6.1)		44.34 (4.79)	
Obtain information related to mental illness	Yes	5 (1.6)	86 (28.7)	188 (62.7)	21 (7)	0.304	45.10 (4.35)	0.001[a]
	No	2 (2.1)	32 (33.3)	60 (62.5)	2 (2.1)		43.50 (3.83)	
Inhabitant	Rural	1 (1.3)	23 (29.9)	51 (66.2)	2 (2.6)	0.612	43.94 (3.86)	0.072[a]
	Urban	6 (1.9)	93 (30.3)	189 (61.6)	19 (6.2)		44.92 (4.31)	
Methods of obtaining health information	Physician/ health care providers	1 (1.2)	32 (40)	44 (55)	3 (3.8)	0.002	43.90 (4.26)	< 0.001[b]
	Internet	1 (0.7)	29 (21.2)	90 (65.7)	17 (12.4)		45.67 (4.58)	
	Newspapers/ magazines	0	4 (23.5)	13 (76.5)	0		44.47 (3.02)	
	Friends and acquaintances	2 (3.8)	20 (37.7)	31 (58.5)	0		43.45 (2.61)	

(Continued)

TABLE 4 (Continued)

Variables		D-lit status; *n* (%)					D-Lit	
		Incorrect response/ don't know	The correct response to 1–7 questions	The correct response to 8–14 questions	The correct response to 15 questions or more	P-value[c]	Mean (SD)	*P*-value
	Book	0	0	15 (100)	0		46.46 (3.71)	
	Radio, television, and satellite	2 (2.5)	28 (35)	47 (58.75)	3 (3.75)		44.96 (4.52)	
	I do not know	1 (6.7)	6 (40)	8 (53.3)	0		41.53 (3.92)	
Methods of obtaining information related to mental illness	Physician/ health care providers	0	25 (33.3)	45 (60)	5 (6.7)	0.002	44.09 (4.41)	0.002[b]
	Psychologist/ Psychiatrist	1 (5.25)	5 (26.3)	12 (63.2)	1 (5.25)		44.31 (4.11)	
	Friends and acquaintances	0	11 (31.4)	24 (68.6)	0		44.51 (3.28)	
	Book	0	1 (11.1)	8 (88.9)	0		46.66 (4.06)	
	Internet	4. (3.1)	22 (17)	89 (69)	14 (10.9)		46.13 (4.38)	
	Radio, television, and satellite	0	23 (54.7)	18 (42.9)	1 (2.4)		43.71 (3.90)	
All participants		7 (1.7)	120 (30)	250 (62.5)	23 (5.8)		-	

[a]Independent sample t-test, [b]one-way ANOVA, [c] Chi-square.

The results in Table 8 show the correlation between variables. According to the results, there was a negative and significant correlation between MHL and depression ($r = -0.236$), anxiety ($r = -0.243$), and stress ($r = -0.155$) ($P < 0.001$). There was a positive and significant correlation between MHL and D-Lit ($r = 0.186$) ($P < 0.001$). There was a negative and significant correlation between D-Lit and depression ($r = -0.192$), anxiety ($r = -0.238$), and stress ($r = -0.156$) ($P < 0.001$). There was a positive and significant correlation between the ability to recognize disorders ($r = 0.163$) and knowledge of self-treatment ($r = 0.154$) with DQOL ($P<0.001$). There was a negative and significant correlation between the state of depression ($r = -0.251$), anxiety ($r = -0.257$), stress ($r = -0.203$), and DQOL ($P < 0.001$) (Table 8).

Discussion

This research showed that MHL was not high and that only 5.8% of patients had high D-Lit scores and were able to answer 15 or more questions correctly. However, in this study, only 7.8% of the patients were free of depression, 5.5% had no anxiety, and 27% were not stressed. In a previous study, the results showed that these patients had insufficient health literacy regarding their illness, and the provision of simple and understandable educational resources for the diabetic population was effective in increasing their health literacy (47). HL assessment is an important prerequisite for reinforcing the proper management of DT2, following treatment, and adopting more flexible health policies (48).

In this study, there was a significant and negative correlation between D-Lit and MHL and the levels of depression, anxiety, and stress. Additionally, there was a significant and negative correlation between levels of depression, anxiety, stress, and the QOL. These results indicate that increasing MHL and D-Lit can decrease the prevalence of anxiety, depression, and stress while improving QOL. These results can be useful for designing educational programs aimed at preventing mental illness and improving T2DM patients' quality of life. Other research indicates that people with low HL are more likely to exhibit depressive symptoms or be considered depressed (49, 50). A previous study found that depressive symptoms affect self-care management and quality of care, negatively affecting health outcomes in people with diabetes (51–53). A previous study also showed that COVID-19 profoundly affects anxiety levels, impacting patients' psychological wellbeing (54). A study from China observed that enhancing D-Lit during the pandemic reduced depression, (55) while another study noted that MHL was negatively correlated with stress and positively correlated with psychological health during the COVID-19 pandemic (56). Therefore, adequate MHL can not only support individuals in critical situations but also play a crucial role in preventing mental disorders.

In this study, there was a positive and significant correlation between knowledge of psychological symptoms, the ability to recognize disorders, and QOL. It appears that people's ability to recognize mental disorder symptoms in the early stages helps them take prompt actions, while awareness of available treatment options facilitates their use of appropriate interventions. As a

TABLE 5 Participants' responses to the D-lit questions.

Subscale	Items	*n* (%)			Mean (SD)	
		Correct response	Incorrect response	Don't know		
F1: Knowledge of the psychological symptoms	1. People with depression may feel guilty when they are innocent. (True)	264 (66)	67 (16.8)	69 (17.2)	11.46 (2.75)	44.69 (4.28)
	2. Loss of confidence and low self-esteem may be signs of depression. (True)	236 (259.15)	101 (25.31)	62 (15.54)		
	3. Too little or too much sleep can be a symptom of depression. (True)	236 (59.1)	83 (20.8)	80 (20.1)		
	4. Eating too much or losing interest in food may be a symptom of depression. (True)	175 (43.8)	125 (31.2)	100 (25)		
	5. People may move more slowly or become agitated due to their depression. (True)	172 (43)	119 (29.75)	109 (27.25)		
F2: Knowledge of the effectiveness of available treatment methods	6. Clinical psychologists can prescribe antidepressant medications. (False)	159 (39.75)	128 (32)	113 (28.25)	8.05 (1.57)	
	7. Many treatments for depression are more effective than antidepressant medications. (False)	154 (38.5)	134 (33.5)	112 (28)		
	8. The effects of counseling are similar to those of cognitive-behavioral therapies for depression. (False)	124 (31.1)	158 (39.6)	117 (29.3)		
	9. The effect of cognitive-behavioral therapies is the same as that of antidepressant medications for mild to moderate depression. (True)	143 (36)	129 (32.5)	125 (31.5)		
F3: Knowledge of cognitive-behavioral symptoms	10. People with depression often speak sporadically and irrelevantly. (False)	100 (25.1)	177 (44.5)	121 (30.4)	11.96 (2.75)	
	11. Reckless and foolhardy behavior is a common symptom of depression. (False)	121 (30.4)	148 (37.2)	129 (32.4)		
	12. Not walking on cracked and broken sidewalks may be a symptom of depression. (False)	126 (31.7)	141 (35.4)	131 (32.9)		
	13. People with depression often hear sounds that are not normally heard. (False)	135 (34.1)	139 (35.1)	122 (30.8)		
	14. Depression does not affect your memory or concentration. (False)	214 (53.6)	96 (24.1)	89 (22.3)		
	15. Having several distinct personalities can be a symptom of depression. (False)	150 (37.5)	136 (34)	114 (28.5)		
F4: Knowledge of taking medications and their side effects	16. Of all the alternative and lifestyle therapies for depression, vitamins are the most beneficial. (False).	158 (39.5)	121 (30.25)	121 (30.25)	8.79 (2.01)	
	17. People with depression should stop taking antidepressant medications as soon as they feel better. (False)	212 (53.1)	82 (20.6)	105 (26.3)		
	18. Antidepressant medications are addictive. (False)	185 (46.5)	118 (29.6)	95 (23.9)		
	19. Antidepressant medications are usually rapid-acting. (False)	183 (45.9)	93 (23.3)	123 (30.8)		
F5: Knowledge of disease severity	20. Most people with depression need to be hospitalized. (False)	202 (50.5)	75 (18.75)	123 (30.75)	4.42 (0.97)	
	21. Many celebrities have suffered from depression. (True)	146 (36.5)	105 (26.25)	149 (37.25)		

result, these proactive measures can reduce the risk of various complications, thereby enhancing QOL. The findings of several studies have reported a significant relationship between the ability to diagnose mental disorders and the seeking of mental health services (57–59). People who are adept at diagnosing various types of mental disorders are more likely to seek mental health services,

TABLE 6 Relationship between demographic variables and diabetes quality of life (DQOL).

Variables		DQOL	
		Mean (SD)	*P*-value
Sex*	Male	55.27 (7.44)	0.152
	Female	54.20 (7.11)	
Age group**	<30	55.77 (11.66)	0.821
	30–50	54.85 (7.03)	
	>50	54.68 (7.12)	
Marital status*	Married	54.65 (7.19)	0.466
	Single	55.35 (7.59)	
Education level**	Illiterate	57 (7.10)	0.111
	Elementary	54.81 (6.65)	
	Secondary	54.75 (7.27)	
	High school	55.26 (7.32)	
	Diploma	53.39 (7.65)	
	Academic	55.81 (7.03)	
Job**	Housewife	53.91 (7.10)	0.143
	Employed	54.80 (7.83)	
	Retired	56.51 (6.51)	
	Self-employed	54.41 (7.41)	
	labor	56.69 (7.25)	
Inhabitant *	Rural	55.36 (6.59)	0.532
	Urban	54.77 (7.59)	
Age the onset of diabetes *	≤40	54.61 (7.48)	0.928
	>40	54.68 (6.70)	
Duration of diabetes **	≤ 5	55.27 (6.70)	0.343
	6–10	54.01 (7.73)	
	>10	54.44 (7.10)	
Obtain information related to mental illness*	Yes	54.84 (7.38)	0.946
	No	54.79 (7.28)	
Methods of obtaining health information**	Physician/health care providers	56.33 (6.91)	0.050
	Internet	55.51 (7.02)	
	Newspapers/ magazines	54.47 (7.07)	
	Friends and acquaintances	54.22 (6.89)	
	Book	55.36 (7.53)	
	Radio, television, and satellite	52.59 (7.93)	
	I do not know	55.27 (8.88)	
Methods of obtaining information related to mental illness**	Physician/Health care providers	55.40 (7.06)	0.042
	Psychologist/ Psychiatrist	53.75 (6.59)	
	Friends and acquaintances	56.76 (6.84)	
	Book	55.83 (6.75)	
	Internet	54.52 (6.89)	
	Radio, television, and satellite	51.68 (8.61)	

*Independent sample t-test, **one-way ANOVA.

allowing for the early diagnosis and appropriate treatment of their conditions (57–59).

This research revealed a statistically significant relationship between age and lower levels of stress and anxiety among people aged 30 years. One study found that early-onset T2DM is associated with mood disorders, anxiety, and stress (60). The findings of another study indicated that younger people exhibit higher levels of depression and anxiety than older people, which is likely due to their low levels of experience in managing the stresses related to treatment and diabetes challenges (61). Additionally, the effect of the disease on physical and mental performance and QOL contribute to higher rates of depression and anxiety among younger patients (61). The findings of our study contrast those reported in the Palizgir study, which indicated different age-related impacts on psychological wellbeing (61). More research is needed to determine whether there is a relationship between age, stress, and anxiety in T2DM. Other factors, such as the stress associated with managing chronic illnesses, may also contribute to stress and anxiety in patients with T2DM.

There was a statistically significant relationship between education level and anxiety, with patients with elementary education exhibiting higher levels of anxiety compared to those with higher academic education, who displayed lower levels of anxiety. The level of education has another protective effect against anxiety, as people with higher education levels tend to use health and treatment services and have no problem finding places that provide such services (62). In addition, higher education levels are associated with a decreased likelihood of engaging in unhealthy behaviors (63, 64). The findings of a previous study showed that a high education level is a protective factor against anxiety and depression (63). Another study found that patients with T2DM who had low education levels were more likely to experience anxiety (65).

There was also a significant relationship between education levels and knowledge of where to find information, with those with higher education levels having higher knowledge. In line with this result, a relationship between education and HL has already

TABLE 7 Relationship between depression, anxiety, and stress with D-Lit, MHL, and DQOL.

Variables		n %	Mean (SD)					
			D-Lit	P-value	MHL	P-value	DQOL	P-value
Depression	Normal	31 (7.75)	46 (4.6)	0.010	81.55 (11.72)	<0.001	58.93 (7.480)	<0.001
	Mild	78 (19.5)	45.79 (4.73)		84.34 (9.18)		55.97 (7.14)	
	Moderate	250 (62.5)	44.31 (4.02)		80.70 (8.52)		54.66 (7.09)	
	Severe	41 (10.25)	43.92 (4.23)		75.34 (8.10)		50.64 (7.08)	
	Extremely Severe	0	0		0		0	
Anxiety	Normal	22 (5.5)	47 (1.02)	<0.001	84.37 (12.92)	<0.001	56.21 (7.87)	<0.001
	Mild	40 (10)	46.17 (4.93)		82.26 (10.26)		58.97 (6.89)	
	Moderate	191 (47.75)	44.95 (4.12)		82.30 (8.28)		55.41 (6.93)	
	Severe	141 (35.25)	43.65 (3.94)		78.36 (8.79)		52.75 (7.40)	
	Extremely Severe	6 (1.5)	42.33 (4.17)		76 (7.32)		52.54 (4.37)	
Stress	Normal	108 (27)	45.78 (4.48)	0.008	82.80 (9.87)	0.001	56.17 (7.94)	0.002
	Mild	168 (42)	44.29 (4.17)		81.56 (8.52)		55.36 (6.60)	
	Moderate	124 (31)	44.28 (4.12)		78.43 (8.91)		52.95 (7.41)	
	Severe	0	0		0		0	
	Extremely Severe	0	0		0		0	

been reported (66). We found a positive relationship between education levels and HL scores, as in other studies (66–68). More educated people have fewer problems finding valid health care and understanding health information.

There was a significant relationship between economic status and MHL; patients with better economic conditions had higher levels of MHL. These results are similar to those of a previous study (69), suggesting that socioeconomic status may be an independent variable that can affect HL directly through education and indirectly through access to digital medical content using tablets and smartphones. In addition, this study found a significant relationship between receiving mental health information and the levels of MHL and D-Lit, and those who received mental health information had higher MHL.

The results of this study can be combined and explained with the mind sponge theory, which was first presented by Vuong and Napier (70). According to the mind-sponge model, the human mind acts like a sponge, absorbing values and information that are compatible with one's mindset and discarding those that are not. This metaphorical sponge consists of several layers, with the mindset encompassing an individual's core values positioned at the center. Information, values, cultural norms, and environmental beliefs are evaluated based on their alignment with these core values, determining their acceptance or rejection (71–74).

According to Jorm's definition of MHL, correct knowledge, beliefs, and attitudes about identifying mental illnesses, their causes, risk factors, and avenues for seeking help are the fundamental components of MHL (75). As a result, by implementing strategies and policies to promote MHL, it can be expected that societal mindsets will evolve over time, leading to the adoption of more correct values, beliefs, and attitudes toward mental issues, replacing erroneous ones. Once the core values concerning mental health issues are corrected. people will be better equipped to judge and use the information around them. More correct information will be absorbed by the "mind sponge," while incorrect information will be rejected. This shift lays the groundwork for adopting correct behaviors, such as seeking professional help when in need. For example, a person experiencing symptoms of depression but possessing a high level of MHL due to correct knowledge, attitudes, and values, is likely to make more accurate cost-benefit analyses. Consequently, while absorbing more accurate information from the environment, such people are more inclined to seek professional help and adopt self-help measures. Conversely, in individuals with low MHL and incorrect values, the absorption of incorrect information, such as methods for suicide attempts or the avoidance of psychological help due to stigmatizing attitudes, can be expected.

As a result, improving MHL, specifically depression health literacy, can facilitate the restructuring of the knowledge, beliefs, values, and attitudes in the mind-sponge mindset of people with diabetes, leading to more correct judgments and, ultimately, more correct help-seeking behaviors. Consequently, the occurrence of mental disorders, such as depression and anxiety, is expected to be prevented. If these disorders occur, the patient is more likely to receive timely treatment and ultimately experience a better quality of life.

Quality of life plays a fundamental role in achieving treatment goals and the early diagnosis of diabetes (76). The significant prevalence of depression, stress, and anxiety among people with diabetes and their potential negative impact on quality

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TABLE 8 Pearson correlation between the variables.

Variables	a.	b.	c.	d.	e.	f.	g.	h.	i.	j.	k.	l.	m.	n.	o.	p.
a. Ability to recognize disorders	1	.														
b. Knowledge of risk factors and causes	0.136**	1														
c. knowledge of self-treatment	0.167**	0.034	1													
d. Knowledge of the professional help available	0.029	−0.056	0.184**	1												
e. Knowledge of where to seek information	0.316**	0.051	0.110*	−0.085	1											
f. Attitudes that promote recognition or appropriate help-seeking behavior	−0.076	−0.107*	0.161**	0.114*	0.031	1										
g. Mental health literacy (MHL)	0.552**	0.179**	0.389**	0.227**	0.553**	0.655**	1									
h. Depression	−0.220**	−0.070	−0.194**	−0.078	−0.218**	−0.010	−0.236**	1								
i. Anxiety	−0.220**	−0.118*	−0.229**	−0.064	−0.267**	0.025	−0.243**	0.729**	1							
j. Stress	−0.195**	−0.144**	−0.099*	0.037	−0.272**	0.102*	−0.155**	0.740**	0.672**	1						
k. Knowledge of the psychological symptoms	0.288**	−0.034	0.340**	0.248**	0.106*	0.117*	0.320**	−0.246**	−0.226**	−0.127*	1					
l. Knowledge about the effectiveness of available treatment methods	−0.128*	−0.131**	−0.006	0.070	0.047	0.098	0.014	−0.038	−0.022	−0.016	−0.099*	1				
m. Knowledge of cognitive-behavioral symptoms	−0.221**	0.013	−0.265**	−0.237**	−0.086	−0.082	−0.252**	0.096	0.028	−0.020	−0.372**	0.090	1			
n. Knowledge of taking medications and their side effects	0.086	−0.070	0.067	0.112*	0.237**	0.073	0.191**	−0.105*	−0.148**	−0.078	0.063	0.136**	−0.050	1		
o. Knowledge of disease severity	0.183**	0.069	0.187**	0.191**	0.116*	0.028	0.209**	−0.144**	−0.148**	−0.089	0.239**	−0.080	−0.238**	0.168**	1	
p. Depression literacy (D- Lit)	0.077	−0.079	0.119*	0.128*	0.167**	0.099*	0.186**	−0.192**	−0.238**	−0.156**	0.450**	0.408**	0.360**	0.566**	0.277**	1
q. DQOL	0.163**	0.073	0.154**	0.092	−0.010	−0.034	0.092	−0.251**	−0.257**	−0.203**	0.303**	−0.062	−0.150**	−0.035	0.069	0.074

*P < 0.05, **P < 0.001.

of life are concerning. The findings of this study suggest that screening and initial assessment of individuals with diabetes at the community-based care level are necessary to address their mental health problems. As a result, it is advisable for primary healthcare providers to regularly evaluate patients' mental health while implementing routine interventions, such as monitoring patients' glycemic status, dietary compliance, and activity levels and referring patients to mental health specialists when necessary. Improving mental health and depression health literacy can form the cornerstone of mental health education for all people with diabetes. Educators, armed with a thorough understanding of the main components of MHL and depression literacy, can provide more targeted, coherent, and useful education, ultimately leading to transformative changes in the values and mindsets of patients. Depression is also associated with an increased risk of hospitalization (for any reason) in patients with diabetes (77). Therefore, nurses and practitioners should not neglect to take the mental history of patients with diabetes into account in addition to initial clinical evaluations. Finally, depression and anxiety contribute to increased healthcare system costs (78), highlighting the need for policymakers to invest in preventive interventions, especially in improving MHL and depression literacy.

This study has limitations that should be considered when interpreting the findings. The cross-sectional nature of this study restricts our ability to establish causal relationships among the variables. Although we observed associations between MHL, psychological status (anxiety, depression, and stress), and quality of life, we cannot definitively conclude that one variable causes the other. Longitudinal studies are required to further investigate the temporal relationships between these variables. In addition, the sample of 400 patients with DT2 from Gonabad, Iran, may not be representative of the entire diabetic population. Consequently, these findings may not be generalizable to patients in other geographic areas or those with different demographic characteristics. Participants' recall accuracy and the potential for socially desirable responses could also skew results. Objective measures, such as clinical assessments, can help address these concerns. The DASS-21 questionnaire, while useful, is used to assess depression, anxiety, and stress; a more comprehensive assessment using in-depth clinical interviews or specialized mental health questionnaires can provide a more accurate understanding of the participants' mental health status.

Conclusion

Our study revealed that lower MHL and D-Lit scores among patients with T2DM were associated with higher levels of anxiety, depression, and stress, as well as a lower quality of life. These findings demonstrate the important role of MHL and D-Lit in promoting psychological wellbeing and overall quality of life in this population. The findings showed that the MHL and D-Lit levels in patients with T2DM were inadequate. Considering the high risk of various mental disorders in patients with T2DM, it is necessary to improve their MHL to detect such disorders in the early stages, seek mental health services, and receive available treatments. In addition, designing preventive programs to improve the mental health of patients with T2DM can prevent the occurrence of mental disorders and improve their QOL. For example, the PATIENT strategy (P: patient's perception; A: assessment; T: tailored approach; I: iterative evaluation; E: education; N: non-pharmacological approach; T: team) used in the previous study can be applied (79).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Gonabad University of Medical Sciences with the code of ethics IR.GMU.REC.1401.017. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. MM: Conceptualization, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. FN: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. MG-G: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. VA: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. KK: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. MN: Conceptualization, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1421053/full#supplementary-material

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Exploring the interconnections of anxiety, depression, sleep problems and health-promoting lifestyles among Chinese university students: a comprehensive network approach

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Background: Anxiety, depression, and sleep problems are prevalent comorbid mental disorders among university students. The World Health Organization (WHO) emphasized a mental health promotion objective, recommending the consideration of protective health-promoting factors in strategies aimed at preventing mental disorders. Integrating theoretically significant constructs (such as protective factors) enhances our comprehension of the intricate mechanisms that underpin mental disorders. This study employed network analysis to first identify core and bridge symptoms within comorbid mental disorders and then explore how health-promoting lifestyles (HPLs) were associated with these disorders. The ultimate goal is to offer health promotion recommendations to enhance students' quality of life.

Methods: A total of 3,896 qualified university students participated in this study. Anxiety, depression, sleep problems, and HPLs were assessed using the GAD-7, PHQ-9, PSQI, and HPLP-II scales. A Gaussian Graphical Model was used to construct the networks. The *Network Comparison Test* was applied to determine whether the associations between HPLs and comorbid symptoms vary by gender, educational level, family sibling, and mental health status.

Results: Low energy (PHQ4) had the highest strength centrality, followed by Daytime dysfunction (PSQI7) and Trouble relaxing (GAD4). Five bridge symptoms were identified: Daytime dysfunction (PSQI7), Self-harm even suicide (PHQ9), Sad mood (PHQ2), Low energy (PHQ4), and Feeling afraid (GAD7). Regarding protective HPLs, Physical activity, Spiritual growth, and Stress management generally emerged as the top three central mental health-promoting behaviors.

Conclusion: Targeting core and bridge symptoms with timely and appropriate interventions can alleviate anxiety, depression, and sleep problems in this population. Moreover, promoting physical activity, fostering spiritual growth, and managing stress are likely to significantly enhance the overall mental health of university students.

KEYWORDS

anxiety, depression, sleep problems, network analysis, health-promoting lifestyles, university students

1 Introduction

The mental health of university students has garnered growing attention. Faced with multifaceted pressures such as academics, social interactions, and career choices, more university students are taking leaves of absence or dropping out due to mental disorders (1). The Global Burden of Disease (GBD) Study highlighted the anxiety and depression have emerged as significant mental health challenges on a global scale (2). According to a systematic review conducted in 2022, the prevalence of anxiety and depression among university students has escalated to 39.0% and 33.6%, respectively (3). Importantly, sleep problems often occur concurrently with anxiety and depression. Since the revision of DSM-III-R by the American Psychiatric Association (APA), sleep disorder has been delineated as a distinct and specific category within DSM-IV, DSM-IV-TR, and DSM-5 (4). A meta-analysis among Chinese university students found a 25.7% prevalence of sleep disorders, with 20.3% dissatisfied with sleep quality and 23.6% exhibiting insomnia (5). During episodes of depression, university students suffer from diminished sleep quality, longer sleep onset latency, and increased daytime sleepiness (6). Furthermore, sleep problems and anxiety may be mediated by a pathogenic mechanism involving hyperarousal, influenced by imbalances in neurotransmitters such as cholinergic and gamma-aminobutyric acid (GABA) (7). In short, mental disorders typically co-occur in individuals rather than manifest independently, with those reporting depression and anxiety simultaneously exhibiting more sleep disturbances (8), a phenomenon referred to as comorbidity in clinical research.

Mental disorders also constitute a risk factor for self-harm and even suicide. Data from the International College Student Health Survey showed that approximately one-third of full-time student respondents have experienced at least one DSM-IV mental disorder (9). Compared to the general adult population, university students exhibit significantly higher rates of suicidal ideation (24% vs 9%) and suicide attempts (9% vs 2.7%) (10). Studies have proved that university students face greater challenges in mental health, highlighting the importance of conducting in-depth research on disorders such as anxiety, depression, and sleep. However, previous research on university students' mental health has primarily relied on total scores from screening scales, often neglecting individual symptoms and the interactions between these symptoms. The network theory of mental disorder (NTMD), as proposed by Borsboom, offers a new perspective to better understand this complexity (11). This theory posits that the persistence of mental disorders are contingent upon the causal relationships among their symptoms. Significant causal relationships may potentially lead to feedback loops among symptoms, perpetuating and exacerbating each other. Using network analysis methods (NAM) in NTMD, symptoms are constructed into an interconnected network where central symptoms are more likely to trigger other symptoms, thereby playing a pivotal role in a disordered state of disease (12). Intervening on central symptoms may accelerate the deactivation of symptom interactions, thus improving peripheral symptoms, which holds considerable practical value (13). Current studies have widely applied this approach to investigate the network structure of mental symptoms among various populations, including the elderly, chronic disease patients, and healthcare workers (14–16).

From a universal health perspective, the World Health Organization (WHO) has proposed a mental health promotion objective, emphasizing that supportive social environment and healthy daily habits can help reduce the incidence of mental illnesses. Moreover, among five primary determinants of human health, lifestyle and behavioral factors contribute 60% (17). Health-promoting lifestyles (HPLs) refer to the multi-dimensional, spontaneous, and sustained daily activities undertaken with the aim of enhancing or promoting individual health and well-being (18). In clinical treatment, promoting the adoption of this adaptive health-promoting lifestyle is also considered a highly cost-effective and potentially applicable non-pharmacological intervention that may alleviate stress and depression (19). It showed that increasing high-intensity physical activity can alleviate the severity of mental health issues or reduce their occurrence among student populations (20). As a factor that promotes better sleep quality, cultivating healthy lifestyle habits is also an effective strategy for improving sleep (21). Certain lifestyles that emphasize mental growth, stress management, and interpersonal relationships are also negatively correlated with anxiety and depression (22). However, the prevalence of healthy behaviors among university students is currently suboptimal, with a considerable number engaging in health-risk behaviors and adopting unhealthy lifestyles (23).

Hence, a comprehensive investigation into the correlation between depression, anxiety, sleep problems, and their protective factors (health-promoting lifestyles) among university students is necessary to better enhance their overall health.

Recently, researchers have also suggested moving beyond symptom measurement within networks. They propose including not only psychiatric symptoms but also a wider range of theoretically relevant components (such as risk or protective factors), to further understand the complex mechanisms promoting or preventing the development of mental disorders (24, 25). Risk factors provide valuable insights into understanding mental illness, yet the importance of protective factors is equally significant. For example, in a sample of 85 remitted depressed patients, resilience was shown to be an important protective factor, predicting fewer residual depression symptoms and less ruminative thinking (26). Eduardo and colleagues examined the relationship between adolescent suicidal behavior and socio-emotional indicators during adolescence, revealing the potential effectiveness of self-esteem and personal well-being in reducing suicide risk (27). By integrating potential health-promoting lifestyle choices with anxiety, depression, and sleep problems, the network model provides a more comprehensive approach to investigate the protective factors operating at the crossroads between health promotion and the development of mental disorders. Furthermore, it's worthwhile to consider the variances concerning gender, educational level, familial sibling, and mental health status. Currently, multi-group network analysis has been developed to use the *Network Comparison Test* (NCT) based on resampling permutation tests to compare global strengths and edge connections between subgroups (28).

Recognizing the complexity of mental health challenges, our first aim is to (a) identify the symptoms that play significant roles in activating, maintaining, and connecting anxiety, depression, and sleep problems within the psychopathology network. Considering the continuously evolution of psychiatric research, our second aim is to (b) explore how comorbid symptoms and protective HPLs are interconnected, discover the central mental health-promoting behaviors, and investigate whether these associations vary by gender, educational level, familial sibling, and mental health status. Ultimately, this may better help educators and healthcare professionals develop evidence-based, more precise health promotion and non-pharmacological intervention strategies to address the mental health problems of university students.

2 Methods

2.1 Study settings and participants

This cross-sectional study, conducted from January 13 to March 18, 2022, was supported by the Psychological Health Education Center at Zhengzhou University. In China, the surveyed location was a Ministry of Education-designated world-class university and a first-class discipline construction university, consistently ranking among the top five nationwide in student enrollment each year, thereby ensuring the representativeness of the survey sample. We employed a multistage sampling method, using seven academic categories (e.g., Medicine, Science, Engineering) as primary units, and degree types (undergraduate and graduate) as secondary units, with stratified sampling throughout. Subsequently, classes served as third-stage units, with cluster sampling randomly selecting students from several classes within each combination of discipline and degree type. Similar to other studies (29, 30), the "Questionnaire Star" program integrated into WeChat was adopted to collect data. An electronic questionnaire was disseminated to 4,952 currently enrolled university students, resulting in the collection and inclusion of 4,698 responses, yielding a response rate of 94.87%. The questionnaire was distributed via the WeChat and Tencent QQ platforms. To ensure data quality, measures implemented: restricting each IP address to a single submission, excluding responses with completion times shorter than 240 seconds or longer than 10 minutes, eliminating incomplete questionnaires, and discarding those with contradictory answers. As a result, a total of 3,896 eligible participants were included. Prior to participation, all subjects provided electronic informed consent. This study received approval from the Ethics Committee of Zhengzhou University (ZZUIRB2022–06).

Power analysis was commonly employed to ascertain the requisite sample size for a study. According to Epskamp and Fried's research (31), we utilized the *netSimulator* function to simulate data within a given network model and anticipated network structure, thereby exploring the appropriate sample size necessary for detecting genuine effect sizes. As the network encompasses a greater number of nodes, a larger sample size is necessitated to achieve an equivalent level of reproducibility. Consequently, we conducted data simulations for a network model encompassing comorbid symptoms and health-promoting lifestyles, with the result shown in Supplementary Figure S1. And when N = 1600, the network's correlation and strength were above 0.9, and the effects on other metrics were also acceptable (above 0.7).

2.2 Measurements

2.2.1 Generalized anxiety disorder scale-7

Using the 7-item Generalized Anxiety Disorder Scale (GAD-7) to measure the severity of anxiety symptoms (32). This scale includes seven items that correspond to the DSM-IV criteria for generalized anxiety disorder, with each item rated on a scale from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 21, with higher scores representing more severe anxiety symptoms, while a score of 5 or above is classified as mild anxiety. The Chinese adaptation of the GAD-7 has undergone thorough validation, establishing its efficacy as a screening tool for anxiety within the general Chinese population (33).

2.2.2 Patient health questionnaire-9

Depression symptoms were evaluated using the Patient Health Questionnaire-9 (PHQ-9) (34), which is based on the nine Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for major depression disorder (35). Participants responded to the items on a 4-point Likert scale ranging from 0 (not at all) to 3 (most of the time or always), resulting in a total score ranging from 0 to 27 across the nine items. For PHQ-9 scores, higher total scores represent more severe depression symptoms, with a score of 5 or above indicating mild depression. Extensively validated in the Chinese population (36), the PHQ-9 serves as an effective tool for assessing depression symptoms. Most previous studies have focused on sleep duration and insomnia symptoms (e.g., difficulty falling asleep or staying asleep), while paying little attention to sleep dimensions (e.g., sleep efficiency, daytime dysfunction, and sleep medication) (37). Therefore, we excluded the third item from this scale and employed the Pittsburgh Sleep Quality Index (PSQI) to comprehensively understand the complexity of sleep problems.

2.2.3 Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the severity of sleep problems (38). Comprising 19 self-assessment items, the PSQI includes seven dimensions: (1) "Subjective Sleep Quality"; (2) "Sleep Latency"; (3) "Sleep Duration"; (4) "Sleep Efficiency"; (5) "Sleep Disturbance"; (6) "Use of Sleep Medication"; and (7) "Daytime Dysfunction". In the Chinese population, a global PSQI score exceeding 7 indicates of poor sleep quality, with a sensitivity of 98.3% and specificity of 90.2% (39).

2.2.4 Health-promoting lifestyle profile-II

The Health-Promoting Lifestyle Profile (HPLP) was developed to quantify the frequency of participation in health-promoting behaviors (40). The HPLP-II was a revision of the HPLP, consisting of a total of 52 items across six dimensions: interpersonal relationship, health responsibility, stress management, nutrition, physical activity, and spiritual growth. It employed a Likert 4-point scoring system, with higher total scores indicating better health behaviors. The Chinese version of the HPLP-II was revised to include 40 items and has been effectively validated in the Chinese population (41). This version was employed in our survey.

2.3 Statistical analysis

All statistical analyses were performed using the R-Studio program (version 4.3.2). First, descriptive statistical methods were used to summarize demographic information and item scores from each scale. Then, we constructed a comorbid network of anxiety, depression, and sleep problems, in addition to a comprehensive network of comorbid symptoms and their association with health-promoting lifestyles. Network analysis can establish bivariate relationship among multiple variables and reveal the structure and nature of entire complex system of mental disorders caused by the causal interactions among variables (including core components, co-occurrence relationships, and critical nodes), which cannot be explained by regression analysis and latent variable analysis (42).

Before constructing the networks, potential item redundancy was checked using the *goldbricker* function from the R package *networktools* (version 1.5.1). Following Jones' manual (43), if the proportion of significantly different central correlations between two variables and other items is less than 25%, then it can be confirmed that these two items measure the same trait or symptom (i.e., redundancy).

2.3.1 Network estimation

The Pairwise Markov Random Field (PMRF) is commonly employed in cross-sectional studies. Given the continuous nature of our dataset, we utilized the Gaussian Graphical Model (GGM) to estimate a network of partial correlation coefficients (44). The partial correlation network is a type of model based on weighted correlation networks. Partial correlation coefficient denotes the correlation between two nodes while holding all other information in the network constant, hence also referred to as "conditional independence correlations". To mitigate spurious connections and enhance the network's comprehensibility, we applied the graphical least absolute shrinkage and selection operator (LASSO) for regularization (45). The Extended Bayesian Information Criterion (EBIC) was used to identify the optimal model fit with a default tuning parameter of 0.5 (46). Additionally, using the Fruchterman-Reingold algorithm to compute the optimal layout of the network, nodes with stronger correlations are positioned closer together, while nodes with weaker correlations are mutually exclusive. For both network estimation and visualization, we relied on the R packages *qgraph* (version 1.9.8) and *bootnet* (version 1.5.6) (44, 47). In graphs, each item is represented as a node, and the connections between nodes are termed edges. The thickness of the edges represents the strength of the association, while the color indicates the direction: green for positive correlations and red for negative correlations.

Quantifying the significance of each node within a network necessitates the computation of centrality metrics, which elucidate the probability that the activation of one node will exert an influence on others (48). Commonly employed measures of node centrality encompass betweenness, closeness, and strength. Nevertheless, prior studies have demonstrated that betweenness and closeness are unreliable for ascertaining node importance (44, 49). Consequently, this study employed strength as the centrality metric. Strength centrality evaluates the aggregate absolute edge weights between a node and all its directly connected nodes, thereby describing the robustness of direct connections between nodes in the absence of intermediary nodes. Hence, nodes with higher strength can be interpreted as more central. Furthermore, bridge centrality metrics (such as bridge strength, bridge closeness, and bridge betweenness) were also evaluated using the bridge function in the R package *networktools* (version 1.5.1) to identify specific nodes that act as conduits connecting different communities within the network (50). Bridge strength quantifies the total absolute edge weight between a community node (such as "physical activity" in health-promoting lifestyles) and all other nodes outside its community. Finally, the R package *mgm* (version 1.2–14) was employed to calculate predictability, which indicates the extent to which the variation of a given node in the network can be predicted by the variation of its connected nodes (51). In the network layout, the area within the surrounding cycle of each node represents its predictability value.

2.3.2 Network stability and accuracy

We assessed network stability and accuracy using the bootstrap method in the R package *bootnet* (version 1.5.6), relying on the following three processes. To ensure the stability of strength and bridge strength, we initially implemented a case-dropping bootstrap procedure (44). This involved selectively discarding portions of data without inducing significant alterations in the existing network, thus affirming its stability. Stability was quantified by computing the Correlation Stability Coefficient (CS-C), indicating the maximum sample proportion that could be removed. Typically, a CS-C value of 0.25 or higher is preferred, with values exceeding 0.5 considered particularly desirable (52). Subsequently, to assess the accuracy of edge weights, we employed a non-parametric bootstrap method to derive confidence intervals (CIs) (53). A narrower confidence interval signifies a more reliable network estimation. Finally, to evaluate potential disparities between edges or nodes, we conducted bootstrapped paired differences in edge weights and centralities of different nodes (44).

2.3.3 Network comparison

To explore potential variances in network characteristics related to comorbid symptoms and health-promoting lifestyles among university students based on gender, educational level, family sibling, and mental health status, we classified gender as “Male” and “Female”; education level as “Undergraduate” and “Graduate”; family sibling status as “Only-child” and “Non-only-child”; mental health status as “Non-mentally disordered” and “At least one mental disorder”. Then, we applied a permutation test with 1000 iterations using the R package *Network Comparison Test* (version 2.2.2) to determine if there are statistical differences in global strength (the absolute sum of all edge weights) as well as network structure (the distributions of edge weights) among subgroups (28). Subsequently, following the adjustment for multiple comparisons using the Bonferroni-Holm correction, the differences in strength at the level of individual edges between both networks were compared.

3 Results

3.1 Study sample characteristics

The demographic characteristics of the overall sample are presented in Table 1. Among the 3,896 participants included in this study, the mean age was 21.92 years (SD = 2.56), with 1,587 (40.7%) being male and 2,309 (59.3%) female. Of these, 1,824 (46.8%) were undergraduates, and 2,072 (53.2%) were graduate students. Altogether, 1,485 (38.1%) reported experiencing anxiety (GAD-7 total score ≥ 5), 1,745 (44.8%) reported experiencing depression (PHQ-9 score ≥ 5), and 629 (16.1%) reported experiencing sleep problems (PSQI total score ≥ 8). Supplementary Table S1 displays the mean, standard deviation (SD), skewness, kurtosis, strength, bridge strength, and predictability of all items across the scales. In both the comorbid network of anxiety, depression, and sleep problems, and the comprehensive network of comorbid symptoms and health-promoting lifestyles, no item was found to be redundant with any other item (i.e., showing less than 25% significantly different correlations).

TABLE 1 Sample demographic characteristics (n = 3896).

Variables	Mean/N	SD/%
Age (year)	21.92	2.56
Gender		
Male	1587	40.7
Female	2309	59.3
BMI (kg/m^2)		
Underweight (≦ 18.4)	544	14
Normal weight (18.5–23.9)	2582	66.3
Overweight (≧ 24)	770	19.7
Residence		
Urban	1889	48.49
Rural	2007	51.51
Academic discipline		
Medical	711	18.2
Non-Medical	3185	81.8
Education level		
Undergraduate Student	1824	46.8
Graduate Student	2072	53.2
Marital status		
Single and without a partner	2868	73.6
Single with a partner	916	23.5
Married	112	2.9
Family sibling status		
Only child	1007	25.8
Non-only child	2889	74.2
Anxiety (GAD-7)		
No anxiety (0–4)	2411	61.9
With anxiety (5–21)	1485	38.1
Depression (PHQ-9)		
No depression (0–4)	2151	55.2
With depression (5–27)	1745	44.8
Sleep problems (PSQI)		
normal sleep (0–7)	3267	83.9
Experiencing sleep problems (8–21)	629	16.1

3.2 Network of anxiety, depression and sleep problems

As illustrated in Figure 1, within the network structure encompassing anxiety, depression, and sleep problems, there are a total of 131 non-zero edges out of 231 possible edges (network density = 0.57), with an average weight of 0.043. The five most prominent edges are all within specific communities: Sleep duration - Sleep efficiency (PSQI3 - PSQI4), Subjective sleep quality - Daytime dysfunction (PSQI1 - PSQI7), Nervousness - Uncontrollable worry (GAD1 - GAD2), Anhedonia - Low energy (PHQ1 - PHQ4), and Abnormal behavior & speech - Self-harm even suicide (PHQ8 - PHQ9) (Supplementary Table S2). Significant edges connecting different communities include Self-harm even suicide - Use of sleep medication (PHQ9 - PSQI6), Low energy - Daytime dysfunction (PHQ4 - PSQI7), and Feeling afraid - Self-harm even suicide (GAD7 - PHQ9) (Supplementary Table S2). Additionally, Excessive worry (GAD3) and Trouble relaxing (GAD4) exhibit the highest predictability (0.747, 0.742), whereas Use of sleep medication (PSQI6) has the lowest predictability (0.173). The average predictability is 0.56, indicating that, on average, more than half of the variance in the nodes can be explained by their adjacent nodes (Supplementary Table S1). Network stability and accuracy tests are shown in Supplementary Figure S4, with both strength and bridge strength centrality being 0.75, exceeding the recommended threshold of 0.5.

The centrality plot (Figure 2A) indicated that Low energy (PHQ4) exhibits the highest strength centrality, followed by Daytime dysfunction (PSQI7) and Trouble relaxing (GAD4), suggesting that these nodes occupy the most significant and influential positions within the comorbidity symptom network. According to Jones' perspective (50), bridge symptoms are selected using the 80th percentile threshold for bridge centrality. As shown in Figure 2B, Daytime dysfunction (PSQI7), Self-harm even suicide (PHQ9), Sad mood (PHQ2), Low energy (PHQ4), and Feeling afraid (GAD7) exhibit the highest bridge strength, identifying them as the pivotal bridge symptoms linking anxiety, depression, and sleep problems comorbidity. The bootstrapped difference test (Supplementary Figure S4) for node strength and bridge strength further corroborate that these nodes are statistically significantly stronger than other nodes within the network.

3.3 Network of comorbid symptoms and health-promoting lifestyles

The network of comorbid symptoms and health-promoting lifestyles is illustrated in Figure 3, with stability and accuracy tests presented in Supplementary Figure S5. Regarding strength centrality, Low energy (PHQ4), Daytime dysfunction (PSQI7), and Trouble relaxing (GAD4) remain the most significant and influential comorbid symptoms, while Physical activity, Health

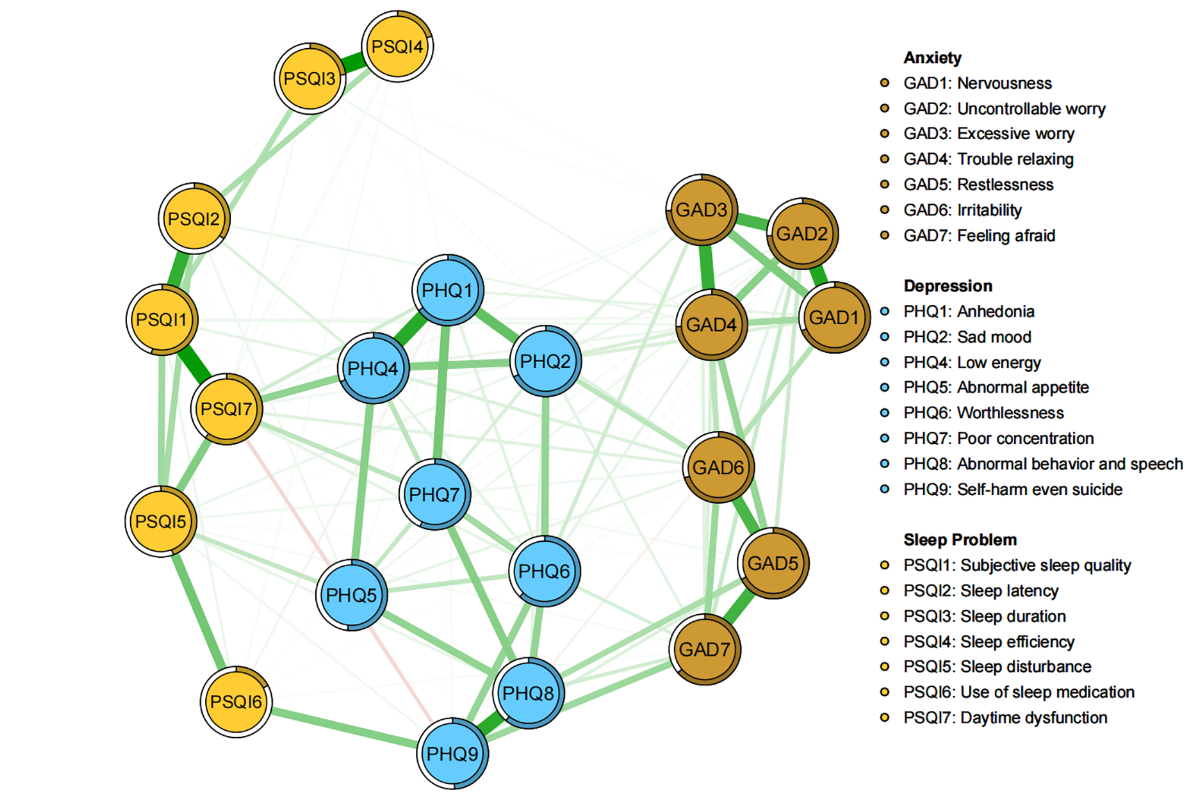

FIGURE 1
Network structure of anxiety, depression and sleep problems among university students.

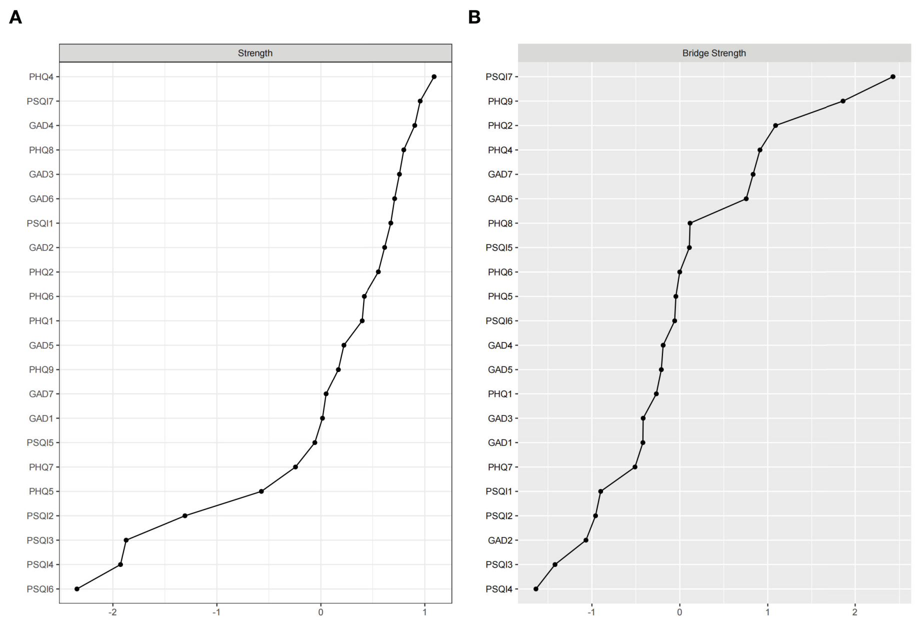

FIGURE 2
Standardized strength and bridge strength centrality of network structure of anxiety, depression and sleep problems among university students (z-scores). **(A)** strength centrality; **(B)** bridge strength centrality.

responsibility, and Stress management are identified as the top three central HPLs (Supplementary Figure S2). In terms of correlations, Spiritual growth and Physical activity exhibit the most negative edges with comorbid symptoms. Moreover, by evaluating the individual connection between each specific protective HPL node and the wider community of comorbid symptoms, Physical activity demonstrated the highest bridge strength. Specifically, Spiritual growth showed the strongest bridge strength with the depression community, Physical activity with the sleep problems community, and both Health responsibility and Stress management with the anxiety community (Supplementary Table S3; Supplementary Figure S3). However, as Health responsibility showed mostly positive correlations with anxiety symptoms. Thereby, Physical activity, Spiritual growth, and Stress management were identified as the central mental health-promoting behaviors.

3.4 Comparisons based on gender, education level, family sibling, and mental health status

NCT revealed the invariances of global strength and network structure among the four groups (Supplementary Figures S6–S9). In terms of global strength comparisons across the four subsamples, significant difference was only found in mental health status (non-mentally disordered: 8.72 vs at least one mental disorder: 13.21, $p = 0.01$). Other comparisons showed no significant differences (male: 13.19 vs female: 12.99, $p = 0.634$; undergraduate: 12.98 vs graduate: 13.43, $p = 0.139$; only-child: 13.23 vs non-only-child: 13.52, $p = 0.733$). Regarding network structure comparisons, significant differences were observed in familial sibling status ($M = 0.16$, $p = 0.030$) and mental health status ($M = 0.28$, $p = 0.01$); The other two subsamples showed no significant differences (gender: $M = 0.13$, $p = 0.129$; educational level: $M = 0.12$, $p = 0.158$). Additionally, after applying the Bonferroni-Holm correction, all edge weights in the three subsamples remained non-significant ($p > 0.05$).

4 Discussion

In the present study, we evaluated the core and bridge symptoms within comorbid network of anxiety, depression, and sleep problems, and identified central mental health-promoting behaviors. Consistent with epidemiological findings in university student populations, at least one in three individuals reported anxiety or depression, and one in every five to six individuals experienced sleep problems. Investigating the relationship between sleep problems and anxiety and depression from sleep dimensions (e.g., sleep efficiency, daytime dysfunction) provides a deep understanding of the complexity of mental health. Health promotion involves enabling individuals to achieve optimal physical and mental well-being, live under healthy habits, and make choices conducive to health (54). By applying a more comprehensive network approach, we can intricately analyze the associations between health-protective factors and specific mental disorders. In the following, we discuss the results of the networks.

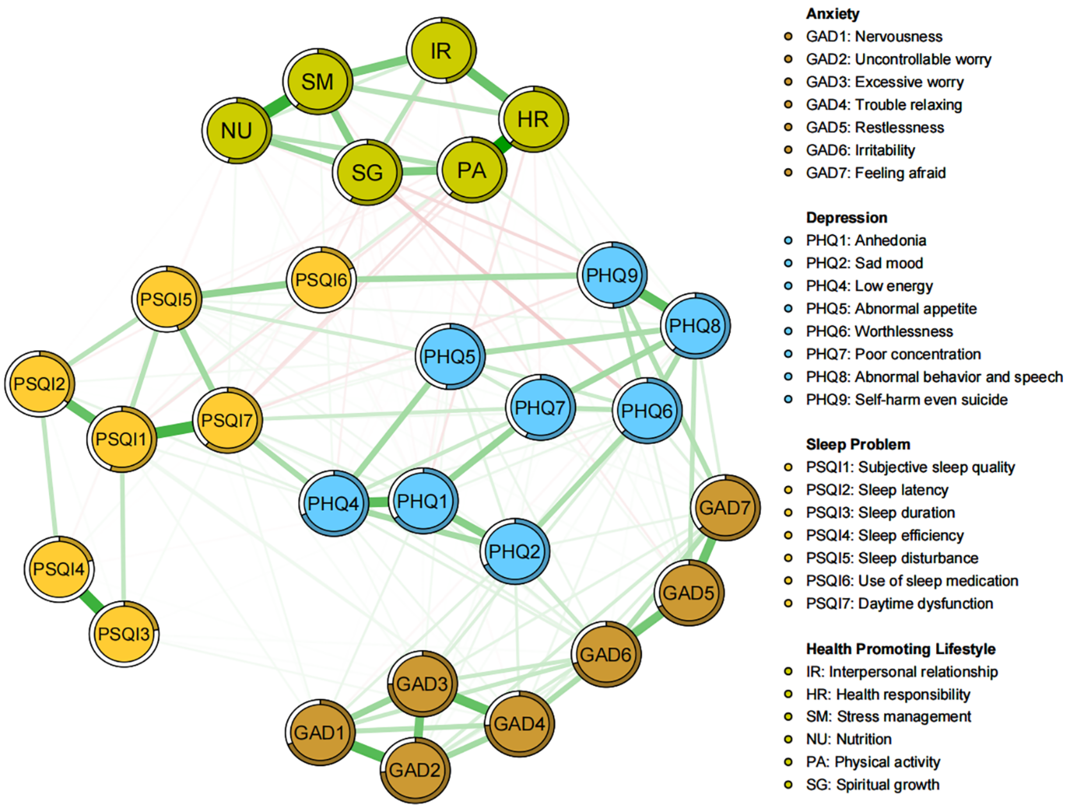

FIGURE 3
Network structure of comorbid symptoms and health-promoting lifestyles among university students.

4.1 Network results for anxiety, depression and sleep problems

Low energy (PHQ4) exhibited the highest strength centrality, indicating its crucial role in activating and sustaining the comorbid network of depression, anxiety, and sleep problems. This phenomenon was also widely observed among Chinese nurses and nursing students and closely associated with Anhedonia (PHQ1) (55, 56). Low energy, manifesting as fatigue or exhaustion, is a core feature of depression (57). During the late stages of the COVID-19 pandemic, the prevalence of fatigue among nursing students reached 67.3% (58). Evidence suggested that this may be associated with the somatization of psychological distress, particularly prevalent among Asian adolescents. This cultural tendency favors physical expression over verbal expression as a coping strategy (55). The cumulative impact of intense academic pressures, limited recreational and social activities, and inadequate sleep on their physical and mental health often manifested as a state of low energy. Ariel et al. found that low energy as a crucial predictor across multiple domains of health and functional impairment, corroborating our findings (59). It may also serve as an early indicator of anhedonia. Neurological evidence indicated that energy depletion may inhibit the neural systems responsible for enhancing the reception of rewarding stimuli (60). Furthermore, as the second most central symptom, Daytime dysfunction (PSQI7) showed strong edge connectivity with Low energy (PHQ4), serving as bridge symptoms. This supported findings from studies on Macau residents, migrant Filipino domestic workers, and clinicians with depression symptoms (61–63). It has been identified as a prominent bridge symptom linking childhood trauma, sleep disorders, and depression in adolescents (64). Exploratory research into sleep structure revealed that sleep problems could be categorized into nocturnal symptoms and daytime consequences, both contributing to dissatisfaction with sleep quantity or quality. However, interference with daytime functioning was centrally positioned and may be a critical outcome measure in insomnia treatment (65). Related studies indicated that students with low energy are more sensitive to stressors, amplifying the negative consequences of insomnia rather than the experience of insomnia itself (66, 67). The clinical significance of Trouble relaxing (GAD4) has been well-documented in insomnia and psychopathology (59). Notably, trouble relaxing was highly correlated with restlessness and clusters within the psychomotor community. Our results also showed that these symptoms have the highest predictability within the network, corroborating Bai et al.'s finding that difficulty relaxing ranks second in EI, with restlessness showing the highest BEI after sleep problems (63). The inability to relax as a core nexus symptom in comorbid PTSD, depression, and anxiety among trauma-exposed samples (68). Outside the classroom and internship settings, interventions such as mindfulness-based approaches and relaxation exercises can alleviate students' physical and mental stress (69).

Node bridge strength centrality may provide insights for identifying critical bridge symptoms in the connection and progression of mental disorders. Beyond low energy and daytime dysfunction, Self-harm even suicide (PHQ9), Sad mood (PHQ2), and Feeling afraid (GAD7) also emerged as bridge symptoms within the current network. As a global health concern, Self-harm even suicide (PHQ9) has consistently been recognized as a key intervention target within adolescent mental disorders (70). Numerous scholars have probed into the nexus between adolescent mental health and suicidal ideation, revealing anxiety as a prospective predictor of suicidal ideation; over 50% of completed suicides and 20%-48% of suicide attempts are attributed to depression (71). We also identified that within the depression community, suicidal ideation is most strongly associated with abnormal behavior & speech (i.e., psychomotor agitation and impulsivity). Among adults experiencing major depression episodes, risk-taking behavior and psychomotor impulsivity were believed to facilitate the transition from suicidal ideation to suicide attempts (72). Our study also identified Feeling afraid (GAD7) as another significant bridge symptom, closely related to suicidal ideation. Epidemiological investigations signify that 75% of lifetime mental disorders manifest before the age of 24, with anxiety disorders typically emerging from early adolescence to young adulthood (73). The factors unique to college students, such as student debt, employment uncertainty, academic pressure, and separation from family, showed that feeling afraid doubles the likelihood of suicidal ideation among those experiencing anxiety symptoms (74). Additionally, Sad mood (PHQ2) played a distinct bridge role in linking anxiety disorders, as corroborated by a bayesian network of anxiety-depression bridges (75). Stigma toward mental illnesses could also lead to the emergence of adolescent emotional problems (76).

4.2 Network results for health-promoting lifestyles

The "Healthy China Action (2019–2030)" plan, formulated by the Healthy China Initiative Committee emphasizes the "big health" concept, integrating prevention and treatment through 15 major health promotion actions, shifting the focus from disease-centric to health-centric approaches. This offered valuable insights for our research. We found that physical activity occupied a central position in the network, potentially at the intersection of mental disorders and health. It remained the most prominent health node when quantifying the degree to which specific health-promoting behaviors correlate with changes in comorbid symptoms. Specifically, physical activity showed a significant negative correlation with sleep problems, potentially reducing the use of hypnotics, alleviating daytime dysfunction, and improving subjective sleep quality. Numerous scholars have corroborated our findings. It enhanced dopamine levels, altering responses to emotional events, and serving as a stress relief mechanism to help individuals return to pre-stress levels more quickly (77, 78). Moreover, adhering to scientific and effective physical exercise can regulate serum cortisol to optimal levels, boost immunity, and serum cortisol is closely linked to the body's circadian rhythm (79). Studies also indicated that while body temperature decreases when falling asleep, evening exercise initially raises deep body temperature and accelerates the rate of temperature decline, thereby improving sleep (80). It's noteworthy that whether a U-shaped relationship exists between physical activity and mental health (81), or the optimal frequency and intensity, requires further research to ascertain.

Spiritual growth can significantly reduce levels of depression. It's strongly negatively correlated with self-harm even suicide, and worthlessness, marking these as the strongest negative edges within the network. Spiritual growth encompasses pursuing long-term life goals, experiencing oneself as positively developing and changing, gaining a sense of belonging, and maximizing the potential for a healthy life through goal-directed efforts (41, 82). Importantly, signs of depression are also characteristic of a lack of spirituality, Leung found that spiritual development significantly reduced depression, anxiety, and stress in adolescents while enhancing their self-confidence (83). It has been observed that young individuals experiencing depression often exhibit intrusive rumination, characterized by involuntary and repetitive contemplation of negative thoughts, which exacerbates their suffering (84). In contrast, spiritual growth can facilitate deliberate rumination, where individuals purposefully reflect on and analyze traumatic events to understand their meaning and impact, thereby promoting psychological growth (85). Additionally, self-efficacy is closely related to spiritual growth and can be viewed as an outward manifestation of it. It also serves as a mediator through which spiritual growth positively influences mental health, significantly reducing symptoms of depression, anxiety, and externalizing behaviors (86). As the third major health-promoting node, stress management showed a significant negative correlation with anxiety symptoms, alleviating trouble relaxing and restlessness. In this study, trouble relaxing was identified as a core symptom of anxiety, and restlessness was closely linked to it. This illustrates how stress management, by targeting core symptoms, can effectively and directly mitigate anxiety. Adolescents who frequently employ stress management strategies and adopt more positive coping and defense mechanisms exhibit fewer anxiety symptoms over time, underscoring the importance of incorporating stress management techniques into mental health programs (87).

The NCT analysis and quantification of centrality indices have confirmed the universal applicability of stress management, physical activity, and spiritual growth as key health-promoting factors for students. Nonetheless, some distinctions emerged when comparing the intensity levels of health-promoting behaviors' effects on mental health symptoms across subgroups. Regarding gender, we found no association between stress management and anxiety in males, while physical activity significantly reduced anxiety and improved sleep quality. This implies that men often employ ineffective strategies for managing stress. Traditional masculine traits, which emphasize strength and control, condition men to suppress vulnerable emotions like fear and sadness, a habit persisting into adulthood (88). Additionally, a report found that men more frequently engage in regular exercise compared to women (89). For graduate students, stress management was the most central health-promoting behavior, surpassing physical activity. Among only-children, stress management strategies were more effective in alleviating anxiety compared to those with siblings. We hypothesize that for individuals experiencing greater and more complex stress, targeted stress management strategies are more direct and effective in reducing psychological issues in the short term. Our findings align with epidemiological surveys on students' mental health (90–92). A higher proportion of women (41.14%) than men (33.71%) experienced anxiety. Anxiety severity was higher among graduate students (8.32) compared to undergraduates (8.09), and higher among only-children (8.75) compared to those with siblings (8.03). Notably, maintaining health responsibility (i.e., continuously attending to physical and mental health and remaining vigilant for potential illnesses) can counterintuitively exacerbate anxiety among women and graduate students. While this represents a form of health responsibility, over attention to health issues in high-stress populations can amplify anxiety, a phenomenon known as "health anxiety". When classified by clinical scores, university students with at least one mental disorder exhibited significantly higher network density (0.44) compared to those without mental disorders (0.33). This elevated connectivity reflects the complexity and interconnection of mental disorders. Moreover, within the network of students experiencing mental disorders, stronger associations were observed among Abnormal behavior & speech - Self-harm even suicide, Spiritual growth - Worthlessness, and Stress management - Restlessness. Self-harm even suicide emerged as the second most central symptom node, following Low energy. Consistent with study on female nursing students (55), this finding suggested that psychomotor symptoms (such as psychomotor agitation/impulsivity and restlessness) and worthlessness may trigger connections within the network and significantly predict suicidal ideation. This also indirectly supports the notion that targeted interventions in stress management and spiritual growth are more directly effective under severe mental disorders.

5 Strengths and limitations

This study, based on Chinese university students, employed network analysis to identify core and bridge symptoms in three prevalent mental disorders. It uniquely integrated health-promoting behaviors into the network, exploring their associations with mental disorders, and identifying optimal nodes for health promotion, aligning with the WHO's mental health promotion objective. The analysis revealed that central health-promoting behaviors predominantly impact the core and bridge symptoms of mental disorders, thereby preventing their development. Network comparison tests were conducted to further understand the differential effects or generalizability of these behaviors within the student population. Moreover, the HPLP-II questionnaire, chosen for its validated advantage in assessing self-maintenance health behaviors in daily life among the Chinese population, proved beneficial.

Despite these strengths, several limitations must be acknowledged. Firstly, the cross-sectional design of the study precludes causal inferences; longitudinal data are required to elucidate the complex mechanisms underlying the interactions between symptoms and health-promoting behaviors. Secondly, future research should incorporate risk factors to gain a comprehensive understanding, as risk factors may exacerbate mental disorders while protective factors might counteract these effects. Thirdly, our study was conducted in a single comprehensive university; despite efforts to mitigate bias, caution is warranted when generalizing the findings. Finally, it must be recognized that all sample information in this study was self-reported, which may affect the accuracy of the analysis.

6 Conclusion

In conclusion, university students are a high-risk group for mental disorders, with at least one in three reporting anxiety or depression, and one in every five to six experiencing sleep problems. Network analysis of the three common mental disorders revealed core symptoms: Low energy (PHQ4), Daytime dysfunction (PSQI7), and Trouble relaxing (GAD4). Bridge symptoms: Daytime dysfunction (PSQI7), Self-harm even suicide (PHQ9), Sad mood (PHQ2), Low energy (PHQ4), and Feeling afraid (GAD7). These symptoms are crucial in activating, maintaining, and interconnecting comorbid conditions. By incorporating health-promoting lifestyles (HPLs) into the network, we explored how protective HPLs are associated with these disorders and examined variations by gender, educational level, family sibling, and mental health status. Our findings highlighted the universal applicability of physical activity, spiritual growth, and stress management as the top health-promoting nodes for students. This study provided insights into common mental disorders and influential health lifestyles, which can aid educators and healthcare professionals in developing evidence-based, non-pharmacological intervention strategies to better promote mental health among university students.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The Ethics Committee of Zhengzhou University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZZ: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis. CS: Funding acquisition, Data curation, Conceptualization, Writing – review & editing, Visualization, Supervision, Resources, Project administration. PZ: Writing – review & editing, Visualization, Supervision, Software, Methodology, Data curation. LW: Writing – review & editing, Visualization, Validation, Supervision, Project administration, Funding acquisition. QZ: Writing – review & editing, Visualization, Supervision, Project administration, Investigation, Funding acquisition. YG: Writing – review & editing, Visualization, Supervision, Resources, Investigation. LG: Writing – review & editing, Visualization, Supervision, Resources, Project administration. YL: Writing – review & editing, Visualization, Supervision, Investigation. PW: Writing – review & editing, Visualization, Supervision, Funding acquisition. BH: Writing – review & editing, Validation, Supervision, Data curation. ML: Writing – review & editing, Validation, Supervision. JD: Writing – review & editing, Validation, Supervision. YW: Writing – review & editing, Validation, Supervision. ZW: Writing – review & editing, Validation, Supervision. YQ: Writing – review & editing, Data curation, Supervision, Project administration.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1402680/full#supplementary-material

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Perceived social support and quality of life in endometrial cancer patients: a longitudinal study

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Objective: This study aimed to assess the influence of medical history, perceived physician-patient communication, and perceived social support on changes in the quality of life (QoL) during the first year of follow-up in patients undergoing surgery for endometrial cancer (EC), the most prevalent gynecological cancer in Western countries, especially in Central and Eastern Europe and North America.

Methods: This prospective longitudinal study included 98 EC patients. All participants completed the Short Form 36 (SF-36) and the Multidimensional Scale of Perceived Social Support (MSPSS) one month and one year after surgery. Additionally, one month after surgery, they responded to a questionnaire designed by the researchers concerning the key aspects of physician-patient communication.

Results: Our findings revealed that patients reporting high social support one month after surgery demonstrated significantly improved emotional well-being (EWB) at both one month and one year after the surgery, with statistically significant higher scores in the dimension of EWB ($p<0.05$). The support from a significant other at one year correlates with greater PF ($p<0.005$), fewer limitations due to physical health ($p<0.05$), less pain ($p<0.05$), less fatigue ($p<0.05$), and better general and EWB ($p<0.05$).

Conclusion: This study underscores the significance of perceived social support for patients cross endometrial cancer. The multifaceted nature of social support, encompassing emotional assistance and information sharing, emerges as a pivotal factor aiding patients in confronting the challenges inherent to EC. This form of support contributes to bolstering psychological well-being and enhancing overall QoL.

KEYWORDS

endometrial cancer, quality of life, social support, radiotherapy, physician-patient communication, well-being, laparoscopy, adjuvant therapy

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in Western countries particularly in Central and Eastern Europe and North America. In 2020, 417,000 new EC cases and 97,000 deaths were reported worldwide (1). In the last decade, its incidence has increased especially in women under the age of 50 (2). Moreover, the incidence of EC is rising in high-income countries, which may be attributable to high rates of obesity, physical inactivity, late menopause, and extended life expectancy. EC is usually diagnosed at early stage because it causes symptoms such as bleeding not related to menstruation and postmenopausal bleeding (3). Therefore, when diagnosed at early stage, EC usually has a favorable prognosis (77% 5-year overall survival [OS]), such that even fertility-sparing treatments are safe (4–7). Conversely, advanced or recurrent disease results in low response to chemotherapy and poor outcome (6–8). EC patients are potentially long-surviving patients, and therefore quality of life (QoL) is a highly relevant topic. In recent decades, QoL has become one of the main outcomes to ensure when choosing cancer treatment (9–11). Quality of Life is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (12). QoL reflects the patient's subjective assessment of all dimensions of their health experience, including physical health, psychological state, level of autonomy, social relationships, personal beliefs, and their relationships to important aspects of the environment (12). In patients suffering from diseases that could reduce survival, both the treatment and the disease itself can impair QoL (9). It has been well documented that many cancer patients report long-term psychological distress (13, 14). Standard treatments such as surgery, chemotherapy, and radiation therapy can impair QoL (9). Different surgical approaches can affect QoL differently. In particular, laparoscopy is associated with less pain, fewer complications and shorter hospital stay than laparotomy, with a better perception of physical well-being (15–17). Emotional well-being (EWB) in patients who have undergone surgery for EC is a multifaceted issue, profoundly influenced by social support (SS) and communication with healthcare providers. These variables are crucial in determining the patients' overall QoL and their ability to cope with the aftermath of their diagnosis and treatment. Social support is a vital factor in the EWB of EC patients. It encompasses the emotional, informational, and practical assistance provided by family, friends, and healthcare professionals. Research by Pasek et al. (18) highlights that SS significantly impacts patients' psychological health by reducing stress and enhancing their ability to manage illness-related challenges. Patients with robust social networks tend to report lower levels of anxiety and depression and exhibit better overall MH. A study by Chan et al. (19) further supports these findings, showing that family and friend support directly influences patients' QoL. Effective SS leads to improved emotional resilience and a more positive outlook, which are crucial for recovery and long-term well-being. According to Smith-Bindman et al. (20), patients who feel understood and supported by their doctors are more likely to experience positive emotional states and lower levels of psychological distress. This underscores the importance of empathy and clear communication in medical practice, especially for patients dealing with life-threatening conditions like EC. Satisfactory information about cancer, the necessary treatment and long-term effects can reduce patients' fears and anxieties, with a positive impact on QoL. Several studies have reported that cancer survivors who are satisfied with the information they received have a better health-related QoL as well as lower levels of depression and anxiety (21). Adequate information increases awareness in the decision-making process by decreasing stress factors and represents an important support factor in the diagnostic and therapeutic path of the disease (22). Similarly, the perception of having received good SS is also an important protective factor in mitigating the negative impact of stressful events and in developing greater resilience, favoring greater individual well-being and a better QoL (22, 23). In this study, we investigated the QoL of patients who underwent surgery for EC treatment. We investigated the change in QoL during the first year of follow-up based on perceived SS (PSS).

We hypothesized that medical history and PSS could have an effect on patients' QoL and general well-being. The increase in the patients' QoL during the study period could be mediated by the socio-personal characteristics of the patients themselves, their clinical history and the quality of PSS. We also wanted to verify whether a better perception of physician-patient communication is associated with a further increase in the well-being of the patients participating in the study.

Methods

The aim of this prospective longitudinal study was to evaluate the impact of medical history, perceived physician-patient communication, and PSS on changes in QoL during the first year of follow-up of patients who had undergone surgery for EC. The standard treatment for EC includes total hysterectomy with bilateral salpingo-oophorectomy. The follow-up or adjuvant treatment is planned according to the risk factors of each case (6).

All EC patients treated at our hospital were evaluated for inclusion and exclusion criteria. Patients were eligible to participate if they had a histological diagnosis of EC, were age >18 years, if they had been treated surgically at our hospital, and if they were able to speak and understand the Italian language. Exclusion criteria were absence of histological diagnosis of EC, absence of standard surgical treatment (e.g. conservative treatment), and inability to speak and understand the Italian language. Self-administered QoL questionnaires were delivered to patients one month and one year postoperatively at the follow-up visit.

Ethics approval and consent to participate

Study number 45/2012, date of approval by the Regional Ethics Committee 16/04/2012. Written informed consent was obtained from all individual participants included in the study.

Data collection

The day of the gynecological check-up visit, a psychologist researcher formally contacted all patients who met the inclusion criteria to explain to them the study protocol and ask for their consent to participate in the study. Patients were included in the study only after obtaining a formal written informed consent. At enrollment, demographic and clinical data were recorded for all patients. At each check-up visit, participants received an envelope containing two questionnaires. They were asked to complete the first questionnaire one month after surgery and the second questionnaire one year after surgery. The investigators were required to provide potential participants with oral and written information about the aim and procedures of the study at enrollment.

Measurement instruments

QoL was measured using the Short Form 36 (SF-36) (24) in the Italian version (25). The SF-36 comprises 36 items and provides scores for eight dimensions of physical and mental health (MH)-related QoL: physical functioning (PF), i.e., the extent to which health interferes with performance in everyday physical activities (e.g., carrying groceries, climbing stairs, and walking); physical role (PR) functioning, i.e., the degree to which health interferes with usual daily activities such as work, housework, or school; bodily pain (BP), i.e., the intensity of bodily pain and the extent to which it interferes with normal work; general health (GH), i.e., the current evaluation of personal health; vitality (VT), i.e., the degree to which a person feels full of energy or worn out and tired; social functioning (SF), i.e., the extent to which health had interfered with normal social activities like visiting friends during the past month; emotional role functioning (ER), i.e., the degree to which emotional problems impede every day activities such as work; and MH, i.e., the extent to which a person feels a positive or a negative mood. The scores range from 0 to 100, with higher scores at each dimension indicating better QoL. In the present study, Cronbach's alpha values for the SF-36 dimensions ranged between 0.70 and 0.87.

Specifically, the present article focuses also on PSS that was measured using the Multidimensional Scale of Perceived Social Support (MSPSS), which was created by Zimet et al. (26) and includes 12 items (using a 5-point scale from "strongly disagree" to "strongly agree"). The MSPSS is divided into three subscales: Friends, Family, and Significant Other, and therefore yields four scores: a total score (range 0–72) for the PSS and three scores for the different sources of PSS (range 0–24), namely, the patient's friends, the patient's family, and the patient's significant other.

In addition, a new questionnaire specially created by the researchers for this study was administered. This questionnaire focused on the salient characteristics of physician-patient communication, designed to test contextual and interpersonal characteristics of the moment of communication itself (see Supplementary Material).

Statistical analysis

All statistical analyses were performed using R software (version 4.2.1).

Differences in categorical and continuous variables were evaluated applying Fisher's exact test and the ANOVA test, respectively. Differences were considered statistically significant with a p value <0.05.

Results

The questionnaires were administered to 127 patients, but only 98 patients returned the questionnaires correctly completed one month and/or one year after surgery. Therefore, 98 patients were included in the analysis. The clinical characteristics of the patients included in this study are summarized in Table 1.

The results of the scores obtained on the SF-36 and MSPSS questionnaires showed that patients who claim to have high social support at one month have more accentuated EWB both one month and one year after the surgery (Table 2), with statistically significant higher scores in the dimension of EWB ($p<0.05$). Patients who reported better SS one year after surgery also scored high on the GH dimension of the SF-36 ($p<0.05$) (Table 2). Particularly, those who reported having high family support had a higher SF score at one month after the surgery ($p<0.05$) (Table 3). Furthermore, one year after the surgery, these patients reported fewer limitations due to emotional problems than those who believe they have had medium to low family support (Table 3). Patients who reported having high family support at one year showed fewer fatigue problems and better SF (Table 3).

The scores also showed that support from a significant other at one year correlates with greater PF ($p<0.005$), fewer limitations due to physical health ($p<0.05$), less pain ($p<0.05$), less fatigue ($p<0.05$) and better general and EWB ($p<0.05$) (Table 4). Moreover, patients who had high friend support at one month reported a higher well-being score than those who felt unsupported by others ($p<0.05$). Patients who felt they had a high degree of friend support at one month reported a higher well-being score than those who felt unsupported by others ($p<0.05$) (Table 5). Social support in its various forms (friend support, significant other support, etc.) correlated with a lower request for extra medical visits in the first year following the surgery (Figure 1A). Correlating clinical data to SF-36 and MSPSS results showed that patients with comorbidities (hypertension, diabetes, hypercholesterolemia) reported higher overall pain, corresponding to a lower score, one year after surgery (Figure 1B). Regarding the body max index (BMI) effect, patients with BMI higher than the median reported a significantly lower score of physical functioning (Figure 1C) and GH (Figure 1D) at one year from surgery.

Patients with grade (G) 3 EC reported a lower score in SF compared with patients with G2 EC (Figure 1E), whereas patients with G2 EC reported a higher score in GH compared with patients with G1 EC (Figure 1F). Regarding surgical treatment, patients who received laparoscopy converted to laparotomy (Figure 1G) and

TABLE 1 Clinical characteristics of the patients.

	Overall (N=98)
Menopausal state	
Post-menopausal	64 (83.1%)
Pre-menopausal	13 (16.9%)
Misses	21
BMI	
Mean (SD)	28.6 (7.5)
Range	19.0 - 49.0
Misses	49
Comorbidies	
No	27 (42.2%)
Yes	37 (57.8%)
Misses	34
Histotype	
Endometrioid	82 (89.1%)
Hyperplasia	3 (3.3%)
Other	7 (7.6%)
Misses	6
Stadio. FIGO	
IA	74 (77.1%)
IB	20 (20.8%)
IIIC	2 (2.1%)
Misses	2
Grading	
G1	55 (61.1%)
G2	28 (31.1%)
G3	7 (7.8%)
Misses	8
Surgery	
Colposcopy	1 (1.0%)
Laparoscopy	62 (63.9%)
Laparotomy	32 (33.0%)
Laparoscopy+Laparotomy	2 (2.1%)
Misses	1
Pelvic lymphadenectomy	
No	65 (66.3%)
Yes	33 (33.7%)
Lomboaortic lymphadenectomy	
No	94 (95.9%)
Yes	4 (4.1%)
Presence of positive lymph nodes	
No	95 (97.9%)
Yes	2 (2.1%)
Misses	1
Surgical time (minutes)	
Mean (SD)	132.8 (45.1)
Misses	3
Days of hospitalization	
Mean (SD)	5.3 (2.0)
Misses	4
Postoperative complications	
No	81 (86.2%)
Yes	13 (13.8%)
Misses	4
Extra visits	
No	87 (91.6%)
Yes	8 (8.4%)
Misses	3

(Continued)

TABLE 1 Continued

SD, standard deviation.

patients who had a longer operation time (Figure 1H) reported a lower PF score at one year. Patients with a longer hospital stay reported a higher GH score at one year after treatment, showing that they felt better than patients who had a shorter hospital stay (Figure 2A). Similarly, patients with postoperative complications reported a higher Energy/Fatigue score one year after treatment, showing that they felt stronger than patients without complications (Figure 2B). The results also showed that patients who received brachytherapy (BRT) had a significantly lower role limitation in regard to PF (corresponding to a higher score) one month from surgery than patients who underwent both BRT and external beam radiation therapy (EBRT) ($p<0.05$) (Figure 2C). Regarding physician-patient communication, 59.8% of the patients reported that they were accompanied by a family member at the time the diagnosis was communicated. In 75.3% of cases, the communication of the diagnosis took place in the gynecological oncology clinic and the patients responded that the time devoted to communication was sufficient (85.6%). It was also shown that most of the participants (82.5%) found an empathetic and supportive attitude, and 93.8% felt supported in their care. 84.5% of participants said that the physicians communicated in clear language, and 91.8% of patients reported that they felt their privacy was protected (91.8%).

TABLE 2 SF36 scores comparison in patients who reported a different general social support.

		Social support Total_scale 1 Month			Social support Total_scale 1 Year		
		Low-medium (N=23)	High (N=74)	p value	Low-medium (N=22)	High (N=72)	p value
SF36 1Month	**Physical functioning**			0.104			
	Mean (SD)	73.6 (20.5)	64.2 (24.4)				
	Role limitation due to physical health			0.822			
	Mean (SD)	20.5 (37.5)	18.6 (33.1)				
	Role limitation due to emotional problems			0.368			
	Mean (SD)	36.4 (42.3)	45.6 (42.2)				
	Energy/Fatigue			0.529			
	Mean (SD)	49.0 (18.0)	52.0 (18.6)				
	Emotional well-being			**0.012**			
	Mean (SD)	50.0 (18.7)	62.0 (18.6)				
	Social functioning			0.106			
	Mean (SD)	61.5 (29.1)	71.7 (24.5)				
	Pain			0.770			
	Mean (SD)	58.5 (22.2)	60.4 (26.9)				
	General health			0.334			
	Mean (SD)	56.4 (25.4)	61.3 (18.6)				
SF36 1 Year	**Physical functioning**			0.478			0.085
	Mean (SD)	73.9 (27.8)	78.3 (24.4)		68.3 (30.6)	79.1 (23.9)	
	Role limitation due to physical health			0.645			0.267
	Mean (SD)	62.0 (43.2)	66.7 (42.4)		55.7 (41.5)	67.4 (43.3)	
	Role limitation due to emotional problems			0.956			0.910
	Mean (SD)	68.1 (44.4)	67.6 (41.2)		69.7 (43.6)	68.5 (41.1)	
	Energy/Fatigue			0.077			0.264
	Mean (SD)	51.7 (21.3)	60.1 (18.8)		53.6 (18.5)	59.0 (20.0)	
	Emotional well-being			**< 0.001**			0.134
	Mean (SD)	52.9 (23.5)	69.4(15.6)		59.8 (18.8)	66.8 (19.0)	
	Social functioning			0.473			0.103
	Mean (SD)	78.3 (24.1)	82.2 (21.5)		75.1 (24.0)	84.0 (21.4)	
	Pain			0.182			0.120
	Mean (SD)	68.4 (27.8)	76.5 (24.0)		66.3 (27.0)	76.1 (25.1)	
	General health			0.363			0.010
	Mean (SD)	59.0 (22.1)	63.6 (20.9)		52.3 (19.7)	65.6 (20.9)	

Scores collected from both questionnaires at 1 month and 1 year from surgery were evaluated and integrated into statistical analyses. SD, standard deviation.
Bold and colored text means significant p-value.

TABLE 3 SF36 scores comparison in patients who reported a different family support.

		Social support Family subscale 1 Month			Social support Family subscale 1 Year		
		Low-Medium (N=23)	High (N=74)	p value	Low- Medium (N=22)	High (N=72)	p value
SF36 1 Month	**Physical functioning**			0.676			
	Mean (SD)	63.8 (28.1)	66.9 (23.4)				
	Role limitation due to physical health			0.618			
	Mean (SD)	14.6 (31.0)	19.9 (34.7)				
	Role limitation due to emotional problems			0.257			
	Mean (SD)	30.6 (41.4)	45.5 (42.4)				
	Energy/Fatigue			0.194			
	Mean (SD)	44.5 (10.4)	52.3 (19.2)				
	Emotional well-being			0.183			
	Mean (SD)	52.4 (19.9)	60.6 (19.0)				
	Social functioning			**0.006**			
	Mean (SD)	50.2 (22.5)	72.1 (25.3)				
	Pain			0.381			
	Mean (SD)	54.3 (22.9)	61.2 (26.0)				
	General health			0.170			
	Mean (SD)	52.9 (21.7)	61.6 (20.0)				
SF36 1 Year	**Physical functioning**			0.833			0.153
	Mean (SD)	75.8 (32.5)	77.5 (24.2)		68.7 (34.5)	78.5 (23.2)	
	Role limitation due to physical health			0.615			0.402
	Mean (SD)	59.6 (45.1)	66.0 (42.3)		56.9 (42.7)	66.4 (43.1)	
	Role limitation due to emotional problems			**0.046**			0.384
	Mean (SD)	46.2 (48.2)	71.1 (40.2)		61.1 (44.7)	70.6 (40.7)	
	Energy/Fatigue			0.108			**0.019**
	Mean (SD)	50.0 (19.7)	59.5 (19.5)		48.12(22.6)	60.1 (18.3)	
	Emotional well-being			0.117			0.060
	Mean (SD)	57.5 (20.2)	66.6 (18.8)		57.6 (18.6)	67.0 (18.9)	
	Social functioning			0.122			**0.008**
	Mean (SD)	72.2 (24.6)	82.5 (21.5)		69.6 (28.5)	84.8 (19.6)	
	Pain			0.690			0.222
	Mean (SD)	76.8 (22.4)	73.8 (25.6)		67.1 (29.6)	75.4 (24.7)	
	General health			0.619			0.077
	Mean (SD)	59.7 (25.8)	62.9 (20.6)		54.4 (22.0)	64.3 (20.8)	

Scores collected from both questionnaires at 1 month and 1 year from surgery were evaluated and integrated into statistical analyses. SD, standard deviation.
Bold and colored text means significant p-value.

TABLE 4 SF36 scores comparison in patients who reported a different support from another significant person.

		Social support Other subscale 1 Month			Social support Other subscale 1 Year		
		Low-Medium (N=18)	High (N=79)	p value	Low- Medium (N=13)	High (N=81)	p value
SF36 1 Month	**Physical functioning**			0.560			
	Mean (SD)	69.4 (25.6)	65.7(23.5)				
	Role limitation due to physical health			0.568			
	Mean (SD)	14.7 (26.6)	19.9 (35.4)				
	Role limitation due to emotional problems			0.273			
	Mean (SD)	33.3 (42.5)	45.7 (42.0)				
	Energy/Fatigue			0.495			
	Mean (SD)	48.4 (21.7)	51.9 (17.7)				
	Emotional well-being			**0.045**			
	Mean (SD)	50.8 (23.2)	61.2 (17.8)				
	Social functioning			0.068			
	Mean (SD)	59.0 (30.2)	71.6 (24.4)				
	Pain			0.946			
	Mean (SD)	60.4 (26.4)	59.9 (25.8)				
	General health			0.089			
	Mean (SD)	52.6 (28.1)	61.9 (17.9)				
SF36 1 Year	**Physical functioning**			0.444			**< 0.001**
	Mean (SD)	73.1 (25.2)	78.2 (25.2)		51.7 (31.1)	80.6 (22.7)	
	Role limitation due to physical health			0.626			**0.043**
	Mean (SD)	61.1 (43.1)	66.6 (42.5)		42.3 (46.1)	68.2 (41.6)	
	Role limitation due to emotional problems			0.748			0.100
	Mean (SD)	64.8 (45.0)	68.4 (41.3)		51.2 (48.4)	71.6 (39.9)	
	Energy/Fatigue			0.430			**0.017**
	Mean (SD)	54.7 (18.5)	58.8 (20.0)		45.8 (21.4)	59.7 (18.8)	
	Emotional well-being			0.054			**0.046**
	Mean (SD)	57.6 (19.3)	67.2 (18.7)		55.4 (20.2)	66.8 (18.6)	
	Social functioning			0.314			0.311
	Mean (SD)	76.5 (24.9)	82.3 (21.4)		76.1 (25.7)	82.8 (21.7)	
	Pain			0.630			**0.006**
	Mean (SD)	71.9 (27.9)	75.1 (24.5)		55.7 (26.5)	76.7 (24.6)	
	General health			0.366			**0.033**
	Mean (SD)	58.4 (25.2)	63.4 (20.1)		50.8 (21.5)	64.3 (20.8)	

Scores collected from both questionnaires at 1 month and 1 year from surgery were evaluated and integrated into statistical analyses. SD, standard deviation.
Bold and colored text means significant p-value.

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TABLE 5 SF36 scores comparison in patients who reported a different support from friends.

		Social support Friends subscale 1 Month			Social support Friends subscale 1 Year		
		Low-Medium (N=18)	High (N=79)	p value	Low-Medium (N=13)	High (N=81)	p value
SF36 1 MONTH	**Physical functioning**			0.841			
	Mean (SD)	66.9 (22.7)	65.9 (24.8)				
	Role limitation due to physical health			0.504			
	Mean (SD)	16.3 (32.8)	21.0 (35.0)				
	Role limitation due to emotional problems			0.718			
	Mean (SD)	41.7 (42.6)	44.8 (42.2)				
	Energy/Fatigue			0.077			
	Mean (SD)	47.2 (16.1)	54.1 (19.4)				
	Emotional well-being			**0.047**			
	Mean (SD)	54.6 (18.1)	62.6 (19.3)				
	Social functioning			0.374			
	Mean (SD)	66.5 (26.7)	71.3 (25.2)				
	Pain			0.106			
	Mean (SD)	54.9 (25.0)	63.6 (26.0)				
	General health			0.152			
	Mean (SD)	56.6 (22.9)	62.7 (18.0)				
SF36 1 YEAR	**Physical functioning**			0.531			0.237
	Mean (SD)	75.4 (26.5)	78.7 (24.2)		73.7 (27.37)	80.17 (24.37)	
	Role limitation due to physical health			0.765			0.818
	Mean (SD)	64.0 (43.0)	66.7 (42.3)		66.9 (40.7)	64.8 (44.8)	
	Role limitation due to emotional problems			0.269			0.223
	Mean (SD)	73.2 (40.3)	63.6 (42.7)		75.2 (37.9)	64.6 (43.8)	
	Energy/Fatigue			0.336			0.294
	Mean (SD)	55.8 (20.9)	59.7 (18.7)		55.814 (19.668)	60.102 (19.242)	
	Emotional well-being			0.114			0.396
	Mean (SD)	61.7 (23.0)	68.0 (15.2)		63.6 (22.4)	67.0 (15.5)	
	Social functioning			0.709			0.975
	Mean (SD)	80.3 (24.0)	82.0 (20.8)		82.7 (22.1)	82.8 (21.3)	
	Pain			0.540			0.187
	Mean (SD)	72.7 (25.3)	75.9 (25.0)		69.8 (25.6)	77.0 (26.1)	
	General health			0.255			0.092
	Mean (SD)	59.5 (23.6)	64.6 (19.1)		58.4 (22.3)	65.9 (19.9)	

Scores collected from both questionnaires at 1 month and 1 year from surgery were evaluated and integrated into statistical analyses. SD, standard deviation.
Bold and colored text means significant p-value.

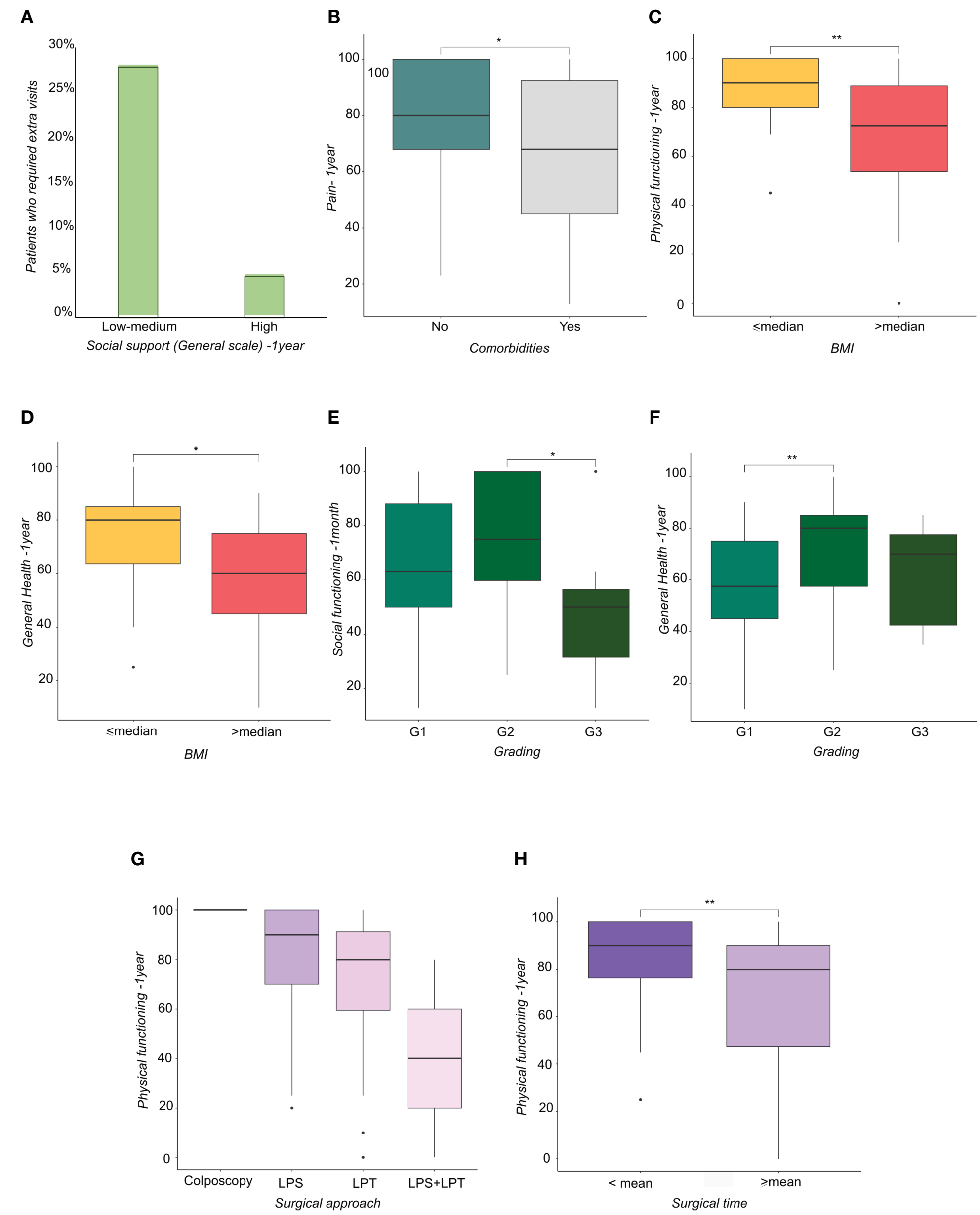

FIGURE 1
(A) Histograms representing the percentage of patients who required extra visits subdivided by social support perception. **(B)** Boxplots representing the distribution of Pain score at one year from surgery in patients subdivided by the presence of comorbidities. **(C, D)** Boxplots representing the distribution of **(C)** physical functioning score at one year from surgery and **(D)** general health at one year from surgery in patients subdivided by Body Mass Index-BMI (lower or higher than median value). **(E, F)** Boxplots representing the distribution of **(E)** Social functioning score at one month and **(F)** General Health score at one year from surgery in patients subdivided by tumor grading. **(G, H)** Boxplots representing the distribution of physical functioning score at one year from surgery in patients subdivided by **(G)** surgical approach and **(H)** surgical time (lower or higher than mean time). * <0.05, **<0.01.

Discussion

The findings of this study reveal a noteworthy trend, namely that patients who perceived robust SS, both at the one-month and one-year junctures following the surgery, showed higher levels of EWB. In particular, high SS at one month is associated with a more accentuated EWB at both one month and one year after the surgery, with statistically significant scores in the dimension of EWB ($p<0.05$). Thus, the positive effect of high SS in the immediate postoperative period was maintained even after one year. Moreover, high PSS one year after surgery also was associated with a high score on the GH dimension of the SF-36 ($p<0.05$). The lack of social contacts, institutional connections and community involvement constitutes social isolation (27, 28). Social isolation has been associated with tumor metastasis, chemoresistance, resistance to radiotherapy and suppression of immune defense (29). Social isolation of cancer patients is associated with reduced OS therefore SS should be guaranteed and promoted in all cancer patients even in EC patients, generally characterized by a better prognosis. EC patients are typically obese, and high BMI and

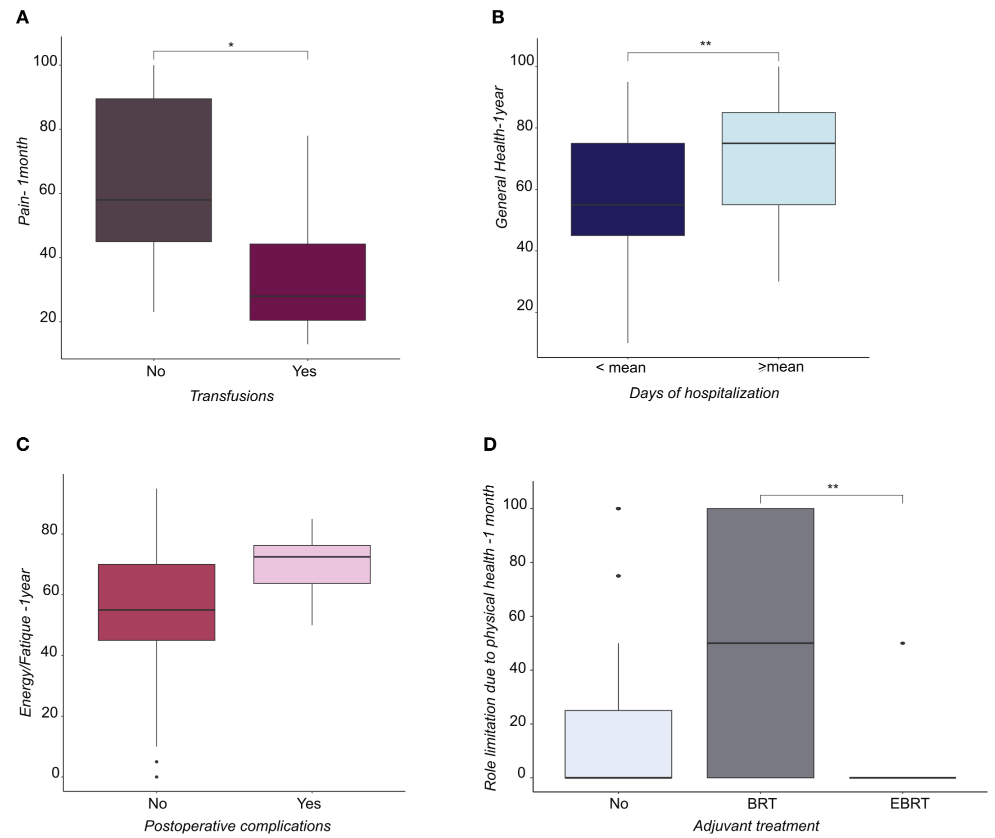

FIGURE 2
(A) Boxplots representing the distribution of pain score at 1 month from surgery in patients subjected or not to transfusions. **(B)** Boxplots representing the distribution of General Health score at 1 year from surgery in patients subdivided by days of hospitalization (lower or higher than mean). **(C)** Boxplots representing the distribution of Energy/fatique score at 1 year from surgery in patients that underwent or not postoperative complication. **(D)** Boxplots representing the distribution of the score related to the role limitation due to physical health at 1 month from surgery in patient not subjected to adjuvant treatment or subjected to brachytherapy (BRT) or external beam radiation therapy (EBRT). * <0.05, **<0.01.

smoking have been reported to affect EWB (30, 31). In our study, the effect of BMI on EWB was confirmed, and in particular, patients with BMI higher than the median reported significantly lower scores of PF and GH at one year from surgery. In a recent study, Karataşli et al. reported that high BMI patients had lower PF scores (32). In a previous systematic review, high BMI showed detrimental effects on physical, social, and role functioning but not on emotional or cognitive functioning (33). Although there is still debate as to whether BMI can influence the risk of EC recurrence (34, 35), providing indications for making lifestyle and dietary changes could be useful for improving QoL regardless of the effect on oncological outcomes (30).

Socioeconomic status (SES) and adjuvant therapy can also affect the EWB of EC patients (36, 37). Patients with a low and intermediate SES reported improved emotional functioning over time, while patients with a high SES reported a higher but stable emotional functioning (36). A recent study reported that BRT is associated with higher EWB than EBRT, and with no lasting effects on emotional and functional health. In contrast, EC patients were still physically affected for years after completion of EBRT (37). In our study, patients who received EBRT combined with BRT showed worse physical role functioning than patients who received only BRT one month after treatment. In more aggressive gynecological cancers such as ovarian cancer, also multiple recurrences significantly decrease mean EWB; on the contrary PWB and FWB were above population norms because of the high levels of social well-being, with over 85% of each group reporting substantial emotional support from their families (38). Patients and their families can be particularly vulnerable when diagnosed with cancer. Cancer patients often turn to their family members to manage their psychological well-being. The support of family members for their EC patient is essential to guarantee any home care but also to facilitate the resumption of routine daily activities. Unfortunately, cancer patients often have difficulty talking about the illness to their family members, and family members may, in the long run, suffer from psychological distress as a result of their cancer patient's illness. Therefore, healthcare professionals must communicate effectively with patients and their families and teach patients and families to communicate with each other even in the event of bad news. Furthermore, it is necessary to support the psychological well-being of people accompanying cancer patients because the psychological well-being of cancer patients is closely connected with that of the people accompanying them (39, 40). In our study, those who reported having high family support had a higher SF score at one month after the surgery ($p<0.05$) (Table 3). Furthermore, one year after the surgery, there were fewer limitations due to emotional problems than those who believed they had had medium to low family support

(Table 3). Other studies have shown that lacking emotional support from expected sources such as family and friends resulted in loneliness and anger (38). A comprehensive analysis of the SF-36 and MSPSS outcomes underscores a compelling association between high SS, notably familial, and a spectrum of favorable outcomes encompassing improved SF, diminished pain perception, reduced fatigue, and enhanced overall general and EWB. Intriguingly, a stronger perception of SS also coincides with a reduction in the need for supplementary medical visits during the year after the surgery. EC patients represent a large portion of patients diagnosed with gynecological cancers, with a large investment of resources. Several studies have shown that minimal in-person or telephone follow-ups can be effective in ensuring adequate surveillance, eliminating unnecessary care (41, 42). Promoting adequate support from the beginning of treatment could be further useful in optimizing resources allocated to oncological follow-ups and enabling healthcare cost savings. Examining the intricate interplay between clinical data and QoL, our study illuminates distinct correlations. Patients grappling with comorbidities report a heightened prevalence of general pain one year after surgery, highlighting the complex interaction between underlying medical conditions and sustained discomfort. Conversely, individuals contending with postoperative complications paradoxically exhibit elevated scores in the Energy/Fatigue dimension, indicative of an augmented sense of vitality. It is conceivable that overcoming a particularly critical condition such as postoperative complications requiring a longer hospital stay can foster, once overcome, greater self-confidence and greater vitality. However, this vitality is juxtaposed by lower scores in the PF dimension, emphasizing the nuanced trade-offs inherent in the relationship between clinical data and patient QoL. Regarding surgical treatment, patients who received laparoscopy converted to laparotomy and patients who had a longer operation time reported a lower PF rate at one year. According to the literature, EC patients undergoing laparoscopy converted to laparotomy have longer operating times, more blood loss, and more intraoperative and postoperative complications (43–45).

Conclusions

According to previous literature (9, 11, 46), this study underscores the significance of PSS for EC patients. The multifaceted nature of SS, encompassing emotional assistance and information sharing, emerges as a pivotal factor aiding patients in confronting the challenges inherent to EC. This form of support contributes to bolstering psychological well-being and enhancing overall QoL.

Ensuring the holistic well-being of EC patients necessitates the provision of comprehensive medical, psychological, and SS throughout the trajectory of the illness.

A significant aspect illuminated by this study pertains to the profound impact of the communication modality on the psychological well-being of women diagnosed with EC. Notably, those who receive a diagnosis accompanied by empathetic communication, comprehensive tumor explanations, and elucidation of available treatment options tend to feel more supported during their treatment journey. Moreover, at the time of planning the surgery, counseling should be provided to improve lifestyle and eating habits.

Sharing treatment strategies with the relative risks and benefits allows for the creation of a therapeutic alliance, obtaining the maximum commitment from patients even in the face of the unforeseen events that each therapeutic path may present. This approach contributes to alleviating anxiety and stress associated with the diagnosis and the perceived loss of control over one's life. On the contrary, a lack of informational support can result in significant uncertainty and fear (41).

The findings of our study not only emphasize the positive influence of social support from loved ones on the psychological well-being of women with EC, but also underscore the pivotal role of healthcare professionals' communication in shaping the perception of the disease experience. Women who feel supported and understood experience reduced isolation and an enhanced ability to confront the challenges linked to their illness. This aspect warrants further investigation.

Assessing and addressing issues related to QoL constitutes an integral facet of modern medical care. Providing compassionate care to the patient, in conjunction with addressing the cancer itself, necessitates an evolving approach aimed at preserving and enhancing both the quality and quantity of life. Social support should be considered an essential component of health care, as it helps improve patients' resilience and QoL during their cancer journey (36).

The evaluation of SS sources should be an integral part of treatment planning, particularly within the family context. Hence, involving spouses and other family members in relevant courses or strategies is recommended. Additionally, healthcare professionals play a pivotal role as sources of SS for women with cancer, necessitating a heightened understanding of these women's unique experiences.

Although the communicative aspect was explored via a non-validated multiple-choice questionnaire, descriptive analysis suggests that a favorable perception of physician-patient communication (empathy, time allocation, setting, presence of a significant other) can positively impact the patient's illness experience. These descriptive results underscore the importance for healthcare personnel to prioritize communicative and relational aspects when communicating the diagnosis and to inquire whether the patient desires information in the presence of a designated caregiver.

Strengths, weaknesses, and future prospects

A key strength of this study lies in its emphasis on SS and the value attributed to patient-healthcare provider communication within the medical journey and illness experience of women with EC. Another notable strength is the discrete analysis of distinct sources of SS, facilitated by the unique instrument chosen for this study. Unfortunately, we do not have data for all patients, so the lack may have weakened our analysis. Any comorbidities or medications may have influenced our variables. However, a principal limitation of the research pertains to the modest sample size and the absence of correlation between responses to the communication questionnaire and data on QoL. Future studies could address these limitations by incorporating larger sample sizes and focusing on the influence of perceived physician-patient communication on psycho-EWB. Although most studies tested patients at four and six months, we decided to administer the questionnaires one year later, to avoid possible effects due to adjuvant therapies following surgery. We hypothesized that one year was a long enough period to evaluate the achievement of emotional balance.

In conclusion, this study provides valuable insights into the pivotal roles of EWB of EC patients is intricately linked to the level of SS they receive and the quality of their communication with healthcare providers. Strengthening these areas can lead to substantial improvements in their MH and overall QoL. The quality of care should always guarantee psychological well-being. Our study highlights that the quality of care already depends on the way in which the diagnosis and oncological pathways are communicated.

In a period in which public health resources are always scarce, investing in tools such as effective communication useful for improving assistance and at the same time reducing health care costs becomes essential (47). These findings underscore the need for comprehensive, patient-centered care that acknowledges the multidimensional facets of patient well-being and the nuanced impact of interpersonal interactions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved byArea Vasta Emilia Nord- Reggio Emilia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ViM: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. MP: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. FT: Data curation, Formal Analysis, Writing – original draft. ER: Writing – original draft, Writing – review & editing. VaM: Data curation, Investigation, Writing – original draft, Writing – review & editing. LA: Investigation, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1447644/full#supplementary-material

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Efficacy of outdoor interventions for myopia in children and adolescents: a systematic review and meta-analysis of randomized controlled trials

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Objectives: The objective of this systematic review and meta-analysis was to evaluate the overall efficacy of outdoor interventions for myopia in children and adolescents, and to provide evidence for the prevention and control of myopia.

Methods: Randomized controlled trials of outdoor interventions for myopia in children and adolescents were identified using electronic databases and manual searches. The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess risk of bias in randomized controlled trials. A mean difference (MD) and a risk ratio (RR) with a 95% confidence interval (CI) were used to combine effect sizes. A sensitivity analysis was performed for each outcome using a stepwise elimination method to assess whether the pooled results were significantly affected by individual studies.

Results: The analysis included seven randomized controlled trials involving a total of 9,437 subjects. The meta-analysis showed marked and statistically significant improvements in spherical equivalent refraction (MD = 0.19; 95% CI 0.14 to 0.25; $p < 0.01$), axial length (MD = −0.09; 95% CI −0.13 to −0.05; $p < 0.01$), and myopia incidence (RR = 0.84; 95% CI 0.78 to 0.91; $p < 0.01$) following outdoor interventions.

Conclusion: Outdoor interventions effectively contributed to the prevention and control of myopia in children and adolescents, positively impacting spherical equivalent refraction, axial length, and myopia incidence. Outdoor interventions were characterized by low risk and high therapeutic benefits and could serve as alternative or adjuvant approaches to medication for the treatment of myopia. Considering the advantages in terms of safety and efficacy, outdoor interventions may be considered as a preferred intervention for the treatment of myopia in children and adolescents, while susceptibility to diseases associated with sunlight, particularly UV exposure, must be taken into account.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, Identifier CRD42024538695.

KEYWORDS

children, adolescents, outdoor interventions, myopia, meta-analysis

1 Introduction

Myopia, as one of the most common public health problem in the world, is a major eye disease leading to visual impairment in children and adolescents (1, 2). In recent years, the way children and adolescents access information has been altered dramatically with the changes in the global economy and social environment, as well as the widespread popularity of smart electronic products and the emergence of online we-media. Significant alterations in the learning pathways, lifestyles and sleeping habits of children and adolescents have had a profound impact on myopia, and the situation for myopia prevention and control has become increasingly challenging (3, 4). The current global prevalence of myopia is estimated to be in excess of 28.3%, with projections indicating that by 2050, the coverage will reach 49.8%, while the prevalence of high myopia will also reach 10% (5, 6). Meanwhile, a substantial body of evidence has indicated that myopia is particularly severe in certain demographic groups, especially among children and adolescents, with an overall myopia incidence exceeding 50% (7–9). It should be emphasized that high myopia increases the risk of pathologic ocular changes, including cataract, glaucoma, retinal detachment, and myopic macular degeneration, which may lead to irreversible vision loss (10, 11).

For children and adolescents, the heavy educational burden and the prevalence of smart electronic products have led to a sharp increase in the need for long-term short-distance use of eyes (e.g., reading, writing, and using electronic devices), thus resulting in a significant increase in the probability of myopia in this group, with a notable increase in the number of cases diagnosed at an early age and with a high degree of severity (12). Several countermeasures have been developed to help children and adolescents effectively prevent and control myopic progression, including Atropine (13), Pirenzepine (14), Orthokeratology (15), Spectacle lenses (16), and Contact lenses (17). However, these medications have certain drawbacks, including the potential for developing drug resistance with prolonged use, the risk of rebound upon discontinuation, and increased susceptibility to keratitis associated with long-term wearing of contact lenses (18, 19). In this context, outdoor interventions may help to address these limitations. As a self-directed health behavior, outdoor interventions (including engaging in outdoor activities and increasing time spent outdoors) have the advantages of being highly participatory and inexpensive, which are difficult to replace with drugs and lenses. While previous evidence suggested outdoor interventions effectively reduce the incidence and progression of myopia in children and adolescents, conflicting findings exist (20–24). Some studies indicated no direct association between outdoor interventions and myopia in this age group (25–27). Therefore, there is no unified consensus among experts on whether or not the progression of myopia in children and adolescents can be effectively prevented and controlled.

Myopia is generally quantified as spherical equivalent refraction (SER), which is commonly defined as the SER of ≤ -0.5 dioptres (D) or less after cycloplegic refraction (1, 28). In addition, axial length (AL) is one of the most important physiological indicators in the progression of myopia, and its change is closely related to refractive status, with longer AL implying more severe myopia (29–32). Therefore, control of AL of the eye during development is crucial for achieving normal vision, and therefore is a primary site for prevention (1). However, published randomized controlled trials (RCTs) of outdoor interventions to prevent and control myopia in children and adolescents provide inconsistent evidence, resulting in different effect sizes. For children and adolescents with an increasing myopia incidence, improving myopia through outdoor interventions rather than medication contributes to their physical and mental health development and quality of life (33, 34). The objective of this systematic review and meta-analysis was to evaluate the overall efficacy of outdoor interventions for myopia in children and adolescents, and to provide evidence for the prevention and control of myopia.

2 Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO), under number CRD42024538695.

2.1 Search strategy

Based on medical subject headings and free-text terms, a search was conducted across six databases: PubMed, Embase, EBSCOhost, Scopus, Web of Science, and APA PsycINFO. Additionally, the Google database was manually searched for relevant studies. The search timeframe was from the inception of each database to April 2024, and the search strategy followed the PICOS principle: (P) population: children and adolescents (ages between 6 and 19 years); (I) intervention: outdoor interventions, including outdoor activities, time spent outdoors, outdoor exposure, etc.; (C) control: control group receiving only routine treatment or appropriate rehabilitation intervention; (O) outcome: any assessment of myopia; (S) study design: randomized controlled trials. The search strategy is presented in Table 1, per the PubMed database.

2.2 Inclusion and exclusion criteria

The criteria for inclusion and exclusion of studies are presented in Table 2.

2.3 Studies selection and quality assessment

According to the predetermined inclusion and exclusion criteria, two independent researchers (ZYM and WFJ) used EndNote 20.6 bibliographic software for evidence selection. Duplicates were excluded when the references were imported into EndNote 20.6 and the remaining duplicates were manually removed. Two independent researchers screened and checked the references based on information such as the title, abstract, and full text. During the study selection process, any controversies were discussed and addressed by consulting the third author (SL).

The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the risk of bias in RCTs, in the following five aspects: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the

TABLE 1 PubMed search strategy.

#1	Myopi* [MeSH Terms] OR Refractive Errors [MeSH Terms]
#2	Myopi* [Title/Abstract] OR Myopia [Title/Abstract] OR Myopias [Title/Abstract] OR Short-sight [Title/Abstract] OR Short-sighted [Title/Abstract] OR Short-sightedness [Title/Abstract] OR Short sight [Title/Abstract] OR Short sighted [Title/Abstract] OR Short sightedness [Title/Abstract] OR Near-sight [Title/Abstract] OR Near-sighted [Title/Abstract] OR Near-sightedness [Title/Abstract] OR Near sight [Title/Abstract] OR Near sighted [Title/Abstract] OR Near sightedness [Title/Abstract] OR Refractive Errors [Title/Abstract] OR Refract* [Title/Abstract] OR Ametropi* [Title/Abstract]
#3	#1 OR #2
#4	Outdoor* [Title/Abstract] OR Outside [Title/Abstract] OR Physical activit* [Title/Abstract] OR Leisure activit* [Title/Abstract] OR Exercise* [Title/Abstract] OR Sport* [Title/Abstract]
#5	Adolescen* [Title/Abstract] OR Teen* [Title/Abstract] OR Youth* [Title/Abstract] OR Child* [Title/Abstract] OR Minor* [Title/Abstract] OR Pupil* [Title/Abstract] OR Pediatric* [Title/Abstract] OR Paediatric* [Title/Abstract]
#6	#3 AND #4 AND #5

TABLE 2 Inclusion and exclusion criteria.

Category	Inclusion criteria	Exclusion criteria
Population	Children and adolescents groups (ages between 6 and 19 years)	Not children and adolescents
Intervention	Outdoor interventions, including outdoor activities, time spent outdoors, outdoor exposure, etc.	Not outdoor interventions
Control	Control group receiving only routine treatment or appropriate rehabilitation intervention	Inappropriate control conditions or control groups
Outcome	Any assessment for myopia, including spherical equivalent refraction, axial length, and myopia incidence	Studies that did not assess myopia
Study design	Randomized controlled trials	Non-randomized controlled trials, such as quasi-randomized controlled trials, study protocols, review, conference abstracts, comments, etc.

outcome, and (5) selection of the reported result. For each eligible study, the overall risk of bias was assessed as either low risk of bias, with some concerns, or high risk of bias. During the quality assessment process, any controversies were discussed and addressed by consulting the third author (SL).

2.4 Data extraction

Using a data extraction form that included relevant information, two independent researchers collected the following data from each included study: (1) basic information, including the first author, country, and year of publication, (2) participant characteristics, including mean (standard deviations) age, sample size, and percentage of boys, (3) intervention and control, and (4) myopia-related outcome measures.

2.5 Statistical analysis

All the outcomes assessed in this systematic review and meta-analysis included spherical equivalent refraction (SER), axial length (AL), and myopia incidence. For continuous variables, the mean difference (MD) with a 95% confidence interval (CI) was used to combine effect sizes as the measurement tools used in different RCTs were the same (35). For binary variables, the risk ratio (RR) was calculated with a 95% CI where the RR represents the ratio of the cumulative incidence of myopia between the intervention and control groups over the entire study period. For all meta-analyses, heterogeneity among studies was assessed using the Chi-square test based on Q-test and I^2 statistics with a significance level of p-value < 0.10 (36). According to the recommendations of Cochrane's handbook, when p-value <0.10 or $I^2 > 50\%$, there was a significant heterogeneity, and a random-effect model was used to merge the results. Otherwise, a fixed-effect model was used to merge the results when there was no significant heterogeneity (p-value >0.10 or $I^2 < 50\%$) (35). All meta-analyses of this study were performed using Stata 18.0 software.

Considering the number of studies included, publication bias was assessed by Egger's test. The small-scale study effects were evaluated by calculating Egger's regression intercepts, with p-value <0.05 as a threshold for statistical significance (37). The trim and fill method was used to assess the stability of the pooled results if there was publication bias (38). A sensitivity analysis was performed for each outcome using a stepwise elimination method to assess whether the pooled results were significantly affected by individual studies (35). The analysis showed that the pooled results remained stable and were not substantially altered by changing the selection of studies included, indicating that the pooled results were robust and insensitive to study selection. In contrast, altering the selection of studies included resulted in statistical changes to the pooled results, suggesting that the pooled results were more sensitive to study selection and less robust. All publication bias tests and sensitivity analyses of this study were performed using Stata 18.0 software.

3 Results

3.1 Literature search and eligible studies

A total of 7,869 studies were identified through database searches, including PubMed ($n = 1,034$), Embase ($n = 1,644$), Web of Science ($n = 2,990$), Scopus ($n = 2084$), EBSCOhost ($n = 56$), APA PsycINFO ($n = 9$), and other sources ($n = 52$). After removing duplicate studies ($n = 3,851$), the titles and abstracts of 4,018 studies were screened for eligibility, and 3,889 references were eliminated due to samples inappropriate ($n = 409$), not RCT studies ($n = 1,165$), non-relevant studies ($n = 1785$), study protocol ($n = 14$), and review/meta-analysis ($n = 516$). Therefore, 129 studies were subjected to full-text review, 122 of which were deemed ineligible because the sample was inappropriate ($n = 9$), no outcomes of myopia ($n = 5$), intervention other than outdoor interventions ($n = 86$), inappropriate control ($n = 3$), incomplete date ($n = 1$), not in English language ($n = 3$), and no full-text such as dissertations ($n = 15$). Finally, 7 studies met the inclusion criteria and were included in the meta-analysis (39–45). A PRISMA flowchart of the literature search is presented in Figure 1.

3.2 Study characteristics

Seven full-text RCTs met inclusion criteria, all of which were conducted in China (39–45). The study populations consisted of students in Guangzhou (one study) (39), Shanghai (one study) (40), Shenyang (one study) (41), Wenzhou (one study) (42), Anyang (one study) (43), Yudu and Jiangxi (one study) (44), and Taiwan (one study) (45). In total, 4,778 subjects were assigned to the intervention group, with a mean age ranging from 6.61 to 10.09 years, while 4,659 were assigned to the control group, with a mean age ranging from 6.57 to 10.25 years. The length of the intervention ranged from 1 year to 3 years, the frequency from 5 to 7 times a week, and the duration from 40 to 60 min. The main characteristics of the seven RCTs are presented in Table 3.

3.3 Assessment of risk bias

Six studies showed a low risk of bias in the randomization process (39–41, 43–45), and one study was assessed as having some concerns owing to the baseline differences (42). For deviations from intended interventions, six studies were considered low risk (39, 41–45), and one study was regarded as having some concerns because of the experimental context (40). For missing outcome data, five studies were considered low risk because the data for the outcome were available for all or nearly all randomized participants (39, 40, 42–44). One study had some concerns and one had high risk due to incomplete collection of participant data and lack of evidence that the result was not biased

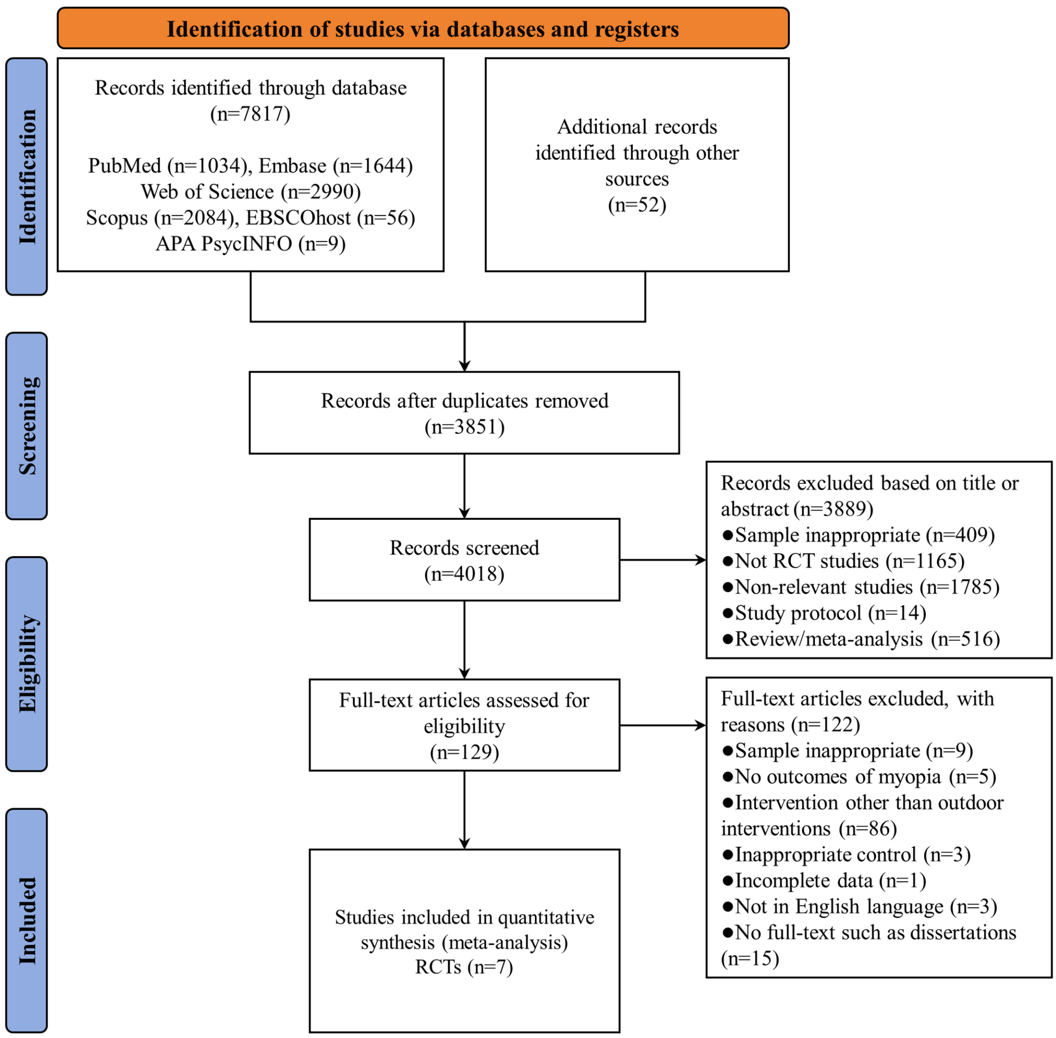

FIGURE 1
Flowchart of studies selection.

TABLE 3 Main characteristics of included randomized controlled trials.

Included studies	Population	Age [Mean (SD)]	Total/M%	Intervention	Control	Outcome
He et al. (39) (China)	Children in grade 1 from 12 primary schools in Guangzhou	T: 6.61 (0.33) C: 6.57 (0.32)	T: 919/52.6% C: 929/54.6%	Time spent outdoors Length: 3 years Freq: 5 times a week Duration: 40 min	Treatment as usual	SER, AL, Myopia incidence
He et al. (40) (China)	Students aged 6–9 years from 24 primary schools in Shanghai	T: 7.30 (0.70) C: 7.20 (0.70)	T: 1878/52.9% C: 1608/52.8%	Time spent outdoors Length: 2 years Freq: 5 times a week Duration: 40 min	Treatment as usual	SER, AL, Myopia incidence
Jin et al. (41) (China)	Students of two primary and two junior high schools in Shenyang	T: 10.09 (2.35) C: 10.25 (2.33)	T: 214/54.2% C: 177/47.5%	Outdoor activities Length: 1 year Freq: 5 times a week Duration: 40 min	No-intervention	SER, AL
Jingyi et al. (42) (China)	Students from three primary schools in Wenzhou	T: NR C: NR	T: 353/NR C: 366/NR	Outdoor activities Length: 1 year Freq: 5 times a week Duration: 60 min	No-intervention	SER, AL
Li et al. (43) (China)	Students from 11 primary schools in Anyang	T: 8.38 (0.34) C: 8.35 (0.30)	T: 135/52.6% C: 133/57.1%	Time spent outdoors Length: 1 year Freq: 7 times a week Duration: NR	Treatment as usual	SER, AL, Myopia incidence
Wang et al. (44) (China)	Children in grades 3 and 4 from 24 elementary school in Yudu and Jiangxi	T: 9.21 (0.62) C: 9.23 (0.62)	T: 1012/50.5% C: 1020/47.2%	Outdoor activities Length: 1 year Freq: 5 times a week Duration: 120 min	No-intervention	SER, AL, Myopia incidence
Wu et al. (45) (China)	Grade 1 schoolchildren in 16 schools in Taiwan	T: NR C: NR	T: 267/55.1% C: 426/50.3%	Time spent outdoors Length: 1 year Freq and Duration: 11 h weekly	Treatment as usual	SER, AL, Myopia incidence

T, test group; C, control group; M%, percentage of boys; SER, spherical equivalent refraction; AL, axial length.

by missing outcome data (41, 45). The measurement outcome bias and selection of the reported result were low risk because all studies used appropriate methods to measure outcomes, and all measurements and data analyses were available in the results. The overall risk was low risk in three studies (39, 43, 44), some concerns in three studies (40, 42, 45), and high risk in one study (41). The Cochrane risk of bias assessment is presented in Figures 2, 3.

3.4 Meta-analysis

A total of seven RCTs were included in the meta-analysis, and heterogeneity was examined using the Chi-square test based on Q-test and I^2 statistics, indicating that the pooled results for SER ($I^2 = 0.00\%$; $Q = 5.10$; $p = 0.53$) and myopia incidence ($I^2 = 0.00\%$; $Q = 0.63$; $p = 0.96$) showed no significant heterogeneity. The pooled results for AL, however, had moderate heterogeneity ($I^2 = 58.78\%$; $Q = 14.56$; $p = 0.02$). There were marked and statistically significant improvements in SER (MD = 0.19; 95% CI 0.14 to 0.25; $p < 0.01$), AL (MD = −0.09; 95% CI −0.13 to −0.05; $p < 0.01$), and myopia incidence (RR = 0.84; 95% CI 0.78 to 0.91; $p < 0.01$) following outdoor interventions. The results of the meta-analysis for each outcome are presented in Figures 4–6.

3.5 Sensitivity analysis

The results of the sensitivity analysis showed that the pooled results for SER, AL, and myopia incidence remained stable after excluding individual studies, indicating that these results were insensitive to study selection. The results of the sensitivity analysis for each outcome are presented in Table 4.

3.6 Publication bias test

For SER and myopia incidence, the *p*-values for Egger's test were 0.24 and 0.13, respectively, indicating that publication bias had no effect on this type of study. For AL, however, the *p*-value for Egger's test was 0.01, indicating that there was publication bias in this result. The results of publication bias test for each outcome are presented in Table 5.

The trim and fill method was used to assess the stability of the pooled result for AL. The results showed that under both the fixed-effects model and random-effects model, the trim and fill adjustment using the linear method produced robust results. Specifically, under the fixed-effects model, the analysis estimated two missing studies

FIGURE 2
Risk of bias graph.

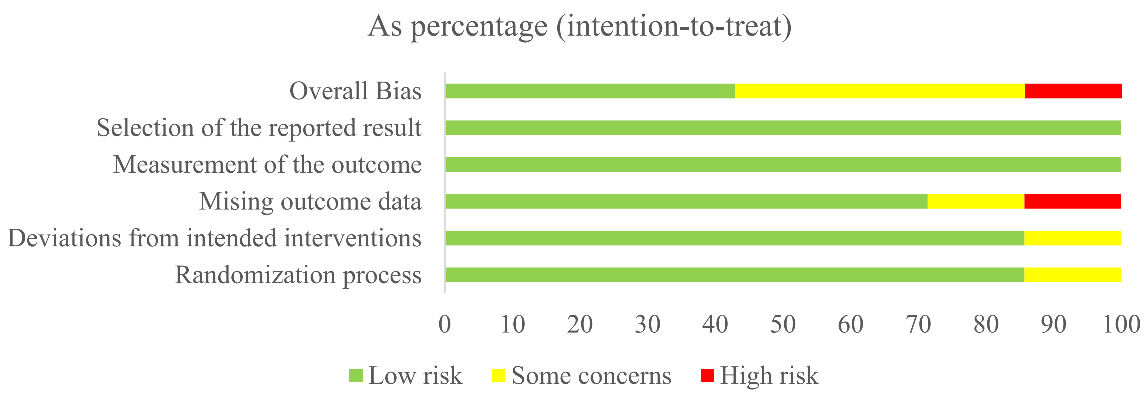

FIGURE 3
Risk of bias summary.

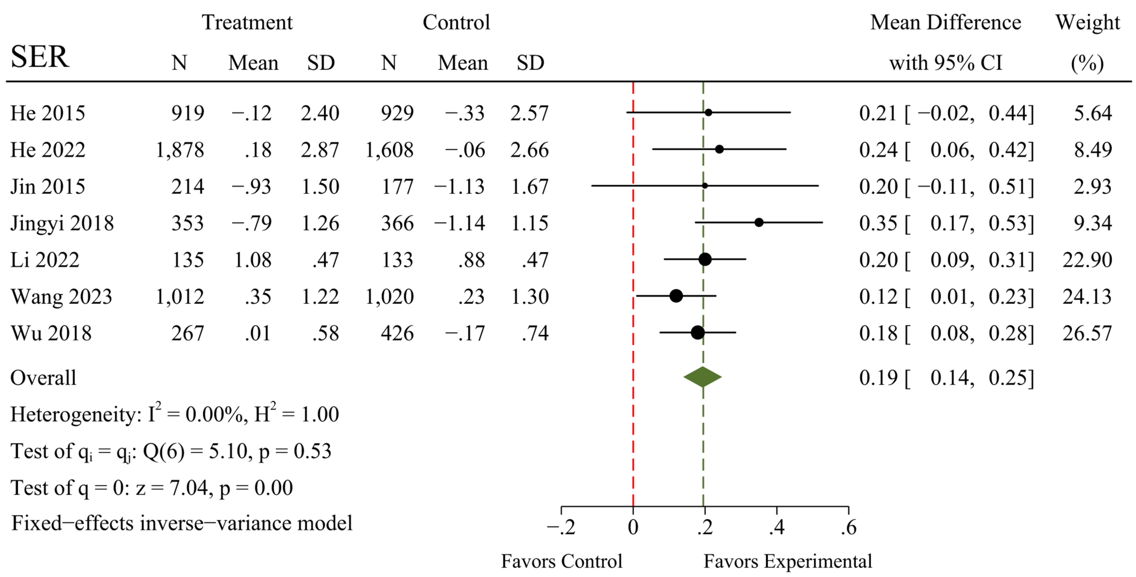

FIGURE 4
Forest plot of the effects of outdoor interventions on SER.

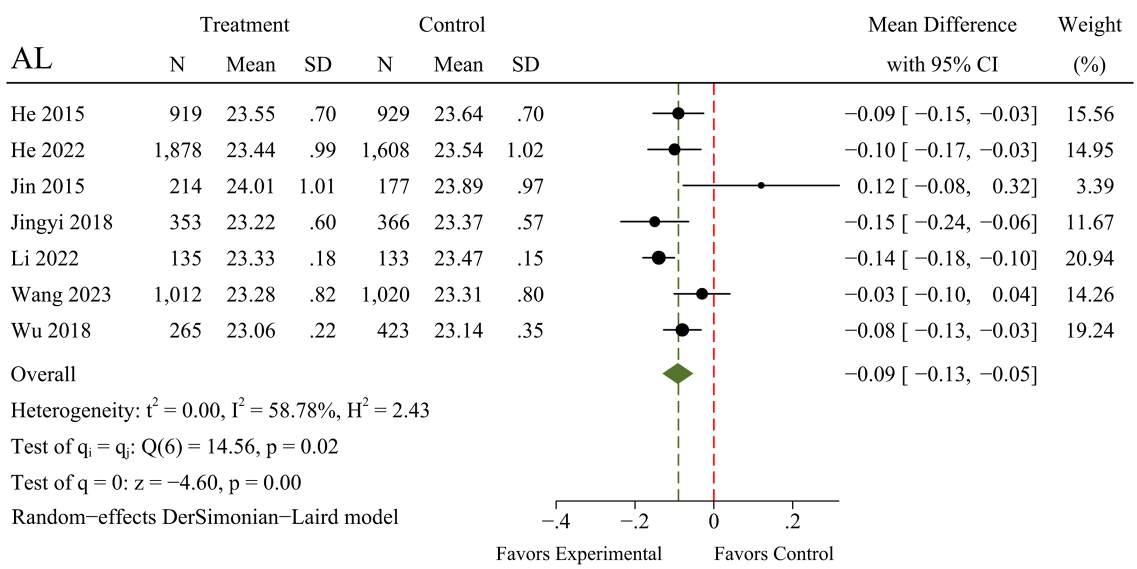

FIGURE 5
Forest plot of the effects of outdoor interventions on AL.

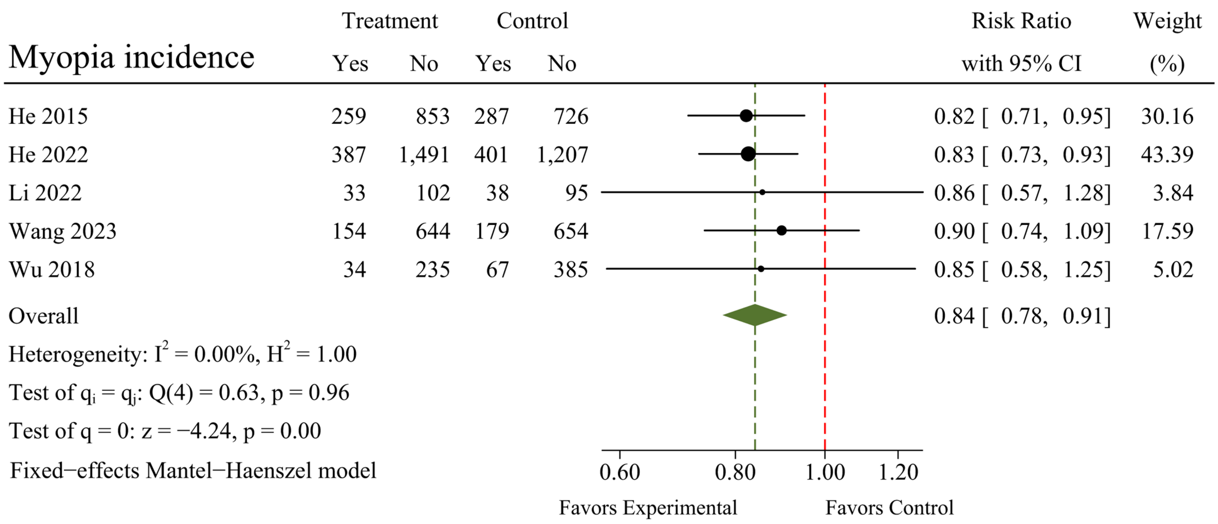

FIGURE 6
Forest plot of the effects of outdoor interventions on myopia incidence.

after two iterations. After imputing these hypothetical studies, there was no statistically significant change in the pooled results. In the random-effects model, the analysis estimated one missing study after two iterations. After the hypothetical study was imputed, the pooled results remained unchanged and stable. The results of the trim and fill adjustment for AL are presented in Table 6.

4 Discussion

The objective of this systematic review and meta-analysis was to evaluate the overall efficacy of outdoor interventions for myopia in children and adolescents, and to provide evidence for the prevention and control of myopia. The pooled results of the meta-analysis demonstrated that outdoor interventions effectively improved SER (MD = 0.19; 95% CI 0.14 to 0.25; $p < 0.01$), AL (MD = −0.09; 95% CI −0.13 to −0.05; $p < 0.01$), and myopia incidence (RR = 0.84; 95% CI 0.78 to 0.91; $p < 0.01$), indicating that outdoor interventions had a beneficial effect on the prevention and control of myopia in children and adolescents. Although there was a moderate heterogeneity and publication bias in some of the pooled results, these results did not change statistically after adjustment using the stepwise elimination and trim and fill methods, implying that the evidence provided by this study was reliable.

Overall, outdoor interventions appear to be a promising approach to preventing and controlling myopia in children and adolescents, and the mechanisms may be explained from several perspectives. Dopamine, a neurotransmitter closely linked to ocular development,

TABLE 4 Sensitivity analysis for outcomes by omitting individual studies.

Outcome	Study omitted	MD/RR	95% CI	
			Lower bound	Upper bound
SER	He et al. (39)	0.19	0.14	0.25
	He et al. (40)	0.19	0.13	0.24
	Jin et al. (41)	0.19	0.14	0.25
	Jingyi et al. (42)	0.18	0.12	0.23
	Li et al. (43)	0.19	0.13	0.25
	Wang et al. (44)	0.22	0.15	0.28
	Wu et al. (45)	0.20	0.14	0.26
AL	He et al. (39)	−0.09	−0.14	−0.04
	He et al. (40)	−0.09	−0.13	−0.04
	Jin et al. (41)	−0.10	−0.13	−0.07
	Jingyi et al. (42)	−0.08	−0.12	−0.04
	Li et al. (43)	−0.08	−0.12	−0.04
	Wang et al. (44)	−0.10	−0.14	−0.06
	Wu et al. (45)	−0.09	−0.14	−0.04
Myopia incidence	He et al. (39)	0.85	0.77	0.93
	He et al. (40)	0.85	0.76	0.95
	Li et al. (43)	0.84	0.77	0.91
	Wang et al. (44)	0.83	0.76	0.90
	Wu et al. (45)	0.84	0.77	0.91

MD, mean difference; RR, risk ratio; CI, confidence interval; SER, spherical equivalent refraction; AL, axial length.

TABLE 5 Results of Egger's test of each outcome.

Outcome	*t*	*p*-value	95% CI	
			Lower bound	Upper bound
SER	1.34	0.24	−0.10	0.32
AL	−4.02	0.01	−0.28	−0.06
Myopia incidence	−2.06	0.13	−0.53	0.11

CI, confidence interval; SER, spherical equivalent refraction; AL, axial length.

TABLE 6 Results of trim and fill adjustment for AL.

Method	Studies	MD	95% CI	
			Lower bound	Upper bound
Fixed	Observed	−0.10	−0.12	−0.08
	Observed + Imputed	−0.11	−0.13	−0.10
Random	Observed	−0.09	−0.13	−0.05
	Observed + Imputed	−0.10	−0.14	−0.06

MD, mean difference; CI, confidence interval.

has been demonstrated to be beneficial in inhibiting the increase of AL (46, 47), and the protective effect of outdoor interventions on myopia in children and adolescents may be mediated through light stimulation of retinal dopamine production and release (48). When children and adolescents are in an outdoor environment, retinal dopaminergic pathways can be activated through the influence of outdoor light and dopamine availability increased (49–51), with the increase of AL being suppressed (52, 53). A RCT examining the relationship between outdoor light intensity and myopia showed that children and adolescents exposed to light intensity of 1,000 lux or higher experienced significant improvements in both SER and AL, in addition to a reduction in myopia incidence compared with the control group (45). Furthermore, a non-negligible explanation for the impact of being outdoors on myopic progression may be the profound differences in the pattern of retinal defocus generated indoors and outdoors (54). Contrasting indoor scenes with outdoors reveals a marked increase in the level of hyperopic defocus for both near and distant fixation while indoors, and this persistent hyperopic defocus contributes to the progression of myopia. In contrast, being outdoors may be protective on the basis that it provides minimal amounts of peripheral defocus and hence may provide a so-called STOP signal for the development of myopia (54).

The pooled results in this study showed that outdoor interventions, including engaging in outdoor activities and increasing time spent outdoors, were effective in preventing and controlling the progression of myopia in children and adolescents compared with the control group, which is promising to resolve the current disagreement in research in this area. The reason for this divergence may stem from the differences in study populations, geographical backgrounds, interventions and outcomes, as well as the definitional criteria employed. The RCTs included in this study were all conducted within China, a country with a high myopia incidence, suggesting that outdoor interventions may exert more substantial preventive and control effects in specific populations. However, this evidence should be extended to a wider range of populations and other countries with lower rates of myopia, and examined for specific applications to comprehensively assess the effectiveness of outdoor interventions for the prevention and control of myopia in different contexts, so as to develop differentiated intervention programs according to the characteristics of different populations and regions.

In addition, although several RCTs have restricted the duration of interventions to 40–60 min, the optimal time for outdoor interventions remains unclear. This ambiguity implies that the "dose–response" relationship between outdoor intervention and myopia-related outcomes is not well understood. Similarly, when should outdoor interventions be implemented (midday versus before and after school)? What is the ideal age for myopia prevention and control? And will myopia rebound after cessation of outdoor interventions? These questions necessitate further investigation in future studies to compare the effectiveness of different intervention modes in the prevention and control of myopia, thereby optimizing the specific implementation strategies of outdoor interventions. Finally, considering that sunlight exposure may serve as a risk factor for certain diseases, including skin cancer or pterygium, it is essential to take environmental conditions (such as light intensity and climate temperature) into account during the implementation of interventions (55, 56). Appropriate preventive measures should be adopted to ensure the safety of interventions, thereby minimizing potential health risks.

In summary, the findings of this study suggest that outdoor interventions effectively contributed to the prevention and control of myopia in children and adolescents, positively impacting SER, AL, and myopia incidence. Children and adolescents are at a critical stage in healthy physical and mental development, and the cumulative effect caused by heavy educational burden and information overflow may increase the risk of myopia in children and adolescents. Outdoor interventions were characterized by low risk and high therapeutic benefits and could serve as alternative or adjuvant approaches to medication for the treatment of myopia. Therefore, considering the advantages in terms of safety and efficacy, outdoor interventions may be considered as a preferred intervention for the treatment of myopia in children and adolescents, while susceptibility to diseases associated with sunlight, particularly UV exposure, must be taken into account. Appropriate medication can be adopted in accordance with specific conditions to further enhance the therapeutic effect, and the improvement in myopia and related indicators can be maximized through this comprehensive treatment in children and adolescents.

4.1 Limitations

The present systematic review and meta-analysis had several limitations. First of all, due to the limited number of RCTs that met the inclusion criteria, sources of heterogeneity between studies may not be explored and discussed. Moreover, this study investigated the overall efficacy of outdoor interventions for myopia in children and adolescents as a whole, and was not divided into myopic and non-myopic children and adolescents to be analyzed separately on this basis. Finally, since the included studies were conducted within China, the generality of the results to other populations and regions needs to be further examined, in order to comprehensively evaluate the efficacy of outdoor intervention on the prevention and control of myopia in different backgrounds.

5 Conclusion

The objective of this systematic review and meta-analysis was to evaluate the overall efficacy of outdoor interventions for myopia in children and adolescents, and to provide evidence for the prevention and control of myopia. Outdoor interventions effectively contributed to the prevention and control of myopia in children and adolescents, positively impacting SER, AL, and myopia incidence. Moreover, outdoor interventions were characterized by low risk and high therapeutic benefits and could serve as alternative or adjuvant approaches to medication for the treatment of myopia. Therefore, considering the advantages in terms of safety and efficacy, outdoor interventions may be considered as a preferred intervention for the treatment of myopia in children and adolescents, while susceptibility to diseases associated with sunlight, particularly UV exposure, must be taken into account.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ZYM: Conceptualization, Data curation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. YZZ: Formal analysis, Software, Validation, Writing – original draft. WFJ: Conceptualization, Formal analysis, Software, Writing – original draft. CFL: Methodology, Resources, Visualization, Writing – original draft. SLL: Data curation, Methodology, Software, Visualization, Writing – original draft. CYC: Conceptualization, Data curation, Resources, Writing – review & editing. SL: Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ultra-overt therapy: a novel medical approach centered on patient consciousness

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Within the realms of human and artificial intelligence, the concepts of consciousness and comprehension are fundamental distinctions. In the clinical sphere, patient awareness regarding medication and its physiological processes plays a crucial role in determining drug efficacy and outcomes. This article introduces a novel perspective on prescription practices termed "Ultra-Overt Therapy" (UOT). A review of current supporting evidence was conducted through a non-systematic search in PubMed and Google Scholar, focusing on concepts such as the "mind–body relationship," "placebo response," "neuroscience," and "complementary medicine." Our findings, rooted in the mechanisms of the "placebo effect," the intricacies of "intersubjective therapy," the potency of "interoceptive awareness," and other domains of medical science, suggest that UOT holds theoretical promise. Future research endeavors focusing on these areas may elucidate the global impact of this method on medical treatment and patient care.

KEYWORDS

overt treatment, mind–body medicine, interoceptive awareness, placebo response, personalized medicine, intersubjective therapy, meaning system, neuroscience

Introduction

The topic of "patient awareness" has an impressive impact on how treatments work and how they are given (Tresker, 2022). Research divides treatments into covert (hidden) or overt (open) based on whether patients know about the medicine they are getting. The overt group, who are told about the drug and how it is given, often feel better because of the placebo effect, unlike the covert group who do not know what they are taking (Colloca et al., 2004). Based on this idea, we introduce the concept of "Ultra-overt therapy" (UOT), suggesting that knowing more about the drug and thinking about how it works can make it works better. This idea leads to examining evidence-based methods and practical research studies to determine whether a third category, termed "ultra-overt," can be added. It is hypothesized that this approach can impact patient treatments. To explore this, we evaluate the role of consciousness and emotion in physiological events within the body and the subsequent placebo response it elicits. The impact of meaning systems on various treatment methods is then discussed, with an overview of relevant neuroscience findings. As practical evidence, several complementary medicine methods are introduced, employing a systematic approach to the body. Finally, three research studies are proposed to assess the hypothesis from different perspectives.

Importance of consciousness and emotions

The idea of "consciousness" involves being aware of both internal and external experiences, including thoughts, feelings, and sensory perceptions (internal), as well as environmental inputs (external). Consciousness also involves wakefulness (level of alertness contrasting with sleep or unconscious states), attention (focusing on specific stimuli or thoughts), perception (interprets sensory information to form an understanding) and self-reflection (think about oneself and one's place in the world) (Tresker, 2022). All these phenomena together integrate information across different brain areas, forming a global workspace where information is broadcasted to other cognitive processes, known as the Global Workspace Theory (Baars et al., 2021). This enhanced cognition leads to "insight," which involves developing a new understanding that enhances self-awareness (Sattin et al., 2021).

In UOT, we aim to promote patient insight into their medication by encouraging them to think deeply about how the drug works in their body and which organs it affects. This process inevitably impacts both the consciousness and emotions of patients in the short and long term and promotes the global workspace of the patient. As these phenomena impose various effects on the body's physiology at both macroscopic and microscopic levels (Dembski et al., 2021; Candia-Rivera, 2022; Friedman et al., 2023), it is valuable to consider the different representations of these impacts in relation to patient health and drug efficacy. By fostering a deeper understanding of the medication's mechanism, patients can experience enhanced therapeutic outcomes and improved overall well-being.

Another critical element in this domain is "emotions." Emotions are complex psychological and physiological states that involve a range of subjective experiences, cognitive processes, and behavioral responses (Lin and Li, 2023). These are closely connected to the body's physical and temporal surroundings, including visual stimuli, social situations, and factors like body position, muscle tension, touch, and pain (Savard et al., 2024). All these signals rapidly disseminate throughout the body to elicit responses via the autonomic nervous system, impacting organs such as the heart, lungs, stomach, facial muscles, and limbs (Jerath and Beveridge, 2020).

Real-life observations and research indicate that distinct emotions often manifest in specific body parts, such as anxiety in the stomach area and love or sadness in the heart area. Interoceptive pathways, along with neural pathways, help send signals from your organs and body to your brain, with the insular cortex playing a key role (Nummenmaa et al., 2014). For instance, the close relationship between the brain and digestive system, facilitated by nerve pathways, underscores the significant influence of emotions on digestion, with emotions like fear, worry, and disgust slowing down digestion in response to perceived threats. The gut, often referred to as the "second brain" due to its numerous neurons, plays a pivotal role in gut feelings and intuition, with the microbiome contributing to the transmission of emotional signals throughout the body. By attending to these cues, individuals can regulate their emotions and navigate various situations, particularly when confronted with illness (Lin and Li, 2023; Savard et al., 2024).

These pathways let you pay attention to your body's signals and focus on what's happening inside you. Recognizing your medication can activate these pathways to bring about a "somatic reappraisal" (Nummenmaa et al., 2014). "Somatic reappraisal" describes processes that arise from focusing on your internal experiences through interoceptive attention. By using cognitive frameworks to understand insights or connections, you can achieve better responses within yourself and with others (Price and Weng, 2021).

Internally, Stimulus-Independent Thoughts (SITs) are mental processes that occur without any external influences. Studies have examined how SITs impact the human body, showing that they take place both when we are at rest and when we are engaged in tasks. Concentrating on the mechanisms of medication within the body is part of UOT, which induces SITs and provides objective effects on the body (Smallwood et al., 2021).

In addition to the somatic reappraisal effect, "embodiment" is another phenomenon resulting from the significance of awareness and emotions in the mind–body relationship. The connection between bodily sensations and emotional responses, often referred to as "embodiment," serves as a potential avenue to strengthen the efficacy of UOT (Price and Weng, 2021). According to Heidegger's perspective, the interrelationship between the mind and body involves a dynamic interplay characterized by reciprocal translation and interaction. Sensations experienced within the body and their subsequent impact on emotions elucidate how physical sensations influence emotional states and vice versa (Fugate et al., 2024).

To explore "embodiment" from another perspective, it is essential to consider therapies that involve sustained focus on the body, guiding individuals to pay attention to specific body parts where emotions are felt, and maintaining that focus with mindfulness. This focused attention is known as an "internal experiential space." The internal experiential space interprets sensory data based on bodily interactions with the environment, leading to the "cognition process" (Price and Weng, 2021). As the extensive impact of the Global Workspace Theory on the body is mentioned before, here we introduce "interoceptive awareness" as a significant phenomenon arising from the interaction between external stimuli and internal cognition (Baars et al., 2021).

"Interoceptive awareness" is about being able to feel and understand what's happening inside your body, such as your heartbeat, breathing, and digestion. This awareness can significantly impact your body's functions by helping you manage stress, control your emotions, and improve your overall well-being. By paying attention to your body's signals, you can better respond to physical and emotional challenges, leading to better health and functioning (Weng et al., 2021). Recent studies show a strong link between interoception and allostasis, which is the process of efficiently managing and regulating emotions (Jerath and Beveridge, 2020; Price and Weng, 2021; Savard et al., 2024). Many complementary medicines are based on this factor, such as meditation, yoga, and breathwork, which are discussed in the related section. However, one worth explaining here in detail is "body scanning exercises" (Simkin and Black, 2014).

One application of "interoceptive awareness" is in body scanning exercises, a type of mindfulness meditation practice. These exercises involve systematically focusing attention on different parts of the body to develop greater awareness of physical sensations. During a body scan, a person mentally scans their body from head to toe, paying close attention to the sensations in each specific part. This technique can lead to various benefits, including stress reduction, emotional regulation, improved sleep, and pain management. By concentrating on specific body parts and altering their relationship with pain, individuals can more effectively manage chronic pain in those areas (You and Ogawa, 2020). Although the scientific basis of this exercise is not yet fully verified (Gan et al., 2022), it offers notable benefits for patients and aligns with the principles of UOT, which aims to cultivate interoceptive awareness in the therapeutic process for targeted organs.

All the aforementioned evidence can be seen as subjective elements, but to consider something more measurable, the placebo effect can be assessed in different domains of medicine.

From placebo effect to placebo response

Delving into the enigmatic realm of the UOT, clinicians' experiences shed light on the placebo's impact on the patient's physiology. The placebo effect is intricately linked to the brain's processes of expectation, anticipation, reward, and learning. However, the mechanisms underlying the brain's generation of the placebo effect largely elude our understanding. Our current understanding is primarily derived from research on pain relief, Parkinson's disease, oxygen deprivation, and immune and hormonal reactions. Unfortunately, there is not much information available about other conditions like mental health disorders and physical illnesses, which are the main focus of this hypothesis (Benedetti, 2008; Kradin, 2011).

During the examination of the ways in which placebos reduce discomfort, we see that they work by activating a brain circuit that controls pain using natural painkillers called endorphins. Advanced brain imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG), show that placebos affect key brain areas just like real painkillers do. Placebo also activates certain brain receptors that respond to opioids (Benedetti, 2008; Rossettini et al., 2020). This raises the question of whether thinking about the drug could release the same natural painkillers. If we can boost these receptors, it might enhance the effectiveness of the medication when taken.

On a molecular level, the natural painkillers triggered by placebos interact with other substances involved in pain signaling, such as cholecystokinin (CCK), which can inhibit the pain relief from these natural painkillers. Blocking CCK could potentially strengthen placebo-induced pain relief. The balance between CCK and natural painkillers determines the efficacy of placebos for pain relief. Some types of placebo pain relief do not respond to naloxone, a drug that blocks natural painkillers, showing that other substances like endocannabinoids are involved. Dopamine also plays a big role in how placebos reduce pain, with increased dopamine and natural painkiller activity in certain brain areas. These changes caused by the placebo effect are driven by positive expectations and emotions (Benedetti et al., 2005; Crawford et al., 2021; Schatzberg, 2022; Talib Hassan et al., 2023). The same effects could happen during UOT.

In Parkinson's disease, placebos can trigger responses that help with symptoms. Placebos cause the brain to release dopamine in certain areas, leading to better symptom control. The amount of dopamine released depends on how much improvement the patient expects. Furthermore, learning also plays a big role in how well placebos work for Parkinson's disease. Placebos do not help new patients with Parkinson's disease, but they do help after repeated exposure to a drug that treats the condition (Benedetti, 2008). This shows that consciousness and repeated thinking about the treatment can lead to better results with UOT.

The placebo effect in the immune and hormone systems is linked to conditioning. Giving a placebo after a standard treatment can cause immune or hormone responses like that established medication. For example, repeated administration of ciclosporin, with a flavored drink as a conditioned stimulus, can lead to placebo-induced immunosuppressive responses. This is demonstrated by alterations in specific immune markers and cell activity. Likewise, administering a placebo following sumatriptan, a serotonin agonist, raises growth hormone levels and reduces cortisol (glucocorticoids) secretion, replicating the effects of the drug (Sonawalla and Rosenbaum, 2002; Benedetti, 2008; Frisaldi et al., 2020; Musavi et al., 2023).

Some scientists have broadened the scope of the placebo effect, conceptualizing it as a placebo response that is closely intertwined with unconscious processes. The placebo response manifests involuntarily and subconsciously, operating independently of conscious intention. It involves intricate interactions involving the inherent reward mechanisms of the nervous system, as well as deeply ingrained procedural memories and imaginative constructs. Clinical observations suggest that placebo impacts are not influenced by consciousness, cognitive effort, or deliberate intent, highlighting their 'automatic' nature. This is associated with the aggregation of imaginal recollections and fantasies, which exert an inherent influence on nervous system functions, including heart rate, respiration, and electrodermal reactions, often occurring spontaneously and without conscious awareness (Stewart-Williams and Podd, 2004; Benedetti et al., 2005; Benedetti, 2008). Imagination plays a key role in UOT, where patients are encouraged to visualize the drug process and its effects within their bodies in a focused manner.

Considering Descartes' dualism, it is proposed that the placebo response functions as a fundamental mind–body pathway that promotes "salutogenesis." This concept emphasizes understanding health through the development of internal resources and strengths, rather than focusing solely on risk factors and vulnerabilities (Brown, 2018). Evidence suggests that the placebo response correlates with central nervous system (CNS) functions, which facilitate the simultaneous emergence of positive emotions and physical sensations that govern mental and physical well-being, especially evident during maternal–infant bonding (Kradin, 2004).

"Salutogenesis" highlights the importance of these internal resources in contributing to health and resilience (Mittelmark et al., 2022). By examining the placebo response through this lens, UOT can offer a unique perspective on how the mind–body connection influences health outcomes (Sattin et al., 2021). Given this intrinsic link between CNS development and the placebo response, it is valuable to explore the neuroscience domain in relation to UOT to deepen our understanding of these interactions.

Neuroscience

Neuroscience integrates knowledge from diverse fields such as psychology, biology, chemistry, and medicine, encompassing various aspects of the nervous system, including neuroanatomy, neurophysiology, neurobiology, and cognitive neuroscience. This integration provides a comprehensive understanding of behavior, cognition, emotions, and sensory experiences (Nebe et al., 2023).

An important aspect of UOT is the impact of the "meaning system" on the body. In human psychology, the "meaning system" refers to the complex network of beliefs, values, expectations, and interpretations that individuals use to make sense of their experiences and the world around them. It encompasses an individual's understanding of themselves, others, and the broader social and cultural context in which they live. The meaning system significantly influences how people perceive events, attribute meaning to them, and respond emotionally, cognitively, and behaviorally (Schore, 2021; Signorelli and Meling, 2021).

Current studies in neuroscience using brain imaging techniques to explore how the brain functions during meaning system process. Researchers are applying machine learning to brain scan data to understand how different cognitive states, such as focused breathing or daydreaming, affect brain activity. This research helps scientists observe how attention shifts during meditation, particularly involving the Prefrontal Cortex, which is active during meditation, focused breathing, and daydreaming (Wang et al., 2023). Imagining how a drug works in the body through mental visualization—an approach used in UOT—can be seen as a form of meditation or daydreaming, potentially sharing similar mechanisms (Bechtel and Huang, 2022). Interestingly, the Prefrontal Cortex is also implicated in Global Workspace Theory (Baars et al., 2021).

Our brain's Default Mode Network (DMN) becomes active when we engage in self-referential thinking or reflect on our thoughts. The anterior insula, part of the Salience Network, plays a crucial role in maintaining awareness of bodily states and facilitating communication between different brain networks. It aids in processing significant events and regulating emotions, often without our conscious awareness, such as when we recall past stressful experiences (Buckner et al., 2008). The DMN includes several key regions: the Posterior Cingulate Cortex (PCC), Precuneus, Angular Gyrus, and Medial Prefrontal Cortex (mPFC). Notably, the mPFC, which is involved in the DMN, also activates during meditation (Signorelli and Meling, 2021; Wang et al., 2023).

On the other hand, some scientists propose that the brain evolves from a foundational neural network established during gestation. This initial neural framework undergoes further development through repetitive stimulation, leading to the formation of additional, interconnected neural networks. These networks engage in temporally linked re-entrant communication, facilitated by components of the secondary neural repertoire, which generates complex brain functions such as perception and consciousness. A discernible psychophysical "neurosignature" emerges from the organized activities of these secondary neural networks. Within this framework, the sense of self develops, encompassing both unique psychological traits and automatic, implicit procedural actions that regulate bodily functions such as metabolism, autonomic balance, and musculoskeletal alignment (Kradin, 2004; Bechtel and Huang, 2022). These robust networks underscore the potential effects of UOT on health by integrating various cognitive and emotional processes.

To explore neuroanatomy further, the amygdala plays a crucial role in our emotional responses by processing sensory information and triggering emotions. It helps us recognize threats and regulate our reactions (Nummenmaa et al., 2014). The amygdala communicates with other brain regions, such as the prefrontal cortex and hippocampus, to coordinate our emotions and behaviors with hormonal signals. Additionally, it releases stress hormones, such as cortisol, in response to perceived threats. Our level of consciousness can influence how hormones and receptors interact, as well as the feedback loop between them (Davis and Whalen, 2001; Bechtel and Huang, 2022). Similarly, UOT can facilitate the molecular and cellular interactions of drugs within targeted organs through analogous neural mechanisms.

Complementary medicine and other approaches

While Western medicine primarily examines how the body's physical pathways influence consciousness, emotions, symptoms, and responses to placebos, the enigmatic mechanisms of complementary methods may also contribute to defining UOT (Orkin, 2021). Although there is no definitive scientific evidence supporting the efficacy of alternative therapies such as energy healing, acupuncture, yoga, and homeopathy, these approaches emphasize the constructive impact of awareness on the mind–body relationship and its potential to aid the healing process (Tangkiatkumjai et al., 2020; Urits et al., 2021).

For instance, many of these therapies focus on specific energy points in the body, such as chakras and Qi, to promote well-being (Khalsa, 2007; Simkin and Black, 2014; Venkatesh et al., 2020; Rogers et al., 2021). Homeopathy, in particular, operates on the belief in a vital force that connects all parts of the body and seeks to enhance this force to restore health. According to this theory, thoughts and emotions can influence this vital force, with positive thoughts strengthening it and negative thoughts weakening it (Mathie, 2015; Aversa et al., 2016). Although these methods have not been fully validated as scientific practices, their historical use and some theoretical mechanisms discussed in literature suggest potential benefits (Adhikari et al., 2018; Deuel and Seeberger, 2020; Urits et al., 2021; Gan et al., 2022).

Turning back to conventional medicine, several traditional approaches can shed light on UOT. For example, "Narrative Medicine" highlights the importance of effective communication with patients. This approach uses storytelling and narrative techniques in clinical practice, medical education, and healthcare research to improve healthcare delivery by incorporating the narratives of both patients and healthcare providers (Remein et al., 2020).

By prioritizing the patient's story, Narrative Medicine acknowledges that illness experiences are deeply personal, shaped by individual life stories, values, beliefs, and cultural backgrounds. Integrating literature, poetry, film, art, and reflective writing into medical education helps healthcare providers develop empathy, creativity, and moral imagination (Loy and Kowalsky, 2024). Given that imagination plays a crucial role in UOT, the principles of Narrative Medicine can also help explain and support the UOT framework.

Another example of the significance of communication in medical practice is the concept of "phenomenology" of disease. This approach allows scholars to delve into patients' lived experiences, offering fresh insights into health, illness, and healthcare delivery. "Medical

Phenomenology" encourages both doctors and patients to reflect on their interactions, exploring moments of connection, misunderstanding, resistance, and growth (Fernandez, 2020). This reflection can lead to a form of "inter-subjective therapy" a psychotherapeutic approach that emphasizes the relational and interactive aspects of the therapeutic process (Stanier and Miglio, 2021).

Inter-subjective therapy centers on the therapeutic relationship between the therapist and the patient, asserting that our sense of self and reality is shaped by our interactions with others. By focusing on the process rather than solely on outcomes, inter-subjective therapy prioritizes understanding and exploring the therapeutic journey within the individual's body (Stanier and Miglio, 2021; Weng et al., 2021).

Delving deeper, the philosophical foundation of "Hermeneutic Medicine" emphasizes the importance of interpretation, dialogue, and contextual understanding in clinical practice, particularly focusing on "meaning-making in diagnosis and treatment." This approach encourages healthcare providers to interpret patients' symptoms and diagnostic results within the context of their unique personal narratives and circumstances, guiding more personalized treatment (Svenaeus, 2022).

Inter-subjective therapy aligns with this perspective by highlighting the relational and interactive aspects of the therapeutic process. Although primarily used for psychological conditions, it can also enhance self-awareness and insight into the healing process when integrated with UOT. By fostering a deeper understanding of the patient's experiences and the therapeutic process, this combined approach can create meaningful engagement, promote transformative change, and ultimately support the healing journey (Stanier and Miglio, 2021; Trevarthen et al., 2023).

If we define UOT as a ritual in which the patient watches or reads about the treatment carefully and then each time thinks about the process of treatment inside his/her body with concentrated focus, it is valuable to consider "Ritual Medicine" and the related literature as a similar approach in medicine.

"Ritual medicine" represents a realm yet to be fully explored, delineating two fundamental roles of rituals in the therapeutic process: an expressive function and a creative function. In its expressive dimension, a ritual communicates essential values and cultural paradigms through symbolic representation, theatrically articulating these foundational principles and imparting them to both active participants and observers (Dallas et al., 2020). Conversely, in its creative capacity, rituals actively shape or reestablish frameworks through which individuals perceive reality, encompassing societal structures, and ethical principles. Rituals, characterized by their performative, standardized, and metaphorical nature, endeavor to translate thoughts into actions, bridge the gap between self and others, and reconcile historical narratives with present experiences (Goli and Farzanegan, 2016).

It is evident that rituals, serving as therapeutic symbolic expressions across verbal, physical, and spatial dimensions, possess the potential to alter focus, memory, and expectations of recovery, thereby instilling a profound sense of potential well-being. Experimental investigations into the configurations and significance of ritual symbols, particularly those intertwined with healing ceremonies, have confirmed that each symbol carries a multitude of connotations for participants, illuminating societal values, organizational structures, and perspectives on natural and supernatural domains. The interpretative framework, preparatory stage, and enactment of a ritual can significantly modulate health perceptions, behaviors, and psychoneuroimmunological reactions through both direct and indirect implications. A significant aspect of this effect is attributed to the emotions elicited by rituals, which harmonize internal, interpersonal, and transpersonal spheres (Goli and Farzanegan, 2016; Apud and Romaní, 2020).

In addition to the guidance provided in the UOT, which instills a sense of ritualistic efficacy in patients, it fosters confidence during treatment, cultivating belief in its effectiveness and ultimately yielding more favorable outcomes imbued with positive emotions (Goli and Farzanegan, 2016; Apud and Romaní, 2020).

Now that we have discussed every element that could be important in the interaction of medicine on a molecular-cellular level in our body relating to the mechanism of UOT, it is time to consider the systemic factors that help achieve better results in understanding UOT.

Systemic factors

To consider the systemic factors in UOT, it is important to think about how drugs distribute in the body and how they are delivered to certain areas more than others at different times. This is influenced by the activation of the sympathetic nervous system (SNS) and the inactivation of the parasympathetic nervous system (PNS), along with the release of certain chemicals like nitric oxide, prostaglandins, and adenosine, which lead to vasodilation (Gibbons, 2019). While the SNS and PNS regulate the involuntary distribution of blood to various parts of the body, a person can influence this distribution intentionally through mental focus, meditation, and biofeedback, as explained above. It is hypothesized that this intentional increase in blood delivery to a specific organ can be achieved consciously or unconsciously through UOT (Kreibig, 2010).

If we consider humans as a combination of genotype and phenotype, "personalized medicine" can also play an additive role in UOT. Personalized medicine customizes medical treatments and interventions according to individual characteristics, such as genetic makeup, lifestyle factors, and environmental influences, to optimize patient outcomes. It selects the most effective and suitable treatments based on each individual's unique traits (Whirl-Carrillo et al., 2021).

The UOT can serve as another manifestation of this scientific approach. Genetic testing, biomarker testing, pharmacogenomics, and patient engagement, which form the foundation of personalized medicine, are all encompassed within the "ultra-overt" method (Hassan et al., 2022). This is because eliciting each patient's consciousness is intertwined with all these parameters individually.

All the ways mentioned above show the immediate effects of consciousness on medication. The long-term effects of the placebo response can vary depending on the person and the condition being treated. Research on how genetics play a role in the placebo effect is still new, and unknown factors may also correlate with UOT (Hassan et al., 2022) (Table 1).

TABLE 1 Supporting evidence for the effectiveness of ultra-overt therapy.

Consciousness	Interoceptive awareness (You and Ogawa, 2020) Embodiment (Fugate et al., 2024) Somatic reappraisal (Price and Weng, 2021) Stimulus-independent thoughts (Smallwood et al., 2021)
Placebo effect	Activating brain areas and related receptors (Benedetti et al., 2005; Rossettini et al., 2020) Secretion of agonists and antagonists (Benedetti, 2008) More efficacy in repeated exposure (Frisaldi et al., 2020) Link to conditioning (Sonawalla and Rosenbaum, 2002)
Neuroscience	Commonalities in neural pathways and neurotransmitters (Signorelli and Meling, 2021) Activity of the prefrontal cortex in both cognition, emotional and physiological processes (Wang et al., 2023) Default mode network (Buckner et al., 2008) Neurosignature (Bechtel and Huang, 2022) Role of amygdala (Davis and Whalen, 2001)
Complementary medicine and other approaches	Energy healing, acupuncture, yoga, meditation and homeopathy (Aversa et al., 2016; Urits et al., 2021) Narrative medicine (Remein et al., 2020) Inter-subjective therapy (Stanier and Miglio, 2021) Hermeneutic medicine (Svenaeus, 2022) Ritual medicine (Goli and Farzanegan, 2016)
Systemic factors	Drug distribution associated with autonomic nervous system (Kreibig, 2010) Personalized medicine (Whirl-Carrillo et al., 2021) Genetics (Hassan et al., 2022)

Clinical study

To test the "ultra-overt" hypothesis, we suggest three research plans for further investigation in this case.

First, to make the ultra-overt treatment work best for patients, we need to educate them fully about the drug's target organ and how it works on a molecular level. We can show them an animation of the drug delivery process and its effects on the tissue, receptors, and organ. To measure the impact, we ask them to watch the animation each time they take the medicine.

First project: amlodipine

One way the ultra-overt method can work is by affecting distribution. To study this, we can use amlodipine to expand its effect on calcium channels in the heart and blood vessels to lower blood pressure, as well as in the bowel muscles which can cause constipation. To see how amlodipine interacts with calcium channels in the heart, blood vessels, and bowel, we can use patch-clamp electrophysiology or radioligand binding assays (Li et al., 2022).

In the first phase, we check the calcium channels in all targeted organs of the patient after amlodipine treatment for a certain time. Then, in the second phase, we inform the patients about amlodipine's effect on heart muscles and show them an animation focusing on how the drug works in the heart to control blood pressure. We then measure the interactions between amlodipine and calcium channels in all organs of the same patients (including blood vessels and bowel) and compare the results to check if knowing about amlodipine's impact on the heart causes a significant change in how it interacts with calcium channels compared to the blood vessels and bowel before and after the intervention.

Second project: metformin

To study the impact on organs, we can use a drug like metformin that targets two organs with different mechanisms. Metformin reduces glucose production in the liver by blocking a pathway called AMP-activated protein kinase (AMPK), and it also makes tissues more sensitive to insulin by improving insulin signaling and glucose uptake in muscles and fat tissue. By looking at these pathways separately, we can see how metformin can affect liver glucose production and insulin sensitivity in muscles by measuring glycogen storage in the liver and muscles using MRI (Shuai et al., 2020; Nourmohammadi et al., 2023).

Like the first project, we check the glycogen storage in the liver and muscles during metformin treatment for a certain time before the ultra-overt education. In the second phase, we tell the patients about metformin's effect on the liver and show them an animation focusing on how the drug works in the liver to reduce glucose production. We then measure the glycogen storage in both targets (liver and muscles) to determine if the patients' awareness of the impact of metformin on the liver causes a significant change in glycogen storage in the liver compared to the muscles before and after the intervention.

Third project: bupropion

This idea can work on a cellular and molecular level by affecting receptors and modulators. Bupropion acts as a norepinephrine-dopamine reuptake inhibitor and a nicotinic acetylcholine receptor blocker, commonly used for depression and quitting smoking. This drug can increase levels of norepinephrine and dopamine in the brain and block nicotinic acetylcholine receptors (Schatzberg, 2022). By studying the patients like the first project and informing them only about bupropion's role in increasing norepinephrine and dopamine, we can measure the increment in these chemicals and the blockage of nicotinic acetylcholine receptors in the brain using PET imaging or radiolabeled ligands before and after the intervention (Gharibkandi et al., 2020). By comparing the changes in dopamine/norepinephrine levels with the change in nicotinic acetylcholine receptor blockage, we can see how knowing about the drug's molecular mechanism affects the function of the drug in the body.

It is important to note that we should seek the "correlation" between the effect of the ultra-overt technique intervention and the final outcome in drug efficacy, rather than focusing on "causation." As mentioned earlier, this technique involves multiple domains and factors within the body, necessitating a comprehensive analysis of the outcomes (Schellenberg, 2020).

Conclusion

In conclusion, the "Ultra-Overt Therapy" (UOT) endeavors to engender "interoceptive awareness" in patients regarding the medications they are using for their ailments and the subsequent physiological responses within their bodies. It is evident that this technique may yield diverse effects depending on the nature of the illness, whether acute or chronic, somatic or psychiatric, and the specific organs involved. As certain aspects of the underlying mechanisms of the placebo effect remain enigmatic, additional clinical investigations are imperative to ascertain the efficacy of UOT comprehensively.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

KS: Conceptualization, Writing – original draft, Writing – review & editing. AL: Investigation, Writing – original draft. SS: Validation, Writing – review & editing. AN: Investigation, Resources, Writing – review & editing. AS: Validation, Writing – review & editing. HNas: Project administration, Supervision, Writing – review & editing. HNam: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Qi stagnation and qi deficiency are associated with depression in college students

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Objective: The current study aims to investigate the correlations between qi stagnation, qi deficiency, and depression levels among college students.

Method: This study investigated 403 college students and measured their levels of depression, qi stagnation, and qi deficiency to analyze the relationship between these three variables. Pearson correlation and linear regression statistical techniques were utilized.

Results: (1) On average, college students reported mild depressive symptoms; (2) college students manifested low levels of qi stagnation and qi deficiency. (3) There exists a strong positive correlation between qi stagnation and qi deficiency; (4) a moderate positive correlation is present between depression and both qi stagnation and qi deficiency among college students. All these results support the mechanism by which qi stagnation and qi deficiency contribute to depression in traditional Chinese medicine theory.

Conclusion: Qi stagnation and qi deficiency are moderately associated with depression levels in college students. It is feasible to use traditional Chinese physical therapy for qi regulation to alleviate depressive symptoms among college students.

KEYWORDS

depression, qi stagnation, qi deficiency, traditional Chinese medicine, college students

1 Introduction

The mental health issue of Chinese college students has emerged as a significant social public health concern. Particularly, the detection rate of depression among college students has been on the rise in recent years (1). The overall prevalence of depression among Chinese university students was found to be 28.4% ($n = 185,787$), with 95% CI from 25.7 to 31.2% (2). Depression symptoms have negative effects on the quality of life and academic achievement of college students (3, 4), and impose a significant medical burden on both families and society (5). In recent years, universities in mainland China have not only introduced mental health courses for all students but have also established psychological counseling centers and formally collaborated with hospitals to address the increasing rate of depression among students.

Traditional Chinese medicine (TCM) plays an important role in interpreting and treating depression symptoms in mainland China (6). TCM therapy has unique efficacy in treating mental disorders, including major depression. The effectiveness of acupuncture in treating depression is well documented (7). Meta-analyses have shown that TCM herbal monotherapy is as effective as antidepressants in reducing depression with fewer adverse events than antidepressants (8). However, there is still a lack of research on the mechanisms of depression from a TCM perspective, which significantly limits the role of traditional Chinese medicine in maintaining mental health.

TCM posits that qi pathological status can lead to various diseases in psychology and physiology. Qi is one of the fundamental substances in the human body and is considered to provide energy and power to the body. The balanced state of qi constitutes an essential foundation for mental well-being. The most prevalent types of qi pathological status encompass qi stagnation and qi deficiency. Qi stagnation is characterized by the sluggish, weak, or obstructed flow of qi in specific parts of the body, viscera, or meridians (9). Qi deficiency refers to the lack of qi in one of the viscera or the whole body, so that it cannot provide sufficient energy and power for physical and mental activities (10). According to TCM, there is a mutual influence between qi deficiency and qi stagnation. Qi deficiency leads to weakened qi movement, which easily results in qi stagnation, while qi stagnation can lead to inadequate production of qi, resulting in qi deficiency. For instance, a study investigated 579 outpatients and revealed a positive association between qi deficiency and qi stagnation ($r=0.48$ in females, and $r=0.61$ in males) (11).

A few studies have quantitatively examined the association between qi stagnation and mental health. For instance, a study with a sample of 2,108 college students aged 18–25 years demonstrated that qi stagnation due to early life maltreatment can lead to a high level of depressive symptoms among college students (12). A case–control study with a sample of 169 participants aged between 16 and 80 years old found a significant association between qi stagnation and insomnia (13). The close connection between qi deficiency and emotional issues has also been verified through limited research. For example, an experimental study with rat models demonstrated that qi deficiency is related to depression (14). A study revealed that qi deficiency was associated with anxiety disorders in both sexes (11). Generally, lack of energy and vitality, lassitude, and mental and physical fatigue can be attributed to qi deficiency (15). According to TCM, regulating liver-qi and invigorating spleen-stomach-qi is a fundamental approach to treating depression (8).

TCM has been acknowledged by the World Health Organization as one of the potentially valuable complementary medicines (16); however, the association between qi and mental disorders (such as depression) has received scant attention from mental health researchers. The primary objective of this study is to explore the mechanism of depression in college students from a TCM perspective and put forward preventive suggestions based on the research findings. Specifically, this study will investigate the degree of correlation between qi stagnation and qi deficiency and depression among college students and propose potential non-herbal intervention approaches to alleviate depression symptoms among college students. Since depression progresses along a continuum (i.e., from subthreshold depression to major depression) (17), the findings of this study will also be conducive to the TCM treatment of depression symptoms.

The present study proposes two hypotheses as follows:

> Hypothesis 1: Qi stagnation is positively associated with depression in college students.
>
> Hypothesis 2: Qi deficiency is positively associated with depression in college students.

2 Research method

The current study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Xichang College (LG202405). Verbal informed consent was obtained from all participants.

2.1 Sampling procedure

The current study is based on cross-sectional data collected from Xichang College, a second-tier university located in Sichuan Province, China. Paper-pencil questionnaires were used, and students were required to provide their student numbers and names for future tracking. The sample consisted of students majoring in business administration, English, primary education, tourism management, and animal science. Students were assured that it was for scientific research and did not pose significant privacy concerns. The survey took place during class breaks from May 20 to 28, 2024. Before the formal survey, the corresponding author coordinated with the teachers in class to help conduct the survey during class breaks.

A total of 452 questionnaires were distributed, and ultimately 403 valid questionnaires were obtained, resulting in an effective rate of 89.16%.

The final valid sample consisted of 97 males (24.07%) and 306 females (75.93%), 315 Han people (78.16%) and 88 individuals from ethnic minorities (21.84%), 306 students from rural registration families (75.93%) and 97 students from urban registration families (24.07%). The age range of the participants was between 17 and 23 years, with a mean age of 19.74 years and a standard deviation of 1.06.

2.2 Research instruments

This study utilized six items to assess qi stagnation and six items to measure qi deficiency. These items were developed based on previous TCM studies (10, 18). Participants were instructed to recollect their physical sensations over the past 3 months and respond to 12 items using a 5-point Likert scale ranging from 1 (never) to 5 (often). One of the items measuring qi stagnation stated, "I sigh for no reason." One of the items assessing qi deficiency stated, "I get tired easily." The Cronbach alpha coefficients for qi stagnation and qi deficiency were 0.81 and 0.85, respectively, indicating high reliability. High mean scores on the scales indicated high levels of qi stagnation or qi deficiency among the students.

This study employed PHQ-9 to assess depression symptoms, which is the depression module of the Patient Health Questionnaire (PHQ), a self-administered instrument to diagnose common mental disorders (19). One of the nine items reads, "I have little interest or pleasure in doing things." Participants were instructed to assess their emotional condition during the previous week and respond on a four-point Likert scale with "0" denoting "not at all," "1" meaning "several days," "2" indicating "more than half the days," and "3" meaning "nearly every day." The Cronbach alpha coefficient of this measurement is 0.84. Higher composite average scores indicate higher levels of depression.

Sleep quality is a control variable in the present study, and it is measured by a single item derived from the study by Snyder et al. (20). This study defines good sleep in the following manner: it is easy to fall asleep when lying down on the bed, rarely being awakened during the night, and feeling refreshed and restored upon waking in the morning. Participants were instructed to retrospectively assess their sleep quality over the past month and evaluate it using a 5-point scale based on the criteria of good sleep. In this 5-point scale, "1" denoted "very poor," while "5" signified "excellent."

Physical exercise is another control variable, measured with a single item adopted from Milton et al. (21)'s study. The present study characterizes healthy physical activity in the following manner: Each session should last a minimum of 20 min and result in at least mild perspiration or breathlessness, and the forms of activities may include brisk walking, table tennis, basketball, badminton, football, running, skipping, dancing, swimming, etc. Participants were asked to retrospectively assess their exercise activity over the past month and evaluate it using a 5-point scale, based on the criteria of healthy physical exercise. In this 5-point scale, "1" means "Less than once a week," "2" means "1–2 times a week," "3" denotes "3–4 times a week," "4" indicates "5–6 times a week," and "5" means "almost every day."

Diet quality was also assessed as a control variable, using a single item adapted from a previous study (22). The study defines a healthy diet in this manner: in addition to staple foods, the daily diet should also include soy products (such as tofu), fruits, milk or other dairy products, eggs, meats (such as pork, chicken, or beef), and seafood (such as fish and shrimp). Participants were asked to rate their diet quality over the past 3 months according to the above definition of a healthy diet, using a five-point scale with "1" representing "very poor" and "5" indicating "very good."

Additionally, considering the significant impact of academic pressure on depression levels, this study also included academic stress as a control variable. Two items assessing academic pressure were adapted from Bedewy and Gabriel (23)'s research. One item required participants to rate their workload in class during the semester using a five-point scale ranging from "1" for "very light" to "5" for "very heavy." The other item asked participants to rate their workload after class during the semester on a five-point scale, with "1" indicating "very little" and "5" indicating "quite a lot." High composite average scores of these two items indicated greater academic pressure. The Cronbach's reliability coefficient for academic pressure in this study was 0.84.

Finally, key personal information of college students was also gathered, including gender (male = 0, female = 1), family registration area (rural = 0, urban = 1), ethnicity (Han = 1, minorities = 1), and age.

3 Results

3.1 Descriptive results

Descriptive statistics of some continuous variables are presented in Table 1.

In this study, the mean depression score was 0.63 on a 4-point scale of 0–3, resulting in a composite sum score of 5.67 (0.63 multiplied by 9). According to Kroenke et al. (24), composite sum scores falling within the range of [5, 9] indicate mild levels of depression. Therefore, the findings suggest that college students, as a whole, experienced mild levels of depression.

On the 5-point scale of 1–5, composite average scores falling in the range of 1.81–2.61 indicate a low level, while scores falling within the interval of 2.62–3.42 indicate a moderate level (25). In this study, the mean values for qi stagnation and qi deficiency were 1.98 and 2.44, respectively. Therefore, overall, college students in this study reported low levels of qi stagnation and qi deficiency symptoms.

The mean values of sleep quality, diet quality, and physical exercise were 3.17, 3.41, and 2.03, respectively, on a five-point scale from 1 to 5. According to Alkharusi (25), these mean scores indicated that college students reported moderate levels of sleep quality and diet quality, as well as low levels of physical exercise.

On the 5-point scale of 1–5, the composite mean values for academic pressure and family economic status are 3.04 and 2.86, respectively. According to Alkharusi (25), these mean values suggest that college students in the current study experience a moderate level of academic pressure and perceive their family's economic status as being at a moderate level.

The violin plots in Figures 1–6 display the score distribution for all measured items and the composite mean distribution for each variable, respectively.

TABLE 1 Descriptive statistics for key variables.

	Min	Max	*M*	SD
DE	0.00	2.56	0.63	0.46
QS	1.00	4.50	1.98	0.73
QD	1.00	5.00	2.44	0.89
PE	1.00	5.00	2.03	0.94
SQ	1.00	5.00	3.17	0.97
DQ	1.00	5.00	3.41	0.80
AP	1.00	5.00	3.04	0.66
FES	1.00	5.00	2.86	0.57

DE, depression; QS, qi stagnation; QD, qi deficiency; PE, physical exercise; SQ, sleep quality; DQ, diet quality; AP, academic pressure; FES, Family economic status; FRA, family registration area; Min, Minimum; Max, Maximum; M, Mean; SD, standard deviation.

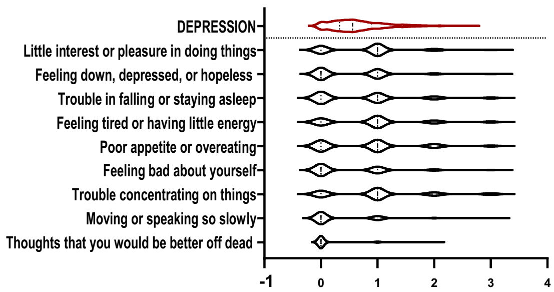

FIGURE 1
The description of depression and its items.

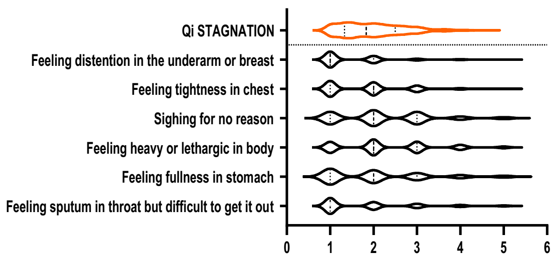

FIGURE 2
The description of Qi stagnation and its items.

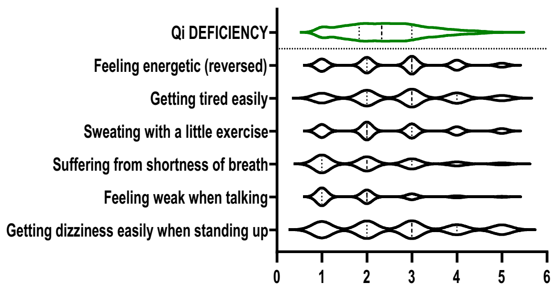

FIGURE 3
The description of Qi deficiency and its itmes.

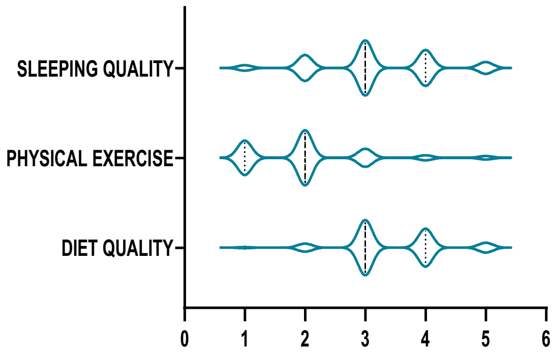

FIGURE 4
The description of life style.

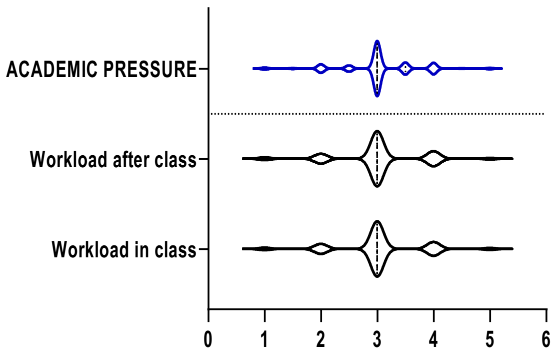

FIGURE 5
The description of academic pressure and its items.

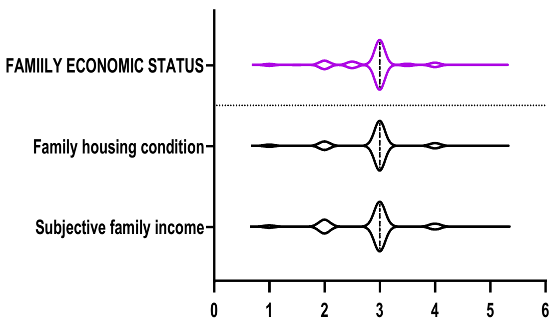

FIGURE 6
The description of family economic status and its items.

3.2 The results of correlational analysis

The current study investigates the magnitude of simple correlations among variables, and the Pearson correlation coefficients are presented in Table 2.

The results presented in Table 1 revealed a positive correlation between qi stagnation and depression ($r = 0.618$, $p < 0.01$), as well as between qi deficiency and depression ($r = 0.633$, $p < 0.01$). The correlation between physical activity and depression did not reach statistical significance ($r = -0.075$, $p > 0.05$), while sleep quality showed a negative correlation with depression ($r = -0.349$, $p < 0.01$). Additionally, diet quality was negatively correlated with depression ($r = -0.272$, $p < 0.01$), and academic pressure was positively correlated with depression ($r = 0.103$, $p < 0.05$). Family economic status showed a non-significant association with depression ($r = -0.088$, $p > 0.05$).

The sample was bootstrapped 1,000 times, and 95% confidence intervals for the main correlation coefficients were obtained (refer to Figure 7).

According to Schober et al. (26), the absolute magnitude of the observed correlation coefficient is categorized as follows: 0.00–0.10 represents negligible correlation, 0.10–0.39 represents weak correlation, 0.40–0.69 represents moderate correlation, and 0.70–0.89 represents strong correlation. In this study, the confidence intervals for the correlation coefficients between depression and qi stagnation, and between depression and qi deficiency were [0.554, 0.675] and [0.571, 0.688], respectively; while the confidence interval for the correlation coefficient between qi stagnation and qi deficiency was [0.734, 0.812]. Therefore, there was a moderate correlation between depression and qi stagnation as well as between depression and qi deficiency; whereas there was a strong correlation between qi stagnation and qi deficiency.

In addition, the confidence interval of the correlation coefficient between depression and sleep quality was [−0.432, −0.260], indicating a weak to moderate relationship; while that between depression and diet quality was [−0.361, −0.180], suggesting a weak association between diet quality and depression.

Finally, the correlations between depression and physical exercise, academic pressure, and family economic status are all at a negligible level.

3.3 Results of regression analysis

Depression is considered the dependent variable, with qi stagnation and qi deficiency as independent variables, while also including control variables in the model. The regression results are presented in Table 3.

In Table 3, the variance inflation factor (VIF) is significantly below 5, indicating the absence of any apparent collinearity issues among the aforementioned variables (27).

It is evident from Table 3 that qi stagnation has a significant impact on depression ($\beta = 0.290$, $p < 0.01$). Additionally, qi deficiency also demonstrates a significant effect on depression ($\beta = 0.389$, $p < 0.01$).

In the realm of lifestyle factors, it was found that diet quality had a significant impact on depression ($\beta = -0.083$, $p < 0.05$), while physical exercise did not exhibit a significant effect ($\beta = 0.033$, $p > 0.05$). On the other hand, sleep quality demonstrated a significant effect ($\beta = -0.162$, $p < 0.01$).

TABLE 2 Correlation coefficients between variables.

	DE	QS	QD	PE	SQ	DQ	AP
DE	1						
QS	0.618**	1					
QD	0.633**	0.776**	1				
PE	−0.075	−0.131**	−0.218**	1			
SQ	−0.349**	−0.250**	−0.239**	0.113*	1		
DQ	−0.272**	−0.230**	−0.241**	0.070	0.298**	1	
AP	0.103*	0.142**	0.202**	−0.090	−0.033	−0.010	1
FES	−0.088	−0.030	−0.049	−0.007	0.141**	0.106*	0.006

**Denotes significance at the 0.01 level; *indicates significance at the 0.05 level. DE, depression; QS, qi stagnation; QD, qi deficiency; PE, physical exercise; SQ, sleep quality; DQ, diet quality; AP, academic pressure; FES, Family economic status; FRA, family registration area; Min, Minimum; Max, Maximum; M, Mean; SD, standard deviation.

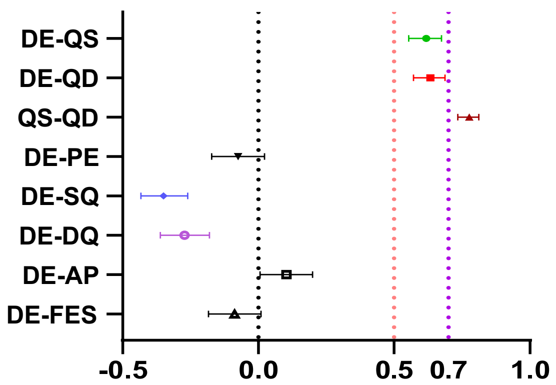

FIGURE 7
The main correlation coefficients bootstrapped 1,000 times with a 95% confidence interval. DE, depression; QS, qi stagnation; QD, qi deficiency; PE, physical exercise; SQ, sleep quality; DQ, diet quality; AP, academic pressure; FES, Family economic status; FRA, family registration area; Min, Minimum; Max, Maximum; M, Mean; SD, standard deviation.

Family economic status ($\beta = -0.004$, $p > 0.05$) and academic pressure ($\beta = 0.009$, $p > 0.05$) had no significant effect on depression.

Among the individual characteristics of age, gender, family registration area, and ethnicity, only gender demonstrated a significant effect on depression ($\beta = 0.154$, $p < 0.01$).

4 Discussion

4.1 Descriptive statistical results

The study demonstrates that, on average, college students exhibit mild symptoms of depression, which aligns with the findings in the study by Du Na et al. (28). Du Na et al. (28) also used the PHQ-9 with a 4-point Likert scale ranging from 0 to 3 to assess college students' depression. Their results revealed a composite mean score of 0.701 on the depression scale (with a composite sum score of 6.38), indicating that, as a whole, college students experienced mild depressive symptoms.

In this study, college students reported low levels of qi stagnation symptoms, with a mean score of 1.98 falling between "never" and "rarely" on the 5-point scale, closely approaching "rarely." Additionally, college students exhibited relatively low levels of qi deficient symptoms, averaging at 2.44, which falls within the range of "rarely" to "occasionally" on a 5-point scale. It is evident that compared to qi stagnation symptoms, college students reported more symptoms of qi deficiency.

The lifestyle of the college students in this study was sub-healthy. Firstly, their diet quality and sleep quality were moderately healthy, consistent with previous research such as Xu Chunyan et al. (29), which reported sub-healthy diet quality and sleep quality among Chinese college students. Secondly, college students reported a low level of physical exercise with merely 1–2 times physical activity per week, and each session lasts more than 20 min. Such a finding aligns with the result in the study by Le Junchao and Guan Yuan (30), revealing that college students engage in sports 1–2 times per week.

The college students in this study perceive their family's economic status to be at a moderate level. This is primarily attributed to the fact that Xichang college is a second-tier university, and the majority of its students come from lower socioeconomic backgrounds. For instance, 75.93% of the students in this study come from rural-registered families.

College students in this study reported moderate levels of academic pressure, which is consistent with the actual situation at Xichang college. As a second-tier university, its academic requirements are not overly rigorous, and the academic competition among students is relatively low.

4.2 The magnitude of correlations in simple correlational analysis

The correlation analysis in this study revealed a strong positive correlation between qi stagnation and qi deficiency. Such a finding is similar to that of Kondo et al. (11), who observed a moderate to strong positive correlation between qi stagnation and qi deficiency in psychological outpatients ($r = 0.48$ in females, and $r = 0.61$ in males).

The Pearson correlation analysis revealed a moderate correlation between qi stagnation and depression, which lends support for Hypothesis 1. Such a finding is in line with the findings in the study by Huang Huiyuan et al. (12), which reported that qi stagnation was moderately associated with depression ($r = 0.556$). There is a moderate

TABLE 3 Regression results of DE on QS and QD.

	B	SE	*β*	*t*	Tolerance	VIF
(Constant)	0.943	0.353		2.674**		
QS	0.185	0.036	0.290	5.107**	0.385	2.594
QD	0.204	0.030	0.389	6.708**	0.370	2.704
PE	0.016	0.018	0.033	0.871	0.891	1.123
SQ	−0.078	0.018	−0.162	−4.237**	0.848	1.179
DQ	−0.048	0.022	−0.083	−2.157*	0.850	1.176
AP	0.006	0.026	0.009	0.243	0.940	1.064
FES	−0.003	0.030	−0.004	−0.099	0.908	1.102
FRA	−0.018	0.040	−0.017	−0.464	0.921	1.086
Gender	−0.167	0.041	0.154	4.090**	0.878	1.139
Ethnicity	0.073	0.042	0.065	1.732	0.878	1.139
Age	−0.030	0.016	−0.068	−1.870	0.941	1.063
	$F = 37.523^{**}$		$Adj.R^2 = 0.500$			

**Denotes significance at the 0.01 level; *indicates significance at the 0.05 level. DE, depression; QS, qi stagnation; QD, qi deficiency; PE, physical exercise; SQ, sleep quality; DQ, diet quality; AP, academic pressure; FES, Family economic status; FRA, family registration area; Min, Minimum; Max, Maximum; M, Mean; SD, standard deviation.

positive correlation between qi-deficiency and depression, supporting Hypothesis 2 very well. This finding is consistent with the findings in the study by Zhang Xiaocong et al. (31) who observed a moderate positive correlation ($r = 0.41$) between qi deficiency and depression among college students.

Regarding control variables, we observed a weak to moderate inverse relationship between depression and sleep quality, which aligns with the findings of Zhang Xin et al. (32) who identified a moderate correlation ($r = 0.41$) between sleep quality and depression levels in Chinese students. In addition, the present study revealed a weak negative association between depression and diet quality, as found in a literature review revealing a weak to moderate negative association between diet quality and depression in diverse population (33). Lastly, there were non-significant negative correlations between physical activity and family economic status with depression, which contrasts with previous studies that found significant negative correlations [e.g., (34, 35)]. This discrepancy may be attributed to the limited number of items used in this study to assess physical activity and family economic status, leading to substantial measurement errors.

4.3 The effects of qi stagnation and qi deficiency on depression in regression analysis

In the regression analysis, we controlled for diet quality, sleep quality, physical exercise, academic pressure, family economic status, and demographic characteristics. The regression results indicated that both qi stagnation and qi deficiency were significant positive predictors of depression level (refer to Table 3; Figure 7); these results also substantiate research hypotheses 1 and 2. These findings are in line with previous research conclusions. For instance, a study comparing adults with and without qi stagnation found higher levels of anxiety and depression among those with qi stagnation (36). Li Xiaojuan et al. (14) exposed the rats to different durations of chronic unpredictable mild stress (CUMS), and found that the rats exposed to 6-week CUMS procedure exhibited significantly similar traits to the phenotypes of LQSSDS (meaning qi stagnation in the liver, and qi deficiency in spleen simultaneously) and depression. According to the TCM theory, the normal state of qi is fundamental to maintaining a healthy mental state; when qi is in a pathological state, mental functions will be hurt, and cognitive decline and emotional disturbances then ensue.

This study further revealed that the effect of qi deficiency on depression was stronger than that of qi stagnation, suggesting that qi deficiency exerts a greater effect on depressive symptoms than qi stagnation in college students. The reason lies in the fact that qi deficiency symptoms were more common among college students compared to qi stagnation symptoms (see Table 1). Insufficient qi is not able to supply adequate nourishment and energy for mental functions. Consequently, qi deficiency has a more significant impact on depression than qi stagnation. In clinical practice of TCM, heart-spleen deficiency (qi deficiency in both heart and spleen) is a common type of depressive disorders, and the patients in this type have more prominent symptoms of qi deficiency than symptoms of qi stagnation (37). A system review showed that among the top three herb formulas for patients with sleep disorder and major depressive disorder during 2007–2011 in Taiwan, Jia-Wei-Xiao-Yao-San came first (38). Jia-Wei-Xiao-Yao-San has been traditionally used to tonify the qi in the spleen and stomach. It is evident that qi deficiency significantly contributes to the development of depression symptoms.

4.4 The effects of control variables on depression in regression analysis

Among the control variables, sleep quality is correlated with depression levels, consistent with previous research findings. For instance, a systematic review found that college students with high levels of depression tend to have poor sleep quality (39). Poor sleep quality is, in fact, a significant symptom of depression.

In this study, diet quality was associated with depression, which is consistent with previous research. For instance, a systematic review of 24 independent cohorts (totaling 1,959,217 person-years) showed higher diet quality is associated with a lower risk for the onset of depressive symptoms (40). According to TCM theory, diet quality is closely associated with the qi in spleen and stomach, and unhealthy diet can lead to inadequate production of qi in spleen and stomach, resulting in qi deficiency and impacting mental functions.

Ultimately, this study revealed that gender was associated with depression levels, with female students exhibiting higher levels of depression than male ones. Such a finding is consistent with previous research [e.g., (41)], possibly due to the significantly higher levels of qi stagnation and qi deficiency in females compared to males (see Appendix 1).

4.5 Limitations of the present study

In this study, cross-sectional data were employed to explore the association between qi stagnation, qi deficiency, and depression symptoms in college students. All hypotheses in this study are well supported, suggesting that this study possesses good internal validity. Nevertheless, this study has the following three drawbacks.

Firstly, the utilization of cross-sectional data restricts the capability to establish causation and only allows for correlation conclusions. Secondly, the small and non-representative sample size, with 75.93% of college students being from rural households and 75.93% being women, limits the external validity of the study. Finally, utilizing a single measure for assessing sleep quality, diet quality, and physical activity may introduce substantial measurement errors and compromise the study's reliability. In future research, we plan to expand our sample size properly, conduct follow-up surveys on participants, and utilize cross-lagged analysis to further explore the impact of qi stagnation and qi deficiency on depression.

5 The implications of the present study

The current study holds both theoretical and practical significance. On the theoretical side, this study offers a distinct perspective on explaining the mechanism of depression symptoms. According to TCM theory, qi is considered as one of the essential material bases for normal mental functions. When qi is in deficiency, it is not able to supply adequate nourishment and energy for mental activities, leading to a decline in mental functions. Qi stagnation refers to slow and idle flow of qi, which can also result in inadequate nourishment for mental activity. 《Simple question. On the theory of pain (素问•举痛论)》 posits that various diseases arise from qi pathological states, indicating that qi stagnation and qi deficiency can lead to numerous kinds of diseases. To summarize, the current study offers support for the TCM theory that depressive symptoms are attributed to qi stagnation and qi deficiency.

In terms of preventing depression, this study suggests that in addition to psychological counseling, using TCM to alleviate symptoms of qi stagnation and qi deficiency can be beneficial for helping college students prevent the onset and progression of depression symptoms. Common health care methods including massage (42), Guasha (scraping) (43), acupuncture (44), and auricular acupressure (45) all can effectively replenish qi and regulate its flow. The integration of TCM health care techniques with psychological counseling can more effectively aid college students in preventing severe depression.

Additionally, according to TCM, a healthy lifestyle (comprising appropriate exercise, a healthy diet, and good sleep) is beneficial for regulating the state of qi (46). Hence, it is indispensable for college students to adopt a healthy lifestyle to prevent and ameliorate depressive symptoms.

6 Conclusion

The findings from this study lend support to the viewpoints in TCM that the healthy state of qi is essential for mental health. Specifically, we revealed that both qi stagnation and qi deficiency are strongly and positively associated with depression symptoms in college students.

The conclusion of this study indicates that the application of certain TCM physiotherapy techniques for regulating and replenishing qi in the body can alleviate depression symptoms among college students. This study is of a correlational rather than causal nature, and we will follow up on these participants in the future to further analyze the connection between qi stagnation, qi deficiency and depressive symptoms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Teacher Education Division of Academic Committee in Xichang University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WX: Conceptualization, Methodology, Writing – original draft. HY: Conceptualization, Investigation, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix 1

Test for the difference between Qi deficiency and Qi stagnation in gender

There is a significant difference in qi stagnation between the sexes, with females ($M = 2.06$, $SD = 0.74$) exhibiting significantly higher levels than males ($M = 1.74$, $SD = 0.63$; $t = -3.81$, $p < 0.01$).

There is a significant difference in qi deficiency between the sexes, with females ($M = 2.54$, $SD = 0.88$) exhibiting significantly higher levels than males ($M = 2.14$, $SD = 0.84$; $t = -3.90$, $p < 0.01$).

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Assessing a measure for Quality of Life in patients with severe Alopecia Areata: a multicentric Italian study

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Objective: The prevalence of anxiety and depression in patients diagnosed with Alopecia Areata (AA) is very high and this significant burden of psychological symptoms threatens the Health-Related Quality of Life (HRQoL) of affected patients. Indeed, AA often does not produce significant physical symptoms, but it nonetheless disrupts many areas of mental health. Clinical assessment of disease severity may not reliably predict patient's HRQoL, nor may it predict the patient's perception of illness. For this reason, considerable effort has been made to apply and develop measures that consider patient's perception and assess the HRQoL of individuals affected by AA. The aim of this multicentric study was to provide the Italian version of the Skindex-16AA and to evaluate its psychometric properties in a clinical sample of consecutive patients with moderate-to-severe AA.

Methods: This is a longitudinal, multicenter, observational study. Patients returned for follow-up visits at 4-, 12-, and 24-weeks. The analyses of the current work aimed to confirm the factorial structure of the Skindex-16AA. In the case of non-fit, an alternative structure for the model was proposed, using an Exploratory Graph Analysis and the Bayesian approach.

Results: The sample was composed of 106 patients with AA. Alopecia Universalis was the most frequently diagnosed type of alopecia at all time points. The analyses on the Skindex-16AA revealed that a two-factor structure with eight items fit the data best (Bayesian Posterior Predictive Checking using 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square values = −6.246/56.395, Posterior Predictive *P*-value = 0.06), and reported satisfactory psychometric properties (i.e., internal consistency and convergent validity).

Conclusion: The Skindex-8AA demonstrated optimal psychometric properties (i.e., convergent and construct validity, and test-retest reliability) measured in a sample of patients with AA, that may suggest that it is an appropriate tool to measure the HRQoL in AA patients. However, further studies are needed in order to confirm and tested other psychometric features of this tool.

KEYWORDS

Alopecia Areata (AA), Quality of Life, Bayesian confirmatory factor analysis, psychodermatology, patients reported outcomes

1 Introduction

Alopecia Areata (AA) is an autoimmune disease with a chronic-recurrent course and a multifactorial pathogenesis, characterized by heterogeneous patterns of hair loss. It represents the second most common form of non-scarring alopecia after androgenetic alopecia, with an estimated lifetime prevalence of 0.10% in the general population worldwide (1); all ages are susceptible; however children and young adults seem to be most commonly more affected (2).

The etiopathogenesis of AA is not yet fully understood, although there is consensus in the literature regarding the involvement of predisposing genetic factors and environmental triggers in determining the onset of the disease (3). Loss of immune privilege by the hair follicle with subsequent activation of CD8 positive T-Lymphocytes seems to be the driver of the disease (4, 5). AA may be associated with various systemic diseases including atopic diseases, thyroid disorders, vitiligo, psoriasis, celiac disease, ulcerative rettocolitis and rheumatoid arthritis (2).

Clinically, AA is characterized by sudden patchy hair loss, involving the scalp or other parts of the body without signs of inflammation or scarring. The most common clinical variants of AA are patchy alopecia, alopecia totalis (AT), alopecia universalis (AU), ophiasis, sisaipho and Marie Antoinette and Thomas More syndrome (3). There are several classification systems for clinical severity of alopecia, however, the Severity of Alopecia Tool (SALT), proposed by Olsen et al., appears to be the most widely used instrument (6). The scoring of the SALT is based on clinician observation and consists of assessing the percentage of scalp area affected by alopecia (i.e., dividing the scalp area into four parts: back 24%, top 40%, both sides 18% of the head). A percentage of involved area >50% results in a score classified as "severe AA" (6).

The prevalence of anxiety and depression in children, as well as in adults, diagnosed with AA is very high (7, 8); furthermore, stress and anxiety can also be considered as triggers of the disease (9). This significant burden of psychological symptoms threatens the Health-Related Quality of Life (HRQoL) of patients. Indeed, AA often does not produce significant physical symptoms, but it appears to disrupt many areas of mental health (10).

Over the years, several disease-specific instruments have been validated to measure the clinical severity of the disease, however, clinical assessment of disease severity does not reliably predict the patient's HRQoL, nor does it predict the patient's perception of illness (11, 12). For this reason, considerable effort has been made to apply and develop measures that consider the patient's perception and assess the HRQoL of individuals affected by AA (13). In fact, a position statement of the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes explicitly stated that the development and validation of AA-specific instruments would be extremely useful to encourage (14). Several generic and dermatology-specific HRQOL instruments have been used, such as Alopecia Areata

Quality of Life Index (15), Alopecia Areata Quality of Life (16), or Alopecia Areata Symptom Impact Scale (17), but they are all lacking of important aspects for their construct validity (13). Moreover, no validation studies for the questionnaires have been proposed on samples of Italian patients. Among different questionnaires proposed, only the Skindex in its different forms (18–20) has been proved to possess satisfactory validity across several, yet different dermatological conditions.

Specifically, the Skindex-16 (13, 21, 22) consists of 16 items that assess the impact of skin disease on three domains: symptoms, emotions, and functioning. Each item is scored on a 7-point Likert scale, ranging from 0 (never bothered) to 6 (always bothered). The total score ranges from 0 to 96, with higher scores indicating greater impairment in quality of life. The Skindex-16 has demonstrated good reliability and validity across various dermatological conditions and has been translated and validated in multiple languages. It serves as a tool for assessing the impact of skin diseases on patients' quality of life in both clinical and research settings (18). The Skindex-16AA was proposed by Gelhorn et al. (20) with slight wording changes respect to Skindex-16 to refer to scalp and AA. This form of the questionnaire was used in the clinical trials BRAVE-AA1 and -AA2, which evaluated the efficacy and safety of baricitinib in AA patients (23). This is a Janus kinase (JAK) inhibitor that modulates immune responses by selectively inhibiting JAK1 and JAK2 enzymes. It is administered orally and it has shown great efficacy in the treatment of AA, being the first drug approved for this condition (24).

Therefore, the aim of the current multicentric study was to provide the Italian adaptation of the Skindex-16AA and to evaluate its psychometric properties (i.e., convergent validity and test-retest reliability) in a real-life clinical sample of consecutive patients with moderate-to-severe AA, among whom a subgroup was treated with baricitinib. Specifically, the main aim was to evaluate the dimensionality of the Skindex-16AA (18) in an Italian clinical sample of patients with AA, and, in case of non-adequacy of the model, to provide an alternative factor structure and/or revision.

2 Materials and methods

2.1 Study participants

Patients were recruited from different Italian centers[1], from the January to October 2023. We enrolled patients aged >18 years, diagnosed with a severe AA (defined as SALT score >50%) by a dermatologist. Baricitinib treatment (4 mm/die, for at least 1 year) was administered to patients unresponsive to conventional systemic treatments (i.e., oral cyclosporine; and topical, oral, intramuscular and intravenous steroids). Participants voluntarily agreed to participate in the study and signed informed consent.

Patients returned for follow-up visits after 4, 12, and 24-weeks (see Table 1 for descriptive statistics both at baseline and follow-up).

The study was approved by the Institutional Ethical Committee of IDI-IRCCS (i.e., Istituto Dermopatico dell'Immacolata-Istituto di Ricovero e Cura a Carattere Scientifico) (protocol number: 739/1).

2.2 Measures

At both baseline and follow-up evaluations, socio-demographic (i.e., age and sex) and clinical variables (e.g., severity of AA, age of diagnosis) were registered (see Table 1), and patients completed the Italian version of the following questionnaire, Skindex-16AA (9, 14) and the Hospital Anxiety and Depression Scale (HADS) (15).

The Skindex-16AA is a 16-item self-report questionnaire assessing measuring the level of quality of life impairment caused by a AA (20). It measures 3 domains, Symptoms (items from #1 to #4), Emotion (items from #5 to #11) and Functioning (items from #12 to #16), and higher score on all dimensions reflect greater impact of AA. The Italian version of the Skindex-16AA was obtained through the conventional back-translation procedure. The content validity of the item has been assessed by one of the Authors (GC) specialized in the treatment of patients with AA, as well as a group of patients ($N = 5$), who were asked if there were difficulties in the understanding of the items. None of the patients declares issues in the comprehension of the items.

The HADS (25) is a 14-item self-report questionnaire measuring anxiety (e.g., "*Worrying thoughts go through my mind*") and depressive (e.g., "*I feel as if I am slowed down*") symptoms. It is commonly used in both clinical and non-clinical samples (26). Both subscales are composed of seven items each, which are rated on a four-point scale (i.e., 0–3), with higher scores indicating more severe depressive and anxiety symptoms. The psychometric properties of the HADS demonstrated satisfactory results (27). Specifically, for the Italian population (28), the HADS demonstrated satisfactory construct validity and internal consistency.

2.3 Statistical analyses

All analyses were performed with JASP (version 0.17.1), Mplus (version 8) (29), and EGAnet (version 1.2.3) for R studio (version 4.2.3). Exploratory Graph Analysis (EGA) (30) and Bayesian confirmatory factor analysis were used to investigate dimensionality of the scale.

Firstly, a Bayesian Confirmatory Factor Analysis (BCFA) was conducted on the Skindex-16AA in order to test the adequacy of the model. In case of non-optimal fit, a more refined exploratory

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TABLE 1 Descriptive statistics of the sample.

Variables	Baseline ($N = 106$)	4-weeks follow-up ($N = 77$)	12-weeks follow-up ($N = 38$)	24-weeks follow-up ($N = 35$)
Sex *N*/%				
Women	77 (72.64%)	56 (72.72%)	28 (73.68%)	27 (77.14%)
Men	29 (27.35%)	21 (27.27%)	10 (26.32%)	8 (22.85%)
Age *M*/(SD)	40.20 (±12.56)	40.80 (±12.28)	41.00 (±12.16)	41.08 (±12.08)
Age diagnosis	27.72 (±15.25)	27.85 (±15.56)	28.07 (±15.25)	29.45 (±17.22)
Type of AA *N*/%				
Alopecia totalis	26 (24.52%)	19 (24.67%)	10 (26.31%)	10 (28.57%)
Alopecia universalis	61 (57.54%)	47 (61.03%)	25 (65.78%)	21 (60%)
Patchy alopecia (≥50%)	19 (17.92%)	11 (14.28%)	3 (7.89%)	4 (11.42%)
Systemic treatment *N*/%	15 (14.15%)	9 (11.68%)	4 (10.52%)	3 (8.57%)
Family history for AA *N*/%	25 (23.58%)	20 (25.97%)	9 (23.68%)	11 (31.42%)
SALT *M*/(SD)	90.79 (±18.85)	84.87 (±22.57)	61.46 (±36.48)	39.64 (±40.09)
HADS-depression *M*/(SD)	8.81 (±11.25)	6.23 (±5.88)	4.14 (±3.44)	6.92 (±6.43)
HADS-anxiety *M*/(SD)	7.83 (±6.08)	7.50 (±6.21)	6.25 (±4.51)	5.75 (±5.34)

N, number count; %, percentage; M, mean; SD, standard deviation; AA, Alopecia Areata; SALT, severity of Alopecia tool; HADS, Hospital Anxiety and Depression Scale.

approach, through the Exploratory Graph Analysis (EGA), was used in order to provide an adequate structure of the questionnaire, by removing problematics items.

EGA is a statistical approach that can identify dimensionality (i.e., communities) in multivariate data using network models. In network models, variables are considered as nodes and they are connected by edges that indicate the strength of the association between these variables (i.e., partial correlation coefficients) (31). In the current analyses, items of the Skindex-16AA were the nodes of the model and the graphical least absolute shrinkage and selection operator (GLASSO) estimation method was used to estimate the model's parameters. The hyperparameter γ was set to 0.5, and the Walktrap community detection algorithm was used to detect the number of dimensions (31). Moreover, a bootstrap approach with 1,000 iterations was used to assess the stability of the solution (30). In the first step of the analyses, EGA assesses consistency of the number and membership of the communities (i.e., how often items are included in the same dimensions). Adequate solutions are obtained when the number of dimensions is stable and when the stability of the items is ≥0.70. Item stability refers to how consistently a node is connected to the others. When unstable items are present in a network they are removed, and all the analyses are performed again until the number and composition of dimensions are stable.

As final step, the model retrieved from the EGA was evaluated through a Bayesian confirmatory factor analysis (BCFA) with a Markov chain Monte Carlo (MCMC) algorithm. We used GIBBS sampling algorithm and 100,000 post burn-in iterations (32). Bayesian analysis is the most appropriate approach when dealing with small sample size (33). Moreover, in the Bayesian approach all parameters are treated as uncertain (i.e., and not as fixed effect like in the frequentist approach), and models can be tested using different prior distribution, which can affect the precision of parameters estimation. In other words, the smaller the prior variance, the higher the precision of parameters estimation (34). Weak informative priors [*N* (0, 1.0)] were used for the hypothesized factor loadings. Sensitivity of the model to priors was inspected comparing the hypothesized model with two competing models which increasingly favor the null hypothesis for factor loadings [*N* (0, 0.25) and *N* (0, 0.10)]. The models fit was evaluated using the Bayesian Posterior Predictive Checking (PPC) and the Posterior Predictive *P*-value (PPP) (35). The fit of the model was based on the PPC confidence interval crossing the zero and PPP > 0.05.

Indices of internal consistency were reported as Cronbach's α and McDonald's ω with their 95% credible intervals (36). As measure of convergent validity, we reported Pearson correlation coefficients with the HADS and also assessed the test-retest reliability of the revised version of the Skindex-16AA at 4, 12, and 24 weeks follow-up. In addition, after obtaining the revised version, we tested the correlation coefficients between the original and the revised version of the Skindex-16AA.

Finally, responsiveness of the revised version of the Skindex-16AA was calculated with *t*-test analysis for paired samples in order to assess the magnitude of the difference in the QoL score between baseline and 24-weeks follow-up. Effect size of 0.20 is considered small, of 0.50 moderate and of 0.80 large (37).

3 Results

3.1 Descriptive statistics

At baseline, the sample was composed of 106 patients (72.64% women), with a mean age of 40.20 years (SD = 12.56); at 4-weeks follow-up of 77 patients (72.72% women), with a mean age of 40.80 (SD = 12.28); at 12-weeks follow-up, of 38 patients (73.68%

women), with a mean age of 41 years (SD = 12.16); and finally, at 24-weeks follow-up of 35 patients (77.14% women), with a mean age of 41.08 (SD = 12.08). Alopecia Universalis was the most diagnosed type of alopecia in the sample at the baseline (57.54%), compared to the Alopecia Totalis (24.52%) and Patchy Alopecia (17.92%). The SALT mean score decreased during the study period, starting from a mean score of 90.79 (SD = 18.85) at the baseline, of 84.87 (SD = 22.57) at 4-weeks follow-up, of 61.46 (SD = 36.48) at 12-weeks follow-up, to 39.64 (SD = 40.09) at 24-weeks follow-up, which reflects an improvement in the extent and severity of hair loss in our sample.

3.2 Exploratory graph analysis

The original model of the Skindex with 16 items (i.e., Skindex-16AA) (18) was not confirmed with the BCFA (Bayesian Posterior Predictive Checking using 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square values = 9.144/115.372; Posterior Predictive *P*-Value = 0.01), and although all items loaded significantly (<0.001) on their hypothesized dimensions, this indicated the presence of problematic items.

Therefore, the model of the Skindex-16AA was further explored with the EGA, which initially suggested a three-factor solution. Stability analysis revealed the presence of eight items which were unstable (item's stability < 0.70; items #5, #6, #9, #11, #12, #14, #15, #16) (see Figure 1). Another EGA analysis was conducted with the remaining 8 items, which suggested the presence of two factors, with four items for each dimension. We named this revised version Skindex-8AA, and all its items reported a high stability (=1.00).

3.3 Bayesian confirmatory factor analysis

The BCFA was performed on the model suggested by the EGA, Skindex-8AA, and reported a good fit to the data (Bayesian Posterior Predictive Checking using 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square values = −15.287/41.715; Posterior Predictive *P*-Value = 0.18), with all items loaded significantly (<0.001) and >0.40 on their hypothesized dimensions (see Table 2; see Supplementary material for the Italian version of the Skindex-8AA).

Sensitivity analysis to priors suggested an effect of priors to parameters estimates. When using informative priors which increasingly favor the null hypothesis for factor loadings [*N* (0, 0.25) and *N* (0, 0.10)], the models indicated the same adequate fit for the moderate informative prior (Bayesian Posterior Predictive Checking using 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square values = −6.246/56.395, Posterior Predictive *P*-Value = 0.06), but a significant model fit for the strong informative prior (Bayesian Posterior Predictive Checking using 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square values = 18.103/96.140, Posterior Predictive *P*-Value =

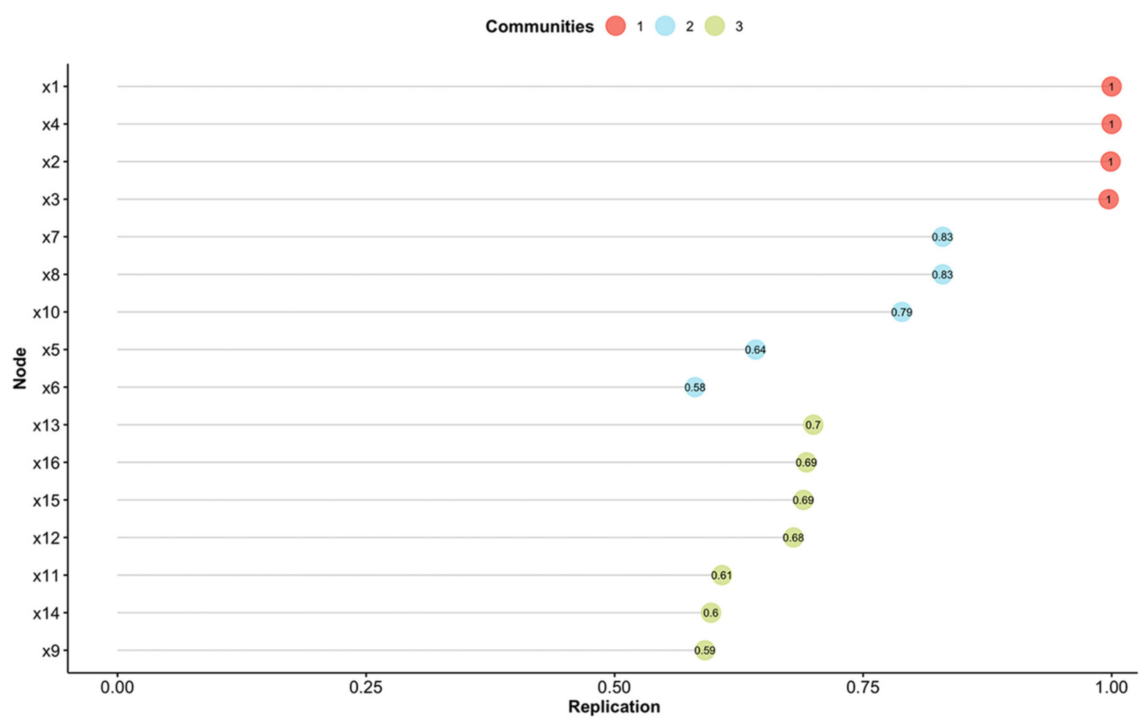

FIGURE 1
Item stability analysis for the Exploratory Graph Analysis. Different colors indicate the different communities found with the Exploratory Graph Analysis. Nodes (i.e., items) with a value < 0.70 are not considered stable.

TABLE 2 Bayesian confirmatory factor analysis of the Skindex-8AA.

	Symptoms	Social-emotional	95% CI
Item 1 (itching)	0.790		0.684–0.866
Item 2 (burning/stinging)	0.917		0.860–0.953
Item 3 (hurting)	0.796		0.684–0.873
Item 4 (irritation)	0.852		0.764–0.911
Item 7 (appearance)		0.881	0.805–0.930
Item 8 (frustration)		0.909	0.846–0.946
Item 10 (ANNOYED)		0.845	0.759–0.904
Item 13 (interactions)		0.852	0.768–0.911
Mean scores (SD)			
Baseline	6.50 (5.23)	15.69 (7.14)	
4-weeks follow-up	5.62 (4.08)	16.21 (7.11)	
12-weekes follow-up	3.57 (2.21)	11.68 (7.78)	
24-weeks follow-up	5.71 (3.67)	11.05 (7.24)	

95% CI, 95% credibility intervals; SD, standard deviation.

0.001). Lastly, changes in estimated factor loadings were all below 10% with both priors.

3.4 Psychometric properties of the Skindex-8AA

The two factors of the Skindex-8AA were named Symptoms and Social-Emotional, respectively. The Symptoms factor had McDonald's ω posterior mean of 0.866 (95% CI = 0.824–0.903, posterior probability $0.70 < \omega < 0.90 = 0.964$; Cronbach $\alpha = 0.867$, 95% CI = 0.827–0.909, posterior probability $0.70 < \alpha < 0.90 = 0.953$) and the Social-Emotional factor had McDonald's ω posterior mean of 0.915 (95% CI = 0.888–0.939, posterior probability $0.70 < \omega < 0.90 = 0.134$; Cronbach $\alpha = 0.919$, 95% CI = 0.896–0.945, posterior probability $0.70 < \alpha < 0.90 = 0.076$), ensuring the construct validity of the Skindex-8AA.

Both factors demonstrated satisfactory and significant convergent validity with the HADS subscales (i.e., depression and anxiety) (Symptoms with HADS depression: $r = 0.38$ $p < 0.01$; Symptoms with HADS anxiety: $r = 0.35$, $p < 0.01$; Social-Emotional with HADS depression: $r = 0.30$, $p < 0.05$; Social-Emotional with HADS anxiety: $r = 0.32$, $p < 0.01$). Finally, Skindex-8AA reported adequate and significant test-retest reliability, at 4, 12, and 24 weeks follow-up (see Table 3).

In addition, the correlations between the Skindex-16AA and the newly proposed Skindex-8AA were found to be very high. The Symptoms subscales had an $r = 1$; the Social-Emotional subscale of the Skindex-8AA had an $r = 0.95$ with the Emotional subscale of the Skindex-16AA and an $r = 0.86$ with the Functioning subscale of the Skindex-16AA. These results indicate that the information provided by the new version proposed (i.e., Skindex-8AA) is practically superimposable to the one of the Skindex-16AA.

Finally, the responsiveness analysis demonstrated that the Social-Emotional subscale of the Skindex-8AA was responsive to change, but not the Symptoms subscale. Mean Skindex-8AA score at baseline was of 16.37 (SD = 7.16) and of 11.05 (SD = 7.24) at 24-weeks follow-up, with an effect size of 1.08 (Cohen's D) ($p < 0.001$), indicating a large significant change in score from baseline to 24-weeks follow-up.

4 Discussion

The main aim of the current study was to provide the Italian adaptation of the Skinde-16AA and study its psychometric properties, in a group of Italian patients with severe AA. However, in case of non-adequacy of the model of the Skindex-16AA, we aimed at proposing an alternative factor structure and/or revision.

The factor analysis did not confirm the original factor structure of the Skindex-16AA (18) due to the presence of problematic items, which were removed from the analyses. The final structure of the questionnaire resulted in two dimensions, that were named Symptoms and Socio-Emotional, composed by four item each, which we named Skindex-8AA. Although the Posterior Predictive P-Value became significant with a strong informative prior, the changes in factor loadings were <10% compared to the model tested with the weaker priors, indicating that the interpretation of the model remained stable with different priors. Moreover, it is important to have short and reliable measure because shorter questionnaires are easier to administer, less time-consuming, and allow for the administration of multiple measures (e.g., for epidemiological studies), thereby reducing the burden on patients.

In our sample, in the first 24 weeks of treatment, our patients experienced a halving of the SALT score, in association with a mild improvement in the mean scores of the anxiety and depression domains of HADS.

Having a specific tool assessing quality of life in patients with AA is of utmost important, since AA significantly affects self-image, and psychosocial factors related to this condition often negatively impact patient QoL, especially in women, as found in the current study and confirmed by literature (29). Moreover, AA is associated with a significant mental health burden including anxiety, depression, suicidal ideation and/or behavior and high rates of psychiatric hospitalizations (21, 38). Whether the psychiatric comorbidity such as anxiety or depression leads to AA or vice versa is still poorly understood. Major depressive disorder was found to increase the risk of developing this condition by 90%, and AA, conversely, was found to increase the risk of subsequently developing major depressive disorder by 34% in adult population (8). Furthermore, the lack of control on the progression and relapses of AA puts patients on a higher risk of feel sad and helpless about their diagnosis, leading to anxiety, worry, fearful, and distress about disease recurrences (10).

TABLE 3 Skindex-8AA test-retest reliability.

Baseline	4 weeks ($N = 79$)		12 weeks ($N = 40$)		24 weeks ($N = 36$)	
	Symptoms	Social-emotional	Symptoms	Social-emotional	Symptoms	Social-emotional
Symptoms	0.68**	0.43**	0.59**	0.31*	0.61**	0.65**
Social-emotional	0.34**	1**	0.40*	0.73**	0.37*	0.77**

$^{**}p < 0.01$; $^{*}p < 0.05$.

The association between hair loss and mood disorders, however, was not demonstrated in pediatric samples. While earlier studies suggested that children may be less prone to developing depression and anxiety symptomatology until they reach an older age, when peers relationships become more salient (39), recent research indicates otherwise. Systematic reviews and studies, such as those by Toussi et al. (21), Vélez-Muñiz et al. (40), and Sinclair (41), have addressed the QoL and the presence of depression, anxiety, and suicide risk in pediatric populations with AA. These studies highlight that children with AA may indeed experience significant psychological distress, challenging the notion that younger children are largely unaffected by their condition in terms of mood disorders.

The psychosocial concern about others' judgment and fear of rejection seem to play a significant role; particularly hair loss in areas that were visible to others were most psychosocially burdensome to patients. Qualitative studies, in fact, suggested that people who suffered from AA frequently reported feelings of insecurity, inadequacy, and lack of self-consciousness due to the changes in their appearance that could impact on the self-identity and self-perception (42). Indeed, the incidence of body dysmorphic disorder is about 13 times higher in patients with AA than in general dermatology patients (43). All these psychological concerns could interfere in the way that patients may rate their condition, so patients tend to rate their AA as more severe and more invariable than dermatologists assessing it by SALT (44). This may explain why depression and anxiety symptoms tend to decrease slower than the SALT score during the treatment, as seen in the quality-of-life scores in psychosocial and symptoms domains.

The Skindex-8AA demonstrated to have an optimal test-retest reliability, over a wide time-frame, which indicates that its factor structure is stable over time.

Overall, specific instruments are usually more responsive than generic tools (45), and may better detect specific characteristics of the patient's illness experience, so it might be useful for clinicians and researchers to consider the use of these questionnaires when evaluating or studying Alopecia Areata.

In conclusion, the Skindex-8AA demonstrated satisfactory psychometric properties (i.e., convergent and construct validity, and test-retest reliability) as assessed in a sample of patients with AA. Future studies are needed to confirm its factor structure on a wider sample, with a more balanced number of women and men, and to assess its congruent validity with another measure of Health-related quality of life tool.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving humans were approved by the Institutional Ethical Committee of IDIIRCCS (protocol number: 739/1). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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GC: Conceptualization, Writing – original draft, Writing – review & editing. GR: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. TS: Visualization, Writing – original draft, Writing – review & editing, Validation. LP: Writing – original draft, Writing – review & editing. FP: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing. LD: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition. FD'O: Writing – original draft, Writing – review & editing. EV: Writing – original draft, Writing – review & editing. MFG: Writing – original draft, Writing – review & editing. RB: Writing – original draft, Writing – review & editing. FA: Writing – original draft, Writing – review & editing. GGi: Writing – original draft, Writing – review & editing. SFR: Writing – original draft, Writing – review & editing. FM: Writing – original draft, Writing – review & editing. LA: Writing – original draft, Writing – review & editing. GGa: Writing – original draft, Writing – review & editing. SR: Writing – original draft, Writing – review & editing. OS: Writing – original draft, Writing – review & editing. SB: Writing – original draft, Writing – review & editing. VB: Writing – original draft, Writing – review & editing. AM: Writing – original draft, Writing – review & editing. LB: Writing – original draft, Writing – review & editing. GM: Writing – original draft, Writing – review & editing. BP: Writing – original draft, Writing – review & editing. MCF: Writing – original draft, Writing – review & editing. DA: Supervision, Writing – original draft, Writing – review & editing. KP: Writing – original draft, Writing – review & editing, Supervision, Validation. Italian Study Group on Cutaneous Adnexal Disease of the Italian Society of Dermatology and Sexual Transmitted diseases (SIDeMaST): Writing – original draft, Writing – review & editing.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1415334/full#supplementary-material

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A longitudinal examination of the effect of physical exercise on the emotional states of college students: exploring the sense of coherence as a mediator through a cross-lagged panel analysis

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Purpose: This longitudinal study aimed to investigate the causal relationship between physical exercise and emotional states among university students, focusing on the mediating role of sense of coherence.

Method: A total of 1,215 university students (aged 18–25 years) were recruited and completed questionnaires assessing physical activity (International Physical Activity Questionnaire-Short Form), emotional states (Positive and Negative Affect Schedule), and sense of coherence (Sense of Coherence Scale-13) at three time points over a three-month period. Preliminary analyses included independent samples t-tests, chi-square tests, and Pearson correlations. Cross-lagged panel mediation analysis was conducted using Mplus 8.3, with bootstrapping employed to test indirect effects.

Results: Results indicated that sense of coherence significantly predicted positive affect ($\beta = 0.259–0.369$, $p < 0.001$). Positive affect, in turn, predicted physical exercise ($\beta = 0.083–0.182$, $p < 0.05$), while negative affect also influenced physical exercise ($\beta = -0.096–0.203$, $p < 0.05$). Physical exercise indirectly influenced positive affect through sense of coherence ($\beta = 0.037$, $p = 0.045$), and positive affect indirectly influenced physical exercise through sense of coherence ($\beta = 0.029$, $p = 0.028$). Other indirect effects involving physical exercise, sense of coherence, and negative affect were non-significant.

Conclusion: This study underscores the importance of sense of coherence in promoting emotional well-being among university students and in the reciprocal relationship between physical exercise and positive emotional states. Findings suggest that interventions targeting sense of coherence may enhance the emotional benefits of physical exercise. Future research should explore other potential mediators and moderators of the relationship between physical exercise and emotions and examine the effectiveness of sense of coherence-based interventions on well-being in this population.

KEYWORDS

physical exercise, emotional states, sense of coherence, longitudinal study, mediation analysis, college students

1 Introduction

The transition to college represents a critical developmental juncture, marked by profound shifts in identity formation, social roles, and psychological maturation (Sawyer et al., 2018; Yikealo et al., 2018; Cage et al., 2021; Liu et al., 2023a). While this period offers significant opportunities for personal growth and exploration, it also presents college students with a myriad of mental health challenges (Kessler et al., 2005; Cao and Liu, 2022). Notably, Chinese college students face a unique set of cultural and societal pressures that can exacerbate these challenges.

Empirical evidence highlights a concerning rise in stress levels among Chinese college students (Cao and Liu, 2022; Liu et al., 2023a). Deeply ingrained traditional family values and parenting norms in Chinese society often place considerable pressure on students as they navigate the transition to college life and grapple with evolving social roles (Ross et al., 1999; Zhang et al., 2012; Hurst et al., 2013). Furthermore, the intensely competitive academic environment, characterized by demanding workloads and a relentless pursuit of achievement, coupled with a fiercely competitive job market, further contribute to heightened stress levels among this population (Hurst et al., 2013; Cao and Liu, 2022).

Critically, longitudinal studies focusing on Chinese college students reveal that mental well-being is not static but rather demonstrates significant fluctuation over time, with notable variations observed across different subgroups (Liu et al., 2023b,c; Xie et al., 2023; Liu et al., 2024). This underscores the importance of identifying and understanding the factors that contribute to these dynamic shifts in mental health among college students.

This study aims to investigate the impact of physical exercise on emotional states among college students, with a particular emphasis on the mediating role of Sense of Coherence (SOC). SOC, a key construct in salutogenic theory, refers to an individual's pervasive orientation to perceive the world and their life experiences as comprehensible, manageable, and meaningful, fostering a belief in their capacity to effectively cope with life's challenges. Emotional states encompass a wide range of affective experiences encountered in daily life, including both the reduction of negative affect (NA) and the cultivation of positive affect (PA) (Lazarus, 1991; Kahneman and Deaton, 2010). PA, in particular, has been linked to a host of cognitive and psychological benefits, including enhanced cognitive flexibility, creativity, and resilience to stress (Fredrickson, 1998, 2001).

Physical exercise, through a complex interplay of physiological and psychological mechanisms, has been shown to reduce NA, enhance PA, and consequently improve overall emotional well-being (Hamer et al., 2012; Mikkelsen et al., 2017; Kandola and Stubbs, 2020). Furthermore, emerging research suggests that physical exercise can foster the development of SOC, equipping individuals with enhanced coping mechanisms to navigate stress and adversity, ultimately promoting emotional well-being (Laudańska-Krzemińska et al., 2020; Soekmawati et al., 2022). However, there remains a dearth of longitudinal research comprehensively examining the dynamic interplay between physical exercise, emotional states, and SOC.

This study aims to address this gap by elucidating the mechanisms through which physical exercise influences emotional states among college students and by examining the mediating role of SOC in this relationship. By shedding light on these complex dynamics, this research seeks to provide a more nuanced understanding of the factors that contribute to emotional well-being among college students, ultimately informing the development of targeted interventions and support programs.

1.1 Relationship between PE and emotional states

Abundant studies have elucidated and sufficiently established the correlation between PE and emotional states while indicating that regular physical activity significantly benefits emotional states, especially among college students. A comprehensive body of research has evidenced that exercise is crucial for mitigating stress and anxiety in this population (Babyak et al., 2000; Ströhle, 2009; Rothon et al., 2010; Bernstein and McNally, 2017; Harvey et al., 2018). For instance, a longitudinal study by Tyson et al. (2010) found that physical activity was associated with lower levels of depression and anxiety among university students. Similarly, Feng et al. (2014) reported that regular exercise significantly reduced stress and improved mood states in Chinese college students.

PE triggers the release of endorphins and dopamine, mood-elevating neurotransmitters (Ransford, 1982; Chaouloff, 1989), boosts circulation (Numaga-Tomita et al., 2019) and oxygen supply (Lai et al., 2007), increases brain efficiency (de Sousa Fernandes et al., 2020), and reduces anxiety and tension (Mahalakshmi et al., 2020; Philippot et al., 2022). Additionally, when PE improves the physical condition and abilities of individuals, it also increases their self-esteem and confidence. These achievements are thus translated into positive emotional states, thereby fortifying affective well-being (Matta Mello Portugal et al., 2013). A study by Liu et al. (2015) demonstrated that physical activity was positively associated with self-esteem among Chinese university students, which, in turn, contributed to better emotional well-being.

PE also stimulates social interaction and teamwork, thereby offering social support and a sense of community. Engagement in group sports or team activities allows for building social connections and reducing loneliness and isolation, which, in turn, boosts emotional states (Parra-Rizo and Sanchís-Soler, 2021). Research by Zhang et al. (2012) indicated that participation in group-based exercise programs enhanced social support and reduced feelings of loneliness among college students, leading to improved emotional well-being. Finally, PE augments neuroplasticity, improving neural connections and communication, enhancing brain structure and function, and thereby increasing emotional regulation and resilience (Mahalakshmi et al., 2020).

1.2 Relationship between PE and SOC

Numerous studies have explored the intricate relationship between PE and SOC. SOC, delineated as individuals' perception of congruence among their behaviors, values, and life aspirations, is pivotal in stress mitigation and disease prophylaxis. Antonovsky (1987) conceptualized that SOC encompasses the aspects of comprehensibility, manageability, and meaningfulness. Being fundamental to individual well-being, SOC captures the persistent and adaptive conviction in individuals' capacities to efficaciously tackle internal and external environmental challenges (Frommberger et al., 1999). According to empirical research, a pronounced correlation exists between PE and SOC among individuals, revealing that those engaged in regular physical activity exhibit elevated levels of psychological well-being (Antonovsky, 1987; Hassmen et al., 2000; Edwards, 2002).

PE mainly facilitates outlining explicit objectives and action frameworks (Karamanian et al., 2020). Individuals performing PE typically need to meticulously strategize their physical training plan, in which weekly exercise frequency, duration, and intensity should be determined before and after training. Individuals' perceptions of autonomy and self-efficacy are bolstered when these objectives are achieved (Olander et al., 2013), which then nurtures SOC. Moreover, physical activity is crucial for endorsing self-identity and self-actualization (Verkooijen and de Bruijn, 2013). Among individuals, it nurtures positive perceptions about one's physical self-image, competencies, and health. Physical activity thus satiates appearance-and well-being-related personal anticipations, thereby magnifying identity gratification and, consequently, SOC. Furthermore, PE is related to improved emotional states and well-being. Neurotransmitters, such as endorphins, secreted during physical exertion elevate mood and well-being (You and Shin, 2017), thereby aligning positive emotional experiences with personal values and aspirations and stimulating SOC. Finally, physical activity promotes social engagement and teamwork among individuals, allowing them to develop social connections, augment social support, and cultivate a sense of belonging (Kim et al., 2021). Integrating team roles and responsibilities with individual behaviors and values further solidifies SOC (Chang et al., 2019).

In summary, using various mechanisms, including promotion of goal specificity, reinforcement of self-identity and actualization, creation of positive affective experiences, and improvement of social connectivity, PE profoundly strengthens SOC. This augmentation of perceived congruence in behaviors, values, and objectives considerably raises psychological well-being levels. Consequently, this study postulates that the degree of PE is positively correlated with SOC.

1.3 Mediating role of SOC in emotional states

SOC and emotional states are profoundly interconnected, and this interconnection highlights the critical role of SOC in stress mitigation, promotion of emotional equilibrium, and protection against psychological and physiological maladies. Because of SOC, individuals perceive internal stability and serenity, which then facilitates the achievement of emotional balance and positive development (Jin et al., 2022). When individuals attain congruity among behaviors, values, and objectives, they experience substantial inner peace and satisfaction, which notably diminishes negative affective experiences such as anxiety and depression, and enhances feelings of joy and fulfillment (Breslin et al., 2006; Julkunen and Ahlström, 2006). Furthermore, SOC augments self-esteem and confidence, thereby serving as a spiritual foundation for traversing life's adversities and stressors, which then advances emotional regulation, and psychological resilience, and substantially improves emotional states (Moksnes et al., 2013; Moksnes and Espnes, 2020). Moreover, SOC promotes self-actualization and contentment, which enables individuals to achieve satisfaction by aligning their behaviors, values, and personal aims with their ideals, thereby enriching emotional experiences and contributing to overall happiness (John and Gross, 2004). SOC is also pivotal for cultivating healthy interpersonal connections by boosting social support and engendering a sense of belonging, offering emotional sustenance and security, effectively preventing negative affect, and bolstering emotional states (Gross and John, 2003; Chang et al., 2020; Fraser et al., 2021).

In summary, the extant literature suggests that PE is positively associated with emotional states and SOC, while SOC, in turn, is positively related to emotional well-being. These findings indicate that SOC may serve as a crucial mediator in the relationship between PE and emotional states among college students. By enhancing SOC, PE may not only directly contribute to improved emotional states but also indirectly foster emotional well-being through the mediating role of SOC.

To further elucidate the dynamic interplay and causal linkages among PE, SOC, and emotional states in college students, the present study employs a longitudinal, cross-lagged panel design. Based on the aforementioned theoretical and empirical foundations, we propose the following research hypotheses (Figure 1):

> *H1*: Physical exercise promotes positive affect among college students.
>
> *H2*: Sense of coherence mediates the relationship between physical exercise and positive affect among college students.
>
> *H3*: Physical exercise reduces negative affect among college students.
>
> *H4*: Sense of coherence mediates the relationship between physical exercise and negative affect among college students.

Figure 1 depicts the hypothesized cross-lagged panel mediation model, illustrating the direct and indirect relationships among physical exercise, sense of coherence, and emotional states (positive and negative affect) across three time points (T1, T2, and T3). The solid lines represent the hypothesized direct effects, while the dashed lines indicate the hypothesized mediating pathways via sense of coherence. The autoregressive paths [e.g., PA(T1) → PA(T2)] and cross-lagged paths [e.g., PE(T1) → SOC(T2)] are also included in the model to account for the stability and reciprocal relationships among the variables over time.

2 Methods

2.1 Participants and procedure

This longitudinal study investigated the relationship between physical exercise, emotional states, and sense of coherence among Chinese college students. Data were collected using the "Maike" digital survey platform at three time points: April, May, and June 2023. A convenience sample of undergraduate and postgraduate students from universities across China was recruited via QR codes disseminated through the WeChat platform. To maximize sample representativeness, recruitment efforts targeted students from diverse geographical locations, academic disciplines, and year levels.

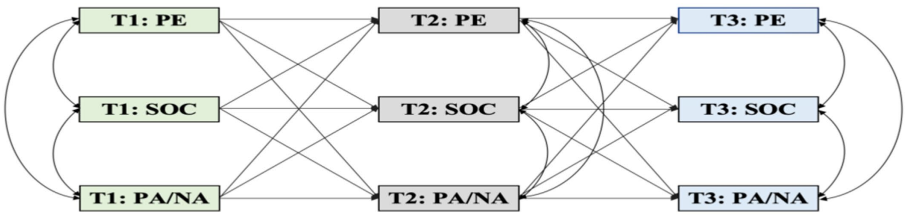

FIGURE 1
Hypothesized model. T1, Time 1 (intake); T2, Time 2 (1 month follow-up); T3, Time 3 (2-month follow-up); PE, physical exercise; SOC, sense of coherence; PA, positive affect; NA, negative affect.

2.1.1 Eligibility criteria

To be eligible for inclusion in the study, participants had to be currently enrolled in an undergraduate or postgraduate program at a Chinese university, have access to a smartphone or computer with internet connectivity, and voluntarily provide informed consent. Individuals were excluded from the study if they reported any physical or mental health conditions that could potentially impede regular exercise participation or completion of the online questionnaires, regardless of whether these conditions were self-reported or medically diagnosed.

Additionally, participants were excluded if their questionnaire data were incomplete (i.e., more than 20% of items missing within any single-time point questionnaire) or if their responses exhibited potentially invalid patterns, such as straight-lining. Questionnaires flagged for potentially invalid response patterns were independently reviewed by two researchers, and exclusion decisions were made via consensus based on pre-established criteria to ensure objectivity. Finally, participants who did not provide informed consent were excluded from all study procedures.

Prior to initiating any study procedures, all potential participants received comprehensive information about the study and provided informed consent. The questionnaire surveys were administered in three phases, spaced 1 month apart, to allow for the examination of changes over time. This study received ethical approval from the Guizhou Normal University Institutional Review Board (approval number: 202300005) and was conducted in accordance with the ethical principles outlined in the latest Declaration of Helsinki.

2.1.2 Sample attrition and bias examination

Initially, 1,215 student participants were enrolled in the study. However, due to attrition, the sample size decreased to 974 and 904 participants at the second and third data collection points, respectively. Complete data across all three time points were available for 533 students, who comprised the final analytic sample.

To assess potential attrition bias, independent samples t-tests were conducted to compare the initial participant pool ($n = 1{,}215$) with the final analytic sample ($n = 533$) on key demographic variables and study variables (physical exercise levels, emotional states, and sense of coherence). The absence of statistically significant differences between these groups suggested that data missingness was random and unlikely to have introduced substantial bias into the study findings. Table 1 provides a detailed overview of the demographic characteristics of the final analytic sample ($n = 533$).

2.2 Measures

2.2.1 Physical exercise

Physical exercise levels were quantified using the Physical Activity Rating Scale-3 (PARS-3) developed by Liang (1994). The PARS-3 consists of three items assessing the intensity, duration, and frequency of physical exercise, each rated on a 5-point Likert scale (1–5). An exercise volume score is calculated using the following formula: Volume = Intensity * Time * Frequency, resulting in a total score ranging from 0 to 100. Based on their scores, students were categorized into three physical activity level groups: low (≤19 points), moderate (20–42 points), and high (≥43 points). The PARS-3 has demonstrated good reliability and validity in Chinese college student samples, with a Cronbach's α of 0.78 and test–retest reliability of 0.82 (Liang, 1994; Wang et al., 2020). Example items include: "How intense is your physical activity in general?," "How long do you usually exercise each time?," and "On average, how many times a week do you engage in physical exercise?"

2.2.2 Sense of coherence

Participants' sense of coherence was assessed using the 13-item Sense of Coherence scale (SOC-13), adapted to Chinese by Bao et al. (2006). The SOC-13 employs a 7-point Likert scale to measure three dimensions: comprehensibility, manageability, and meaningfulness. Higher total scores indicate a stronger sense of coherence. The Chinese version of the SOC-13 has shown good psychometric properties, with Cronbach's α ranging from 0.76 to 0.91 and test–retest reliability of 0.78 (Bao et al., 2006; Zhang et al., 2011). Example items include: "When you face difficult situations, do you feel you are able to find a way to handle them?" and "Do you have the feeling that your life has a purpose and meaning?"

2.2.3 Emotional states

Positive and negative emotional states were evaluated using the Chinese version of the Positive and Negative Affect Schedule (PANAS), developed by Huang et al. (2003). This scale comprises two 10-item subscales, each rated on a 5-point Likert scale (1 = very slightly or not at all, 5 = extremely), measuring the intensity of positive and negative emotional experiences, respectively. Higher scores on each subscale indicate greater intensity of the corresponding emotional experience. While overall emotional state was considered, positive and negative affect were also analyzed as relatively independent constructs. The Chinese version of the PANAS has demonstrated good reliability and validity, with Cronbach's α of 0.85 for the positive affect subscale and 0.83 for the negative affect subscale (Huang et al., 2003; Li et al., 2015). Example items include: Positive

TABLE 1 Internal consistency testing of study variables ($n = 533$).

Scales	Items	Cronbach's alpha		
		T1	T2	T3
PANAS	20	0.808	0.876	0.875
Positive affect (PA)	10	0.851	0.903	0.903
Negative affect (NA)	10	0.887	0.905	0.899

T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); PA and NA belongs to PANAS.

affect—"Excited, interested, strong, enthusiastic, alert"; Negative affect—"Distressed, upset, scared, nervous, hostile."

2.3 Statistical analysis

Data analysis for this study was conducted in three primary stages. First, to ensure the data met the assumptions of multivariate normality, a Doornik-Hansen test was performed in Stata 16.1, examining the key variables of age, physical exercise, sense of coherence, positive affect, and negative affect. The significance level for this test was set at $p < 0.05$, with only data meeting this criterion considered to fulfill the assumption of multivariate normality and suitable for further analysis.

Next, preliminary analyses were conducted using SPSS 26.0 to gain a comprehensive understanding of the sample characteristics and relationships between variables. Specifically, independent samples *t*-tests and chi-square tests were employed to compare participants included and excluded from the study on key variables, ensuring sample representativeness. Descriptive statistics, including means, standard deviations, and frequencies, were calculated and analyzed. Pearson correlation coefficients were calculated to examine the bivariate associations between study variables. Cronbach's α coefficients were also computed to assess the reliability of the scales, with values greater than 0.7 considered acceptable for further analysis. To facilitate interpretation, Pearson correlation coefficients were categorized into five levels based on Cohen's (2013) criteria: negligible (≤0.19), low (0.20–0.39), moderate (0.40–0.59), moderate-high (0.60–0.79), and high (≥0.80).

Finally, to examine the hypothesized causal relationships and mediating effects among the variables, a cross-lagged panel mediation model was analyzed using Mplus 8.3. Path coefficients, representing the magnitude and direction of effects between variables in the model, were estimated. Total, indirect, and direct effects were also calculated to quantify the influence of variables on each other. A bias-corrected bootstrapping procedure with 5,000 resamples was employed to test the significance of the indirect (mediating) effects. A 95% confidence interval that did not include zero was considered to indicate a statistically significant mediating effect.

3 Results

3.1 Test of common method biases

When the singular survey method was used for data collection, a potential spurious covariance was introduced among the variables. Therefore, the Harman single-factor test was applied to the initial dataset ($N = 1,215$) to evaluate common method biases (Livingstone et al., 1997). The foremost principal component only contributed to 20.749% of the total variance from the 36 extracted components without rotation, which was well beneath the 40% threshold. This result confirms that common method biases were not a significant problem in this study. In later survey rounds, adjustments were also made in the questionnaire item sequence as a precautionary measure.

3.2 Descriptive analysis

The sample consisted of 533 university students (average age: 19.38 ± 1.22 years) from different Chinese provinces, and 50.28% of these participants were female students. The dropout rate was 56.13%. Table 2 presents the demographic details of participants and the outcomes of the dropout analysis. Chi-square tests conducted to examine ethnic background and economic status unveiled no statistically significant differences between the groups included and excluded from the study, evidenced by p values for ethnicity ($\chi^2 = 1.958$, $p = 0.162$) and economic status ($\chi^2 = 0.812$, $p = 0.666$). Furthermore, independent samples t-tests conducted on SOC, emotional states, and PE levels at T1 revealed no statistically significant differences for PA ($t = -0.050$, $p = 0.960$), NA ($t = 0.148$, $p = 0.883$), and PE ($t = 1.847$, $p = 0.065$). However, a significant difference was found in SOC at T1 between the included and excluded groups ($t = 2.031$, $p = 0.043$), with the excluded group having a slightly higher SOC score (54.69 ± 9.11) than the included group (53.67 ± 8.04). These findings suggest that participant attrition was largely random, with the exception of a small difference in baseline SOC scores, which should be considered when interpreting the study's conclusions.

Key variables were evaluated here at three-time intervals: PA, NA, SOC, and PE (Table 3). A comparative analysis across these time points revealed notable statistical differences in PA, NA, and SOC among the groups at each measurement stage. Nonetheless, PE exhibited no statistically significant differences among the groups ($F = 2.834$, $p = 0.059$).

As shown in Table 4, the most frequently reported exercise intensity at baseline (T1) was "small strength, not too nervous movements" (EI-2, 31.89%), followed by "intense and sustained exercise of moderate intensity" (EI-3, 30.96%). Follow-up assessments at 1 month (T2) and 2 months (T3) revealed a similar pattern, suggesting that the distribution of exercise intensity remained relatively stable over the study period.

3.3 Bivariate analysis

To investigate the relationships between PE, PA, NA, and SOC over three-time points, Pearson correlation coefficients were calculated. PE at Time 1 [PE(T1)] and SOC at Time 2 [SOC(T2)] were significantly correlated ($r = 0.177$, $p < 0.001$). Similarly, PE(T1) and PA at Time 2 [PA(T2)] were significantly correlated ($r = 0.346$, $p < 0.001$). Furthermore, SOC at Time 1 [SOC(T1)] and PA at Time 2 [PA(T2)] were significantly related ($r = 0.179$, $p < 0.001$), whereas SOC(T1) and NA at Time 2 [NA(T2)] exhibited a significant negative correlation

TABLE 2 Demographic characteristics of the participants ($N = 1,215$).

Variable		Included data ($n = 533$)	Excluded data ($n = 682$)	x^2/t	p-value
		Mean±SD or n (%)			
Sex	Male	265 (49.72)	408 (59.82)	12.365	<0.001
	Female	268 (50.28)	274 (40.18)		
Age		19.38 ± 1.22	20.10 ± 1.78	8.066	<0.001
Ethnicity	Han	296 (55.53)	406 (59.53)	1.958	0.162
	Minorities	237 (44.47)	276 (40.47)		
Household	City	126 (23.64)	203 (29.77)	6.939	0.031
	Town	102 (19.14)	136 (19.94)		
	Rural	305 (57.22)	343 (50.29)		
Grade Level	Freshman	482 (90.43)	413 (60.56)	139.775	<0.001
	Sophomore	28 (5.25)	132 (19.35)		
	Junior	17 (3.19)	82 (12.02)		
	Senior	0	18 (2.64)		
	Graduate	6 (1.13)	37 (5.43)		
Major	Sociology	270 (50.66)	271 (39.74)	51.390	<0.001
	Science	132 (24.77)	175 (25.66)		
	Engineering	113 (21.20)	131 (19.21)		
	Art and Sport	18 (3.37)	105 (15.39)		
Economic conditions	Low	212 (39.77)	267 (39.15)	0.812	0.666
	Intermediate	318 (59.66)	408 (59.83)		
	High	3 (0.57)	7 (1.02)		
SOC(T1)		53.67 ± 8.04	54.69 ± 9.11	2.031	0.043
SOC(T2)		54.37 ± 7.29			
SOC(T3)		53.00 ± 6.52			
PA(T1)		30.05 ± 5.53	30.03 ± 6.08	−0.050	0.960
PA(T2)		28.90 ± 6.66			
PA(T3)		29.62 ± 6.01			
NA(T1)		24.11 ± 6.17	24.16 ± 6.20	0.148	0.883
NA(T2)		23.13 ± 6.68			
NA(T3)		25.29 ± 6.01			
PE(T1)		21.89 ± 19.11	24.03 ± 20.78	1.847	0.065
PE(T2)		20.76 ± 18.56			
PE(T3)		19.27 ± 16.34			

T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); SD, standard deviation; SOC, sense of coherence; PA, positive affect; NA, negative affect; PE, physical exercise.

($r = -0.237$, $p < 0.001$). Additional correlation findings are detailed in Figure 2.

3.4 Path analysis of PE and emotional states

In this study, cross-lagged models were used to rigorously explore the dynamics between PE, PA, NA, and SOC across three temporal intervals (T1, T2, and T3), thereby concentrating specifically on their influence on emotional states. Based on preliminary correlational findings, a cross-lagged mediation model was constructed to evaluate the interactive association between PE and emotional states—comprising both PA and NA—while demographic factors such as gender, place of residence, and economic status were integrated as control variables into the model so as to mitigate potential confounding influences.

Autoregressive coefficients for emotional state-related variables exhibited statistically significant continuity across the study phases. The path analysis (Figure 3) revealed that from T1 to T2 and T2 to T3, SOC exerted a significant predictive effect on PA, thereby highlighting the substantial causal impact of SOC on emotional states over time

TABLE 3 The comparison of baseline data for the study variables across different periods ($n = 533$).

Variable	T1	T2	T3	F	p-value
	Mean ± SD				
PE	21.90 ± 19.11	20.76 ± 18.56	19.27 ± 16.34	2.834	0.059
SOC	53.67 ± 8.04	54.37 ± 7.29	53.00 ± 6.52	4.730	0.009
PA	30.05 ± 5.53	28.89 ± 6.66	29.62 ± 6.01	4.907	0.008
NA	24.11 ± 6.17	23.13 ± 6.68	25.29 ± 6.01	15.735	<0.001

T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); SD, standard deviation; SOC, sense of coherence; PA, positive affect; NA, negative affect; PA and NA belongs to PANAS; PE, physical exercise.

TABLE 4 Frequency distribution of exercise intensity ($n = 533$).

Exercise intensity (EI)	T1		T2		T3	
	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
EI-1	86	16.14	92	17.26	85	15.95
EI-2	170	31.89	168	31.52	184	34.52
EI-3	165	30.96	172	32.27	170	31.89
EI-4	95	17.82	86	16.14	81	15.20
EI-5	17	3.19	15	2.81	13	2.44

T1, Time 1 (intake); T2, Time 2 (1 month follow-up); T3, Time 3 (2-month follow-up); EI-1, Light exercise; EI-2, Small strength not too nervous movements; EI-3, Intense and sustained exercise of moderate intensity; EI-4, Shortness of breath, sweating a lot of great strength, but not lasting movement; EI-5, Shortness of breath, sweating a lot of great intensity of lasting movement.

(T1 → T2: $\beta = 0.259$, $p < 0.001$; T2 → T3: $\beta = 0.369$, $p < 0.001$). Concurrently, the model demonstrated that PA made a statistically significant contribution to PE across both intervals (T1 → T2: $\beta = 0.182$, $p < 0.001$; T2 → T3: $\beta = 0.083$, $p = 0.032$), whereas the predictive capacity of SOC on PE was not statistically significant. This finding indicated that PA sustains a unidirectional predictive relationship with PE, and SOC alone impacts emotional states, delineating the meticulous interplay among physical activity, SOC, and the spectrum of affective experiences.

Moreover, the path analysis further elucidated (Figure 4) that NA significantly influenced PE across both T1 to T2 and T2 to T3 intervals (T1 → T2: $\beta = -0.096$, $p = 0.022$; T2 → T3: $\beta = 0.203$, $p < 0.001$). Yet, the predictive capacity of SOC on both PE and NA was not statistically significant (SOC(T1) → PE(T2): $\beta = 0.035$, $p = 0.358$; SOC(T1) → NA(T2): $\beta = 0.213$, $p < 0.001$; SOC(T2) → PE(T3): $\beta = 0.129$, $p = 0.002$; SOC(T2) → NA(T3): $\beta = 0.016$, $p = 0.723$), which revealed a unidirectional causal relationship between NA to PE. This accentuates that the components of emotional states and PE are intricately related over time. These insights imply that while SOC significantly influences the positive dimensions of emotional states, it seems to exert more constrained direct effects on PE and NA, which highlights the complex interplay among various aspects of emotional states and physical activity.

The subsequent analysis (Table 5) uncovered that path coefficients for the mediating role of SOC in the PE–PA relationship were statistically significant, which indicates meaningful indirect effects (PE(T1) → SOC(T2) → PA(T3): $\beta = 0.037$, 95% CI [0.001, 0.073], $p = 0.045$). Path coefficients highlighting the mediating role of SOC in the PA–PE dynamic relationship were also statistically significant (PA(T1) → SOC(T2) → PE(T3): $\beta = 0.029$, 95% CI [0.003, 0.055], $p = 0.028$). Conversely, path coefficients concerning the SOC-mediated influence of PE on NA through SOC and the SOC-mediated reciprocal influence of NA on PE were not statistically significant (PE(T1) → SOC(T2) → NA(T3): $\beta = 0.002$, 95% CI [−0.014, 0.018], $p = 0.791$; NA(T1) → SOC(T2) → PE(T3): $\beta < 0.001$, 95% CI [−0.013, 0.012], $p = 0.961$). This result thus underscores the differential mediating effects of SOC between the positive and negative dimensions of emotional states and PE.

To further test the complete mediation effect of SOC, we compared the fit indices of the hypothesized model with alternative models that included direct paths from PE(T1) to PA(T3) and from PA(T1) to PE(T3). The results showed that adding these direct paths did not significantly improve the model fit [$\Delta\chi^2(2) = 3.641$, $p = 0.162$], suggesting that SOC fully mediated the relationships between PE and PA over time.

4 Discussion

This study delves into the interplay of emotional states, physical exercise (PE) levels, and sense of coherence (SOC) among university students.

4.1 Results discussion

A negative association between negative affect (NA) and PE levels was observed from the first time point (T1) to the second (T2), aligning with previous research suggesting that reducing negative emotions may enhance individuals' willingness to engage in physical activity (Modolo et al., 2011; Liu X. et al., 2023). Interestingly, this trend reversed from T2 to T3, with increased negative affect corresponding to higher PE levels. This reversal might reflect the structured physical education courses prevalent in Chinese

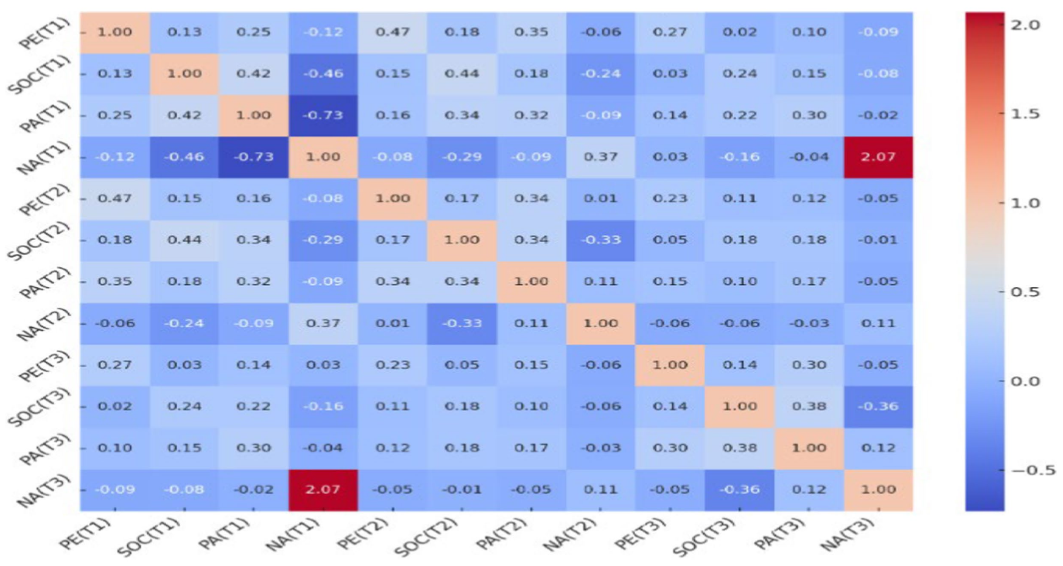

FIGURE 2
Heatmap of the correlation matrix. The correlation coefficients among various variables are shown, with the intensity of the color reflecting the strength and direction of the correlation. Positive correlations are depicted in warmer colors, while negative correlations are indicated in cooler colors.

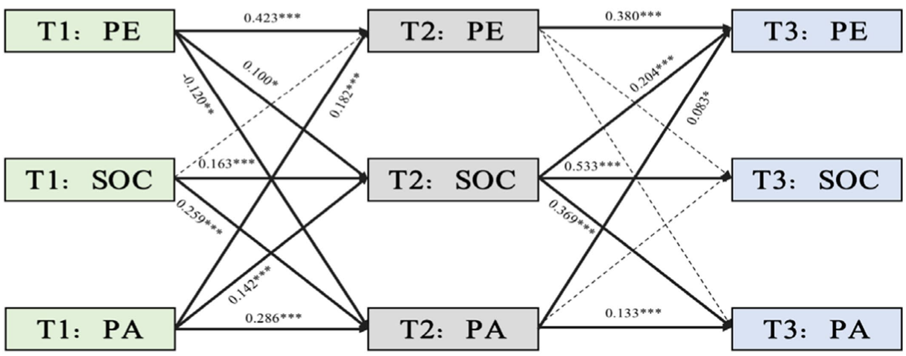

FIGURE 3
A standardized cross-lagged path model among PE, SOC, and PA. T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); SOC, sense of coherence; PA, positive affect; PE, physical exercise. Solid lines indicate significance, and dotted lines signify non-significance. The residuals are not shown; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

universities, particularly for non-sports majors. Integrated into academic evaluations, these courses aim to promote physical well-being and cultivate lasting exercise habits, potentially serving as a stress-relief mechanism toward the semester's end (Baghurst and Kelley, 2014). This finding also aligns with some studies suggesting that, under specific circumstances, negative emotions can motivate physical exercise (Eklund and Crawford, 1994). However, the expected mediating role of SOC on the relationship between PE levels and NA was not observed. Further exploration of the conditions under which SOC might influence this dynamic relationship is warranted.

Furthermore, our findings confirmed the consistent, positive influence of positive affect (PA) on PE levels across the observation period, corroborating a direct causal relationship between positive emotions and PE levels. This aligns with previous findings demonstrating that positive emotional states can significantly motivate individuals to participate in physical activity (Helfer et al., 2015).

This study also highlighted the significant mediating role of SOC in the relationship between PE levels and PA, underscoring the importance of SOC for emotional well-being among university students. Higher SOC levels were significantly associated with higher PA, consistent with research identifying SOC as a determinant of positive affect (Oztekin and Tezer, 2009). However, no predictive relationship of PE levels on SOC was found, similar to a longitudinal study on community-dwelling older adults where SOC did not significantly influence physical activity levels (Kukihara et al., 2018). This suggests that the relationship between PE levels and SOC is complex and influenced by factors not covered in this study, such as the nature of exercise, individual perceptions of coherence, and other mediating variables. Future research should

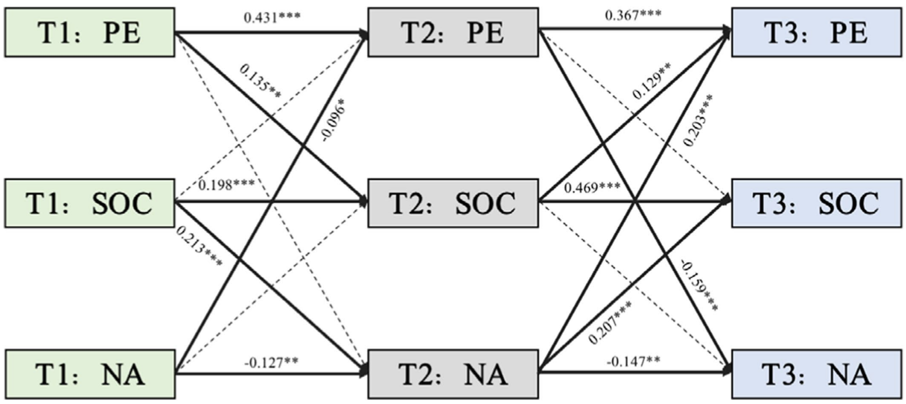

FIGURE 4
A standardized cross-lagged path model among PE, SOC, and NA. T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); SOC, sense of coherence; NA, negative effect; PE, physical exercise. Solid lines indicate significance, dotted lines indicate non-significance. The residuals are not shown; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

explore these factors to better understand the conditions under which PE levels might impact SOC.

4.2 Research significance

This study revealed a crucial mediating role of SOC in the relationship between PA and PE levels, indicating that SOC is essential for enhancing the positive impact of PE levels on emotional states. This finding expands on previous research by highlighting the importance of considering SOC when examining the emotional benefits of PE for university students. This suggests that interventions aimed at enhancing SOC among university students could be significantly beneficial to their mental and physical well-being by fostering self-esteem and confidence, fulfilling needs for self-actualization, and providing social support (Posadzki et al., 2010).

By investigating the mechanisms through which PE levels influence emotional well-being among university students, this longitudinal study provides empirical evidence for addressing emotional health challenges within this population. The findings have important theoretical and practical implications. Theoretically, this study contributes to the existing literature by providing a more nuanced understanding of the dynamic relationships between PE, SOC, and emotional states among university students. Practically, the findings suggest that interventions aimed at enhancing SOC and promoting PE could be effective strategies for improving emotional well-being among university students. Universities should consider incorporating such interventions into their student health and well-being programs.

4.3 Limitations and future directions

While this study offers valuable insights into the intricate relationships between PE levels, emotional states, and SOC among university students using a cross-lagged model, it has limitations.

Participants were primarily recruited from a single university, limiting the generalizability of the findings. Future research should recruit a more diverse sample from multiple universities to enhance the representativeness of the findings. The study relied on self-reported measures, which are susceptible to potential biases, including recall inaccuracies, social desirability effects, and response bias, potentially compromising the objectivity and accuracy of the collected data. Incorporating objective measurement techniques, along with other data collection techniques like direct behavioral observation and physiological assessments, could provide a more comprehensive and accurate portrayal of the studied phenomena. The study's limited time span might have masked long-term dynamic relationships and influences between PE levels, emotional states, and SOC. The two-month follow-up period might be insufficient to capture the full range of changes in these variables over time. Future studies should employ longitudinal designs with longer timeframes to explore the enduring effects of these variables over time more thoroughly. Furthermore, future research must explore the role of cultural and social contexts in shaping the interplay between PE levels, emotional states, and SOC. Valuable insights can be gained regarding how cultural norms, societal expectations, and educational practices influence these variables and their interrelationships when investigating these relationships across diverse cultural backgrounds.

Despite these limitations, this study significantly contributes to our understanding of the dynamic relationships between PE, emotional states, and SOC among university students. Addressing the identified limitations and incorporating the suggested methodological refinements in future research can significantly enrich the field, providing more profound, actionable insights and practical implications for promoting emotional and physical well-being among individuals in university settings and beyond.

5 Conclusion

This study illuminates the significant predictive power of a sense of coherence on positive emotional states, highlighting its crucial role in emotional well-being. Furthermore, the study reveals a positive feedback loop between positive emotional states and physical exercise. These findings suggest that interventions such as mindfulness training, stress management workshops, and social support programs could enhance students' sense of coherence, thereby maximizing the positive effects of

TABLE 5 Standardized path analysis among variables at different time points.

PA path	Coefficient (β)	S.E.	*p*-value	95%CI
PE(T1) → PE(T2)	0.423	0.036	<0.001	0.354 ~ 0.493
PE(T1) → SOC(T2)	0.100	0.043	0.020	0.016 ~ 0.184
PE(T1) → PA(T2)	−0.120	0.040	0.003	−0.200 ~ −0.041
SOC(T1) → PE(T2)	0.002	0.039	0.960	−0.074 ~ 0.078
SOC(T1) → SOC(T2)	0.163	0.043	<0.001	0.079 ~ 0.246
SOC(T1) → PA(T2)	0.259	0.039	<0.001	0.181 ~ 0.336
PA(T1) → PE (T2)	0.182	0.040	<0.001	0.104 ~ 0.026
PA(T1) → SOC(T2)	0.142	0.044	0.001	0.055 ~ 0.229
PA(T1) → PA(T2)	0.286	0.041	<0.001	0.206 ~ 0.366
PE(T2) → PE(T3)	0.380	0.036	<0.001	0.309 ~ 0.450
PE(T2) → SOC(T3)	0.017	0.036	0.629	−0.053 ~ 0.088
PE(T2) → PA(T3)	0.046	0.040	0.242	−0.031 ~ 0.124
SOC(T2) → PE(T3)	0.204	0.038	<0.001	0.129 ~ 0.278
SOC(T2) → SOC(T3)	0.553	0.030	<0.001	0.494 ~ 0.612
SOC(T2) → PA(T3)	0.369	0.037	<0.001	0.297 ~ 0.442
PA(T2) → PE(T3)	0.083	0.039	0.032	0.007 ~ 0.159
PA(T2) → SOC(T3)	−0.015	0.036	0.684	−0.086 ~ 0.056
PA(T2) → PA(T3)	0.133	0.040	0.001	0.055 ~ 0.210
PE(T1) → SOC(T2) → PA(T3)	0.037	0.018	0.045	0.001 ~ 0.073
PA(T1) → SOC(T2) → PE(T3)	0.029	0.013	0.028	0.003 ~ 0.055
NA path	**Coefficient (β)**	**S.E.**	***p*-value**	**95%CI**
PE(T1) → PE(T2)	0.431	0.038	<0.001	0.356 ~ 0.506
PE(T1) → SOC(T2)	0.135	0.046	0.003	0.045 ~ 0.224
PE(T1) → NA(T2)	0.078	0.045	0.086	−0.011 ~ 0.166
SOC(T1) → PE(T2)	0.035	0.038	0.358	−0.040 ~ 0.110
SOC(T1) → SOC(T2)	0.198	0.042	<0.001	0.117 ~ 0.280
SOC(T1) → NA(T2)	0.213	0.041	<0.001	0.133 ~ 0.294
NA(T1) → PE (T2)	−0.096	0.042	0.022	−0.178 ~ −0.014
NA(T1) → SOC(T2)	−0.002	0.046	0.958	−0.093 ~ 0.089
NA(T1) → NA(T2)	−0.127	0.046	0.005	−0.217 ~ −0.038
PE(T2) → PE(T3)	0.367	0.036	<0.001	0.297 ~ 0.437
PE(T2) → SOC(T3)	−0.003	0.035	0.931	−0.072 ~ 0.066
PE(T2) → NA(T3)	−0.159	0.042	<0.001	−0.241 ~ −0.076
SOC(T2) → PE(T3)	0.129	0.041	0.002	0.048 ~ 0.210
SOC(T2) → SOC(T3)	0.469	0.035	<0.001	0.401 ~ 0.538
SOC(T2) → NA(T3)	0.016	0.046	0.723	−0.074 ~ 0.107
NA(T2) → PE(T3)	0.203	0.041	<0.001	0.122 ~ 0.283
NA(T2) → SOC(T3)	0.207	0.038	<0.001	0.132 ~ 0.281
NA(T2) → NA(T3)	−0.147	0.046	0.001	−0.237 ~ −0.057
PE(T1) → SOC(T2) → NA(T3)	0.002	0.008	0.791	−0.014 ~ 0.018
NA(T1) → SOC(T2) → PE(T3)	<0.001	0.006	0.961	−0.013 ~ 0.012

T1, Time 1 (intake); T2, Time 2 (one-month follow-up); T3, Time 3 (2-month follow-up); SOC, sense of coherence; PA, positive affect; NA, negative affect; PE, physical exercise.

physical exercise on emotional states. The age of artificial intelligence presents opportunities to leverage these technologies to develop personalized mindfulness training applications, intelligent stress monitoring tools, and social platforms. These resources can provide more precise and effective support and interventions for university students, ultimately improving their sense of coherence and emotional well-being.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Ethics Committee of Guizhou Normal University, China (Approval No.: 202300005). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. LL: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pain, mindfulness, and placebo: a systematic review

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Introduction: Pain is a complex phenomenon influenced by psychosocial variables, including the placebo effect. The effectiveness of mindfulness-based interventions (MBIs) for pain has been demonstrated in experimental studies and systematic reviews, but the mechanisms of action are only starting to be established. Whether the expectations of individuals experiencing pain can be manipulated during MBIs remains to be systematically evaluated, and what role placebo effects might play remains to be explored.

Methods: To evaluate the literature analyzing placebo effects in MBIs for pain, we performed a systematic review based on searches conducted in PubMed, Web of Science, and SCOPUS databases. Our search revealed a total of 272 studies, of which only 19 studies were included (10 acute pain and nine chronic pain), considering the inclusion and exclusion criteria related to expectations and placebo effects.

Results: From the 19 included studies, six measured placebo effects only in relation to the pharmacological intervention used in the study and not to an MBI.

Discussion: The results of the few studies that focused on the placebo effects of the MBIs indicate that placebo and expectations play a role in the MBIs' effects on pain. Although expectations and placebo effects are frequently discussed in the context of mindfulness and pain research, these results show that these factors are still not routinely considered in experimental designs. However, the results of the few studies included in this systematic review highlight a clear role for placebo and expectancy effects in the overall effects of MBIs for both acute and chronic pain, suggesting that routine measurement and further consideration in future studies are warranted. Additional research in this fascinating and challenging field is necessary to fully understand the connection between MBIs, placebo/expectations, and their effects on pain relief.

KEYWORDS

expectations, cognitive-behavioral therapy, pain measurements, placebo effects, mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), meditation therapy

Introduction

Pain is a multidimensional phenomenon with a significant biopsychosocial dimension. According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential damage" (Raja et al., 2020). The biopsychosocial dimension of pain is fully recognized in the first note attached to the abovementioned pain definition. It determines the individuality of the pain experience: "Pain is always a ***personal*** experience that is influenced to varying degrees by biological, psychological, and social factors" (Raja et al., 2020). This subjective response to pain is dynamically modulated by complex interactions between sensory, cognitive, and affective factors (Price, 2000; Auvray et al., 2010). Pain is challenging to treat, and chronic pain is considered a medical issue

(Turk, 2002; Cohen et al., 2021; Knopp-Sihota et al., 2022). Pain treatment is also an ethical issue since many patients fail to receive adequate pain relief (Hall and Boswell, 2009; Gatchel et al., 2014). Each pain patient is unique, and it is crucial to consider the individual behind the pain. The principles of autonomy, non-maleficence, beneficence, and justice are necessary to assist patients and their families in pain management (Swenson, 2002; Reeves and Jones, 2022). The use of cognitive-behavioral approaches in pain management is growing, as these methods help improve the patient's relationship with a painful experience (Moisset et al., 2020; Brandel et al., 2022; Yang et al., 2022).

Among cognitive-behavioral approaches, mindfulness-based interventions (MBIs) are increasingly used (Baminiwatta and Solangaarachchi, 2021). By defining mindfulness as the "awareness that arises through paying attention, on purpose, in the present moment, non-judgmentally," Kabat-Zinn laid the foundation for using MBIs in pain management and other medical areas (Kabat-Zinn, 1982; Ludwig and Kabat-Zinn, 2008). Despite numerous studies on the efficacy of MBIs in pain management, the extent of their efficacy varies (Mcclintock et al., 2019; Shires et al., 2020; Schmidt and Pilat, 2023). Notably, the efficacy of MBIs is predominantly observed in reducing the aversive component of pain rather than its sensory component (Jinich-Diamant et al., 2020).

The variability in the efficacy of MBIs for pain can be attributed to some of the challenges in their design (Leca and Tavares, 2022; Cardle et al., 2023). The challenges include the lack of active controls in MBIs, the need for better reporting of important parameters such as the background of the meditation instructors, the wide diversity of evaluated outcome domains, and the lack of agreement on the operational definition of MBIs (session lengths, number of sessions, frequency of sessions, and duration of the intervention). One significant issue to consider in MBIs for pain management is the placebo effect. Several studies show that the efficacy of MBIs in pain management is lower when active controls (i.e., an experimental group that controls for the placebo effect) are used instead of passive controls (Goldberg et al., 2018; Shires et al., 2020; Hohenschurz-Schmidt et al., 2023a,b). Furthermore, the more specifically the active control is matched to the treatment (i.e., the better it controls for the placebo effect), the smaller the observed efficacy of MBIs is.

Placebo effects in pain responses are well-established (Coleshill et al., 2018; Bingel, 2020; Rossettini et al., 2020; Van Lennep et al., 2021). The term "placebo" originates from the Latin word "placere," which means "to please" (Schedlowski et al., 2015; Meissner and Linde, 2018). The placebo effect involves the improvement of symptoms or physiological conditions following an inert treatment. It can be influenced by various factors, such as the natural progression of a disease, symptom fluctuations, response biases, the effects of co-interventions, and statistical phenomena. The placebo response, defined as the "outcome caused by a placebo manipulation," depends on emotional and cognitive aspects.

Factors such as patient expectations, the quality of the doctor–patient relationship, and other variables were shown to significantly affect the placebo response (Schedlowski et al., 2015; Meissner and Linde, 2018).

The importance of the placebo effect is well-recognized, and its effects may be manipulated. It is well-established that the placebo effect may confound the specific actions of active compounds in pharmacologic studies (Scott et al., 2008). In clinical pharmacological trials, the placebo arm groups and the interference of non-specific effects are considered to fully evaluate the specific effect of a new treatment (Pollo and Benedetti, 2009; Enck et al., 2013). Recent research has advanced our understanding of the neural mechanisms underlying placebo effects. The potential to harness the placebo effect (Scott et al., 2008; Bingel et al., 2011) to influence therapy outcomes and benefit patients is currently being considered and discussed (Pollo and Benedetti, 2009; Enck et al., 2013).

Pain is modulated by a network of brain areas known as the supraspinal endogenous pain modulatory system. The understanding of this system has evolved considerably to include the dynamic interaction of pain with other interconnected dimensions, such as emotion and cognition (Tracey and Mantyh, 2007; Heinricher et al., 2009). Furthermore, the dynamic balance between inhibition and facilitation of top-down descending modulation is recognized, and an imbalance toward facilitation is considered to contribute to chronic pain (Tracey and Mantyh, 2007).

Among the brain areas of the endogenous pain modulatory system, the periaqueductal gray (PAG) plays a key role in top-down modulation by conveying most of the input from higher brain areas, such as the prefrontal cortex (PFC), which is involved in cognitive and executive control, and the amygdala, which is involved in emotional responses (Martins and Tavares, 2017; Ng et al., 2018). There are, however, direct effects on the spinal cord, such as direct cortico-spinal pathways from the anterior cingulate cortex (ACC), which facilitate the transmission of nociceptive information (Chen et al., 2018).

Regarding the neurobiological networks that may underlie the effects of MBIs on pain, a reduction in the activity of areas involved in emotional reactions to pain, such as the amygdala, may account for the reduction in aversion to the noxious event (Zeidan and Vago, 2016). Regarding the placebo effect, a neural network between the rostral ACC (rACC) and brain stem areas, including the PAG, has been proposed to account for placebo responses, showing similar activation patterns during opioid analgesia (Petrovic et al., 2002). In addition to the cingulofrontal brain regions, placebo analgesia is associated with activation in other areas, such as the PAG, hypothalamus, and amygdala.

The unique role of the ACC and its connections with the emotional components of the limbic system and the cognitive PFC is interesting due to the emotional and cognitive components of the placebo effect. The PFC also plays an important role in this network (Wager et al., 2004; Lui et al., 2010). Neuroimaging studies have also shown a negative correlation between the magnitude of placebo analgesia and the activation of the rACC, contralateral insula, primary somatosensory cortex (S1), and thalamus (Wager et al., 2004; Eippert et al., 2009).

Regarding expectations and their relation to the placebo effect, the manipulation of expectations modulates pain through endogenous opioidergic release (Case et al., 2021). In contrast, conditioned placebo responses to pain do not appear to be mediated by opioids (Amanzio and Benedetti, 1999). Interestingly, reappraisal-based manipulations based on mindfulness are postulated to reduce pain through non-opioid mechanisms (Zeidan et al., 2016; May et al., 2018; Wells et al., 2020).

Based on the abovementioned literature, we hypothesize that the efficacy of MBIs in pain may be affected by placebo effects and that the expectations of the participants may affect the outcome of these interventions. Therefore, it is important to systematically evaluate the literature to understand the mechanisms specific to mindfulness that are not activated by a placebo intervention. To this end, we conducted a systematic review to assess the evidence for the evaluation of placebo effects in MBIs for pain and to analyze if the expectations of the participants were considered in the studies and if the involvement of opioid mechanisms was examined.

Materials and methods

The present research was conducted in accordance with the Cochrane recommendations on systematic reviews and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Higgins et al., 2011). The review protocol was not preregistered in the International Prospective Register of Systematic Reviews (PROSPERO).

For this project, three different databases, namely Pubmed, Web of Science, and SCOPUS, were searched until May 2024. The search was performed between 1 November and 30 November 2022 and updated on 30 May 2024. For the present systematic review, the population, intervention, comparison, outcomes (PICO) question was: "What is the evidence for the evaluation of placebo effects of participants in MBI studies for pain?" No *a priori* distinctions were made between the types of MBI interventions or the duration of pain (acute or chronic).

The following MeSH terms were used in all the databases: "placebo," AND "pain," AND "mindfulness," with no restrictions applied to the results. Initially, we included all articles that met our search criteria. All the articles were organized in a table specifying the name, author, and study design. Two authors (AL and IT) examined the titles and abstracts of the selected studies. Review articles were excluded, and all the original articles were considered eligible for further analysis.

The full text of these original articles was extracted, and after analysis by both authors, it was consensually agreed that an additional six articles should be discarded for not meeting the inclusion criteria (studies using MBIs for pain). In the end, we were left with a total of 19 articles. For each of these articles, both authors analyzed the population (the inclusion and exclusion criteria), experimental design, the type of pain studied, the type and duration of the MBIs, the characteristics of the instructors providing the interventions, the communication between the research team and participants, participant expectations (if they were considered), and the study of placebo and outcomes. The selection process followed the recent PRISMA guidelines (Page et al., 2021; Figure 1).

To assess the risk of bias, both authors used the *Cochrane Risk of Bias Tool* for randomized controlled trials (Higgins et al.,

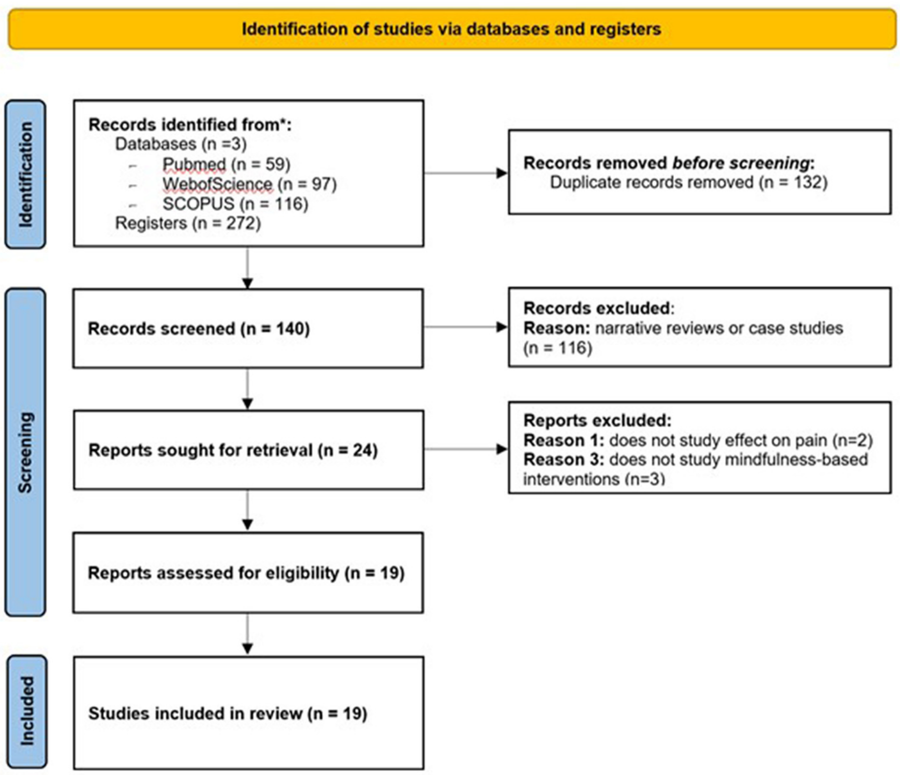

FIGURE 1
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. *Means registered databases.

2011) and the *Newcastle-Ottawa Scale* for non-randomized studies (Wells et al., 2021). The *Cochrane Risk of Bias Tool* for Randomized Controlled Trials evaluates six different criteria. An article was considered to have a low risk of bias if all criteria were met, a moderate risk of bias if one criterion was missing or two criteria were not followed, and a high risk of bias if two or more criteria were missing.

The *Newcastle-Ottawa Scale* evaluates eight different criteria, which are grouped into three categories: selection (a maximum of four stars), comparison (a maximum of two stars), and result/exposition (a maximum of three stars). For classifying the articles, an article was considered to have a low risk of bias if it had three or four stars in the selection category. It was considered to have a moderate risk of bias if it had two stars in the selection category, one or two stars in the comparison category, and two or three stars in the result/exposition category. An article was considered to have a high risk of bias if it had zero or one star in the selection category, zero stars in the comparison category, and zero or one star in the result/exposition category.

Results

A total of 272 articles were collected from all databases, namely 59 from PubMed, 67 from Web of Science, and 116 from SCOPUS databases. After removing duplicates, we were left with 140 different results. After screening the titles and abstracts of these studies, only original articles were considered eligible, and all reviews were excluded, resulting in a total of 25 articles proceeding to the inclusion phase. Both authors analyzed the full text of these 25 studies and agreed to eliminate six additional articles for not meeting the inclusion criteria: two articles did not focus on the study of pain and three did not use an MBI. In the end, we were left with a total of 19 articles.

For each of these 19 articles, both authors analyzed the population of participants concerning the inclusion and exclusion criteria, specifically regarding their previous experience in meditation and mindfulness, as it could affect the answer to the main question of our study. We also extracted data regarding the experimental design, the type of pain studied, the type and duration of MBIs, the experience and possible conflicts of interest of the instructors guiding the MBIs, the communication between the research team and the participants, whether the expectations of the participants were considered, and the study of placebo effects. The main outcomes analyzed were the effects on pain, both in sensory intensity and unpleasantness (Table 1). Table 1 presents the results of the 19 analyzed studies concerning (1) the effects of MBIs on pain; (2) the involvement of endogenous opioids in the effects of MBIs on pain; and (3) participant expectations and analysis of placebo effects.

Regarding the effects of MBIs on pain, it should be noted that the studies evaluated mostly acute pain (i.e., experimentally induced pain), with 10 out of the 19 analyzed studies focusing on this type of pain. Among these studies, noxious heat was the predominant stimulus applied in seven studies, followed by cold (one study), ischemic stimulation (one study), and electric stimulation (one study). For chronic pain, several types of pain were analyzed, with a predominance of migraine/headache (three studies). Other types of chronic pain studied included musculoskeletal pain, such as arthritis (two studies), fibromyalgia (one study), low back pain (one study), diabetic neuropathy (one study), and diverse types of chronic pain (one study).

Information regarding the duration of chronic pain and the occurrence of pain co-morbidities, such as cognitive deficits and emotional imbalances, could not always be retrieved from the analyzed papers. A randomized controlled trial (Westenberg et al., 2018) studied the effect of a brief 60-s mindfulness video exercise on musculoskeletal pain in upper extremity patients and concluded that there were improvements in momentary pain, anxiety, depression, and anger. Three studies focused on the effect of mindfulness therapies on headaches. One of them was conducted in a population of adolescents using adaptations of MBSR and MBCT and revealed that the intervention resulted in reduced headache frequency and medication intake, disability, trait anxiety, symptoms of depression, and catastrophizing (Grazzi et al., 2021). The other two studies were conducted with adults and demonstrated that mindfulness reduced headache frequency, headache-related disability (Seminowicz et al., 2020), and decreased pain severity (Namjoo et al., 2019).

Mindfulness-based interventions have been proven to improve the quality of life in patients with painful diabetic neuropathy, with better results observed when combined with vitamin D supplementation (Davoudi et al., 2021). Additionally, they reduced pain in rheumatoid arthritis patients, with greater benefits observed in patients with recurrent depression (Zautra et al., 2008). However, when focusing on a population of fibromyalgia patients, the analyzed study (Schmidt et al., 2011) did not support the improvement of quality of life in patients receiving MBSR. Overall, regarding the net effects of MBIs, the results indicate the benefits of MBIs in acute and chronic pain.

Regarding the neurobiological mechanisms involved in MBIs' effects on pain, particularly concerning endogenous opioids, the majority of the results indicate that mindfulness meditation pain relief is not mediated by endogenous opioids (Zeidan et al., 2016; Esch et al., 2017; May et al., 2018; Wells et al., 2020). However, this finding was not supported by another study (Sharon et al., 2016), which concluded that the effects of mindfulness meditation on pain relief were mediated by endogenous opioids. Notably, the result of the latter study was based on a small population size ($n = 14$). The remaining studies did not analyze opioid involvement in MBIs for pain in detail. Collectively, the analyzed literature predominantly suggests that the effects of MBIs on pain are not mediated by endogenous opioids.

Finally, regarding participants' expectations and the analysis of the placebo effect, the analyzed literature presented a variety of results. Information about collecting participants' expectations concerning the pain relief they could receive from MBIs was sparse. Five studies clearly evaluated the expectations of the participants. The studies of the Davies group (Davies et al., 2021, 2022, 2023) analyzed in detail the initial expectations of the participants, including manipulating expectations to test the effects of the MBIs (Davies et al., 2022). One of the studies (Vencatachellum et al., 2021) hypothesized that mindfulness could reduce cue-induced hypoalgesia and hyperalgesia and found evidence supporting the

TABLE 1 Summary of the main findings of the analyzed studies (in alphabetic order).

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Case et al. (2021) Study type: secondary analysis of previous work	Population: 78 (39 ♂/39 ♀) Mean age: 27 ± 7 Experimental groups: Meditation + naloxone Control + naloxone Meditation + saline Control + saline Previous experience in MBI: Not referred	Duration: Acute Modality/type: Noxious heat (35–49°C)	Type: Mindfulness-based mental training Duration: 4 sessions of 20 min Instructors: - Formation/experience: not referred - Conflicts of interest/Disclosure of Instructors/Authors: Referred: none	Referred: - Participants were told that: "the study would assess whether meditation was associated with the release of naturally occurring opiates" - They would receive intravenous administration of saline or naloxone, a relatively safe drug that blocks the transmission of opioid activity	Evaluated: Yes Remarks: In a scale of 0–10 how much do you expect that meditation will be effective in reducing your pain?	Placebo of the MBI intervention: Placebo saline for naloxone	- MBI lowered pain during saline and naloxone infusion - Higher expected pain- relief from MBI predicted lower pain intensity - Relation between meditation-related expectations and reduction of pain intensity during naloxone infusion, but not saline - Expectations for book-listening based analgesia did not significantly predict pain changes during saline or naloxone infusion in the control group.
Davies et al. (2021) Study type: RCT	Population: 93 (34 ♂/59 ♀) Mean age: 21 ± 9 Experimental groups: - Mindfulness - Sham mindfulness - No treatment Inclusion criteria: Fluent in English Pain-free (<3/10) - Meditation naïve Not pregnant/breastfeeding - Not under analgesic or psychotropic medication. Previous experience in MBI/meditation: Meditation naïve	Duration: Acute Modality/type: Heat	Type: "Mindfulness of Breath and Body" (MBCT adaptation for chronic pain) Duration: Four sessions of 20-min training in home practice of an audio recording Instructors: Formation/experience: not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred: None	Referred: Informed consent: Yes; No details provided	Evaluated: Yes Remarks: At the beginning of the project "no suggestion was made regarding mindfulness being effective for pain in any study materials or procedures, including the meditation training" and "How effective do you think mindfulness is for reducing pain?" At the end of the project "Do you think you were practicing a guided mindfulness meditation?"	Placebo of the MBI intervention: Sham-intervention group delivered as MBI	- Sham MBI produced equivalent credibility ratings and expectations of improvement as MBI, but did not influence mindfulness-related processes. - MBI increased "observing" (but none of the other four mindfulness facets) relative to no treatment, but not sham. - MBI and sham moderately increased pain tolerance relative to no treatment, with no difference between mindfulness and sham. - No effects in pain threshold. - Neither MBI nor sham reduced pain intensity or unpleasantness relative to no treatment, although MBI reduced pain unpleasantness relative to sham.

(Continued)

TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Davies et al. (2022) Study type: RCT	Population: 153 (42 ♂/111 ♀) Mean age: 22 ± 93 Experimental groups: - Mindfulness with expectancy (mindfulness treatment and told mindfulness); - Mindfulness without expectancy (mindfulness treatment and told sham); - SHAM+(sham treatment and told mindfulness) - SHAM- (sham treatment and told sham), with an additional comparison against a no treatment control group. Inclusion criteria: - Fluent in English - Pain free - Not pregnant, breastfeeding - Not taking analgesic or psychotropic medications. Previous experience in MBI/Meditation: Mindfulness naïve	Duration: Acute Modality/type: Noxious heat	Type: Focused attention mindfulness (breath and body) Duration/place: Six daily sessions lasting 20-min of audio guided training; first and last session in the lab and the remaining home Instructors: - Formation/experience: Not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred: none	Referred: - Several moments of communication with the participants to determine expectations. - Instructions displayed on the computer screen (and reiterated in a short audio introduction) revealed the group allocation to the participant (i.e., mindfulness, sham mindfulness, or no treatment, as per cover story) without the researcher's knowledge (to maintain blinding). Informed consent: Yes; Details provided	Evaluated: Yes The study evaluates expectancy so that it can be manipulated to test the effect of intervention. Remarks: Participants were asked in several moments questions like "How effective do you think mindfulness meditation is for reducing pain?" and "How effective do you think your training will be for reducing pain?"	Placebo of the MBI intervention: Balanced placebo designs allowing for manipulation of both treatment and instruction (expectation)	- MBI improved pain outcomes (unpleasantness, intensity, and tolerance) in comparison to control. - The instruction manipulation increased expectation for pain relief in those told mindfulness relative to those told sham. - There were no main effects or interactions of treatment or instruction on pain outcomes. - Irrespective of actual intervention received, the belief of receiving mindfulness predicted increased pain threshold and tolerance, with expectancy fully mediating the effect on pain tolerance.

(Continued)

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Davies et al. (2023) Study type: RCT	Population: 169 (28 ♂/138 ♀) males; 3 other Mean age: 32 ± 8 Experimental groups: - Mindfulness of Breath/Body - Specific sham mindfulness - General sham mindfulness - Audiobook control Inclusion criteria: - 18 years of age or older, - Understand English, - Chronic or recurrent pain as clinical guidelines Previous experience in MBI/Meditation: Not referred	Duration: Chronic pain/recurrent pain Modality/type: Diverse (arthritis, muscle pain, headache, menstrual, neuropathic, other)	Type: Mindfulness of Breath and Body Duration: one 20-min session Instructors: - Formation/experience: experienced meditation instructor - Conflicts of interest/Disclosure of Instructors/Authors: Referred: "The authors have no conflicts of interest to declare." After setup, the research team had no involvement in the running of the RCT, which was entirely automate ("the study was ostensibly double blind").	Referred: Yes - Participants were asked to numerically rate the current intensity and unpleasantness of pain. - The analogy of listening to a song on the radio was used to help participants differentiate between intensity and unpleasantness. Informed consent: Yes	Evaluated: Yes Remarks: "We assessed pre-to-post changes in placebo-related (response expectancy and hope) processes to assess potential differential effects of mindfulness, specific sham, and general sham relative to audiobook control." Expectancy was assessed at baseline by asking participants: "How effective do you think mindfulness meditation is for reducing pain?"	Placebo of the MBI intervention: - Specific sham mindfulness: condition developed and validated to explicitly control for non-specific factors present in the "Mindfulness of Breath and Body"; characterized by a facilitator voice, attention paid to the intervention, body posture and instructions designed to give the meditator the sense that they were practicing a guided meditation, except for instructions that explicitly or implicitly suggested training attention on present moment experience or brought mindfulness metacognitive qualities to attention General sham mindfulness: Did not include any mindfulness instructions.	- Mindfulness not superior to sham in reduction of pain intensity/unpleasantness. - Mindfulness and sham reduced pain unpleasantness (but not pain intensity) relative to audiobook control, with expectancy most strongly associated with this effect. - Treatment expectancy associated with decreases in pain intensity and unpleasantness after mindfulness and sham training. - Specific and general sham with equivalent expectancy and credibility ratings to each other and the mindfulness intervention (suggesting that all three interventions were likely to engage placebo-related processes equally) - Mindfulness and sham equally reduced pain catastrophizing relative to audiobook control - No differences in pain reappraisal between mindfulness, shams, and audiobook control.

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Davoudi et al. (2021) Study type: RCT	Population: 225 (133 ♂/92♀) Mean age: 56 ± 25 Experimental groups: - Mindfulness and placebo - Placebo - Mindfulness - Vitamin D - Mindfulness + Vitamin D Inclusion criteria: Patients referred to the hospital. - Lack of major co-morbid disease - Age of 20–70 years Willingness to participate in studying - Vitamin D insufficiency or deficiency Previous experience in MBI: Not referred	Duration: Chronic Modality/type: Diabetic neuropathy	Type: modified mindfulness manual based on pain relief protocols Duration: 12 weeks (90 min per session) Instructors: - Formation/experience: trained psychotherapist - Conflicts of interest/Disclosure of Instructors/Authors: Referred: none	Referred: They were blinded about study aims and other groups' existence (VDs and other mindfulness groups). Informed consent: Not referred	Evaluated: No Remarks: Not referred	Placebo of the MBI intervention: similar drops in shape (without any VD) and duration.	- Improvement of QOL in all groups except the "placebo only" group for outcome variables. - There was no difference between VD and MBI groups (within and not combined with placebo) in improvement of QOL - "VD + MBI" has a greater improvement in QOL rather than VD and mindfulness groups. - Reduction in pain disability and pain severity in all groups except "placebo." No difference between MBI and VD groups to reduce pain disability and pain severity. Yet, the "vitamin D + mindfulness" group showed the higher improvement.

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Esch et al. (2017) Study type: RCT	Population: 31 (8 ♂/24♀) Mean age: 27 ± 8 Experimental groups: - Passive control condition (no intervention) - Combined breathing/mindfulness meditation technique Inclusion criteria: - At least 18 years old Language proficient - No visual impairments Previous experience in MBI: Meditation naïve volunteers	Duration: Acute Modality/type: Ischemic arm pain (tourniquet test)	Type: combined breathing/mindfulness meditation technique (bodyscan, attention to breath (ATB), attention to senses (ATS), open awareness/attention to experience (ATE), and walking meditation—with focused breath awareness as a steady anchor) Duration: daily group sessions of 1.5 h each Instructors: - Formation/experience: The trainer (TE) had 20 years of meditation experience, and is a professional meditation/mindfulness teacher, and researcher in the field. - Conflicts of interest/disclosure of Instructors/Authors: none	The topic of pain (e.g., pain awareness or pain perception) was intentionally and carefully avoided in this course. Participants were informed about their individual group assignment—intervention or control—(to get to know whether they would be required to show-up for intervention training) after the completion of assessments on day 2 by a person otherwise not interacting with the participants. Informed consent: Yes	Evaluated: No Remarks: It was measured the self-attributed minfulness by the *Freiburg Mindfulness Inventory*	Placebo of the MBI intervention: Placebo saline for naloxone	- The MBI group meditation group produced fewer errors in ANT (Attention Network Test) - Increases in pain tolerance occurred in both groups (accentuated in control), and correlated with reported mindfulness - Naloxone showed a trend to decrease pain tolerance in both groups.
Grazzi et al. (2021) Study type: Open Label Study	Population: 37 (2 ♂/35 ♀) Mean age: 15 ± 2 Experimental groups: Participants completed 6 weekly group sessions of guided meditation, and one booster session 15 days later. Inclusion criteria: Adolescents (12–18) chronic or high-frequency migraine without aura. Previous experience in MBI: meditation naive	Duration: Chronic Modality/type: Migraine	Type: Adaptation of MBSR and MBCT programs, by shortening these programs Duration/place: 6 weeks group sessions with 1 h duration followed by one booster session 15 days after	Referred: Not explicitly mentioned. Informed consent: Yes: for adolescents and their parents; details not available	Evaluated: No	Placebo of the MBI intervention: Not performed but authors refer as a limitation intrinsic to an open-label study	- MBI decreases headache frequency MBI had effects on medication intake, disability, trait anxiety, symptoms of depression and catastrophizing

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Khatib et al. (2024) Study type: RCT	Population: 59 (29 ♂/30 ♀) Mean age: 46 Experimental groups: - Mindfulness - Sham mindfulness-meditation Inclusion criteria: - Not positive for opioids - Not pregnant - Meditation naive - Responsive to the straight leg-raise test, - Not having back surgery within a year of the enrollment - Not concurrently enrolled in other experiments - Not initiating new pain therapies during the study period. Previous experience in MBI/meditation: Mindfulness naive	Duration: Chronic Modality/type: Low back pain	Type: Mindfulness based mental training Duration: Four 20-min sessions Instructors: - Formation/experience: certified meditation instructors. - Conflicts of interest/Disclosure of Instructors/Authors: Referred: Drug assignment blinded to patients, nurses, and experimenters. Only the physicians, pharmacist, and coordinator aware of drug assignment. Participants were compensated $400 for study completion.	Referred: Yes - In Straight leg-raise 1 (non-meditation rest), patients were instructed to "rest with your eyes closed" and after 7 min, pain ratings were collected. - In pre-intervention bolus control, patients were instructed to "continue resting with your eyes closed" (8 min). - In all 4 mindfulness sessions, instructions acknowledging arising thoughts, feelings, and/or emotions, that such sensations and emotions were "momentary" and "fleeting," and to "return their attention back to the breath" whenever such discursive events occurred. During training day 4, participants were asked to practice while lying in the supine position and wearing a face mask to emulate the conditions in the post-intervention testing sessions. - During each sham mindfulness-meditation training session, the participants were told, approximately every 2–3 min, to "take deep breaths as we sit in meditation."	Evaluated: No Remarks: Not referred	Placebo of the MBI intervention: Sham-mindfulness meditation (train individuals to "take slow, deep breaths" in a meditative posture but omits the mindfulness-specific instructions non-reactive attention to breath sensations—hypothesized to mediate pain relief); Placebo saline for naloxone	- After the interventions, mindfulness and sham mindfulness-meditation effectively attenuated induced pain. - Mindfulness-meditation with lower pain before and after the straight leg-raise test when resting and during meditation when compared to the sham mindfulness-meditation group. - Mindfulness and sham mindfulness-meditation associated with significant reductions in back pain during saline and naloxone infusion when compared to rest (non-meditation). - Meditation directly reduces evoked chronic pain through non-opioidergic processes - Mindfulness group with lower straight leg-raise induced pain than the sham mindfulness-meditation group during rest (non-meditation) and meditation. - Mindfulness and sham mindfulness-meditation training was also associated with significantly lower Brief Pain Inventory severity and interference scores - Mindfulness and sham mindfulness-meditation training associated with significant improvements in pain interference and pain catastrophizing after 80-min of mental training

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
May et al. (2018) Study type: RCT	Population: 32 (18 ♂/14 ♀) Mean age: 52 ± 52 Experimental groups: - Saline - Naloxone Inclusion criteria: - Pain-free adults with established meditation practice - From the local community Previous experience in MBI/meditation: Experienced meditators	Duration: Acute Modality/type: Electric current 5 Hz	Type: Open Monitoring/Awareness but the background of the experienced meditators was very diverse. Duration/place: 10 min prior to nociceptive stimulation Instructors: - Formation/experience: Not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred in detail	Referred: The researcher described the protocol taking into account the specificities of the sessions and participants gave their consent Informed consent: Yes; in two different moments; Details not available	Evaluated: Yes The authors referred that "the participants had a variety of expectations of the drug effect". Remarks: - Participants were kept blind as to the naloxone or saline administration. - They were subsequently asked "in which session they believed they received naloxone" and "in your opinion what does naloxone do"	Placebo of the MBI: No; the placebo effect focuses on naloxone/saline administration	- MBI induced analgesia (lowered pain intensity and pain unpleasantness) - Naloxone increased meditation-induced analgesia (lower pain intensity and pain unpleasantness)
Namjoo et al. (2019) Study type: RCT	Population: 85 (29 ♂/56 ♀) Mean age: 36 ± 7 Experimental groups: - MBCT - Attention Placebo Control Inclusion criteria: - >19 years - Headache experience at least - 3 days/month and for > 3 months) due to a primary headache - Reading and writing skills to understand and complete worksheets Previous experience in MBI/meditation: Not referred (just "engaging in other psychotherapies for pain condition")	Duration: Chronic Modality/type: Headache	Type: MBCT (the first half of the protocol focused on the preferment of awareness of patients about mind default mode; in the second half of treatment, enhanced awareness converted to automatic skills and patients learn to choose intentionally to respond to their experiences rather than to react. Duration 8-weekly 2 h group program Instructors: - Formation/experience: Superior in MBCT fibromyalgia patients. - Conflicts of interest/Disclosure of Instructors/Authors: Referred: none	Referred: No Informed consent: Yes	Evaluated: No Remarks: Not referred	Placebo of the MBI intervention: Attention Placebo Control −8 weekly 2 h sessions; participants received attention and therapist's empathy and participated in group discussion.	- Change of scores across the two groups over time (for pain severity and for pain interference (pleasing result for researchers who claim that MBI can affect pain perception) - MBI resulted in a higher rate of pain openness and a lower rate of pain focus compared to the APC group from baseline to follow-up. - MBI resulted in a higher rate of pain distancing compared to the APC group from baseline to post-test and the reappraisal scores decreased in the follow-up—MBI was ineffective and could not make any changes on pain diversion

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Schmidt et al. (2011) Study type: RCT	Population: 177 (0 ♂/177 ♀) Mean age: 52 ± 5 Experimental groups: - MBSR - Active control procedure (o que é?) Wait list Inclusion criteria: - 18–70 years of age - Currently with fibromyalgia diagnosis (criteria of the American - College of Rheumatology) - Command of the German language - Motivation to participate Previous experience in MBI/meditation: Not referred	Duration: Chronic Modality/type: Fibromyalgia	Type: MBSR (mindfulness meditation and mindful yoga exercises) Duration: 8-week group program (one 2.5-h session every week, and an additional 7-h all-day session on a weekend day.) Instructors: - Formation/experience: at least 7 years of previous experience teaching MBSR - Conflicts of interest/Disclosure of Instructors/Authors: Referred: none	Referred: "Informational brochures were provided that briefly described the 2 interventions as alternative behavioral treatments potentially capable of enhancing the wellbeing in fibromyalgia patients. - No suggestion was made about the superiority of either treatment." - "Patients in the intervention arms were told that 2 new innovative treatments were to be compared, one based on the concept of mindfulness (entailing meditation and yoga lessons, as well as homework), and the other based on health support techniques (entailing relaxation and stretching exercises, as well as homework). The active control group was referred to as the relaxation group. All patients participating in one of the 2 active treatment arms were also offered participation in their treatment of choice after completion of the trial." Informed consent: Yes	Evaluated: Yes Remarks: "Pre- and post-intervention 1-h personal interviews were conducted by each instructor to establish rapport and to help patients formulate realistic individual goals for the intervention."	Placebo of the MBI intervention: The active control is considered the placebo. 8-week group of size and weekly format similar to that of the MBSR program taught by a single instructor; Equivalent amounts of social support and weekly topical educational discussions; use of Jacobson Progressive Muscle Relaxation training (PMR), and fibromyalgia- specific gentle stretching exercises; homework assignments were similar in duration and intensity to those in the MBSR group; patients received compact discs (CDs) with instructions for daily exercises	- No significant differences between groups on primary outcome (health related quality of life), but patients overall improved in HRQoL at short-term follow-up. Only MBI manifested a significant pre-to-post- intervention improvement in HRQoL - Multivariate analysis of secondary measures (disorder-specific quality of life, depression, pain, anxiety, somatic complaints, and a proposed index of mindfulness) indicated modest benefits for MBSR patients. MBSR yielded significant pre-to-post-intervention improvements in 6 of 8 secondary outcome variables, the active control in 3, and the wait list in 2.
Seminowicz et al. (2020) Study type: RCT	Population: 98 (9 ♂/89 ♀) Mean age: 36 Experimental groups: MBSR Stress management for headache (o que é?) Inclusion criteria: - 18–65 years of age - Diagnosis of migraine (International Classification of Headache Disorders for migraine with/without aura) - ≥1 year history of a migraine diagnosis Previous experience in MBI/meditation: Meditation naive	Duration: Chronic Modality/type: Migraine	Type: MBSR vs. stress management (active control) Duration/Place: 12 group sessions over 4 months, including 8 weekly sessions followed by 4 biweekly sessions. Instructors: - Formation/experience: Two experienced, certified instructors (10 and 40 years of meditation experience) - Conflicts of interest/Disclosures of Instructors/Authors: Referred: none	Referred: Not explicitly mentioned. Informed consent: Yes; details not available	Evaluated: No Remarks: Authors state that the study accounts for the influence of expectations and non-specific effects of intervention but it is not mentioned how the expectations were evaluated	Placebo of the MBI intervention: The active control is considered the placebo. This intervention included 12 sessions over 4 months with on didactic content about the role of stress and other triggers in headaches in a similar format of the intervention group, minus the retreat.	- MBI decreased headache and migraine frequency and intensity - MBI decreased headache-related disability, as well as yielded a higher treatment response rate, in comparison to the active control

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Sharon et al. (2016) Study type: RCT	Population: 14 Mean Age: not specified Experimental groups: - Intravenous naloxone (0.1 mg/kg) - Intravenous saline Inclusion criteria: Same meditation practice Previous experience in MBI/meditation: Experienced meditators	Duration: Acute Modality/type: Cold stimulus (2–4°C water)	Type: Sitting mindfulness meditation with Shamatha or Vipassana meditation Duration/place: The details of the mindfulness practice (duration, guidance, groups) during the intervention are unclear Instructors: - Formation/experience: Not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred: None	Referred: No details Informed consent: Not referred	Evaluated: No Remarks: Not referred	Placebo of the MBI intervention: No; the placebo effect focuses on naloxone/saline administration	- MBI and placebo reduced pain and unpleasantness scores - Naloxone did not reverse MBI-induced induced analgesia - Positive correlation between pain scores following naloxone vs. placebo and participants' mindfulness meditation experience (reduced response to placebo with increasing experience).
Vencatachellum et al. (2021) Study type: Mixed factorial design	Population: 62 (31 ♂/31 ♀) Mean age: 26 ± 85 Experimental groups: - Mindfulness-meditation - Suppression (o que é?) Inclusion criteria: - 18 years or older - Healthy - Acute and chronic pain free Previous experience in MBI/meditation: Not referred	Duration: Acute Modality/type: Noxious heat (43–49.5°C)	Type: Mindfulness meditation: open awareness to sensations, thoughts and emotions; Audio recording Suppression: Mentally blocking out any arising sensations, thoughts and emotions and concealing any external manifestation of current experiences Duration: 10 min Instructors: - Formation/experience: not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred: none	Referred: A research staff member provided instructions. Informed consent: Yes; details not available	Evaluated: No Remarks: The authors state that mindfulness leads to a prioritization of current sensory information over previous expectations, which were not evaluated	Placebo of the MBI intervention: Lack of MBI reduction of conditioned hyperalgesia is interpreted as absence of placebo effect	- Pain Intensity: reduced conditioned hypoalgesia in the MBI group compared to the suppression group - Pain Unpleasantness: smaller conditioned hypoalgesia magnitudes in the MBI group compared to the suppression group

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Wells et al. (2020) Study type: RCT	Population: 60 (30 ♂/30 ♀) Mean age: 27 ± 7 years old Experimental groups: - Mindfulness-meditation ($n = 19$) - Sham-mindfulness meditation - Slow-paced breathing Inclusion criteria: - 18 years or older Healthy - Acute and chronic pain-free Previous experience in MBI/meditation: Meditation-naive	Duration: Acute Modality/type: Noxious heat (49°C)	Type: Mindfulness meditation: non-reactive attention to breath sensations Duration: 4 separate sessions, 20 min each Instructors: - Formation/experience: Certified Meditation Teachers - Conflicts of interest/Disclosures of Instructors/Authors: Referred in detail	Referred: Participants were informed of their experimental group. Participants of the sham group were lead to believe "they were practicing mindfulness meditation without instructions related to mindfully attending to the breath in a non-evaluative manner. Participants were first told they were randomly assigned to the mindfulness meditation group." Informed consent: Yes; details not available	Evaluated: No Referred: The sham group was intentionally lead to belied that they were practicing mindfulness breathing	Placebo of the MBI intervention: Sham-mindfulness meditation; Slow Breathing; Saline	- MBI reduced pain unpleasantness, but not pain intensity, after naloxone or saline infusion sessions when compared to rest. - Slow-paced breathing reduced pain intensity and unpleasantness ratings during naloxone, but not saline infusion. - Sham-mindfulness meditation reduced pain unpleasantness during saline infusion which was reversed by naloxone. - Sham-mindfulness did not lower pain intensity. - Self-reported "focusing on the breath" is a feature associated with the mindfulness-meditation and slow paced- breathing, but not sham-mindfulness meditation.

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Westenberg et al. (2018) Study type: RCT	Population: 125 (63 ♂/62 ♀) Mean age: 55 ± 15 Experimental groups: - Mindfulness-based video exercise - Education pamphlet Inclusion criteria: Attending an appointment with the orthopedic Previous experience in MBI/meditation: Meditation naive	Duration: Chronic Modality/type: Musculoskeletal pain	Type: Visualization practice of identifying stress full thoughts/feeling and releasing with the breath using a video support Duration/place: 60-second mindfulness; waiting room Instructors: - Formation/experience: Background of the instructors not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred: none	Referred: Not explicitly mentioned. Informed consent: Yes; details not available	Evaluated: No Remarks: Participants were kept blind to the intervention. They were told that a comparison of 2 pain and stress management interventions was being performed without specifying the intervention.	Placebo of the MBI intervention: Attention placebo control with an educational pamphlet about pain and stress with the same duration as MBI.	- MBI improved momentary pain, anxiety, depression, and anger patients in the waiting room (high levels of psychologic distress)
Zautra et al. (2008) Study type: RCT	Population: 144 (46 ♂/98 ♀) Mean age: 52 ± 12 Experimental groups: - Mindfulness-meditation - Cognitive Behavioral Therapy - Education only Inclusion criteria: - >or 18 years - Self/Clinical- Diagnosis of rheumatoid arthritis	Duration: Chronic Modality/type: Rheumatoid arthritis	Type: Adaptation of MBSR and MBCT to chronic pain; examining and promoting emotion regulation and adaptation in chronic pain. Duration: 8 weeks program (MBSR/MBCT format) but shorter (no retreat; 10 min sitting meditations). Instructors: Formation/experience: not referred (doctoral-level psychologist; student level)	Referred: Not explicitly mentioned. Informed consent: Yes; details not available.	Evaluated: No Remarks: The authors state that "a direct assessment of expectation of improvement and satisfaction with treatment would be import to assess equivalence between groups"	Placebo of the MBI intervention: Education group used as an attention placebo control	- MBI improved self- reported pain, dependent on depression history and pain assessment method - Patients with recurrent depression benefited most from MBI, in the affective dimension and along with physicians' ratings of joint tenderness

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Zeidan et al. (2015) Study type: RCT	Population: 75 (38 ♂/37 ♀) Mean age: 27 ± 6 Experimental groups: - Mindfulness meditation Placebo conditioning - Sham mindfulness meditation - Book-listening control Inclusion criteria: - Healthy - Pain-free - Right-handed volunteers Without any prior meditative experience Previous experience in MBI/meditation: Meditation naïve	Duration: Acute Modality/type: Noxious heat (35–49°C)	4 days of Mindfulness intervention vs. 4 days of a placebo conditioning regimen. Type: Mindfulness-based mental training: training day 1: focus on the breath sensations occurring "at the tip of the nose." Training day 2: expansion of the focus to the "full flow of the breath," including bodily sensations training days 3 and 4: minimal meditation instructions. Duration: 4 sessions in 4 days; 20 min Instructors: - Formation/experience: not referred - Conflicts of interest/Disclosures of Instructors/Authors: Not Referred	Referred: Participants were told that they were participating in an "experimental trial of a new formulation of a topical, local anesthetic being tested for its pain reducing effects over time." They were told that the drug's name is "lidocaine" and that it "has been proven effective at progressively reducing pain after multiple applications in preliminary studies at other universities." Informed consent: Yes; Details provided	Evaluated: No Remarks: The sham group was intentionally lead to belied that they were practicing mindfulness breathing	Placebo of the MBI intervention: A placebo- conditioned regimen was designed and tested	- All cognitive manipulations (i.e., MBI, placebo conditioning, sham MBI) attenuated pain intensity and unpleasantness ratings when compared to rest and the control condition. - MBI produced greater pain relief than placebo and sham MBI by engaging different brain mechanisms from those of placebo and sham induced analgesia - The cognitive state of mindfulness meditation deactivated brain regions that facilitate low-level sensory and nociceptive processing including the thalamus and PAG compared with rest and the main effects of placebo and sham MBI. - Compared with placebo manipulation, MBI produced greater activation in brain regions that mediate the cognitive control of pain. Placebo produced greater activation in several brain areas in comparison to MBI. - Sham MBI induce overlapping activation of some brain areas with MBI, and deactivation of brain regions associated with the default mode network of the brain. - Some brain areas presented higher activation during sham MBI compared with MBI, whereas other had the opposite response

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TABLE 1 (Continued)

References Study type	Participants	Pain	MBI	Communication research team/participants	Participants expectations	Analysis of placebo effects	Outcomes
Zeidan et al. (2016) Study type: RCT	Population: 78 (39 ♂/39 ♀) Mean age: 27 ± 7 Experimental groups: - Meditation + naloxone - Control + naloxone - Meditation + saline - Control + saline Inclusion criteria: - Healthy - Pain-free Meditation-naive - Recruited from the local community Previous experience in MBI/Meditation: Meditation naïve volunteers	Pain duration: Acute Pain modality: Noxious heat (35–49°C)	Type: Mindfulness-based mental training: training day 1: focus on the breath sensations occurring "at the tip of the nose." Training day 2: expansion of the focus to the "full flow of the breath," including bodily sensations training days 3 and 4: minimal meditation instructions (no instructions for practice tice outside training sessions). Duration: 4 sessions of 20 min. Instructors: - Formation/experience: not referred - Conflicts of interest/Disclosures of Instructors/Authors: Referred in detail	Referred: Participants in the meditation group were instructed to "begin meditating until the end of the experiment." Participants in the control group subjects were told to "close your eyes and relax until the end of the experiment"	Evaluated: No Remarks: Not referred	Placebo of the MBI intervention: Placebo saline for naloxone	- MBI during saline infusion significantly reduced pain intensity and unpleasantness ratings when compared to the control+saline group. - Naloxone infusion failed to reverse meditation-induced analgesia (pain intensity and unpleasantness ratings) - No significant differences in pain intensity or pain unpleasantness reductions between the meditation+naloxone and the meditation+saline groups. - MBI during naloxone produced significantly greater reductions in pain intensity and unpleasantness than the groups.

MBCT, Mindfulness based Cognitive Therapy; MBSR, Mindfulness-Based Stress Reduction; RCT, Randomized Controlled Trial.

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role of mindfulness in the reduction of cue-induced hyperalgesia. Another study was a secondary analysis of a previous study (Zeidan et al., 2016; Case et al., 2021) and demonstrated that participant expectations about MBIs-induced effects on pain relief predicted pain reductions, with this correlation being higher during opioid antagonism (naloxone).

Some studies indicate that the placebo effect plays an important role in MBIs' pain relief and that expectancy is the strongest predictor of decreases in pain unpleasantness and intensity, as well as increases in pain tolerance (Davies et al., 2021, 2022). One study indicates that mindfulness meditation produces greater pain relief than a placebo intervention (Zeidan et al., 2015) while engaging different brain mechanisms. According to this study, mindfulness is associated with the activation of brain areas responsible for the cognitive modulation of pain, such as the ACC, bilateral anterior insula, and putamen nucleus, and the deactivation of nociceptive and sensory areas, including the thalamus and PAG. In contrast, the placebo effect is associated with greater activation in the bilateral dorsolateral PFC, PAG, thalamus, cerebellum, posterior cingulate cortex, and superior frontal gyrus. SHAM mindfulness activates brain areas that partially overlap with those activated and deactivated by mindfulness, producing greater activation in the thalamus, periaqueductal gray, bilateral dorsolateral prefrontal cortex, and cerebellum and a minor activation in the posterior cingulate cortex and right globus pallidus.

We also conducted a specific analysis of the control groups in the studies, considering acute (Table 2) and chronic (Table 3) pain separately, given the diversity of the analyzed outcomes. Two of the 19 studies were not included in the analysis because they did not have a control group (Grazzi et al., 2021; Vencatachellum et al., 2021) and were longitudinal evaluations of the interventions. As previously mentioned, the main aims of the studies varied, such as evaluating the opioid-mediated mechanisms of MBIs and/or the MBIs themselves. Therefore, the control groups were specifically designed, including saline infusion (e.g., Zeidan et al., 2016; Esch et al., 2017; May et al., 2018; Namjoo et al., 2019; Wells et al., 2020; Case et al., 2021; Khatib et al., 2024) or a specific placebo (Davoudi et al., 2021).

Interestingly, the analysis of the control groups when the interventions were MBIs frequently included interventions such as passive controls, book listening, or educational programs (Zautra et al., 2008; Zeidan et al., 2016; Esch et al., 2017; Case et al., 2021). Controls more closely related to MBIs were also designed to equate the non-specific features of the MBI (general Sham mindfulness), stress management, or slow breathing techniques (Zeidan et al., 2015; Seminowicz et al., 2020; Wells et al., 2020; Davies et al., 2021, 2022, 2023; Khatib et al., 2024). A recent study included an experimental group specific to the MBI, in which all conditions matched the structural features of the MBI (e.g., attention to the intervention and instructions designed to give the meditator the sense that they were practicing a guided meditation) but lacked the instructions to provide attentional stability and meta-awareness (Davies et al., 2023).

The studies varied widely in terms of outcomes, covering sensory (intensity and threshold) and cognitive-emotional (e.g., catastrophizing, anxiety, and depression) aspects. Among the 11 studies that specifically controlled for the MBI (and not the pharmacologic intervention), MBIs had a similar effect to the control intervention in at least one of the analyzed parameters. These parameters included sensory aspects (Sharon et al., 2016; Davies et al., 2021, 2022, 2023; pain intensity), emotional components (pain unpleasantness; Davies et al., 2023), medical consumption (Davies et al., 2023), and multifactorial parameters (quality of life; Schmidt et al., 2011).

MBIs had a higher effect than the sham intervention in sensory parameters (Zautra et al., 2008; Zeidan et al., 2015; Westenberg et al., 2018; Seminowicz et al., 2020; Wells et al., 2020; Case et al., 2021; Khatib et al., 2024; pain intensity) and several cognitive/emotional aspects of pain (Zautra et al., 2008; Zeidan et al., 2015; Westenberg et al., 2018; Davies et al., 2021). In none of the analyzed studies did sham interventions have a higher effect than MBIs.

To assess the quality of the studies included in this review, the *Cochrane Risk of Bias Tool* for Randomized Controlled Trials was used (Higgins et al., 2011), as well as the *Newcastle-Ottawa Scale* for non-randomized studies (Tables 4, 5). Most of the studies reviewed have a moderate risk of bias, and therefore, the sample of articles analyzed may be considered of good quality.

Discussion

To the best of our knowledge, this is the first systematic review evaluating the possible effects of expectations and the placebo effect on the outcomes of MBIs for pain management. Systematic reviews support the efficacy of MBIs in pain management, suggesting that these cognitive-behavioral therapies could be useful (Hilton et al., 2017; Mcclintock et al., 2019; Pardos-Gascon et al., 2021). However, these studies highlight the need for further research due to the variability in the effects observed. This need is also supported by the present systematic review since all analyzed studies showed an effect of MBIs on pain management. Notably, the studies often evaluated the effects of MBIs on both the sensory and emotional dimensions of pain by measuring pain intensity and pain unpleasantness, which is commendable given the multidimensional nature of pain (Price, 2000; Raja et al., 2020).

Further research is needed to understand the mechanisms of MBIs in pain, considering the established effects of expectations and placebo on pain and their neurobiological mechanisms (Zunhammer et al., 2021; Benedetti et al., 2022). In this study, we attempted to systematically evaluate whether participant expectations of MBIs for pain were evaluated and whether the potential for MBI-derived placebo effects was considered. Previous systematic reviews and meta-analyses have suggested that the mechanisms of action should be studied (Hilton et al., 2017; Mcclintock et al., 2019; Pardos-Gascon et al., 2021). Given the knowledge of placebo-induced analgesia, we hypothesized that MBI-induced placebo effects could have an effect.

Despite the growing body of research on MBIs, the "next generation of mindfulness-based intervention research" (Rosenkranz et al., 2019) emphasizes the need for better experimental designs to investigate the underlying mechanisms of MBIs' beneficial effects. In general, studies on MBIs, not only

TABLE 2 Comparison of the effects of MBIs and sham (control) interventions in the acute pain studies, focusing on the main pain outcomes.

References	Main mechanisms	Type of sham intervention	Pain outcomes			
			Intensity/ threshold	Tolerance	Unpleasantness	Catastrophizing
Case et al. (2021)	Opioid-mediated modulation of expectations	- Active (Book Listening) or Passive control - Saline infusion	MBI>Controls	N/A	N/A	N/A
Davies et al. (2021)	Placebo effects of MBIs	Specific Sham mindfulness	MBI=Control	MBI=Control	MBI>Control	N/A
Davies et al. (2022)	Role of expectations in placebo effects of MBIs	Specific Sham mindfulness	MBI=Control	MBI=Control	MBI=Control	N/A
Esch et al. (2017)	Opioid modulation	- Passive control - Saline infusion	N/A	MBI=Control	N/A	N/A
May et al. (2018)	Opioid modulation	Saline infusion	MBI>Control	N/A	MBI>Control	N/A
Namjoo et al. (2019)	Opioid modulation	Saline infusion	MBI>Control	N/A	N/A	N/A
Sharon et al. (2016)	Opioid modulation	Saline infusion	MBI=Control	N/A	MBI=Control	N/A
Wells et al. (2020)	Opioid modulation	- Slow-paced Breathing or Sham Mindfulness Meditation - Saline infusion	MBI>Control	N/A	MBI=Control	N/A
Zeidan et al. (2015)	MBI vs. placebo analgesia	- Placebo conditioning - General Sham Mindfulness (GSM) - Active control (Book listening)	MBI>active controls (GSM)>Book listening	N/A	MBI>active controls (GSM)>Book listening	N/A
Zeidan et al. (2016)	Opioid modulation	- Active (book listening) - Saline infusion	MBI>Control	N/A	MBI>Control	N/A

MBI>Control means that the effect of MBI was significantly higher than the sham intervention.

for pain, should prioritize longitudinal evaluations and active controls, as well as account for the instructors' experience and the participants' expectations (Caspi and Burleson, 2007; Davidson and Kaszniak, 2015; Van Dam et al., 2018). Additional research using matched sham interventions is necessary in this field.

In a recent review of MBIs' effects on fibromyalgia, we identified several study limitations (Leca and Tavares, 2022), confirming that experimental design concerns also apply to pain studies. Further studies with adequate experimental designs are needed to better evaluate the effects of MBIs, particularly regarding the instructors' experience. In the present study, we found similar constraints in the 19 analyzed studies, particularly regarding the instructors' experience. A total of eight of the 15 analyzed studies did not report the experience of the instructors. It was shown that the experience of the instructors and their time of practice may influence the outcomes of some MBIs (Davidson and Kaszniak, 2015; Van Dam et al., 2018).

Attempts to contact authors for missing information were unsuccessful. Two studies (Zeidan et al., 2015; Sharon et al., 2016) did not have instructors, as their aims differed from the others, reducing the number of relevant studies to 15 instead of 17 studies.

Other studies only mentioned that the instructors were psychologists with expertise in mindfulness practices (Wells et al., 2020; Davoudi et al., 2021), which is also vague information.

Some studies referred to both the extent of the instructors' experience and the type of practice (Schmidt et al., 2011; Namjoo et al., 2019). One additional constraint in the analyzed studies is the lack of reporting and/or evaluation of participants' previous experience with mindfulness or meditation in six of the analyzed studies (Zautra et al., 2008; Schmidt et al., 2011; Namjoo et al., 2019; Case et al., 2021; Davoudi et al., 2021; Vencatachellum et al., 2021). This is a challenging issue since participants' prior experience with mindfulness or meditation may prompt them to recognize if they are receiving a sham intervention. Consequently, these participants may not experience the same placebo effect as those who believe they are receiving active treatment. This bias could be mitigated by selecting participants who are completely naive to mindfulness. Addressing these issues in future research would be an important step in better understanding the factors that influence MBIs' effects on pain. Among the 19 analyzed studies, 10 used acute stimuli, while the remaining studies evaluated various chronic pain conditions such as recurrent headaches/migraines,

TABLE 3 **Comparison of the effects of MBIs and sham (control) interventions in the chronic pain studies, focusing on the main pain outcomes.**

References	Main aim	Type of sham (control) intervention	Main chronic pain outcomes				
			Severity/ intensity/ frequency	Pain-related disability	Quality of life (health related/ neuropathic-specific)	Medication consumption	Emotional distress (unpleasantness/ catastrophizing/ anxiety/ depression/ coping)
Davies et al. (2023)	Effects of Specific- and General- sham interventions	- General Sham mindfulness (GSM) - Specific Sham mindfulness (SSM)	MBI=Controls (both GSM and SSM) GSM=SSM	N/A	N/A	MBI=Controls (both GSM and SSM) GSM=SSM	MBI=Controls (both GSM and SSM) GSM=SSM
Davoudi et al. (2021)	Vitamin D effects	Pharmacologic placebo	MBI>Control	MBI>Control	MBI>Control	N/A	N/A
Khatib et al. (2024)	Opioid effects in MBI and Sham-MBI	- Sham-matched mindfulness - Saline infusion	MBI> sham mindfulness	N/A	N/A	N/A	N/A
Schmidt et al. (2011)	MBSR in fibromyalgia	General Sham Mindfulness (GSM)	N/A	N/A	MBI=GSM[a]	N/A	N/A
Seminowicz et al. (2020)	MBSR in headache	Stress management	MBI>Control	N/A	N/A	N/A	N/A
Westenberg et al. (2018)	Mindfulness-based video exercise	Attention placebo control	MBI>Control	N/A	N/A	N/A	MBI>Control
Zautra et al. (2008)	Mindfulness in arthritis	Attention placebo control (education)	M>Control[b]	N/A	N/A	N/A	MBI>Control[b]

MBI>Control means that the effect of MBI was significantly higher than the sham intervention.

[a]General Active Sham (Active Control) had statistically significant effects in secondary outcomes in longitudinal analysis and comparison with passive control.

[b]Dependent on history of recurrent depression.

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TABLE 4 Analysis of risk of bias for randomized controlled trials (*Cochrane Risk of Bias Tool*).

References	Random and sequential sample selection	Blinded allocation (the researcher does not know the treatment of the next patient)	Single blinded or double blinded sample/patients and/or investigators	Blinded evaluation of the results	Justification for the cases of withdrawal of the study	Report of all results (do not select only positive results)	Risk of bias
Case et al. (2021)	Yes	Yes	Yes	-	Yes	-	Moderate
Davies et al. (2021)	Yes	Yes	Yes	-	Yes	Yes	Moderate
Davies et al. (2022)	Yes	Yes	Yes	-	Yes	Yes	Moderate
Davies et al. (2023)	Yes	Yes	Yes	-	Yes	Yes	Moderate
Davoudi et al. (2021)	Yes	-	Yes	-	No	Yes	High
Esch et al. (2017)	Yes	Yes	Yes	-	No	Yes	Moderate
Khatib et al. (2024)	Yes	Yes	Yes	-	No	Yes	Moderate
May et al. (2018)	Yes	Yes	Yes	-	Yes	Yes	Moderate
Namjoo et al. (2019)	Yes	No	Yes	-	Yes	Yes	Moderate
Schmidt et al. (2011)	Yes	Yes	Yes	No	Yes	Yes	Moderate
Seminowicz et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Low
Sharon et al. (2016)	Yes	Yes	Yes	-	Yes	-	Moderate
Wells et al. (2020)	Yes	Yes	Yes	-	Yes	Yes	Moderate
Westenberg et al. (2018)	Yes	No	Yes	-	Yes	Yes	Moderate
Zautra et al. (2008)	Yes	Yes	Yes	-	No	Yes	Moderate
Zeidan et al. (2015)	Yes	No	No	-	Yes	-	High
Zeidan et al. (2016)	Yes	Yes	Yes	-	Yes	-	Moderate

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TABLE 5 Analysis of risk of bias for non-randomized studies (*Newcastle-Ottawa Scale*).

References	Selection				Comparison	Result/exposition			Risk of bias
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	According to the methodology	Verification of the exposition	Same methods for cases/controls	No response rate	
Grazzi et al. (2021)	*	*	*	-	*	*	-	*	Moderate
Vencatachellum et al. (2021)	*	*	*	*	*	*	*	-	Low

diabetic neuropathy, and musculoskeletal/articular pain. However, acute and chronic pain may differ in terms of the mechanisms of mindfulness. Due to neuroplastic changes in the nervous system from acute to chronic pain and the specificities of chronic pain types, caution is needed when translating MBIs for pain management in both acute and chronic pain.

There are still very few articles focusing on the role of expectations in MBIs' pain relief. There is a considerable gap in the field of pain research, given that the role of expectations in MBIs for other conditions has been demonstrated. The label "mindfulness" in a study has been shown to drive expectancy (Ghanbari Noshari et al., 2023), potentially leading to the placebo effect. Since pain has a cognitive dimension and lacks objective biomarkers, MBIs primarily rely on self-reported experiences. Therefore, understanding patients' expectations and the information they received about the intervention is crucial. However, our analysis revealed that most studies did not clearly specify the type of information provided to participants.

The information in the three studies that analyzed the effects of MBIs on pain responses was clear. Two of these studies concluded that the placebo effect plays a role in pain responses during MBIs, with expectancy being the strongest predictor of decreases in pain unpleasantness and intensity and increases in pain tolerance (Davies et al., 2021, 2022). In one study, investigators created a cover story, informing the participants that they would be allocated to one of two groups (mindfulness or no treatment), while they were allocated to one of three groups (mindfulness, sham mindfulness, or placebo; Davies et al., 2021).

In another study, participants were informed that the aim of the study was to test a newly developed MBI that integrated highly effective elements of existing MBIs for pain and was expected to greatly reduce pain. A similar cover story was used, but participants were allocated to one of three groups (mindfulness, sham mindfulness, or no treatment), while they were, in fact, allocated to one of five groups (MM+: told they were receiving mindfulness and actually received mindfulness; MM-: told they were receiving sham but actually received mindfulness; SHAM+: told they were receiving mindfulness but actually received sham; SHAM-: told they were receiving sham and actually received sham; and no treatment control). This design demonstrated the effects of patients' expectation on MBI results for pain and the occurrence of a placebo effect (Davies et al., 2022).

For a placebo effect to be accurately measured and controlled for, the sham intervention must fulfill two roles. First, it must *match in credibility* (i.e., from a participant's or patient's perspective, it must be indistinguishable from actual mindfulness), as evidenced by equivalent scores on credibility or manipulation checks. Second, the sham intervention must elicit expectations of benefit equal to those receiving mindfulness, as evidenced by equivalent expectancy ratings post-exposure or by pre-exposure and post-exposure changes in expectancy ratings across both groups. In this regard, defining sham-mindfulness interventions or even sham-mindfulness interventions with specific MBI features is crucial (Davies et al., 2023) and may provide new insights into the specific mechanisms of MBIs.

Two studies focused on the effect of expectation on MBIs' pain relief. One of them hypothesized that mindfulness could reduce cue-induced hypoalgesia and hyperalgesia and found evidence to support the role of mindfulness in reducing cue-induced hyperalgesia (Vencatachellum et al., 2021). The other study was a secondary analysis of a previous study (Zeidan et al., 2016) and demonstrated that the expectations of the participants about MBI-induced pain relief predicted pain reductions, with the correlation being higher during opioid antagonism (naloxone). Collectively, the results of studies that properly control MBIs for factors such as expectations show that these expectations should be considered. The studies by the Davies group (Davies et al., 2022, 2023) provide a solid ground for collecting and numerically measuring participant expectations to manipulate them and evaluate the placebo effect.

It should be noted that only a few studies have properly measured and manipulated pain expectancies. Therefore, the intentions of the participants in MBIs and their expectations regarding pain improvement should be evaluated using appropriate questionnaires before and after the interventions.

One study investigated the neurobiological mechanisms underlying MBIs' pain relief and whether they were similar to those mediating the placebo effect (Zeidan et al., 2015). This study concluded that MBIs produce greater pain relief than a placebo intervention while engaging different brain mechanisms. The differences in the magnitude of the effects and the underlying brain structures indicate that the MBIs' effects on pain relief are not entirely mediated by placebo, although placebo plays a role. However, the limited number of studies, along with some of the abovementioned pitfalls in the experimental design, prevents solid conclusions to be drawn about the influence of expectations on "MBIs-induced" pain relief. Further studies are necessary to allow additional systematic reviews and meta-analyses on this fascinating issue in neuroscience, psychology, and medicine.

Overall, this systematic review indicates that certain aspects of MBIs for pain management need to be considered before this type of cognitive-behavioral intervention is widely adopted for pain management. For example, it is important to determine the expectations of the participants in the interventions, as these may be manipulated to maximize placebo effects and better establish the mechanisms behind the beneficial effects of MBIs. The importance of including adequate sham controls should be highlighted in the experimental design of MBIs for pain management. Regarding the neurobiological mechanisms underlying the effects of MBIs on pain management, such as opioid involvement, future neuroimaging studies may be important. Due to the neuroplastic changes induced by chronic pain and its impact on human suffering, it is crucial to continue studying chronic pain rather than focusing predominantly on acute pain. Evaluating the long-term impact of MBIs and assessing the durability of treatment effects is also essential, particularly for chronic pain conditions.

Limitations of the present study

This study presents some limitations. The small number of studies that actually evaluated the effects of expectations was much smaller than the 19 analyzed studies, which impairs the ability to conduct a meta-analysis. Nevertheless, the large majority of the studies were of good quality, as demonstrated by the risk of bias assessment. Another limitation was the inability to consistently retrieve data regarding the population, such as age and gender, which considerably affect pain responses and responses to psychological interventions such as MBIs.

It is important for researchers in MBIs for pain to openly discuss the limitations and constraints of the current available interventions to evaluate the mechanisms of the placebo effect in MBIs for pain. Replicating studies that show that the placebo effect plays a role in MBIs for pain (e.g., Zeidan et al., 2016; Davies et al., 2022) would be important. There is a clear need for better development, validation, and reporting of the sham interventions used in MBIs. Longitudinal studies of novice and expert meditators are necessary to evaluate how specific (mindfulness) and non-specific (placebo) effects change over time with more training and expertise.

Currently, there is a significant scope in MBIs for pain to develop useful and specific placebo interventions, as the concept of a "universal placebo" does not exist in MBIs. The present systematic review also highlights the need to continue analyzing the neurobiological basis of MBI to gain a better understanding of the pain modulatory mechanisms, other than opioids, that may support controlled therapeutic interventions of MBIs in pain management.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AL: Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Methodology, Software. RS: Supervision, Validation, Writing – review & editing. IT: Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Resources, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Differences in brain connectivity between older adults practicing Tai Chi and Water Aerobics: a case–control study

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Background: This study aimed to investigate the neural mechanisms that differentiate mind–body practices from aerobic physical activities and elucidate their effects on cognition and healthy aging. We examined functional brain connectivity in older adults (age > 60) without pre-existing uncontrolled chronic diseases, comparing Tai Chi with Water Aerobics practitioners.

Methods: We conducted a cross-sectional, case–control fMRI study involving two strictly matched groups ($n = 32$) based on gender, age, education, and years of practice. Seed-to-voxel analysis was performed using the Salience, and Frontoparietal Networks as seed regions in Stroop Word-Color and N-Back tasks and Resting State.

Results: During Resting State condition and using Salience network as a seed, Tai Chi group exhibited a stronger correlation between Anterior Cingulate Cortex and Insular Cortex areas (regions related to interoceptive awareness, cognitive control and motor organization of subjective aspects of experience). In N-Back task and using Salience network as seed, Tai Chi group showed increased correlation between Left Supramarginal Gyrus and various cerebellar regions (related to memory, attention, cognitive processing, sensorimotor control and cognitive flexibility). In Stroop task, using Salience network as seed, Tai Chi group showed enhanced correlation between Left Rostral Prefrontal Cortex and Right Occipital Pole, and Right Lateral Occipital Cortex (areas associated with sustained attention, prospective memory, mediate attention between external stimuli and internal intention). Additionally, in Stroop task, using Frontoparietal network as seed, Water Aerobics group exhibited a stronger correlation between Left Posterior Parietal Lobe (specialized in word meaning, representing motor actions, motor planning directed to objects, and general perception) and different cerebellar regions (linked to object mirroring).

Conclusion: Our study provides evidence of differences in functional connectivity between older adults who have received training in a mind–body practice (Tai Chi) or in an aerobic physical activity (Water Aerobics) when performing attentional and working memory tasks, as well as during resting state.

KEYWORDS

Tai Chi, longevity, self-regulation, fMRI, functional connectivity, mind–body, embodied cognition, Stroop

1 Introduction

There is a growing interest in identifying effective strategies to promote healthy brain aging and preserve cognitive abilities (United Nations, 2019; World Health Organization, 2017). Among them, aerobic physical activities and mind–body practices play a fundamental role in preserving structural and functional health of the brain and they are widely acknowledged as protective factors for maintaining cognitive function and promoting healthy aging in older adults (Erickson et al., 2011; Song et al., 2017; Stillman et al., 2020; Erickson et al., 2022). They can exert beneficial effects on the brain via processes of neuroplasticity (e.g., changes in functional connectivity) which may converge into improvements in cognitive performance (Voss et al., 2013; Li et al., 2022). Tai Chi (a mind–body practice) and Water Aerobics (an aerobic physical activity) were the practices compared in the present study and they were described below in more detail.

Tai Chi is a mind–body practice that combines gentle flowing movements, with refined movement control; it includes controlled breathing, and focused attention, promoting a state of relaxed alertness and integrating the mind and body. As a result, Tai Chi has gained recognition for offering distinct advantages for both physical and mental health (Kong et al., 2019; Birdee et al., 2009) and enhancing brain function (Cui et al., 2021; Port et al., 2018; Yang et al., 2020). Studies have addressed its capacity to improve cognitive performance in older adults (Wayne et al., 2014). Moreover, mind–body practices like Tai Chi enhance interoception, which refers to the perception and awareness of bodily sensations (Farb et al., 2013; Farb et al., 2015). Interoceptive awareness and sensorimotor control are recognized as central to mind–body regulation (Khalsa et al., 2018; Quadt et al., 2018) and they play a significant role in Tai Chi training.

Water Aerobics also has benefits for health aging. It is an aerobic physical activity that stands out as an effective way to maintain a healthy body weight and prevent muscle and joint injuries (Tamin and Loekito, 2018). It is effective in treating patients with hemorrhagic stroke (Li and Chen, 2021), it has been associated with reduced anxiety and depression, improved functional independence, and decreased oxidative stress among older adults with depression (da Silva et al., 2019). Moreover, a systematic review has highlighted the benefits of Water Aerobics for patients with fibromyalgia (Bidonde et al., 2014). We would like to highlight that in contrast to Tai Chi interoceptive attentional focus, Water Aerobics involves repetitive movements and externalized attention focused on following the instructor's motions. Furthermore, in Water Aerobics neuromuscular activity required from antigravity muscles is reduced (Pereira Neiva et al., 2018; Barbosa et al., 2009; Butts et al., 1991) while Tai Chi works with grounding or antigravity muscles. Besides, Tai Chi works with previous choreographed and memorized movements while Water Aerobics works with repetitive and copied movements. Therefore, Water Aerobics was chosen as an active control group for Tai Chi practice.

While one ages, changes occur in brain structure and function, including alterations in connectivity patterns within neural networks (Grady, 2012). These networks are shaped by the anatomical links among many brain regions, representing the exchange of information among them. Through functional brain connectivity, one can identifiy correlations between spatial regions of interest by employing linear temporal correlations based on parameters of neuronal activity (Xie et al., 2021; Smitha et al., 2017). Changes in functional connectivity have been utilized to identify age-related differences, with connectivity patterns within Salience Network (SN), Frontoparietal Network (FN), and Default Mode Network (DMN), serving as potential indicators of healthy or pathological brain aging (Buckner et al., 2005; Gardner et al., 2013; Seeley et al., 2009; Tomasi and Volkow, 2012; Zhou et al., 2012). Thus, engaging in exercise training and in practices that require centered attention and promote mind–body integration, such as Tai Chi may induce neuroplastic changes that could counteract age-related declines in memory, executive function, attention, abstract reasoning skills, and problem-solving abilities (Erickson et al., 2011; Tang et al., 2015; Tang et al., 2010).

Previous studies have shown that aerobic physical activities increase the size of hippocampus and improve memory (Erickson et al., 2011) and that mind–body practices, including meditation and movement meditation like Tai Chi, can influence brain networks associated with attention, emotional regulation, and cognitive control (Brewer et al., 2011). Mind–body practices have been linked to enhanced functional connectivity and structural changes in regions involved in self-referential processing and attentional control (Port et al., 2018; Tang et al., 2010; Kozasa et al., 2012). However, the neural mechanisms that distinguish mind–body practices from aerobic physical activities and elucidate their advantages in healthy aging remain unclear. Little is known about the differences that mind–body practices and physical practices may present on brain connectivity in adults over 60 years of age, without pre-existing diseases. This exploration might also aid in the development of targeted specific interventions to promote healthy aging and improve cognitive well-being in older adults. We observed differences in activation within regions linked to self-awareness, alongside enhanced efficacy in areas associated with attention and memory in the Tai Chi group compared to Water Aerobic group in a previous study, however a sample size of 16 participants did not allow robust conclusions (Port et al., 2018). Thus, in this study, which builds up on the findings of our previous study, we aimed on recruiting a higher number of participants.

Our hypothesis was that, due to the combination of conscious attention to movements and interoceptive training, Tai Chi practitioners would present heightened brain connectivity among areas linked to cognitive control, sensorimotor control, and interoception compared with Water Aerobics practitioners. This study aimed to explore differences in functional brain connectivity among older adults (age > 60) participating in interoceptive, attentional, and movement control training, specifically Tai Chi, or an aerobic physical activity, such as Water Aerobics. Participants performed N-Back and Stroop tasks during magnetic resonance imaging (MRI) scans.

2 Methods

2.1 Study design

This is a case control cross-sectional study conducted at the Brain Institute of Hospital Israelita Albert Einstein, São Paulo, Brazil. This work was approved by our institutional ethics committee (CAAE: 38602714.7.0000.0071).

Out of 57 volunteers contacted, 44 took part in the study (were evaluated), and among those, 32 met the pairing criteria. Both groups were paired in terms of sex, age, education, and the time of practice.

After signing of the informed consent form, volunteers underwent neuropsychological assessment and then underwent functional magnetic resonance imaging.

2.2 Participants

To assure that characteristics of volunteers were compatible to inclusion and exclusion criteria, the researcher responsible for contacting the participants has also interviewed the Tai Chi and Water Aerobics instructors during data collection. We took special care to ensure that the chosen Tai Chi participants refrained from practicing any other mind–body techniques, such as yoga, various meditation styles, karate, or Qigong. Similarly, we ensured that the Water Aerobics volunteers were not involved in any of these other mind–body practices. Furthermore, we verified that the volunteers did not fall under the category of obesity, and they were carefully paired based on their individual gender, age, education and years of practice. While the stringent criteria and precise selection criteria led to the smaller sample size, they facilitated a controlled matching process, resulting in a distinct sample of older adults free from pre-existing conditions or with controlled chronic diseases trained in each activity.

2.2.1 Inclusion criteria

Male or female aged>60; not obese (BMI < 30); who had practiced one of the two activities for at least 3 years, at least 1 h twice a week; non-practitioners of other mind–body activities; not colorblind; right-handed.

2.2.2 Exclusion criteria

We excluded individuals who were interested in participating in the study if they had alterations or diseases involving the vestibular system, had uncontrolled chronic diseases such as diabetes or hypertension, had altered neurological conditions that resulted in spasticity or involuntary movement, had a neurological or psychiatric condition that hindered their ability to perform the tasks, were taking benzodiazepines or analgesic medications at doses that interfered with their attention span, had undergone orthopedic surgeries and/or received botulinum toxin injections in the last 6 months, met any criteria that contraindicated them from having a magnetic resonance imaging (such as having a cardiac pacemaker or cochlear implants), had dental artifacts, or had tremors or dystonia in the head and neck region.

The participants were interviewed by experienced nurses specialized in clinical studies to check the inclusion and exclusion criteria and after that they answered the questionnaires and scales.

2.3 Questionnaires and scales

The neuropsychological assessment was designed to probe whether group differences in memory skills, attention, executive functions, learning, recall skills, well-being and psychomotor efficiency. We conducted the assessment using the following tests in paper and pencil version:

World Health Organization Well-Being Index (WHO-5): A brief questionnaire consisting of 5 simple, noninvasive, and positively phrased statements used to assess subjective well-being. Participants rated each statement on a 6-point Likert scale, ranging from 5 (all the time) to 0 (at no time), indicating how they felt during the last 2 weeks. The internal consistency is 0.78 in a Brazilian sample (Fleck et al., 2000).

Pittsburgh Sleep Quality Index (PSQI): This scale evaluates sleep quality over the past 30 days through objective questions related to sleep schedule, nighttime awakenings, and daytime state. Each of the 19 self-reported items belongs to one of seven subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. There are five additional questions, rated by the respondent's roommate or bed partner, which are included for clinical purposes and are not scored. The Cronbach's alpha in a Brazilian sample is 0.71 (Buysse et al., 1989).

Self-Report Questionnaire-20 (SRQ-20): An inventory consisting of 20 questions used to detect psychiatric symptoms and assess mental health. The cutoff value was 7/8, with 86.33% sensitivity and 89.31% specificity. The score range is 0–20 (Scholte et al., 2011).

Beck Depression Inventory (BDI): The BDI assesses depression symptoms using 21 items, with each item scored on a scale from 0 to 3. The total score range is 0–63, and a cutoff value of 20 points discriminates mild to moderate symptoms of depression, with a sensitivity of 0.77 and specificity of 0.95 (Beck et al., 1988b).

Beck Anxiety Inventory (BAI): The BAI measures anxiety symptoms with 21 items, rated on a scale from 0 to 3, resulting in a total score range of 0–63. The internal consistency was 0.91, and the test–retest reliability was 0.99 for a sample of the Brazilian population (Beck et al., 1988a).

2.4 Neuropsychological tests

Trail Making Test Part A and Part B: Part A involves connecting 25 numbers, while Part B requires connecting numbers and letters in alternating ascending order using a pencil line. The examiner records the number of errors committed and the time taken to complete each task. They measure sustained and selective attention, respectively (Spreen and Strauss, 1998).

Stroop Color and Word Test: This paper-pencil task measures selective attention, cognitive flexibility, and the ability to suppress habitual responses in favor of unusual responses. The subject must quickly name the colors of four rectangles printed in green, blue, black, and red. The examiner records the number of errors and the time taken to complete the task (Spreen and Strauss, 1998).

Rey's Auditory Verbal Learning Test (RAVLT): The RAVLT is a paper-and-pencil measure of verbal memory for unstructured information (word lists). The examinee is presented with a list of 15 unrelated concrete nouns (List A) and is asked to recall as many words as possible. This process is repeated four more times, followed by the presentation and recall of List B. After approximately 25 min, the examinee is asked to recall List A again. The score is based on the number of words recalled at each stage. The estimated average application time for the first part (presentation of Lists A and B and immediate recall of List A) is 10 to 15 min, and the second part (delayed recall) takes approximately 10 min. The RAVLT provides 10 basic scores, including the number of words recalled in each attempt and the recognition of words from List A and List B (Salgado et al., 2011).

Verbal Fluency F.A.S. (COWA): This test measures the ability to recall words within specific categories. The examinee is asked to generate as many words as possible starting with each of the letter's F, A, and S within a specified time while following certain rules. The scores are obtained for each letter and a general score representing the total number of words evoked for the three letters (Spreen and Strauss, 1998).

Mini Mental State Examination (MMSE): The MMSE assesses various cognitive functions through questions categorized into seven areas: time orientation, location orientation, three-word registration, attention and calculation, three-word recall, language, and visual construction capacity. The MMSE score ranges from 0 to 30. It is a screening tool for cognitive deficits. Its Cronbach alpha is 0.71 and kappa is 0.79 for a Brazilian sample (Bertolucci et al., 1994).

Digit-Symbol (DS WAIS-III): This test evaluates processing speed, visual-motor response, and association between numbers and symbols within a 2-min duration. The score range is 0–133, and the test–retest reliability for the Brazilian sample was 0.84 (Wechsler, 2004).

2.5 Functional magnetic resonance imaging

All functional magnetic resonance imaging (fMRI) scans were performed using a 3.0 T "Discovery MR750w GE Healthcare®" equipment with a 32-channel head coil. The scans were conducted at the Department of Diagnostic and Preventive Medicine—Sector of Image of Hospital Israelita Albert Einstein. The NNL system (NNL, Norway) with a dedicated algorithm (Eprime) was used for stimulus presentation and acquisition of behavioral responses. This system utilizes independent binocular projection.

2.5.1 Acquisition parameters

The fMRI evaluation was performed using paradigms prepared specifically for the evaluation of certain brain functions. The parameters of the acquisition sequences, sensitive to the BOLD effect (blood oxygen level dependent) were TR = 2000 ms, 40 slices with 3.3 mm thickness and 0.3 spacing between them. FOV = 240 mm, 64×64 matrix. The acquisition of the N-Back paradigm task had a total of 104 volumes (duration 3 min 28 s), and that of the Stroop task, 154 volumes (duration 5 min 8 s), and Resting-State had a total of 200 volumes (6 min 40 s).

T1-weighted Volumetric SPGR with axial acquisition, TR = 5 mss, TE = 1.7 ms, Matrix: 256 × 256, FOV 21.6 cm, Flip angle: 7, Thickness: 1.0 mm with 176 slices covering the entire cephalic segment, (duration 6 min 20 s). Axial FLAIR: TR = 1,000 ms, TE = 140 ms, IR = 1000s, FOV = 24 cm, Thickness = 5 mm, Spacing = 2.5 mm, 20 levels, for potential identification of other co-morbidities, t = 4:40s.

2.5.2 Description of tasks for functional assessment

Participants familiarized themselves with the tasks prior to the fMRI sessions and were scanned while performing adapted versions of the Stroop Word-Color Task (SWCT) and N-Back task. The SWCT was presented before the N-Back task.

2.5.2.1 Attention paradigm (Stroop word—color task)

The SWCT is a classic task used to study attention and inhibition and has been used in fMRI as a paradigm for understanding cognitive control mechanisms (Peterson et al., 1999). During this task, participants were instructed to communicate the color (blue, red, or green) of isolated words by pressing one of the three buttons, corresponding to these colors. Words were presented in three conditions: congruent (for example, the word "BLUE" painted in blue), neutral (color and words are not related), and incongruent (for example, the word "BLUE" painted in green). Each condition was presented in five blocks of trials, with 10 trials within each block. Each word/stimulus was presented for 1 s, with 1 s of inter-stimulus interval. Conditions were presented sequentially, without rest in between them, and always in the following sequence: congruent, neutral and incongruent. There were 8 s of waiting period before the first block of trials for a total of 154 TRs (5 min and 8 s).

2.5.2.2 N-Back task memory paradigm

The N-Back task has been frequently used in the investigation of the neural correlates of the working memory process (Owen et al., 2005). In the "2-back" (remember) condition, the target letter was a repeated letter, separated by another letter. The "0-back" (find) condition is a baseline task to control attention and motor movement, where participants were instructed to respond whenever the letter 'X' was displayed. Each condition was presented in five blocks of trials, each with 10 trials, alternating between "0-back" and "2-back" conditions. No rest periods were introduced between these blocks. Letters were presented for 1 s, with a 1 s inter-stimulus interval. There were 8 s of waiting period before the first block of trials for a total of 104 TRs (3 min 28 s).

2.5.3 Data analysis

2.5.3.1 Activation data analysis

Functional activation analysis was performed using the FSL program (Oxford, University 2010. FSL, Oxford England) which provides several routines for processing fMRI images.

The processing of the FMR images was performed with the FEAT tool (FMRI Expert Analysis Tool), version 6.0 integrated with the FSL software (FMRIB's Software Library). The following image pre-processing sequence was performed: the first four initial volumes were removed because they represented acquisition calibration parameters, two step high-resolution registration to the MNI152 2 mm standard space image is carried out using FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001) affine registration with 12 degrees of freedom, motion correction using MCFLIRT (Jenkinson et al., 2002) removal of non-brain tissue with the BET tool (Smith, 2002) slice-timing correction using Fourier-space time-series phase-shifting, spatial smoothing with a Gaussian kernel of FWHM 5 mm, intensity normalization of the general mean in the 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 100 s). Time-series statistical analysis is carried out using FILM with local autocorrelation correction (Smith, 2002). The recording of the functional image on the high-resolution T1-weighted anatomical image and the subsequent normalization to the standard brain Montreal Neurological Institute (MNI) 152, with 2 mm resolution were performed with the FLIRT tool (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

2.5.3.2 Functional connectivity data analysis

Data pre-process and analysis was conducted using CONN Toolbox 20.b version standard pipeline and parameters. We conducted functional connectivity analysis on the Resting-state, Stroop and N-Back fMRI data without segmenting for each stimulus condition. Consequently, the Stroop task analysis incorporated data from congruent, incongruent, and neutral conditions, while the N-Back analysis included the 0-back and 2-back conditions. We made this choice because there were insufficient data points in the fMRI data to perform connectivity analyses for each stimulus separately (Parkes et al., 2018). Operational procedure consisting in realignment, unwarping deformation, slice time correction, segmentation, normalization, *outliers*' detection and smoothing. Confounding variables were based on head movement (discarding volumes with displacement >2 mm and global signal z-value >9; no subjects were excluded), realignment parameters, white matter, and cerebrospinal fluid signals. Bandpass filtering (0.008 to 0.09 Hz) was applied to filter out physiological noise, and confounding variables were removed using a simultaneous bandpass approach. For this functional connectivity study, we conducted a seed-to-voxel analysis, using Salience and Frontoparietal networks as seeds. We did a functional connectivity analysis between the seed regions and the whole brain voxels. We set a *p*-value of 0.05 (FDR-corrected) for significant differences between groups.

2.5.3.3 Regions of interest

We used Salience network including Anterior Cingulated Cortex (x = 0, y = 22, z = 35), left Anterior Insular Cortex (x = −44, y = 13, z = 1), right Anterior Insular Cortex (x = 47, y = 14, z = 0), left rostral Prefrontal Cortex (x = −32, y = 45, z = 27), right rostral Prefrontal Cortex (x = 32, y = 46, z = 27), left Supramarginal Gyrus (x = −60, y = −39, z = 31) and right Supramarginal Gyrus (x = 62, y = −35, z = 32).

The Frontoparietal Network included left Lateral Prefrontal Cortex (x = −43, y = 33, z = 28), right Lateral Prefrontal Cortex (x = 41, y = 38, z = 30), left Posterior Parietal Lobe (x = −46, y = −58, z = 49) and right Posterior Parietal Lobe (x = 52, y = −52, z = 4; Whitfield-Gabrieli and Nieto-Castanon, 2012). All networks and ROIs were defined based on networks provided by the CONN Software.

2.6 Statistical analysis

2.6.1 Demographic and neuropsychological statistical analysis

We used the Mann–Whitney's test to analyze differences between groups in age, weight, height, body mass index and practice time. For the schooling category (elementary school, high school, under degree and graduate) we used a Fisher's exact test to compare whether both groups were paired in terms of schooling. To test differences between groups in neuropsychological assessment, we used Mann–Whitney's test. We set a *p*-value of 0.05 for statistical difference between groups. We conducted the statistical analysis using JASP Team (2024).

2.6.2 Behavioral statistical analysis

We conducted an analysis of variance (ANOVA) to test whether the groups differed in terms of response time (in milliseconds) and accuracy (ratio of correct answers to total attempts) in the Stroop and N-Back tasks. Only attempts with correct answers were considered for the response time calculation. We set a p-value of 0.05 for statistical differences in the interaction between groups and stimuli, corrected by Bonferroni. *Post-hoc* analyzes were performed to describe variables between groups. Behavioral statistical analyses were conducted using JASP (Version 0.19.0).

2.6.3 Activation statistical analysis

Statistical analysis was based on the massive univariate approach, using a General Linear Model (GLM), modeling the response in each voxel to the experimental conditions of the task. The activity of each of the two conditions of interest (Stroop: incongruent and neutral; N-Back: remember) were modeled as blocks of activity. The regressor for each of the conditions was modeled with a custom function, with duration established through the average of the trials of each task, inserted in a file containing three-column regressors. Next, each regressor was convoluted with a gamma function (time to peak = 5 s, standard error = 2.8 s). In addition to the repressors of interest, head movement parameters were also included as repressors of non-interest. In each participant, the contrast between the remember and find conditions was performed (remember > find for the N-Back task). For the Stroop task, the baseline was established by the congruent condition, resulting in contrasts incongruent > neutral and neutral> incongruent. It was evaluated using a t test for one sample, and the t values converted to Z. The group analysis was performed with a mixed effects model, using FLAME (FMRIB's Local Analysis of Mixed Effects; Woolrich et al., 2001). Differences between groups were assessed by a two-tailed t test for independent samples for each of the contrasts. To control for false positive results, the Z statistic maps were initially thresholded using voxel clusters determined by Z > 3.1, and the cluster corrected significance threshold of $p = 0.05$ (Figure 1).

3 Results

3.1 Demographic and neuropsychological results

Table 1 shows demographic comparison between groups. There were no significant differences in age, year of practice and height. We found significant difference in Body Mass Index and Weight, however none of the participants were obese (BMI < 30). There were no differences in level of education ($p = 0.139$) and most of participants had a college degree. We found no significant differences between groups in the neuropsychological tests (BAI, BDI, COWA, MMSE, RAVLT, PSQI, Who-5, Stroop, Trail Making, Digit-Symbol and SRQ-20). Descriptive and inferential statistics regarding each task and group is available as Supplementary Table 1.

3.2 Behavioral tests performed in fMRI

N-Back Task: We found no significant interaction effects between groups and stimuli in the ANOVA analysis for either accuracy ($p = 0.338$) or response time ($p = 0.951$). Detailed descriptive statistics (mean and standard deviation) for each group and stimulus, along with the corresponding inferential statistics (*p*-values and effect sizes), are provided in Supplementary Table 2.

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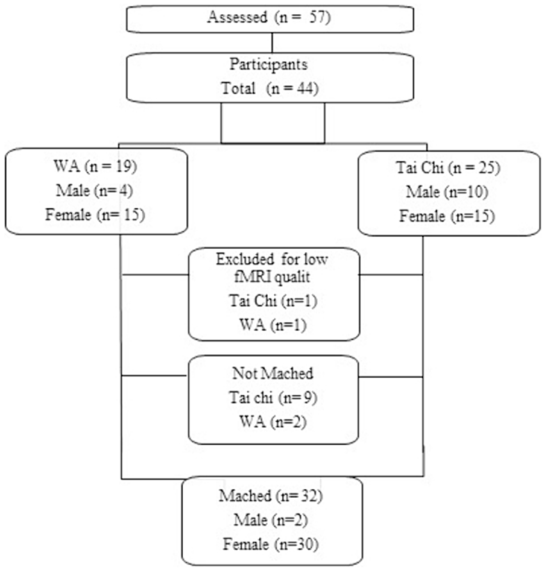

FIGURE 1
Study flowchart.

TABLE 1 Demographic results comparison between Tai Chi and Water Aerobics practitioners.

	Group	N	Mean	SD	p-value	Cohen's D
Years of Practice	1	16	13.750	10.976	0.108	0.584
	2	16	8.563	6.099		
Age	1	16	68.063	6.658	0.583	0.066
	2	16	68.500	6.491		
Hight	1	16	1.576	0.077	0.151	0.449
	2	16	1.611	0.079		
Weight	1	16	57.938	7.646	< 0.001	1.448
	2	16	70.250	9.277		
BMI	1	16	23.386	3.075	0.002	1.256
	2	16	27.046	2.745		

BMI, Body Mass Index; 1, Tai Chi group; 2, Water Aerobics; SD, Standard Deviation.

Stroop Task: The ANOVA analysis of the Stroop Word Color Task revealed no significant interaction effects between groups and stimuli for either accuracy ($p = 0.582$) or response time ($p = 0.29$). Comprehensive descriptive statistics (mean and standard deviation) for each group and stimulus, as well as the corresponding inferential statistics (p-values and effect sizes), can be found in Supplementary Table 3.

3.3 fMRI activation analysis in N-Back and Stroop task

There were no differences between groups in the activation results. Notably, during Stroop task, we found consistent activation in occipital and frontal cortex areas. When comparing incongruent and neutral conditions, we identified a greater number of activation clusters, indicating the presence of the Stroop effect. (Supplementary Table 3 for N-Back; Table 2 for Stroop).

3.4 Functional connectivity comparison between groups: results for N-Back and Stroop tasks

3.4.1 Resting state

Tai Chi > Water Aerobics: During Resting State, using the salience network as seed, Tai Chi group exhibited a higher correlation of Anterior Cingulate Cortex (ACC) with two clusters, one covering the Right Central Opercular Cortex: 4 voxels (57%) and the other in the right Insular Cortex: 3 voxels (43%; Figure 2; Table 3).

3.4.2 N-Back task

Tai Chi > Water Aerobics: During the N-Back using salience network as seed, Tai Chi group showed a higher correlation of left Supramarginal Gyrus with three clusters, one covering the Cerebellum Crus 2 left: 49 voxels (42%), other covering Cerebellum 7b left: 19 voxels (16%) and Cerebellum Crus 2 right: 12 voxels (10%; Figure 3; Table 3).

3.4.3 Stroop task

Tai Chi > Water Aerobics: During the Stroop task using Salience Network as seed, Tai Chi group demonstrated a higher correlation of the Left Rostral Prefrontal Cortex with the right occipital pole: 312 voxels (44%), and inferior division of the right lateral occipital cortex: 205 voxels (29%), and the superior division of the right lateral occipital cortex: 114 voxels (16%). **Water Aerobics > Tai Chi**: Additionally, during the Stroop task using Frontoparietal network as seed, Water Aerobics group exhibited a higher correlation of the left posterior parietal lobe with 3 cerebellar clusters, Cerebellum Crus 1 left: 226 voxels (73%), Cerebellum Crus 2 left: 83 voxels (27%), and Cerebellum 6 left: 2 voxels (1%; Figure 4; Table 3).

4 Discussion

Our study investigated differences in functional activity and connectivity in adults over the age of 60, without reporting uncontrolled pre-existing chronic diseases, involved in mind–body training (Tai Chi), compared with adults of the same age involved in an aerobic physical activity (Water Aerobics), with a strict matching criterion for gender, age, education, and time of practice. There were no differences in neuropsychological tests and these results confirm that there were no statistically significant differences in measures of cognitive performance between groups. This concern in pairing allowed us to have as similar active groups as possible, valuing the observed differences. The recruitment process was therefore, challenging.

At first participants underwent neuropsychological tests, then were assessed during a working memory task (N-Back task) and an attention and inhibitory control task (Stroop task). We performed a seed-to-voxel analysis using Salience and Frontoparietal networks as seeds.

Contrary to our expectations, our findings revealed no behavioral variances between groups in either the Stroop or N-Back tasks. The

TABLE 2 fMRI activation analysis for Stroop task, no comparison between groups.

Contrast	Cluster	Index	Voxels peak	x	y	z	Area
Tai Chi (neutro>congruent)	4	191	4.07	−50	4	30	64% Precentral Gurys
	3	161	3.82	−44	−66	−10	41% inf. Lateral Occiptal Cortex
	2	159	4.07	8	−64	−12	45% R Cerebellum VI
	1	130	4.29	−64	−4	0	24% Superior Temporal Gyrus
WA (neutro>congruent)	No siginficant						
Tai Chi (incongruent>congruent)	4	12,891	5.51	−38	−38	40	27% Supramarginal Gyrus
	3	436	4.32	18	−72	58	58% Lateral Occiptal Cortex
	2	372	5.04	38	2	54	47% Middle Frontal Gyrus
	1	297	4.35	46	10	32	31% Precentral Gyrus
WA (incongruent>congruent)	2	392	4.29	−26	−96	16	61% Occiptal Pole
	1	201	4.2	−30	−58	46	33% Superior Parietal Lobule
Tai Chi [incongruent>congruent] > [neutro>congruent]	6	5,346	4.9	0	−64	52	60% Precuneous Cortex
	5	1,269	4.73	42	20	24	23% Middle Frontal Gyrus
	4	369	4.15	−42	12	32	44% Middle Frontal Gyrus
	3	231	4.28	56	−46	12	36% Middle Temporal Gyrus
	2	173	4.25	0	20	50	26% Superior Frontal Gyrus
	1	162	4.13	−36	2	54	44% Middle Frontal Gyrus
WA [incongruent>congruent] > [neutro>congruent]	2	260	4.53	14	−90	0	18% Occiptal Pole
	1	145	3.83	−36	−56	50	30% Superior Parietal Lobule

The table shows the clusters (voxels) that had activation by group, during task conditions for Stroop. Coordinates (x, y, z) are in MNI space. WA, Water Aerobics.

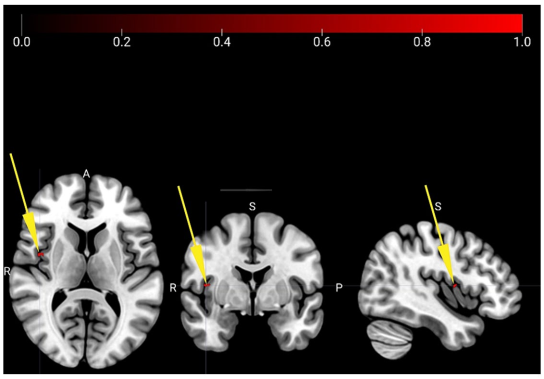

FIGURE 2
Resting State connectivity analysis comparison between groups. Tai Chi group exhibited an increased correlation between the seed of anterior cingulate cortex with the clusters central opercular cortex right and insular cortex right. Peak-cluster shown in red. Yellow arrows indicate localization of peak-cluster in MRI space (x = 42, y = 02, z = 18).

groups' shared characteristics of good health, comparable education (years of schooling), and the same amount of physical exercise (engaging in physical activity for over 3 years, at least twice weekly). This outcome indicates the study's efficacy in reducing inter-group variations.

4.1 Brain activation

Our investigation into brain activation revealed no discernible differences between groups during cognitive testing, which contradicts our initial hypothesis. These results are particularly notable given a prior study that identified differences in brain activation between Tai Chi and Water Acrobatics groups within a subset sample (Port et al., 2018). However, our current findings suggest a uniformity in brain activation across groups during task performance, hinting at potential similarities in neural processing despite differences in training interventions. Future studies with a larger sample size are necessary to buttress (or refute) our observations.

Despite the absence of group differences in brain activation, our analysis shows consistent activation patterns in the Stroop task in both groups. Notably, we observed activation in both occipital and frontal cortex areas, known for their involvement in visual processing and executive control functions, respectively (Huang et al., 2020). This observation aligns with existing literature on the neural correlates of the Stroop task, supporting the reliability of our neuroimaging methodology. Despite the absence of group differences in brain activation, our analysis shows consistent activation patterns in the Stroop task in both groups. Notably, we observed activation in both occipital and frontal cortex areas, known for their involvement in visual processing and executive control functions, respectively (Huang et al., 2020). This consistency aligns with existing literature on the neural correlates of the Stroop task, supporting the reliability of our neuroimaging methodology.

TABLE 3 Connectivity comparison between Tai Chi and Water Aerobics groups.

Task	Seed	Correlation	Contrast	Cluster (x, y, z)	Size p-FDR
Resting State	Salience Anterior Cingulate Cortex	1. Central Opercular Cortex right: 4 voxels (57%) covering 0% of Central Opercular Cortex right 2. Insular Cortex right: 3 voxels (43%), covering 0% of Insular Cortex right.	TC > WA	(+42, +02, +18)	0.040456
N-Back	Salience Left Supramarginal Gyrus	1. Cerebellum Crus 2 left: 49 voxels (42%) covering 3% of Cerebellum 2 left 2. Cerebellum 7b left: 19 voxels (Farb et al., 2015) covering1% of Cerebellum 7b left 3. Cerebellum Crus2 right: 12 voxels (10%) covering 15 of Cerebellum Crus2 right	TC > WA	(−4, −76, −38)	0.021126
Stroop	Salience Left Rostral Prefrontal Cortex	1. Occipital Pole right: 312 voxels (44%) covering 12% of Occipital Pole right 2. Inferior Lateral Occipital Cortex right: 205 voxels (29%) covering 10% of Inferior Lateral Occipital Cortex right 3. Superior Lateral Occipital Cortex right: 114 voxels (16%) covering 2% of Superior Lateral Occipital Cortex right	TC > WA	(+16, −94, −04)	0.0000001
	Frontoparietal Left Posterior Parietal Lobe	1. Cerebellum Crus 1 Left: 226 voxels (73%) covering 10% of Cerebellum Crus 1 Left 2. Cerebellum Crus 2 left: 83 voxels (27%) covering 4% of Cerebellum Crus 2 left 3. Cerebellum 6 left:2 voxels (1%) covering 0% of Cerebellum 6 left	WA > TC	(−30, −70, −32)	0.000311

The table shows the clusters (voxels) that had correlation differences, in the comparison between the groups and the nodes within the networks chosen a priori. TC refers to Tai Chi group and WA refers to Water Aerobics group. The networks chosen were the Salience and Frontoparietal networks. *p*-FDR refers to value with False Discovery Rate correction. Coordinates (x, y, z) are in MNI space.

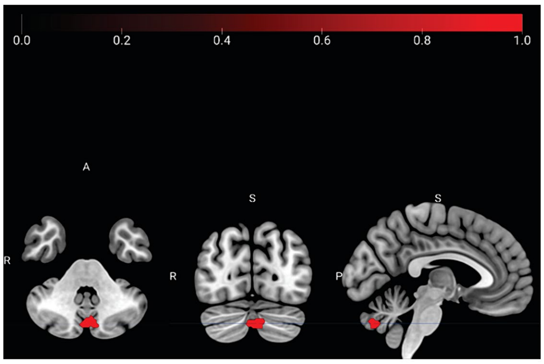

FIGURE 3
N-Back connectivity analysis comparison between groups. The Tai Chi group exhibited an increased correlation between the seed of left supramarginal gyrus and the clusters of cerebellum crus 2 left, cerebellum 7b left and cerebellum crus 2 right. Peak-cluster shown in red with coordinates in MNI space (x = −4, y = −76, z = −38).

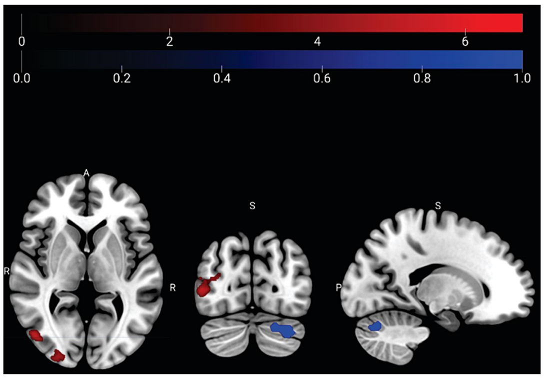

FIGURE 4
Stroop connectivity analysis comparison between groups. Using salience network, the Tai Chi group exhibited an increased correlation between the seed of the rostral left prefrontal cortex and the right occipital pole, the anterior division of the right lateral occipital cortex, and the superior division of the right lateral occipital cortex. Peak cluster shown in red at x = 16, y = −94, z = −04 in MNI space. Using frontoparietal network, Water Aerobics group exhibited increased correlation between the seed of the left posterior parietal lobe and the cerebellum crus 1 left, cerebellum crus 2 left, and cerebellum 6 left. Peak clusters shown in blue at x = −30, y = −70, z = −32.

4.2 Connectivity

4.2.1 Resting state

Supporting our initial hypothesis, our findings revealed that Tai Chi group presented increased connectivity between Anterior Cingulate Cortex (ACC), Insular Cortex (IC), and Central Opercular Cortex (insular area) during resting state, compared to Water Aerobics group. The Central Opercular Cortex, along with Frontoparietal areas, is involved in cognitive control (Marek and Dosenbach, 2018). The Anterior Cingulate Cortex and Insular Cortex are crucial components of Salience Network, consistently co-activated in response to salient stimuli, whether external or internal, irrespective of their emotional valence (Craig, 2009a). These regions play a significant role in interoceptive processes and, consequently, in physiological regulation (Chong et al., 2017). For example, the ACC is involved in both bodily arousal and interoceptive accuracy and sensitivity. Accuracy refers to the objective precision of bodily events such as heartbeats and temperature, while interoceptive sensitivity is the subjective interpretation of internal states of the body such as restlessness, confusion, and calmness (Pollatos et al., 2007). In turn, Insular Cortex, especially the Anterior Insular Cortex (AIC), is crucial for integrating internal and external signals and plays a role ranging from affective and sensory processing to higher cognitive processes (Menon et al., 2022). According to Craig (2003) the AIC performs a meta-representation of primary afferent interoception in humans, forming the basis for the subjective image of the "self," for feelings, cognitive awareness, and emotions (Marek and Dosenbach, 2018).

Connections between the ACC and IC appear to play a central role in sensorimotor, affective, and cognitive interplay and are crucial for the link between body and subjectivity, interoception, and self-regulation. Disruptions in connectivity of these areas are associated with emotional fragility and affective dysregulation implicating psychiatric disorders such as anxiety, panic and narcissistic personality disorder (Schimmelpfennig et al., 2023; Stein et al., 2007; Pannekoek et al., 2013). Additionally, as central areas in salience network, the ACC and IC act as a filter between internal and external stimuli, which is related to maintaining goal-directed behavior (Menon, 2011). Changes in connectivity between these areas can compromise the switching of activation between default mode network (DMN) and executive control network (FN), leading to alterations in cognitive function and age-related dysfunctions (Menon, 2011).

Our results indicated increased connectivity between the ACC and IC in Tai Chi group, corroborating previous studies showing that Tai Chi is associated not only with plasticity in functional brain networks during resting state but also with changes in insular connectivity (Cui et al., 2021; Xu et al., 2020; Yue et al., 2020).

Consistent with other studies, we found that combined body and cognition training, as observed in Tai Chi, is associated with increased brain connectivity between areas that are particularly relevant to interoceptive accuracy during rest (Chong et al., 2017). This training is also related to areas involved in regulation of body physiology (Duquette, 2017) self-regulation skills, cognitive control, and motor organization of subjective aspects of experience through IC and ACC (Craig, 2011; Craig, 2009b; Vago and Silbersweig, 2012).

4.2.2 N-Back

Our findings revealed a stronger correlation between the left Superior Marginal Gyrus (LSMG) and cerebellum (Crus I and II) in Tai Chi group compared to Water Aerobics group during N-Back task, using Salience Network as seed region. The LSMG is known to play a causal role in cognitive processing and is a key area in short-term memory network, crucial for retention and sequencing of abstract representation information (Guidali et al., 2019). Moreover, the LSMG is associated with temporal sequencing of movement, adaptation to environmental changes, sustaining attention, sequential memory retrieval, and embodiment (Cabeza et al., 2008; Hartwigsen et al., 2012).

Tai Chi involves slow and choreographed movements performed in specific sequences and rhythms, synchronized with breathing, and requires attentional regulation and movement awareness, and this cognitive aspect of Tai Chi is likely responsible for the increased connectivity observed in the LSMG of the Tai Chi group (Jiang et al., 2021).

Cerebellum is known to contribute to affectivity by regulating emotions, as well as the rhythm and precision of movement (Guell et al., 2018). It plays a crucial role in psychophysiological regulation, as motor effort and movement qualities are essential factors (Balasubramaniam et al., 2021). Increased connectivity between the LSMG and cerebellum suggests that conscious movement, a characteristic of Tai Chi and other contemplative practices involving movement, may be associated with this type of regulation.

Recent research on the cerebellum highlights its integration with interoceptive training and sensorimotor control. Crus I of the cerebellum is associated with mirroring, while Crus II is specialized in mentalizing, social cognition, and emotional self-perception (Van Overwalle et al., 2014; Van Overwalle et al., 2020). Additionally, cerebellum is involved in complex functions such as strategy formation, cognitive flexibility, and working memory (Schmahmann, 2019). It modulates cognition like it modulates the motor system and is implicated in interoceptive sensitivity (Smith et al., 2022).

4.2.3 Stroop

In the Stroop task group comparison, salience network seed exhibited a more robust correlation with the Left Rostral Prefrontal Cortex (R-PFC), Right Occipital Pole, Right Lateral Occipital Cortex (Anterior Division), and Superior Division of the Right Lateral Occipital Cortex in Tai Chi group in contrast to Water Aerobics group.

Previous studies suggest that the Rostral Prefrontal Cortex (R-PFC) plays a role in sustaining attention and prospective memory, and it is known to mediate attention between external stimuli and internally maintained intentions (Benoit et al., 2012; Burgess et al., 2000). Occipital pole is responsible for integration and perception of visual information and integrates the visual association cortex, which interprets visual images (Rehman, 2022). In a review, posterior occipital and temporal areas were also associated with selective attention (Cabeza and Nyberg, 2000). These functions are important for inhibitory control and stimulus recognition, which are relevant to Stroop task. Other studies have linked visual areas of the brain to interoceptive sensitivity (Smith et al., 2022; Kuehn et al., 2016). In addition, interoception has been associated with prefrontal cortex activation and attention regulation (Vago and Silbersweig, 2012).

The increased correlation between prefrontal and visual areas involved in the integration of internal and external information, inhibitory control, and stimulus recognition in Tai Chi group, during Stroop task, is likely to the fact that Tai Chi practice encompasses elements of meditation and martial art. During Tai Chi, internal attention is sustained while simultaneously maintaining external attention, along with the execution of slow movements based on attack and defense actions. Thus, Tai Chi integrates attention to both internal states and external factors, involving salient stimulus discrimination (or imminent danger) and internal impulse control directed toward effective action (attack or defense). These findings support Tai Chi as a cognitive training for selective attention, sustained attention, and inhibitory control. Additionally, Tai Chi encompasses movements for combat training, enhancing bodily awareness, potentially optimizing sensorimotor regulation of affective states (Critchley, 2005). Interoception also appears to be involved in the development of these regulatory functions (Critchley et al., 2004).

When using Frontoparietal network as seed for Stroop task, Water Aerobics group showed a stronger correlation between the Left Posterior Parietal Lobe (LPPL) and Crus I and Crus II of cerebellum compared to Tai Chi group. The LPPL is the region consistently activated in functional neuroimaging studies related to conceptual processing (Binder et al., 2009). In conceptualization tasks, such as word comprehension, the LPPL acts convergently, integrating information from various perceptual modalities (Damasio, 1989). This suggests that Water Aerobics group utilized a less specialized and more generalized perception in the attention task, unlike Tai Chi group, which exhibited correlations with interoceptive awareness areas (sensitivity, discrimination, and accuracy).

Water Aerobics group showed a stronger correlation between the LPPL and Crus I of cerebellum. The LPPL is specialized in representing motor actions and motor planning directed at objects (Kiefer and Pulvermüller, 2012). And Crus I is an area of cerebellum linked to object mirroring (Schmahmann, 2019). This object mirroring suggests an externally focused strategy, a motor representation strategy based on shape recognition related to word meaning (Kuhnke et al., 2020).

This could be attributed to Water Aerobics emphasis on imitating the instructor's movements. Our results indicate that, to perform an attention and conflict resolution task, Water Aerobics group exhibited increased connectivity between areas related to mirroring and exteroception, while Tai Chi group showed increased connectivity between areas involved in sustained attention, prospective memory, and interoceptive sensitivity.

4.3 Limitations

Although we revealed differences in brain connectivity between Tai Chi and Water Aerobics during Resting State, N-Back and Stroop tasks, some limitations must be addressed. We did not have a control group without practicing physical activities, which probably had health issues. We had a small sample size due to our strict group matching criteria which allowed us to compare participants with similar characteristics beyond their practices. This rigid pairing values the specificity of the differences found. Due to the cross-sectional design of our study, we cannot establish causal relationships between interventions and outcomes, precluding claims on which type of intervention may exert more pronounced effects on brain function.

5 Conclusion

Our study provides evidence for differences in functional connectivity patterns between older adults who have engaged in a mind–body practice (Tai Chi) or in an aerobic physical activity (Water Aerobics) when performing attentional and working memory tasks, as well as during resting state.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética em Pesquisa do Hospital Israelita Albert Einstein. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

APP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. AJP: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. RA: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. SL: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. JR: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. DS: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. EK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2024.1420339/full#supplementary-material

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Online eurythmy therapy for cancer-related fatigue: a prospective repeated-measures observational study exploring fatigue, stress, and mindfulness

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Introduction: Cancer is a debilitating disease with an often chronic course. One of the most taxing and prevalent sequelae in this context is cancer-related fatigue (CRF) resulting from the disease and/or associated treatments. Over the last years mindfulness-based interventions such as eurythmy therapy (ERYT), a mindful-movement therapy from anthroposophic medicine, have emerged as promising adjunct therapies in oncology. This prospective study investigated an online implementation of ERYT for CRF using a single arm repeated-measures design based on two consecutive studies.

Method: Study 1 consisted of an initial assessment before, during, after, and at follow up of a 6-week online ERYT-based program in a mixed sample of N=165 adults with or without cancer diagnosis. Study 2 involved a similar design with an adapted 8-week online ERYT-based program in a sample of N=125 adults who had been diagnosed with cancer. Outcomes were assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue, Perceived Stress Scale, Mindful Attention Awareness Scale, and Insomnia Severity Index (for Study 1 all, for Study 2 only the former three). We additionally performed an exploratory analysis regarding practice frequency and duration. Data were analyzed using Linear Mixed-Effect Models per outcome; ANOVA was used for practice times.

Results: For Study 1, mixed-effects model estimates showed no significant effect on fatigue, but pointed to significantly improved emotional and physical well-being, reduced stress, as well as increased mindfulness (mixed subjects). Functional and social well-being or sleep quality did not change significantly. Study 2 model estimates on the other hand showed significantly improved CRF in conjunction with the ERYT-based online intervention, as well as improved stress and mindfulness scores (cancer-diagnosed subjects).

Conclusion: Taken together, while our results should be interpreted with caution given the single-arm design and relatively high dropout, they suggest online ERYT may be associated with a reduction in fatigue for individuals diagnosed with cancer, an increase in mindfulness, and benefits for stress and certain well-being indicators. The online group format is advantageous in view of affordability and accessibility, the latter being particularly relevant for individuals who due to high symptom severity cannot leave their homes. Randomized-controlled studies will be needed to confirm these findings.

KEYWORDS

fatigue, cancer, cancer-related fatigue, mindful movement, mindfulness-based, eurythmy therapy, integrative medicine, online intervention

1 Introduction

Cancer is a complex and debilitating disease with an often chronic course, affecting millions of individuals worldwide (Tran et al., 2022; Sung et al., 2021). One of the most prevalent and taxing sequelae in this context is cancer-related fatigue (CRF), a general and persistent lack of energy not relieved by rest, which results from both the disease and associated treatments (Bower, 2014; Cleeland et al., 2013). Reported prevalence rates of CRF depend on type of treatment, population, and assessment methodology, but may range between 25 and 99% (Bower, 2014) or 14–100% (Ma et al., 2020), with the latter meta-analysis reporting a pooled prevalence of 52% based on 84 studies.

Mind–body therapies and particularly mindfulness-based movement practices such as Yoga, Tai Chi, Qi Gong, or Feldenkrais, which combine bodily movements (and often also breath) with focused attention, have emerged as promising adjunct therapies in oncology to improve common sequelae like CRF, sleep disturbances, reduced quality of life, or stress (Chen et al., 2024; Firkins et al., 2020; Mayden, 2012; Zhang et al., 2019; Wu et al., 2022; Desveaux et al., 2015; Raman et al., 2013; Gouw et al., 2019; Wang et al., 2013; Hillier and Worley, 2015; Cramer et al., 2012b; Vergeer et al., 2021; Miller et al., 2020; Stephens and Hillier, 2020; Wang and Szabo, 2020; Cocchiara et al., 2020). Eurythmy therapy (ERYT) is an integrative movement-based therapy in this context rooted in anthroposophic medicine, which involves integrated sequences of movements, performed with arms, hand, legs, or the whole body, in a state of focused concentration and intentionality (Kirchner-Bockholt, 1977; Kienle et al., 2013). Guided by a trained therapist, the technique is said to develop mindfulness to outer movement, inner sensation, and the connection between the two (Berger et al., 2015), a process engaging both proprioceptive and interoceptive awareness. Generally speaking, ERYT protocols can be practiced individually or in groups, and consist of movement sequences based on a core set of principles which are then tailored to a given disease or patient at hand (Hamre H. J. et al., 2007). Emerging scientific evidence points to benefits for a range of conditions (Lötzke et al., 2015) such as stress (Berger et al., 2015; Kanitz et al., 2011), depression (Hamre et al., 2006; Hamre et al., 2013), anxiety (Schwab et al., 2011; Hamre et al., 2009), or chronic pain (Hamre H. et al., 2007; Michalsen et al., 2021). Indeed, ERYT has also been applied in complementary cancer care, with promising first results (Kanitz et al., 2013). A challenge in this context however remains that disease- and treatment-related symptoms, including CRF, often restrict patients' ability to travel to practice sessions (Kim et al., 2020). Online delivery of ERYT could hence be a promising avenue in oncology, as it allows patients to engage in the therapeutic activity without requiring them to leave their homes. Indeed, online applications of other mindful movement practices, such as Tai Chi or Qi Gong, have been shown to present useful alternatives in similar and other relevant contexts (Oh et al., 2021; Gao et al., 2022; Sohl et al., 2024; Brosnan et al., 2021; Gravesande et al., 2023; Teo et al., 2024). Nonetheless, research assessing the online delivery of ERYT in particular to our knowledge has not yet been conducted.

The current study thus assessed an online intervention based on ERYT to improve CRF and associated symptoms. More specifically, using an exploratory approach with repeated-measures design based on two consecutive observational studies, we aimed to assess changes in CRF (main outcome), sleep quality, stress, quality of life indicators, and mindfulness (secondary outcomes) during and after an online ERYT-based intervention for adults diagnosed with cancer. The study was conducted by the University of Bern (Institute of Complementary and Integrative Medicine) in collaboration with a healthcare provider specializing in ERYT.[1]

2 Study 1: exploratory assessment (mixed subjects)

2.1 Study 1 methods

2.1.1 Study design and setting

The first study (11/2022–2/2023) involved an observational assessment with repeated-measures design on a mixed subjects sample, focusing on fatigue, sleep quality, mindfulness, quality of life indicators, and perceived stress as outcomes. The study included five measurement points, namely t1 at baseline, t2–t3 during the intervention, t4 just after completion of the intervention, and t5 at follow up. All surveys were conducted online and in full anonymity of participants. Anonymous self-generated codes were used to link an individuals' repeated measures between assessment times. Given the design was observational and no potentially identifying data were collected (no names, email or IP addresses, birthdates, etc.), ethics approval was not required for this study according to the responsible Ethics Committee guidelines and the Federal Act on Research involving Human Beings (Human Research Act, 2011).

2.1.2 Participants and procedure

Information about the intervention as well as the study were announced on the health provider's website, newsletters, in psychology networks, adverts in clinics also practicing anthroposophic medicine, physicians' practices, and social media. All individuals who registered for the two cycles of the intervention (one held in German and one in English) between November and December 2022 were invited to participate in the study. They were thoroughly informed about the study, specifying that participation was voluntary and that opting not to take part in the study would not impact their enrollment and participation in the intervention itself. In view of the exploratory aim of Study 1, we included all individuals who registered for the program

1 *Eurythmy4you.*

and agreed to participate in the study. This meant that also individuals who did not have a cancer diagnosis but enrolled in the program for other reasons (e.g., relatives of cancer patients) and agreed to participate were included. Except for the intervention itself (free of charge), no compensation was offered to participants. All participants were asked to fill in the baseline survey at the outset of the intervention (t1), 2 weeks later (t2), 4 weeks later (t3), 6 weeks later (t4, which marked the completion of the intervention), as well as at follow-up (t5) after 14 weeks (i.e., 8 weeks after completion).

2.1.3 Measures

The online survey was made of a set of validated psychological questionnaires programmed by means of SoSci Survey (Leiner, 2023) for anonymous computer-assisted implementation, and was available in German and English. For the validated scales the recall period was set to the last 7 days. The survey further included single items to indicate age, gender, cancer status, motive for enrolment, and practice times. For self-reported practice times we used the following quantitative items (t2–t5 assessment: *how many days in the last 2 weeks*/at follow-up: *per week on average*; *were you able to do the exercises?* answer options: *0–2 days*, *3–5 days*, *6–8 days*, *9–11 days*, *12–14 days*; and, respectively, *0–1 days*, *2–3 days*, *4–5 days*, and *6–7 days*). They were also asked how much time they have spent on the exercises per practice day (*1–10 min*, *11–20 min*, *21–30 min*, *more than 30 min*, or *not done*). *Functional Assessment of Chronic Illness Therapy - Fatigue:* To assess CRF and associated quality of life/well-being indicators we used the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; Cella, 1997, validated German version: Montan et al., 2018; facit.org, 2022). The 40 items of this instrument were rated on a five-point Likert scale ranging from 0 (*not at all*) to 4 (*very much*). The overall FACIT-F score was calculated by summing the item scores (range 0–160), with higher scores indicating less fatigue/higher quality of life. The instrument includes five subscales, namely Fatigue (FA; 13 items), Physical Well-Being (PWB; 7 items), Social/Family Well-Being (SWB; 7 items), Emotional Well-Being (EWB; 6 items), and Functional Well-Being (FWB; 7 items). Most pertinently here, the FA subscale can range from 0 to 52, with lower scores implying more fatigue (clinical cut-off at 36; Alexander et al., 2009). *Mindful Attention Awareness Scale:* The Mindful Attention Awareness Scale (MAAS; Brown and Ryan, 2003; Carlson and Brown, 2005, validated German version: Michalak et al., 2008) is a widely used brief mindfulness questionnaire that showed good psychometric properties in cancer patient samples (Tseng, 2024). It is made of 15 items, each presenting a statement related to mindful awareness rated on a scale from 1 (*almost always*) to 6 (*almost never*). The MAAS score is the mean of all items and ranges from 1 to 6, with higher scores indicating higher mindfulness. *Perceived Stress Scale:* The Perceived Stress Scale (PSS-10; Cohen et al., 1983, validated German version: Klein et al., 2016; Copyright © 2022 Mapi Research Trust) is a well-established validated questionnaire for assessing perceived stress, which has also been extensively used in the context of cancer patients (Yılmaz Koğar and Koğar, 2024; Tseng, 2024; Chui, 2021; Chrobak et al., 2023; Trojnar et al., 2024; Soria-Reyes et al., 2023). Each of the 10 items is rated on a five-point Likert scale from 0 (*never*) to 4 (*very often*), with higher scores indicating greater perceived stress (total score calculated by summing the items, range: 0–40). PSS-10 total scores can be interpreted as low (0–13), moderate (14–26), or high (27–40) stress (Adamson et al., 2020). *Insomnia Severity Index*. The Insomnia Severity Index (ISI; Morin et al., 2011; Morin, 1993, German version: Dieck et al., 2018; Copyright © 2022 Mapi Research Trust) is a 7 item instrument assessing the perceived severity of insomnia. It has been frequently used in research on cancer populations with good validity and reliability (Yusufov et al., 2019; Lin et al., 2020; Michaud et al., 2021; Savard et al., 2005). Each item is rated on a five-point Likert scale from 0 to 4. The total score (calculated by summing the items) ranges from 0 to 28, with higher scores indicating greater severity (i.e., worse sleep quality).

2.1.4 Intervention

The mindful movement-based intervention consisted of weekly online group sessions (90 min) and guided self-practice between sessions over six consecutive weeks. In the online sessions participants were familiarized with a specific sequence of ERYT exercises tailored to address cancer-related symptoms and CRF (for further information on ERYT in the context of cancer and CRF, see Kröz et al., 2013; Meier-Girard et al., 2020; Kröz et al., 2017), conveyed step by step over the course of the program. In a given session, the facilitator (an experienced and certified eurythmy therapist; TH) demonstrated each of the exercises at full length live on camera, while also verbally describing the specifics of the movements and pointing out relevant meaning content. After some initial rounds of demonstration, participants were encouraged to actively join the facilitator, gradually imitating the movements until they were able to perform the exercise independently. This practice time (30–40 min) was followed by a short resting period (5 min), during which the facilitator guided participants through a body scan, aimed to enable them to sense directly in their body the impact of the exercise. Participants then had the opportunity to ask questions. The facilitator finally provided instructions on how to perform the exercise on their own in their forthcoming self-practice during the time lapse between sessions, including what to pay specific attention to, context of practice, and duration, with a recommendation of 10–15 min of daily self-practice. In the subsequent session, the facilitator encouraged participants to discuss their experiences and ask questions if needed. Furthermore, participants had access to video recordings of the live sessions and of demonstrations of specific ERYT exercises, as well as to an online group forum for exchange.

2.1.5 Data analysis

All statistical analyses were performed using *R* version 4.4.0 (R Core Team, 2024). For all inferential statistics the significance level was set to $\alpha < 0.05$. Surveys that had been filled in outside the defined time windows (for t1 more than 1 week after intervention onset, for t2–t4 less than one or more than 3 weeks apart, and for t5 outside the required period of 4–10 weeks post intervention end) where excluded from the analysis. To analyze time-dependent changes in the outcome variables and test for significance we performed Linear Mixed-Effects Models (LMM) (Brown, 2021) using the *R* packages *lme4* (Bates et al., 2015) and *nlme* (Pinheiro et al., 2023). We opted for LMM among other reasons due to its capacity to calculate accurate models in spite of missing data, a common challenge in longitudinal studies (Gabrio et al., 2022). Models were calculated for each outcome separately, with all models adjusted for age, gender, and survey language. Finally, to test the effect of self-practice time on the outcomes we performed explorative one-way Analysis of Variance (ANOVA) with Tukey post-hoc tests for practice frequencies and duration for each measurement point, starting with t2.

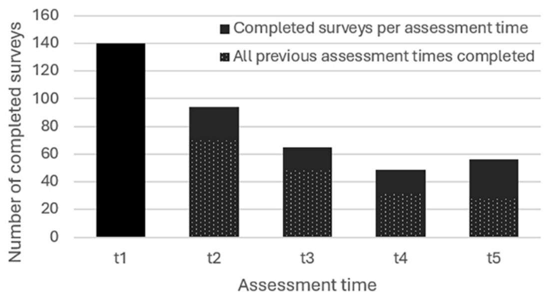

FIGURE 1
Number of completed surveys per assessment time (Study 1).

TABLE 1 Age and gender of subjects (Study 1).

	n
Age groups (in years):	
21–40	11
41–50	32
51–60	39
61–70	56
71–97	25
n.a.	2
Mean sample age (*SD*)	59.0 (12.24)
Gender	
Female	127
Male	17
Diverse	0
n.a.	21

n.a., response not available.

2.2 Study 1 results

2.2.1 Subjects

Of the 283 individuals who registered for the program in Study 1 (187 for the English and 96 for the German iteration), $N = 165$ agreed to participate in the study and filled in at least one questionnaire (57.6% filled in at least two questionnaires and 17% filled in all five questionnaires, see Figure 1). About two thirds of participants ($n = 99$) filled in the English version of the survey, the rest used the German version ($n = 66$). Sociodemographic characteristics of Study 1 participants are given in Table 1. The mean age was 59 years ($SD = 12.2$), a large majority being female. Nearly a third ($n = 52$) reported to have received a cancer diagnosis during their lifetime, of which 26 participants indicated to be currently in treatment. Means and standard deviations of Study 1 outcome variables at each of the five assessment times can be found in Table 2. The subjects' baseline FACIT-F FA score was above 36 and can thus be considered non-clinical (Alexander et al., 2009). Baseline PSS-10 scores pointed to moderate stress levels (Adamson et al., 2020), and baseline MAAS scores can be considered within the normative range based on a large-scale norming study (Brown and Kasser, 2005; Carlson and Brown, 2005). Finally, the subjects' baseline ISI scores suggest mild to moderate severity of insomnia as per clinical benchmarks (Morin et al., 2011).

2.2.2 Time-dependent changes in outcome variables

Figure 2 shows significant changes in the outcomes over time found in Study 1. *CRF and quality of life indicators.* There was a significant improvement in the FACIT-F physical well-being ($F(4, 197) = 2.764$, $p = 0.029$) and emotional well-being ($F(4, 158) = 5.181$, $p < 0.001$) scales (Figures 2A,B, respectively). The FACIT-F fatigue subscale score also improved, but not significantly ($F(4, 198) = 1.948$, $p = 0.104$). The same was the case for social ($F(4, 180) = 1.831$, $p = 0.125$) and functional ($F(4, 199) = 1.227$, $p = 0.301$) well-being and the overall FACIT-F score ($F(4, 144) = 2.362$, $p = 0.056$). For EWB all estimates were significant relative to t1 at $p < 0.001$, except for t2 ($p < 0.01$) and t3 ($p < 0.05$). For PWB only t2 ($p < 0.05$) and t3 ($p < 0.01$) estimates were significant relative to t1. *Perceived stress.* Figure 2C shows changes in the PSS-10 scores, pointing to a significant reduction in stress over the course of the intervention ($F(4, 198) = 4.110$, $p = 0.003$). Except for t2 (n.s), all estimates were significant relative to t1 at $p < 0.01$. *Mindfulness.* Time-dependent changes in mindfulness are visible in Figure 2D, with MAAS scores increasing significantly over the course of the intervention ($F(4, 200) = 12.467$, $p < 0.001$). The estimates were significant relative to t1 at $p < 0.001$, except for t3 ($p < 0.01$) and t2 (n.s.). *Sleep.* Sleep quality as per ISI did not significantly change in conjunction with the intervention ($F(4, 201) = 1.724$ $p = 0.146$).

2.2.3 Effects of self-practice frequency and duration

In Study 1, the frequency of practice (number of days practiced during the past 2 weeks/during 1 week on average in case of t5) had a significant effect on stress levels as per ANOVA at t4 ($F(4, 41)$, $p = 0.031$), with post-hoc tests showing significantly lower stress if 12–14 rather than 6–8 days had been practiced ($p = 0.021$). The duration of self-practice (minutes per day) in the preceding weeks also had a significant effect on stress at t4 ($F(4, 41) = 3.038$, $p = 0.028$), but only a trend of higher stress if over 30 min per day were practiced compared to 11–20 min ($p = 0.073$). As with stress, practice frequency of preceding weeks also had a significant effect on SWB at t4 ($F(4, 40) = 2.738$, $p = 0.042$). Post-hoc tests showed significantly higher SWB if 9–11 rather than 6–8 days had been practiced ($p = 0.041$). Furthermore, the duration of self-practice had a significant effect on SWB at t2 ($F(4, 65) = 3.316$, $p = 0.016$), with significantly higher SWB if they had practiced 1–10 min per day ($p = 0.009$) or 11–20 min per day ($p = 0.035$) during preceding weeks rather than no practice at all. Similarly, practice duration had a significant effect on FWB at t4 ($F(4, 42)$, $p = 0.021$), with significantly lower FWB if they had practiced more than 30 min compared to 11–20 min during preceding weeks ($p = 0.022$). Finally, self-practice duration had a significant effect on sleep quality at t2 ($F(4, 71)$, $p = 0.034$), with significantly better sleep quality if they had practiced 11–20 min compared to no practice at all ($p = 0.033$), and a significant effect at t4 ($F(4, 43)$, $p = 0.010$) in which sleep quality was worse if they had practiced more than 30 min compared to 11–20 min during preceding weeks ($p = 0.009$).

2.3 Study 1 discussion

Study 1 assessed outcomes of a 6-week online intervention employing ERYT for CRF. While we found significant improvements in emotional and physical well-being, perceived stress, as well as

TABLE 2 Means and standard deviations of all outcome variables per measurement point (Study 1).

	t1		t2		t3		t4		t5	
	n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
FACIT-F total	128	116.41 (24.92)	62	117.8 (22.93)	47	117.11 (23.42)	35	117.57 (25.47)	41	119.1 (25.12)
–PWB	133	22.76 (5.32)	84	23.86 (4.13)	61	23.86 (4.52)	48	23.14 (5.25)	52	23.35 (4.39)
–SWB	128	18.50 (6.18)	74	17.36 (6.58)	60	19.03 (6.15)	45	18.44 (7.02)	49	19.10 (5.63)
–EWB	132	17.46 (5.05)	65	18.61 (3.94)	49	18.64 (3.58)	37	18.64 (4.20)	47	19.11 (3.84)
–FWB	132	19.59 (6.18)	80	20.04 (4.98)	62	19.92 (5.23)	47	20.23 (4.84)	54	20.35 (5.35)
–Fatigue	132	37.95 (10.20)	80	39.72 (8.89)	62	39.11 (9.58)	47	40.27 (9.41)	53	38.93 (9.72)
PSS-10	130	15.42 (6.87)	80	13.81 (5.82)	63	13.65 (6.74)	46	13.00 (6.08)	52	13.37 (6.11)
MAAS	128	4.22 (0.86)	79	4.40 (0.81)	63	4.53 (0.79)	48	4.81 (0.78)	54	4.67 (0.71)
ISI	128	8.36 (5.85)	81	7.45 (5.74)	62	8.27 (5.62)	48	7.27 (5.72)	54	8.13 (6.47)

FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue (facit.org, 2022), total score range: 0–160; PWB, Physical Well-Being (range 0–28); SWB, Social Well-Being (range 0–28); EWB, Emotional Well-Being (range 0–24); FWB, Functional Well-Being (range 0–28), Fatigue (range 0–52); PSS-10, Perceived Stress Scale (Cohen et al., 1983), range 0–40; MAAS, Mindful Attention Awareness Scale (Brown and Ryan, 2003; Carlson and Brown, 2005), range 1–6; ISI, Insomnia Severity Index (Morin, 1993; Morin et al., 2011), range 0–28. t1 = baseline, t2/t3 = during, t4 = at completion, t5 = follow-up.

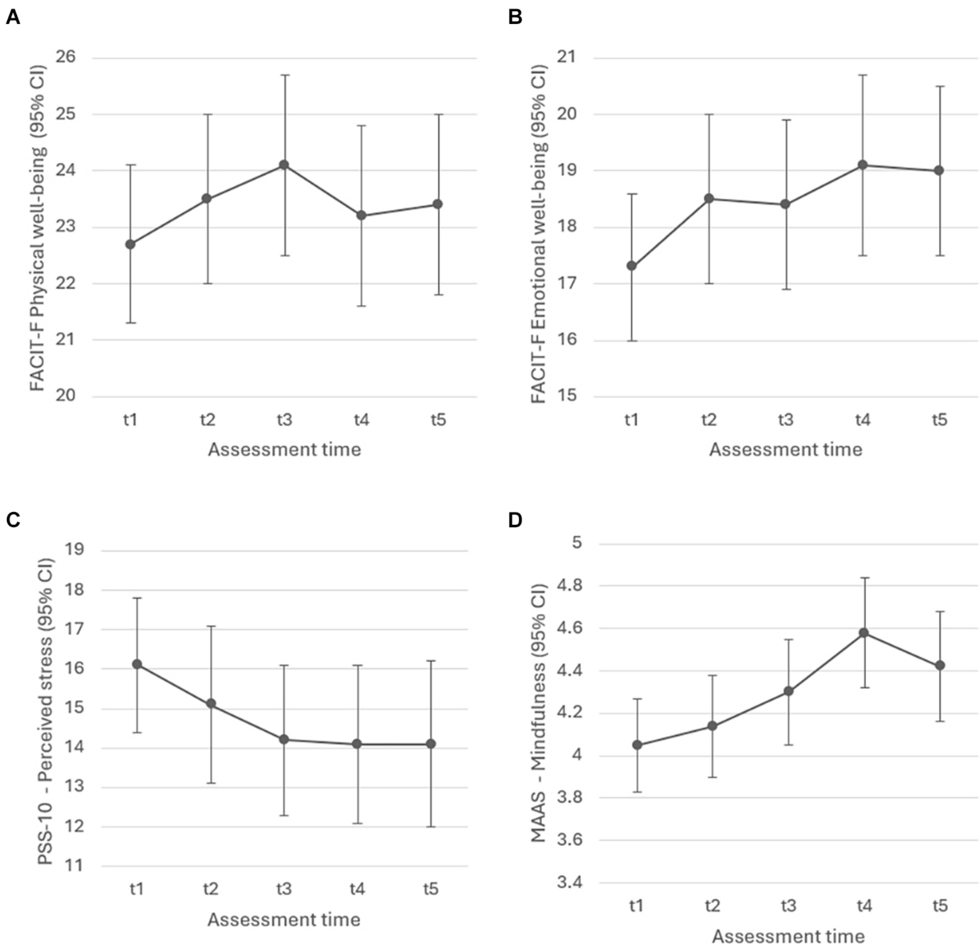

FIGURE 2
Study 1: Liner Mixed-Effect Model estimates with **(A)** physical well-being ($p = 0.029$), **(B)** emotional well-being ($p < 0.001$), **(C)** perceived stress ($p = 0.003$), and **(D)** mindfulness ($p < 0.001$) as outcomes.

mindfulness, there were no significant changes in fatigue, sleep quality, or social and functional well-being. The lack of significant changes in fatigue could be related to the subjects' non-clinical degree of baseline fatigue. The sample's baseline scores pointed to slightly more fatigue compared to normative values from healthy adults (Webster et al., 2003) but slightly less fatigue (although only by one point) than cancer-specific reference scores from a large-scale population survey (Butt et al., 2010). Indeed, the rather small proportion of cancer patients/survivors in the sample does not allow conclusions regarding CRF *per se*, a limitation of Study 1 which we subsequently addressed in Study 2. A further limitation of the study was the relatively high dropout between assessment times, which is common in online survey-based research, but could potentially give rise to bias and hence advises caution for the interpretation of the data. As with fatigue, baseline PSS-10 scores were somewhat above general population norms (Cohen, 1988) but below reference scores based on a breast cancer sample (Soria-Reyes et al., 2023). ISI scores were in contrast largely in line with cancer-specific normative values (Savard et al., 2005). Finally, the frequency and duration of self-practice of ERYT exercises beyond the practice during the guided online sessions appeared to play a role in shaping the magnitude of beneficial effects. While in several cases more frequent or longer self-practice times seemed to exert a favorable impact on the outcomes, this did not hold for all intervals, assessment times, or outcomes. Moreover, practice durations larger than 30 min in some cases even had a detrimental impact on sleep quality and functional well-being in the assessment thereafter, bearing in mind however that the exploratory design and modest number of cancer-diagnosed participants do not allow definitive conclusions with reference to causality and in general. Further research will be needed to establish optimal practice frequencies and durations per intervention phase. Taken together, the results suggest the online ERYT-based CRF intervention to merit further investigation; the findings from the first study were taken into account in the design of Study 2.

3 Study 2: assessment of CRF intervention (cancer-diagnosed subjects)

3.1 Study 2 methods

3.1.1 Study design and setting

Study 2 (9/2023–2/2024) employed a similar design as the first study but focused on a sample diagnosed with cancer, with the assessment schedule and intervention adapted to the clinical requirements of the subjects at hand: In order to reduce participant burden we shortened the survey by limiting the FACIT-F to the fatigue subscale and dropping the ISI. Furthermore, by omitting one of the two assessment times during the intervention we reduced the number of surveys to be completed from 5 to 4. As in Study 1, all survey data was collected online and in full anonymity of participants (including anonymous self-generated codes to link the repeated measures) without collecting any potentially identifying information; the study hence did not require ethics approval. The main outcome of Study 2 was CRF, with stress and mindfulness as secondary outcomes.

3.1.2 Participants and procedure

The study was announced in the same fashion as in Study 1. All individuals who registered to one of two cycles of the intervention (one held in German, one in English, and the latter also being simultaneously translated to Chinese and Indonesian with the support of two professional interpreters) between September and November 2023 were invited to participate in the study. As in Study 1, no compensation was offered to participants except for the free of charge intervention. They were thoroughly informed about the study, specifying that participation was voluntary and that opting out would not impact their participation in the intervention itself. Only those who indicated that they had been diagnosed with cancer within the last 5 years were included in the study. The choice of a 5-year period was based on evidence that CRF may persist for up to 5 years after treatment, or longer (Bower, 2014). All participants were asked to fill in the baseline survey at the outset of the intervention (t1), 4 weeks later (t2), 8 weeks later (t3–completion of the intervention), and 16 weeks later (i.e., 8 weeks after the end of the intervention) as a follow-up assessment (t4).

3.1.3 Measures

We used the same measures as in Study 1 to assess CRF, stress, and mindfulness, using the original recall periods for all instruments. In addition to the English and German language versions, a Chinese version of the survey was prepared using validated translations of the FACIT-F fatigue subscale (facit.org, 2022; Cai et al., 2023), the PSS-10 (Jiang et al., 2023), and the MAAS (Chen et al., 2012). Finally, we again asked about frequency and duration of self-practice (e.g., *On average, how many days per week were you able to do the exercises*?).

3.1.4 Intervention

Like in Study 1, the intervention consisted of weekly online group sessions, but the overall duration was extended to 8 weeks. Furthermore, the specific ERYT exercises shown to the participants were adapted to target fatigue more specifically and match an 8-weeks program, and additional behavioral exercises designed to foster mindfulness and self-awareness based on anthroposophic medicine (Haas, 2017) were incorporated into the intervention. As in Study 1, participants were encouraged to practice the learned exercises by themselves during the subsequent week, with a recommendation to practice at least 15 min daily, and were invited to use the video-recorded demonstrations of the exercises and a group forum.

3.1.5 Data analysis

Except for the outcome variables that were dropped, the data analysis protocol was identical to the one described in Study 1. The defined time windows for filling in Study 2 surveys were adapted to match the number of measurement points; namely, surveys were excluded from the analysis if t1 survey was filled in more than 1 week after intervention start, t1–t3 surveys less than 3 or more than 6 weeks apart from each other, or t4 survey outside the required 4–10 weeks after t3 survey.

3.2 Study 2 results

3.2.1 Subjects

Of the 303 individuals who registered for the intervention in Study 2 (242 for the English, 61 for the German iteration), $N = 125$ agreed to participate in the study and filled in at least one survey. Of these subjects, 48% filled in at least two surveys and 24.8% filled in all four surveys (see Figure 3). About half of them used the English version of the survey ($n = 64$), slightly more than a third used the German ($n = 46$), and the remainder the Chinese version ($n = 15$). Table 3 shows sociodemographic characteristics of Study 2

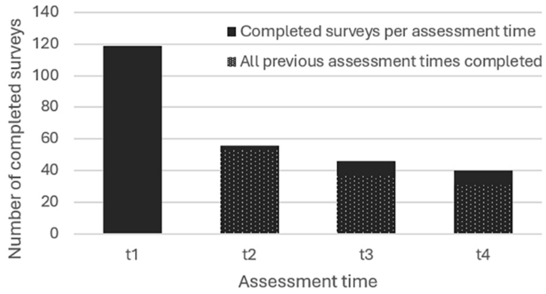

FIGURE 3
Number of completed surveys per assessment time (Study 2).

TABLE 3 Age and gender of the sample (Study 2).

	n
Age groups (in years)	
23–40	9
41–50	34
51–60	36
61–70	28
71–82	18
Mean sample age (*SD*)	56.57 (11.87)
Gender:	
Female	105
Male	16
Diverse	0
n.a.	4

n.a., response not available.

participants. As in the former study, a large majority of participants were female, and the mean age was 56.57 years ($SD = 11.87$). Means and standard deviations of Study 2 outcome variables at all assessment times are found in Table 4. The subjects' baseline FACIT-F fatigue subscale scores were below the cut-off of 36 (Alexander et al., 2009) which suggests a clinically significant degree of fatigue; they were also below reference values from a large cancer patients sample (Butt et al., 2010) and norms for healthy adults (Webster et al., 2003). Baseline PSS-10 scores were indicative of moderate stress levels (Adamson et al., 2020) comparable to reference scores of a large-scale cancer patients sample (Soria-Reyes et al., 2023) and above general population norms (Cohen, 1988). Finally, baseline MAAS scores of participants were somewhat below general population normative values (Brown and Kasser, 2005), as well as a large-scale sample of cancer patients (Carlson and Brown, 2005).

3.2.2 Time-dependent changes in outcome variables

Cancer-related fatigue. Fatigue as assessed by the FACIT-F fatigue subscale showed a significant decrease over the course of the intervention ($F(3, 119) = 23.618$, $p < 0.001$) in Study 2, as can be seen in Figure 4A. *Perceived stress.* Similarly, scores on the PSS-10 showed a significant reduction in stress over time ($F(3, 129) = 22.414$, $p < 0.001$), as depicted in Figure 4B. *Mindfulness.* Finally, Figure 4C shows MAAS scores per assessment time, pointing to a significant increase in mindfulness over the course of the intervention ($F(3, 128) = 24.323$, $p < 0.001$). For all three Study 2 outcomes, estimates (t2, t3, t4) were significant relative to t1 at $p < 0.001$.

3.2.3 Effects of self-practice frequency and duration

As per ANOVA, the mean number of days per week of self-practice over the past 4 weeks/8 weeks in case of t4 (frequency) had a significant effect on stress in Study 2 at t3 ($F(3, 42) = 4.248$, $p = 0.010$), with 4–5 days of practice in the preceding weeks associated with less stress compared to 0–1 days ($p = 0.006$). Conversely, at t4 ($F(3, 36) = 2.925$, $p = 0.047$) 4–5 days of self-practice during the preceding weeks was associated with higher stress compared to 2–3 days of self-practice ($p = 0.037$). Self-practice frequency had a significant effect on mindfulness at t3 ($F(3, 41) = 3.951$, $p = 0.015$), with 4–5 days of self-practice associated with higher mindfulness scores than precedent self-practice of only 2–3 days ($p = 0.045$). Finally, the mean duration of self-practice per day in the preceding weeks had a significant effect on fatigue at t2 ($F(4, 45)$, $p = 0.037$), with significantly more fatigue in conjunction with a practice of longer than 30 min compared to no practice at all ($p = 0.024$).

3.3 Study 2 discussion

Using a repeated-measures design with four assessment times (follow-up at 8 weeks post intervention) in subjects diagnosed with cancer (past 5 years), Study 2 found significantly improved CRF, stress, and mindfulness scores in conjunction with the adapted ERYT-based online intervention. The exploratory analysis of practice frequency and duration yielded inconclusive results. As with the former study, the interpretability of our findings is challenged by relatively high dropout rates, a common problem of online survey-based research. A detailed discussion of findings follows in the subsequent section.

4 General discussion

Persistent fatigue is one of the most common and taxing sequelae of cancer (Bower, 2014) and presents a challenge in a series of other chronic illnesses (Whitehead, 2009). Using an exploratory single-arm repeated measures design based on two consecutive studies, the current work assessed an online application of ERYT to address CRF and associated symptoms. Study 1 consisted of a preliminary assessment in a mixed subjects sample of $N = 165$ adults with or without cancer diagnosis. Mixed-effects model estimates of the repeated measures before, during, after, and at follow up of the 6-week ERYT online program pointed to significantly improved emotional and physical well-being, reduced stress, and increased mindfulness, but had no effect on fatigue, functional and social well-being, or sleep quality. However, given the low proportion of cancer patients and survivors in this first sample, conclusions regarding CRF could not be drawn based on Study 1. Study 2 therefore involved a similar design with a sample of $N = 125$ adults who had been diagnosed with cancer within the past 5 years. Model estimates showed significant improvements of CRF, stress, and mindfulness scores in conjunction with the adapted 8-week long ERYT-based online intervention.

To our knowledge this is the first study examining an online application of ERYT. Taken together, our results suggest that online ERYT may reduce CRF in individuals diagnosed with cancer, may

TABLE 4 Means and standard deviations for all outcome variables (Study 2).

	t1		t2		t3		t4	
	n	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*	*n*	*M (SD)*
FACIT-F Fatigue	118	27.49 (11.11)	52	33.60 (9.61)	44	33.91 (10.27)	32	35.28 (10.09)
PSS-10	118	20.47 (6.63)	52	16.54 (6.08)	46	16.22 (6.20)	40	15.85 (6.67)
MAAS	117	3.84 (0.90)	51	4.19 (0.80)	45	4.27 (0.81)	40	4.47 (0.89)

FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue subscale (facit.org, 2022); PSS-10, Perceived Stress Scale (Cohen et al., 1983), range 0–40; MAAS, Mindful Attention Awareness Scale (Brown and Ryan, 2003; Carlson and Brown, 2005), range 1–6; t1 = baseline, t2 = mid-term, t3 = at completion, t4 = follow-up.

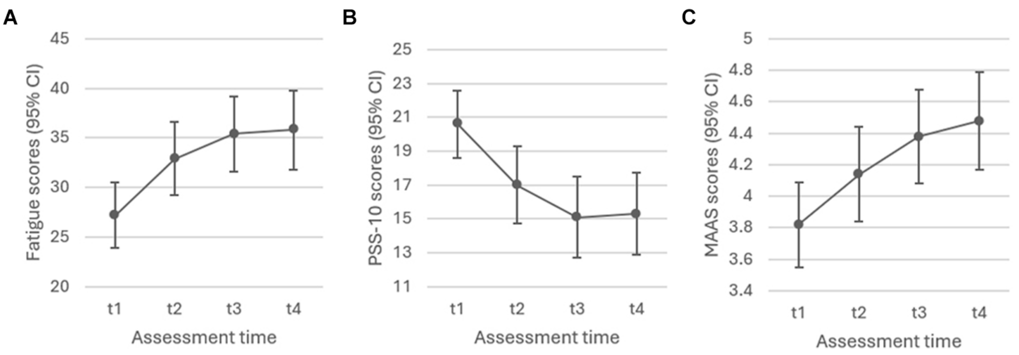

FIGURE 4
Study 2: Liner Mixed-Effect Model estimates with **(A)** fatigue ($p < 0.001$), **(B)** perceived stress ($p < 0.001$), and **(C)** mindfulness ($p < 0.001$) as outcomes.

involve an increase in mindfulness, and could be associated with benefits for stress and well-being. However, controlled clinical trials will be needed to confirm and further elaborate these findings. Clinical research on ERYT in general is still scarce, but our results are in line with the few existent face-to-face ERYT studies that found reduced CRF in breast cancer patients and survivors (Oei et al., 2021; Kröz et al., 2023). Another study found reduced fatigue scores in moderately stressed adults after receiving ERYT (Kanitz et al., 2012), and a systematic review on the effectiveness of ERYT in various clinical populations (e.g., cancer, hypertension, chronic low back pain, anxiety, and other indications) concluded the implementation of ERYT as an adjunct therapy to be associated with improvements in health (Lötzke et al., 2015). Furthermore, our results are in line with findings on other mindful-movement based practices: Meta-analyses and reviews on Yoga, Tai Chi, and Qigong for instance concluded that these practices were able to relieve CRF in cancer patients/survivors (Dong et al., 2019; Sadja and Mills, 2013; Cramer et al., 2012a; Armer and Lutgendorf, 2019; Liu et al., 2020; Song et al., 2018; Yin et al., 2020; Zeng et al., 2019), but described magnitude of effects varied from study to study. Furthermore, our results converge with meta-analytic findings reporting significantly reduced CRF in RCTs of Mindfulness-Based Stress Reduction (MBSR, Kabat-Zinn, 2003) and similar interventions in oncology populations (Johns et al., 2021; Chayadi et al., 2022; Xie et al., 2020; Zhang et al., 2019; McCloy et al., 2022), although one meta-analysis found improved stress and sleep but no significant effects on fatigue or quality of life in conjunction with MBSR (Wu et al., 2022). In several of the former meta-analyses results regarding sleep quality were less consistent (Zhang et al., 2019; McCloy et al., 2022), which was perhaps mirrored in our Study 1, although, as mentioned before, the sample did not allow conclusions regarding oncology populations. Finally, we found a series of significant but inconclusive effects of differential practice times (frequencies and durations) of ERYT on CRF, stress, and mindfulness (Study 2), as well as sleep and well-being indicators (Study 1), but only for selected assessment times, and the optimal amount of self-practice appeared to differ in relation to the various assessment times and outcome variables. While further research with systematic comparisons of self-practice times will be needed to elucidate these findings, the current exploratory assessment suggests a tendency of more/longer self-practice associated with benefits, although in a few instances the opposite was the case. Given the latter occurred particularly in the context of extended self-practice times, it is not inconceivable that lengthening practice beyond a certain optimum could turn benefit into detriment. Several reviews of mindfulness-based interventions report positive associations between home practice and intervention outcomes in both general and cancer-affected populations (Parsons et al., 2017; Baydoun et al., 2021; Kang et al., 2021), but research in this context is scarce, and a consensus on optimal practice times in view of treatment effectiveness and adherence remains to be established.

Although single-arm evaluations are an important step in exploratory research, the lack of a control condition and randomization was a limitation of the current work and will be necessary to confirm beneficial effects of online ERYT. Furthermore, due to the voluntary nature of participation and hence self-selection of participants we cannot rule out sampling bias, which limits the generalizability of our findings. Finally, response and survey completion rates per assessment time

(Figures 1, 3) were relatively low, which is however not unusual for online studies based on voluntary and non-compensated participation (Rostaminezhad et al., 2013; Bawa, 2016; Fish et al., 2016; Meyerowitz-Katz et al., 2020), but nonetheless speaks for cautious interpretation of results. Indeed, the possibility of dropout effects represents a notorious challenge for clinical research relying on longitudinal assessments; such effects may compromise interpretability of findings in particular, in cases in which the dropout-related missingness is non-random (Bell et al., 2013), which is generally difficult to rule out, but for which mixed-effect models are considered a method of choice, given their capacity to minimize dropout bias in longitudinal research with both random or non-random missingness (Mallinckrodt et al., 2001; Bell et al., 2013). Although our findings provide promising first indications, future studies should hence attempt to reduce dropout (Meyerowitz-Katz et al., 2020), include controlled designs, as well as systematic comparisons of varying practice times and subgroups (e.g., individuals currently in treatment vs. cancer survivors). In addition, assessing the duration of disease and/or remission period as well as therapeutic protocols per participant would be favourable for an enhanced contextualization of CRF levels and other outcomes at the various assessment times. Strengths of the current work include the novelty of the approach and its potential to expand the still limited toolkit for addressing CRF in oncology populations, as well as the limited research on ERYT in general. Furthermore, the group format and online delivery imply affordability and scalability, which along with the adaptability of ERYT exercises, renders the intervention more broadly accessible, also in locations in which ERYT therapists are not readily available, and, pertinently, for individuals who are unable to leave their home due to debilitating cancer treatment side-effects (e.g., dizziness, nausea, swollen joints; Kim et al., 2020) and not least CRF itself (Bower, 2014). A recent meta-analysis of online interventions involving mindfulness-based practices for cancer patients concluded online delivery to be both feasible and acceptable to manage cancer-related symptoms (Fan et al., 2023), with similar conclusions reiterated in studies examining online delivery of specific mindfulness-based movement practices, such as Tai Chi and Qigong (Oh et al., 2021; Gao et al., 2022; Sohl et al., 2024). Online ERYT may be an additional such option, with promising first results that should be further investigated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans given full anonymity of participants at all stages of the research (fully encrypted survey via anonymous self-generated codes, no collection of IP or E-Mail addresses, no collection of identifying participant data). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because participants were thoroughly informed in written form about the study and the voluntary nature of participation; they provided implied informed consent by completing the online survey (opt-in).

Author contributions

ET: Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. YK: Data curation, Writing – review & editing. TH: Conceptualization, Funding acquisition, Writing – review & editing. IB: Writing – original draft, Writing – review & editing. UW: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

TH works as a therapist at the health provider *Eurythmy4you* but was not involved in the collection, handling, or analysis of data in this study, which was done independently by the scientific authors.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Psychosomatic health status and corresponding comorbid network analysis of college students in traditional Chinese medicine schools

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Introduction: Depression, anxiety, and somatic symptoms are highly comorbid and represent the most prevalent psychosomatic health issues. Few studies have investigated the network structure of psychosomatic symptoms among traditional Chinese medicine (TCM) students. This study aims to investigate the psychosomatic health status of college students in TCM universities, while simultaneously constructing a network structure of common somatic symptoms and psychological symptoms.

Methods: Online investigation was conducted among 665 students from a university of Chinese medicine. Health Status Questionnaire, Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-2 (PHQ-2) were used to assess the mental symptoms and physical status of participants. With the R software processing, a network model of psychosomatic symptoms was constructed. Specifically, we computed the predictability (PRE), expected influence (EI), and bridging expected influence (BEI) of each symptom. Meanwhile, the stability and accuracy of the network were evaluated using the case-deletion bootstrap method.

Results: Among the participants, 277 (41.65%) subjects exhibited depressive symptoms, and 244 (36.69%) subjects showed symptoms of anxiety. Common somatic symptoms included fatigue, forgetfulness, sighing, thirst, and sweating. Within the psychosomatic symptoms network, " worrying too much about things ", "uncontrollable worries" and "weakness" exhibited the high EI and PRE, suggesting they are central symptoms. " Little interest or pleasure in doing things," " feeling down, depressed, or hopeless," " dyssomnia," and "sighing" with high BEI values demonstrated that they are bridging symptoms in the comorbid network.

Conclusion: The psychosomatic health status of college students in traditional Chinese medicine schools is concerning, showing high tendencies for depression, anxiety, and somatic symptoms. There exists a complex relationship between somatic symptoms and psychological symptoms among students. " Worrying too much about things ", "uncontrollable worries" and "weakness" enable to serve as comorbid intervention targets for anxiety, depression, and somatic symptoms. Addressing " little interest or pleasure in doing things," " feeling down, depressed, or hopeless," " dyssomnia," and "sighing" may effectively prevent the mutual transmission between psychological and physical symptoms. The network model highlighting the potential targeting symptoms to intervene in the treatment of psychosomatic health.

KEYWORDS

college students, psychosomatic health, anxiety, depression, somatic symptoms, comorbidity, network analysis

1 Introduction

Mental health is considered as the foundation of human health in the "Mental Health Action Plan (2020-2030)" of the World Health Organization (1). Nowadays, mental health issue is the leading cause of disability and a major public health concern worldwide. Depression and anxiety are important indicators of mental health, which are closely associated with somatic symptoms. Researches indicate that patients with anxiety and depression often exhibit somatic symptoms in clinical settings (2). Usually, somatic symptoms give raise to the impairment in daily life and work, as well as a primary reason for seeking medical care. Many of these symptoms are purely subjective discomfort without organic pathology, serving as outward manifestations of impaired mental health (3). Somatic symptoms, anxiety and depression constitute the three most common psychosomatic health issues. At least one-third of individuals with somatic symptom disorders concurrently experience anxiety and depression, highlighting a high comorbidity among these conditions (4, 5). The comorbid mechanisms among anxiety, depression, and somatic symptoms need to be further investigated. Menkes et al. found that some exogenous interferons can induce depression by inhibiting serotonin synthesis, thereby leading to fatigue and somatic symptoms (such as limb pain) (6). Rudolf et al. discovered that patients with anxiety disorders exhibited lower autonomic nervous system adaptability compared to healthy individuals, with more abnormal neuroregulation. As a result, the lower perception threshold for external stimuli is obtained for the patients, causing their central nervous system to struggle in accurately distinguishing whether the received stimuli are related to anxiety or neutral stimuli (7). Meanwhile, research shows a gradual increase in psychosomatic health issues among adolescents (8, 9).The somatic and psychological problems has became the significant components of mental disorders (10).

Current research on anxiety, depression, and somatic symptoms mostly relies on traditional latent variable theories in which the symptoms of mental disorders are interpreted as outcomes of underlying common factors (11). However, from this perspective, the co-occurrence or random clustering of different symptoms in mental disorders is attributed to the latent common factors that cannot be directly observed (12). Therefore, these methods based on the latent variable theories usually capture common differences among all symptoms. They overlook information related to the individual development of mental disorders (13, 14).

Recently, the network analysis has provided a new insight to understanding psychopathological symptoms (15). The network theory of psychopathology no longer regards mental disorders as underlying entities behind symptoms, but rather considers symptoms as integral components of mental disorders (16). It explores the interactions among individual psychopathological symptoms to reveal connections among individual variables (15, 17). In network analysis, nodes represent symptoms, and edges (lines between nodes) denote connections between symptoms. The weight of an edge signifies the strength of the association. The nodes connected with more edges and with larger weights suggest their higher centrality (18). Researchers often focus on nodes with higher centrality because these nodes can bring about prominent influence or can be used to predict other nodes. Additionally, network analysis offers a fresh perspective on the mechanisms of comorbidity in mental disorders, providing an intuitive depiction of the relationships among symptom clusters (19, 20). The "bridge variables" are established to connect different symptom clusters, which are beneficial to understand interactions between symptom clusters and identify targets for targeted interventions (20–22). Numbers of studies have utilized network analysis in mental disorders. Yang et al., explored the correlation among personality traits, anxiety and depression in college students (23). Luo et al., analyzed the comorbid characteristics of anxiety and depression symptoms in the student groups (14). Liu et al., used network analysis to explore bridging symptoms between depression and anxiety in HIV patients (24). However, the network analysis between psychosomatic symptoms needs to be further explored. Constructing networks of psychosomatic symptoms allows exploration of the relationship between somatic symptoms and psychological symptoms from a comorbidity perspective, thereby bridging research gaps between physical and psychological fields.

College students are a critical transitional stage from late adolescence to early adulthood, which are a high-risk group for physical and mental illnesses. Compared to other countries, the incidence of psychosomatic health issues among Chinese university students is relatively high (25–27), which may be owing to the large population, significant competitive pressure, and limited resources for mental health education. Among undergraduate students in Chinese comprehensive universities, 11.8% of them exhibited severe or moderate somatic symptoms; the students with severe anxiety symptoms accounted for 7.8% of the surveyed students; and severe depression symptoms are reported by 23.3% (28). Medical schools are a relatively unique category within universities, characterized by specialized programs, longer durations, extensive coursework, and high employment pressures. These characteristics of medical schools contribute to greater stress for medical students. Research suggested that 20% to 67% of medical students experience varying degrees of psychosomatic health issues, which was significantly higher than the 10% to 30% observed in regular college students (29).Within medical schools, Traditional Chinese Medicine (TCM) universities represent a unique presence because of blending elements of medical education with both natural and humanistic sciences. Meanwhile, TCM universities are widespread across nearly every province of China. However, there is currently limited research on the psychosomatic health characteristics of college students in TCM universities.

In this work, taking the TCM college students as objects, their psychosomatic status was investigated by a comprehensive questionnaire survey. Based on the investigation results, we constructed a network model (Psychosomatic Symptoms Network Model) which comprised somatic symptoms and anxiety-depression symptoms. The central and bridging symptoms within this network were also explored to elucidate important connections between somatic symptoms and psychological symptoms. This work describes the current psychosomatic health status of TCM college students. In addition, the network model we proposed provides theoretical insights into specific pathways linking somatic symptoms with psychological symptoms.

2 Materials and methods

2.1 Participants

An online survey was adopted via the survey links (www.wjx.cn), and the survey link was distributed to college students from Beijing University of Chinese Medicin. Participants were briefed on the purpose of survey and how to complete the questionnaire. The informed consents were obtained from participants. A total of 665 participants completed the survey from April to May 2024. The survey consisted of conventional information of the participant, Health Status Questionnaire, Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-2 (PHQ-2). This work strictly adhered to the principles of "Helsinki Declaration" and received approval from the Ethics Committee of BUCM (No. 2024BZYLL0105)

2.2 Measures

2.2.1 Health status questionnaire

The health status questionnaire was revised based on literature research and expert consultation. It is a self-assessment questionnaire that includes 30 relevant symptoms (items) categorized into overall symptoms, head-face-neck symptoms, chest-abdomen symptoms, diet, sleep, bowel movements, etc. All items are presented in clear and understandable description. Each item employs a 4-point rating scale: 0 points for "none," 1 point for "occasional," 2 points for "sometimes," and 3 points for "frequent". For example, "Do you feel dizzy?" Responses such as "none," "occasional," "sometimes," and "frequent" correspond to 0 points, 1 point, 2 points, and 3 points respectively. Previous research has confirmed that this questionnaire has good reliability and validity, accurately reflecting the participants' physical health status (30). In this investigation, the Cronbach's α for health status questionnaire was 0.92.

2.2.2 Generalized anxiety disorder-7

The GAD-7 is a common tool for evaluating anxiety symptoms, developed by Spitzer et al (31). This investigation employed the version of GAD-7 revised by He et al. The version is suitable for the Chinese context and has demonstrated good reliability and validity among Chinese populations (32, 33). The GAD-7 consists of 7 items including excessive worry, difficulty relaxing, feeling restless, irritability, and fear. Each item employs a 4-point Likert scale: 0, 1, 2, 3 points representing "not at all," "several days," "more than half the days," and "nearly every day," respectively. A total score of ≥ 5 on the GAD-7 indicates an anxiety state (34). In this investigation, the Cronbach's α for the GAD-7 was 0.91.

2.2.3 Patient health questionnaire-2

The PHQ-2, developed by Kroenke et al., is a brief and widely used screening tool for depression (35). The PHQ-2 consists of 2 items: "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless". Similarly, a 4-point Likert scale was employed for each item: 0, 1, 2, 3 points indicating "not at all," "several days," "more than half the days," and "nearly every day," respectively. A total score of ≥ 2 on the PHQ-2 suggests the depression (36). Related studies have confirmed that the PHQ-2 has good reliability and validity in screening for depressive symptoms (36). In this investigation, the Cronbach's α for the PHQ-2 was 0.72.

2.3 Statistical analysis

2.3.1 General information statistics

Descriptive statistics of the participants were conducted by SPSS 26.0. The classification data was expressed in terms of frequencies and component ratios. The mean ± standard deviation was used for the description of continuous variables. Bivariate correlations between psychological symptoms and somatic symptoms were obtained by Spearman correlation analysis.

2.3.2 Network model construction

The qgraph package in R software (version 4.4.0) (37) was employed to construct symptom networks based on EBICglasso function and Spearman correlation analysis. The EBICglasso function combines the least absolute shrinkage and selection operator (LASSO) regularization with extended Bayesian information criterion (EBIC) (23). In this work, the EBIC hyperparameter γ was set to 0.5 (19). The Fruchterman-Reingold layout was utilized (38). The network was divided into the somatic symptom community and the anxiety-depression community. Nodes in each community represent somatic symptoms or items from GAD-7 and PHQ-2 scales. In the visualized network, blue edges between nodes indicate positive correlations, while red edges indicate negative correlations. Thicker edges signify stronger correlations between adjacent nodes (39).

The expected influence (EI) of each node was also calculated by qgraph package, which sums the values of all edges connected to that specific node. A higher EI value demonstrates the greater importance of the node within the network (40). Meanwhile, the bridge expected influence (BEI) of each node is calculated to identify bridging symptoms (41). The BEI is the sum of edge weights between a specific node and nodes in other communities (20). A larger BEI suggests the stronger influence of that node on another community (41). Nodes can be forecasted through their neighboring nodes. Predictability (PRE) of each node was obtained by R-package mgm (42). With PRE ranging from 0 to 1, the node with higher PRE indicates the stronger predictive ability of this node (43).

Network robustness test were assessed using the bootnet package, which includes the stability and the accuracy of the network (19). With a non-parametric bootstrap (1000 bootstrap samples), the accuracy of edge weight was evaluated via computing 95% confidence intervals (CI). Case-deletion bootstrap was employed to calculate the stability coefficient, with coefficients above 0.5 to indicate good stability of centrality indices (19). Bootstrap difference tests (1000 bootstrap samples, $\alpha = 0.05$) were employed on edge weights, EI, and BEI to examine differences between two edge weights or two nodes.

3 Results

3.1 Demographic characteristics and descriptive statistics

Among 665 participants, there were 193 males (29.02%) and 472 females (70.98%). The age ranged from 18 to 32 years old, with an average age of 22.38 ± 3.20 years. Among them, 443 (66.62%) participants were undergraduates and 222 (33.38%) participants were graduate students.

3.1.1 Mental health

Varying degrees of anxiety and depression were discovered among participants, with 244 (36.69%) experiencing anxiety and 277 (41.65%) experiencing depression. Based on the GAD-7 and PHQ-2, the total scores, mean (M), standard deviation (SD), as shown in Table 1. Node numbers, Pre, EI, and BEI of items were also listed Table 1.

3.1.2 Somatic symptoms

About 30 somatic symptoms were investigated, and their frequencies were studied, as shown in Table 2. Common somatic symptoms (> 50%) among participants included fatigue, forgetfulness, sighing, thirst, and sweating in order of frequency.

The correlation between somatic symptoms and anxiety/ depression was shown in Table 3. Symptoms such as fatigue, forgetfulness, sighing, stool abnormity, dyssomnia, weakness, pant, stomach distension, chest tightness, palpitations, and soreness of waist had correlation coefficients r ≥ 0.5 with depression or anxiety, indicating strong relationships among these variables. Moreover, all symptoms were analyzed in the comorbid

TABLE 1 Item's total score, M, SD, Pre, EI, BEI values.

Item	Number	M ± SD	PRE	EI	BEI
PHQ-2 total score		1.25 ± 1.19			
Little interest or pleasure in doing things	P1	0.59 ± 0.70	0.54	0.57	0.42
Feeling down, depressed, or hopeless	P2	0.66 ± 0.65	0.63	0.83	0.42
GAD-7 total score		3.86 ± 4.31			
Feeling nervous, anxious or eager	G1	0.80 ± 0.69	0.59	0.05	0.28
Uncontrollable worries	G2	0.56 ± 0.81	0.67	1.61	0.22
Worrying too much about things	G3	0.65 ± 0.83	0.69	1.51	0.11
Trouble relaxing	G4	0.60 ± 0.83	0.6	0.71	0.17
Unable to sit still due to restlessness	G5	0.37 ± 0.69	0.52	-0.71	0.17
Easily annoyed or irritable	G6	0.53 ± 0.77	0.59	0.39	0.21
Feeling afraid as if something awful might happen	G7	0.37 ± 0.68	0.54	-0.82	0.13

TABLE 2 Somatic symptoms and corresponding frequency.

Item	Frequency	Item	Frequency	Item	Frequency
fatigue	82.86%	pant	44.36%	soreness of waist	35.49%
forgetfulness	73.38%	eating disorder	43.91%	fever	35.34%
sighing	68.27%	bellyache	41.81%	cough	31.88%
thirst	61.96%	xerophthalmia	40.45%	foreign body sensation	30.08%
sweating	56.24%	headache	40.30%	anal burning	28.87%
stool abnormity	47.22%	stomach distension	38.64%	abdominal distension	28.57%
dyssomnia	47.21%	chest distress	37.90%	frequent micturition	28.12%
weakness	46.47%	dizzy	37.59%	nausea	25.71%
lumbago	46.32%	cold	36.69%	tinnitus	24.66%
alopecia	46.17%	palpitation	35.94%	hiccup	23.60%

network to calculate their scores (M, SD) and parameters (PRE, EI, and BEI), as outlined in Table 4.

3.2 Network structure

Figure 1A depicts the network structure of somatic symptoms with anxiety-depressive symptoms. The network structure (average weight of 0.048) includes 129 non-zero edges, and edge weights range from 0.00 to 0.38. Within the network, 52 edges (40.31%) bridge the somatic symptoms and the symptoms of anxiety/depression, and these52 bridging edges are all positively correlated. These edges with the top three weights are the bridge between "Feeling down, depressed, or hopeless" and "sighing" (edge weight = 0.24), the bridge between "Feeling nervous, anxious or eager" and "fatigue" (edge weight = 0.14), and the bridge between "Little interest or pleasure in doing things" and "dyssomnia" (edge weight = 0.12). The correlation matrix of the network is also shown in Supplementary Table S1 of Supplementary Material. Bootstrap estimation of edge weights shows relatively narrow CI, indicating reliable evaluation of these edge weights, as depicted in Supplementary Figure S1. Testing differences of edge are also shown in Supplementary Figure S2. Additionally, predictability of node is represented by circle around this node. PRE values of nodes range from 0.28 to 0.69 in this network. The nodes of "Uncontrollable worries" and "Worrying too much about things" exhibit the high predictability, indicating that 67% and 69% of their variances can be explained by adjacent nodes, respectively.

The expected influences among somatic manifestations and symptoms of anxiety/depression are shown in Figure 1B. In the network, the nodes of "Uncontrollable worries", "Worrying too much about things", and "weakness" exhibit the large EI values (1.61, 1.51, and 1.15, respectively). Statistically, these three symptoms have the highest associations in comorbid network, considered as the central symptoms. Bootstrap difference test reveals a stable coefficient of 0.75 for the EI, suggesting the stability of EI evaluation (Supplementary Figure S3). Furthermore, bootstrap difference tests of EI demonstrate significant differences among the central symptoms and the majority (≥50%) of other symptoms, as shown in Supplementary Figure S4.

The bridging expected influences among somatic manifestations and symptoms of anxiety/depression are depicted in Figure 1C. Larger BEI values indicate stronger bridging centrality. The nodes of "dyssomnia", "Little interest or pleasure in doing things", "Feeling down, depressed, or hopeless", and "sighing" are identified as bridging symptoms because of their high BEI (0.46, 0.42, 0.42, and 0.39, respectively). Bootstrap difference test obtains a coefficient of 0.67 for the stability of BEI evaluation (Supplementary Figure S5). Meanwhile, bootstrap difference tests of BEI demonstrate significant differences among the bridging symptoms and most other nodes (Supplementary Figure S6).

4 Discussion

In this study, the proportion of depression among college students was 41.65%, and anxiety was 36.69%. These proportions are significantly higher than the average rates of 32.74% for depression and 27.22% for anxiety among medical students in China, respectively (44). The differences of proportions may be attributed to variations of subjects, measurement tools, methods, and geographical factors. The high proportions reflect the serious states of depression and anxiety among college students of TCM universities. Compared to general medical students, TCM students face unique challenges such as learning both TCM and Western medicine, high academic pressures, and intense competition in employment. With the challenges exceeding their coping abilities, they are more prone to developing mental health issues (i.e. depression and anxiety). For physical health, we found various somatic symptoms with high frequencies (> 20%) among college students. Furthermore, the frequencies of some somatic manifestations (such as fatigue, forgetfulness, sighing, thirst, and

TABLE 3 Correlation among somatic symptoms, depression, and anxiety.

Item	Depression	Anxiety
total score	0.798*	0.717*
fatigue	0.573*	0.531*
forgetfulness	0.504*	0.468*
sigh	0.598*	0.575*
stool abnormity	0.510*	0.423*
dyssomnia	0.691*	0.551*
weakness	0.599*	0.536*
pant	0.519*	0.459*
stomach distension	0.500*	0.474*
chest distress	0.588*	0.539*
palpitation	0.509*	0.487*
soreness of waist	0.539*	0.491*
thirst	0.481*	0.478*
sweat	0.492*	0.489*
lumbago	0.452*	0.417*
alopecia	0.368*	0.351*
eating disorder	0.455*	0.381*
bellyache	0.388*	0.370*
xerophthalmia	0.388*	0.344*
headache	0.489*	0.418*
dizzy	0.461*	0.426*
cold	0.310*	0.314*
fever	0.332*	0.296*
cough	0.290*	0.263*
foreign body sensation	0.308*	0.278*
anal burning	0.375*	0.303*
abdominal distension	0.456*	0.425*
frequent micturition	0.399*	0.389*
nausea	0.405*	0.382*
tinnitus	0.323*	0.261*
hiccup	0.409*	0.390*

* means $P < 0.05$, which has statistical significance.

TABLE 4 Item's M, SD, Pre, EI, BEI values.

Item	Number	M ± SD	Pre	EI	BEI
fatigue	S1	1.45 ± 1.06	0.56	0.77	0.14
forgetfulness	S2	1.20 ± 1.03	0.44	-1.15	0.09
sighing	S3	1.00 ± 0.93	0.59	0.46	0.39
stool abnormity	S4	0.67 ± 0.84	0.28	-1.88	0.17
dyssomnia	S5	0.69 ± 0.88	0.42	-1.34	0.46
weakness	S6	0.66 ± 0.94	0.57	1.15	0.18
pant	S7	0.62 ± 0.83	0.41	-0.72	0.1
stomach distension	S8	0.54 ± 0.79	0.35	-1.18	0.13
chest distress	S9	0.51 ± 0.79	0.53	0.47	0.21
palpitation	S10	0.45 ± 0.69	0.43	-0.53	0.15
soreness of waist	S11	0.49 ± 0.77	0.49	-0.19	0.13

sweating) exceed 50%. These physical discomforts have become prevalent issues affecting academic performance and daily lives of students, demanding significant attention.

From a causal systems perspective (CSP), this study investigated the interactions among psychosomatic symptoms in TCM university students. Compared with the traditional common cause perspective (CCP), this work attributed comorbidities to direct interactions among symptoms, providing an alternative explanation (14). The work identified the symptoms of " worrying too much about things ", "uncontrollable worries" and "weakness" as central symptoms in the network. Both symptoms of "uncontrollable worries" and " worrying too much about things " refer to a persistent state of anxiousness, which are the common central symptoms in existing anxiety and depression network models. Cai et al. reported that the symptom of "worrying too much about things" was the central symptom of the anxiety-depression network adolescents in the later stages of the COVID-19 pandemic (45). Zhang et al. discovered that the symptoms of "uncontrollable worries" and "worrying too much about things" were the core symptoms in the anxiety-depression network of Chinese elderly diabetic patients (46). Similar results have been reported in investigations on new university students of China (14). The recurring presence of "uncontrollable worries" or "worrying too much about things" as the central symptom across different groups highlights the significance in psychological manifestations. With insighting into the neuroendocrine perspective, persistent worry results in overactivity of hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol secretion, thereby leading to a range of somatic symptoms (i.e. dizziness, headaches, fatigue and palpitations) (47, 48). Therefore, the modulation of unnecessary worry is crucial for improving the psychosomatic health of college students. As another central symptom in this network, the somatic manifestation of "weakness" means a persistent feeling of tiredness and lack of energy. This sensation can significantly impact the activities in daily life, which also exhibits a relatively high occurrence (46.47%) among college students. College students often face high academic demands, such as complex subject knowledge, heavy assignments, and exam tasks. This pressure can lead to long study hours, insufficient rest and relaxation, ultimately resulting in weakness. Weakness can be classified into physiological and pathological types. Physiological weakness is usually caused by factors such as excessive exertion, lack of sleep, or poor nutrition, while pathological weakness may be a symptom of certain diseases. Psychological disorders (especially depression and anxiety) often accompany weakness, which affects not only the body but also

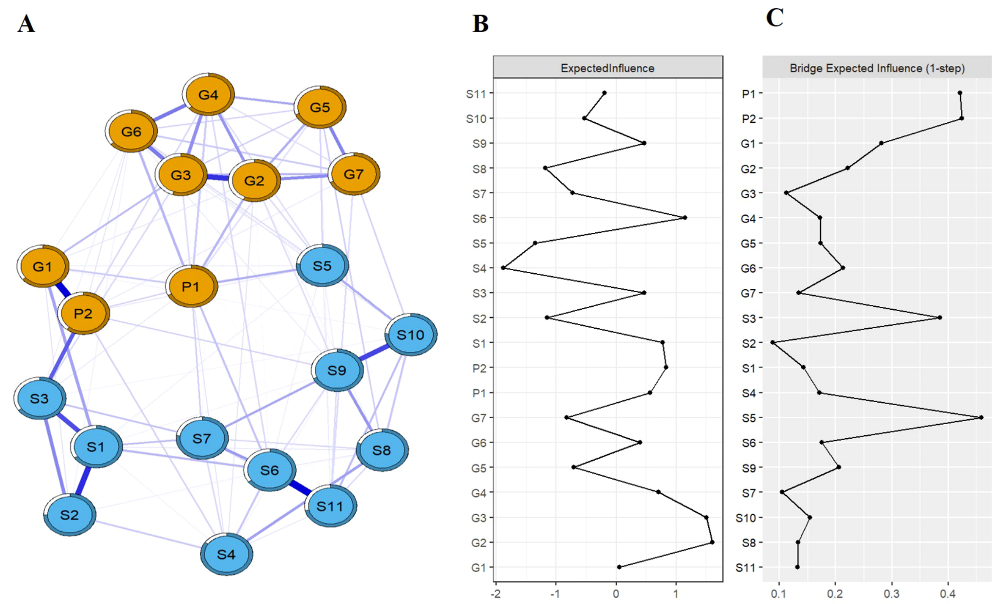

FIGURE 1
Psychosomatic symptom network structure and node EI/BEI value.

emotional states. Additionally, weakness also contributes to psychological health issues. Chronic tiredness may lead to mood disturbances, anxiety, and depression, thereby creating a vicious cycle. From a psychopathological perspective, the comorbid mechanisms of weakness and psychological disorders involve complex interactions among neurobiological, inflammatory, sleep quality, and psychosocial factors. Within the comorbid network, these three symptoms are strongly associated with other symptoms because of their high EI values, playing a crucial role in activating and maintaining the network. Intervening in central symptoms of network can effectively reduce the overall severity of symptoms, thereby promoting treatment and prevention (49, 50).

BEI is an indicator for identifying bridging symptoms, and in this study the four symptoms with the highest BEI values were identified: "little interest or pleasure in doing things", "feeling down, depressed, or hopeless", "sighing" and "dyssomnia". In network analysis, bridging symptoms have cross-diagnostic significance as they serve to connect symptom networks from two different communities. Although there is a lack of network analysis studies on psychosomatic symptoms, in anxiety-depression network models, symptom of "feeling down, depressed, or hopeless"and "little interest or pleasure in doing things" appears as bridging symptoms among Chinese new college students (14). During the COVID-19 pandemic, symptoms of "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless" were identified as bridging symptoms in the anxiety-depression network of nursing students (51). Additionally, "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless" were also typical symptoms for diagnosing major depression (52). The above studies highlight the importance of bridging symptoms "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless" in psychological clinical manifestations, which matches the findings in this network analysis. In this study, these two symptoms also demonstrated their significant impact on physical manifestations, specifically their strong capacity to increase the risk of somatic symptoms. The somatic symptoms of "sighing" and "dyssomnia" are two additional bridging symptoms identified in this network, which exhibit the strongest ability to increase the risk of anxiety and depression contagion. Sighing is an external manifestation of anxiety/depression, and individuals may sigh to alleviate inner tension and repression when feeling anxious or depressed. However, frequent sighing enables to lead individuals to focus more on their negative emotions, worsening anxiety and depression. The serious influence makes sighing an important link in psychosomatic symptoms. Another bridging symptom is " dyssomnia," which aligns with previous research findings. A systematic review indicates that dyssomnia is bidirectionally associated with anxiety and depression in adolescents, adults, and the elderly (53). Meanwhile, the somatic manifestations of "dyssomnia" were also identified as a bridging symptom in the network of anxiety, depression, and insomnia for clinical practitioners with depressive symptoms (54). In terms of psychopathology, brain neurotransmitters are considered a common underlying mechanism linking dyssomnia with depression/anxiety. Imbalances in neurotransmitters such as norepinephrine, serotonin, and dopamine can affect mood and sleep. Furthermore, a lack of sleep can reversely disrupt these neurotransmitters, yielding a negative feedback loop. As mentioned, bridging symptoms play a crucial role in the generation of comorbidities, which give raise to the onset and persistence of mental comorbidities. Intervening in bridging symptoms can effectively prevent or alleviate comorbid symptoms (55, 56).

The average node predictability of the network is 0.52, indicating a moderate level of self-determination (43). The predictability of nodes can reflect the controllability of the network and determine the effectiveness of the planned treatment (43). In this study, "uncontrollable worry" and " Worrying too much about things" showed high predictability values that could be controlled by intervening in their adjacent nodes. However, symptoms with lower predictability, like " stool abnormity" and " stomach distension" may require direct control or intervention from external factors outside the network (39).

The study exhibits limitations. The investigation employed convenience sampling from a single TCM university with an uneven gender ratio. Recruiting participants from different regions on a larger scale will be considered. Meanwhile, it is also a cross-sectional study, preventing examination of dynamic or causal relationships among symptoms. Future longitudinal studies should explore these relationships. In addition, the use of brief scales (PHQ-2 and GAD-7) may have limited the ability to capture the full spectrum of psychological symptoms. The study found that the effect between somatic symptoms and psychological symptoms was relatively weak, which may indicate that the actual effect is limited. Future intervention trials targeting central and bridging symptoms are needed to validate its effectiveness.

This work investigated the psychosomatic health status of college students of TCM, thereby establishing a network model of psychosomatic symptoms. Within the comorbid network, the centrality, bridging role, and predictability of symptoms were explored. We found that the psychosomatic health of these students is concerning, showing tendencies towards high levels of depression, anxiety, and somatization symptoms. After comorbid network analysis, the symptoms of " worrying too much about things ", "uncontrollable worries" and "weakness" were identified as central symptoms in the network model. Targeting these central symptoms for intervention could further relieve overall somatic presentations and reduce the severity of anxiety or depression. Simultaneously, interventions of targeting nodes with high predictability ("uncontrollable worry" and " Worrying too much about things") can be achieved by intervening in their adjacent nodes. Bridging symptoms (" little interest or pleasure in doing things," " feeling down, depressed, or hopeless," " dyssomnia," and "sighing") can effectively prevent or alleviate the symptoms of comorbidity. This study will serve as a reference for psychosomatic health interventions among college students in TCM universities.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1467064/full#supplementary-material

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Association between sleep duration and chronic musculoskeletal pain in US adults: a cross-sectional study

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Background: This study aims to explore the association between sleep duration and the prevalence of chronic musculoskeletal pain (CMP).

Methods: A cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2009–2010, which involved multiple centers across the United States. The study included 3,904 adults selected based on age and complete data availability. Demographic variables such as gender, age, race, and socioeconomic status (represented by the poverty-to-income ratio) were considered.

Results: Of the participants, 1,595 reported less than 7 h of sleep, 2,046 reported 7–8 h, and 263 reported more than 9 h of sleep. Short sleep duration was associated with higher odds of CMP (OR, 1.611, 95% CI: 1.224–2.120, $p = 0.005$). Long sleep duration also showed a higher prevalence (OR, 1.751; 95% CI, 0.923 to 3.321; $p = 0.059$), although this result was not statistically significant. A U-shaped relationship emerged (Effective degree of freedom (EDF) = 3.32, $p < 0.001$), indicating that 7 h of sleep was associated with the lowest odds of CMP. In individuals with sleep durations less than 7 h, each hour increment correlated with 22.8% reduced odds of CMP (OR, 0.772; 95% CI, 0.717–0.833; $p = 0.002$). Beyond 7 h, each hour increment was associated with 38.9% increased odds of CMP (OR, 1.389; 95% CI, 1.103–1.749; $p = 0.049$).

Conclusion: The findings suggest that both insufficient and excessive sleep durations are linked to a higher prevalence of CMP, highlighting the importance of optimal sleep duration for musculoskeletal health.

KEYWORDS

sleep duration, chronic musculoskeletal pain, low back pain, NHANES, cross-sectional study

1 Introduction

Chronic musculoskeletal pain (CMP) affects over 20–33% of the global population, according to the World Health Organization (WHO), resulting in significant health and socio-economic burdens (1). Sleep plays a crucial role in maintaining physical well-being, with an optimal duration generally ranging from 7 to 9 h (2–4). Poor sleep habits are linked to various adverse health effects, including cardiovascular events (2, 5, 6), diabetes mellitus (DM) (5), Alzheimer's Disease (4, 7), and increased mortality risk (2).

In the United States, about one-third of the population frequently experiences sleep difficulties, a condition even more prevalent among those with concurrent pain symptoms (8, 9). Observational data indicate a link between sleep disturbances and the onset, progression, and persistence of pain symptoms (8, 10–12). Chronic pain and sleep disturbances often co-occur, highlighting a clinically important reciprocal relationship. Various epidemiological studies have indicated that poor sleep quality and not getting enough sleep are correlated with a higher prevalence of chronic pain (10, 13). Conversely, experiencing chronic pain can also disrupt an individual's sleep patterns (14).

Understanding the potential mechanisms behind this reciprocal relationship is crucial for developing new treatments for chronic pain. However, the precise relationship between sleep duration and chronic pain remains unclear. Most studies suggest a link between short sleep duration and higher prevalence of chronic pain (14), but research demonstrating a connection between excessive sleep and chronic pain is limited. This study aims to conduct a large-scale population study to explore the relationship between sleep duration and chronic pain by analyzing retrospective data from the National Health and Nutrition Examination Survey (NHANES). Specifically, we assessed the link between self-reported sleep duration and the presence of chronic pain and investigate the potential effects of age, gender, Body Mass Index (BMI), race, poverty-to-income ratio (PIR), alcohol use, smoking, DM and sleep disorders. This research offers valuable insights into understanding the intricate relationship between sleep and chronic pain, with implications for chronic pain prevention and treatment.

2 Methods

2.1 Study population

The protocols for NHANES, a cross-sectional survey, were approved by the ethics review board of the National Center for Health Statistics, and all participants provided written informed consent. It was in accordance with the policy of the National Institutes of Health that analysis conducted using de-identified data not directly involving participants was not classified as a human subject study, thus not requiring institutional review board review.

NHANES participants undergo demographic assessments, laboratory examinations, and extensive interviews, covering measures of sex, age, race, PIR, clinical profiles, and personal behaviors. The sampling structure of NHANES allows it to effectively represent the non-institutionalized population of the United States after adjustments for sex, age, race, and ethnicity were made. We primarily focused on two indicators, including sleep behavior and musculoskeletal pain. Data from NHANES 2009–2010 which included an arthritis questionnaire were obtained. We excluded 48 participants who were pregnant. Participants missing information on sleep duration, pain, or other important covariates (e.g., smoking, alcohol consumption, diabetes, PIR) were excluded. Finally, data from 3,904 participants were included in the analysis (Supplementary Figure S1).

2.2 Measurement

2.2.1 Outcome ascertainment

CMP is defined as pain persisting or recurring for more than 3 months (15). To define this group, pain-related questions from the Arthritis Questionnaire Section (ARQ) provides interview data were utilized. Participants were classified into chronic musculoskeletal pain group if they reported experiencing "neck pain," "upper back pain," "mid back pain," "low back pain," "buttocks pain," "hip pain," or "rib cage pain" for at least three months.

2.2.2 Exposure measurement

Participants provided self-reported information regarding their typical sleep duration on weekdays or workdays. Between 2009 and 2010, NHANES participants were requested to disclose their usual sleep duration on weekdays or workdays with the question: "How much sleep do you usually get at night on weekdays or workdays?" The distribution of the number of participants in each sleep duration group is shown in Supplementary Figure S2. The sleep duration data was segmented into three categories: less than 7 h, 7 to 8 h, and 9 h or more.

2.2.3 Covariate assessment

Covariates were selected based on existing literature. Standardized questionnaires were utilized to gather data on various factors, including: age, sex, race, education level, PIR, BMI, waist circumference, smoking habits, alcohol consumption, hypertension, diabetes, sleep disorders.

Race was classified as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other. Education level was categorized as below 12th grade, high school graduate or equivalent, and college or above.

Height, weight, and blood pressure were measured following established protocols. BMI was computed by dividing weight in kilograms by height in meters squared (kg/m^2).

Participants were grouped as never smokers, former smokers or current smokers based on their responses regarding smoking history and current behavior. Alcohol consumption status was determined by the question "Have you had at least 12 drinks of any type of alcoholic beverage in any one year?." Hypertension was identified by self-reporting a history of high blood pressure diagnosis. Diabetes was established through self-reporting a diagnosis of diabetes or sugar diabetes, excluding gestational diabetes. Sleep Disorders was defined based on the questions "Have you ever told a doctor you had trouble sleeping?" and "Have you ever been told by a doctor you have a sleep disorder?." These covariates were included to account for potential confounding variables in the relationship between sleep duration and pain.

2.3 Statistical analysis

This study utilized sample weights provided by NHANES for weighted analysis to accurately reflect the actual distribution of the U.S. population, ensuring a high level of accuracy and representativeness in assessing the connection between sleep duration and chronic pain. The data was presented as survey-weighted mean (95% confidence interval [CI]) for continuous variables and survey-weighted percentage (95% CI) for categorical variables. The population with missing data in the variables was excluded from the analysis. A comparison of baseline characteristics was conducted among participants with different sleep durations (< 7 h, 7 to 8 h, and ≥ 9 h) using one-way ANOVA for continuous variables and the chi-square test for categorical variables.

We selected these confounders on the basis of their association with the outcomes of interest or changes in effect estimates of more than 10% (16). After considering the clinical significance, we adjusted for the following covariates: age (years), sex, BMI, race, PIR, alcohol consumption, smoking habits, diabetes, and sleep disorders. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for prevalent CMP and low back pain (LBP) using weighted logistic regression model. To further assess the impact of excluding missing data, we conducted a sensitivity analysis. We compared the results from the complete dataset with those from the dataset after excluding individuals with missing data. To assess the nonlinear relationship between sleep duration and prevalent CMP and LBP, a generalized additive model (GAM) was employed. The effective degrees of freedom (EDF) provide insight into the curvature of the smoothing curve (17, 18). An EDF value of 1 indicates a linear relationship, while an EDF value greater than 1 suggests a more complex relationship between chronic pain and sleep duration. By analyzing the smoothing curve, a weighted two-piecewise linear regression model (19, 20) was developed to identify any potential threshold effect. The model adjusted for possible confounders, and the results were presented as odds ratios (ORs) with corresponding 95% CIs. Additionally, we conducted stratified analyses for gender, age, smoking, BMI, diabetes, and sleep disorders to validate the results.

All analyses were conducted using the R statistical software (The R Foundation[1]) and EmpowerStats software (X&Y solutions, Inc. Boston MA[2]) running on R software. A two-sided p-value < 0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics of the study participants

Among the 3,904 participants in the study, 1,956 were male and 1,948 were female. Sleep duration is categorized into three distinct groups: those sleeping less than 7 h, those sleeping 7 to 8 h, and those sleeping 9 h or more. Compared with the group that slept for 7 to 8 h, participants with shorter sleep durations were more often male, had a lower PIR, and exhibited higher BMI or waist circumferences. They were also more likely to smoke and to have comorbid hypertension, diabetes, and sleep disturbances. In contrast, participants with longer sleep durations, as opposed to the 7–8 h group, were predominantly female, had a lower PIR, and had lower BMI or waist circumferences. They were also smokers and frequently had diabetes, but less frequently had hypertension and reported alcohol use. A detailed summary of the baseline characteristics of the subjects is provided in Table 1.

3.2 Impact of short and long sleep durations on chronic musculoskeletal pain and low back pain

Table 2 depicts the prevalence of pain in different anatomical regions. Both longer sleep durations (≥9 h) and shorter sleep durations (<7 h), compared to the standard sleep duration (7–8 h), are linked to increased pain prevalence across all examined anatomical regions (neck, upper back, mid back, low back, buttocks or hips). Table 3 shows the results of weighted logistic regression model construction between sleep duration and CMP and LBP, detailing odds ratios (ORs) and 95% CIs for both conditions across short and long sleep durations versus the normal sleep duration. In the unadjusted model, short sleep duration was associated with 97% higher odds of CMP (OR = 1.970 [95% CI 1.648, 2.354], p < 0.001), and long sleep duration with 79% higher odds compared to normal sleep duration (OR = 1.797 [95% CI 1.201, 2.690], p = 0.013). For LBP, the ORs were 1.844 ([95% CI 1.527, 2.228], p < 0.001) for short sleepers and 1.911 ([95% CI 1.233, 2.963], p = 0.012) for long sleepers. After adjusting for confounders, the adjusted ORs for CMP were 1.611 (95% CI 1.224, 2.120, p = 0.005) for short and 1.751 (95% CI 0.923, 3.321, p = 0.059) for long sleep durations. For LBP, the adjusted ORs were 1.428 (95% CI 1.085, 1.879, p = 0.015) for short and 1.818 (95% CI 0.883, 3.741, p = 0.069) for long sleep durations. Results derived from the analysis of data with missing covariates corroborated the findings observed in the full dataset of the study (Supplementary Table S1).

3.3 Threshold effect analysis for sleep duration on chronic musculoskeletal pain and low back pain

Figure 1 illustrates a U-shaped relationship between CMP (EDF = 3.32, p < 0.001), LBP (EDF = 2.86, p < 0.001), and sleep duration post adjustment for confounders based on the generalized additive models. We further conducted a threshold effect analysis using the cut-off value of 7 h and found that the odds of CMP decreased with sleep duration until it reached a minimum at 7 h (OR = 0.772 [95% CI 0.717, 0.833], p = 0.002). Conversely, exceeding 7 h of sleep led to a significant increase in CMP odds (OR = 1.389 [95% CI 1.103, 1.749], p = 0.049) (Table 4). Similarly, the odds of LBP decreased with sleep duration until it reached a minimum at 7 h (OR = 0.776 [95% CI 0.663, 0.906], p = 0.006). However, surpassing 7 h of sleep resulted in an odds elevation (OR = 1.419 [95% CI 0.904, 2.228], p = 0.069).

When stratified by gender, age, BMI, smoking, diabetes, and sleep disorders, a curvilinear relationship between sleep duration and musculoskeletal pain was still observed. Female, aged 40–65, smokers, obese individuals, those with diabetes, and individuals with sleep disorders have a high prevalence of CMP (Figure 2).

4 Discussion

In this population-based cross-sectional investigation, we discovered an independent relationship between sleep duration and a higher prevalence of chronic musculoskeletal pain. Our analysis revealed a non-linear correlation between sleep duration and pain prevalence, with significant increases in pain odds observed at extreme sleep durations. The optimal sleep duration for mitigating pain odds was identified as 7 h, highlighting the importance of maintaining this balance to reduce the likelihood of chronic musculoskeletal pain.

1 http://www.R-project.org
2 www.empowerstats.com

TABLE 1 Selected characteristics of NHANES 2009–2010 participants 20 ≤ aged ≤69 years (n = 3,904).

Characteristics	All participants (n = 3,904)	Short sleep (< 7 h) (n = 1,595)	Normal sleep (7–8 h) (n = 2046)	Long sleep (≥ 9 h) (n = 263)	P-value
Gender (%)					0.0204
Male	50.57 (49.01, 52.13)	53.66 (49.87, 57.40)	49.32 (46.87, 51.78)	43.70 (37.80, 49.79)	
Female	49.43 (47.87, 50.99)	46.34 (42.60, 50.13)	50.68 (48.22, 53.13)	56.30 (50.21, 62.20)	
Age (year)	43.61 (42.87, 44.35)	43.95 (43.00, 44.89)	43.47 (42.43, 44.50)	42.93 (40.87, 45.00)	0.6654
Age, n (%)					0.2926
< 40	39.84 (37.15, 42.60)	38.33 (34.77, 42.01)	40.87 (37.18, 44.66)	39.45 (32.36, 47.02)	
40–65	53.15 (50.63, 55.66)	55.44 (52.25, 58.59)	51.89 (48.59, 55.18)	51.14 (44.58, 57.65)	
≥65	7.00 (6.17, 7.94)	6.23 (4.79, 8.08)	7.24 (5.95, 8.77)	9.41 (5.88, 14.73)	
BMI (kg/m^2)	28.92 (28.62, 29.22)	29.51 (28.99, 30.04)	28.61 (28.16, 29.07)	28.20 (27.17, 29.22)	0.0301
BMI, n (%)					0.0043
<18.5	1.80 (1.22, 2.65)	2.21 (1.58, 3.09)	1.50 (0.95, 2.36)	2.19 (0.70, 6.64)	
18.5–25	28.37 (25.26, 31.71)	24.44 (21.29, 27.89)	30.09 (25.60, 35.01)	35.92 (28.09, 44.58)	
25–30	33.08 (30.60, 35.65)	31.73 (29.08, 34.50)	34.37 (29.44, 39.65)	29.22 (21.92, 37.78)	
>30	36.75 (34.58, 38.97)	41.62 (37.96, 45.38)	34.04 (30.47, 37.80)	32.67 (25.00, 41.40)	
Waist	98.32 (97.43, 99.22)	99.87 (98.43, 101.31)	97.53 (96.37, 98.69)	96.40 (93.92, 98.88)	0.0170
Race/ethnicity, n (%)					<0.0001
Mexican American	8.39 (4.71, 14.48)	8.28 (4.85, 13.78)	8.29 (4.60, 14.47)	9.90 (4.21, 21.57)	
Other Hispanic	4.75 (2.81, 7.91)	5.79 (3.68, 8.99)	4.00 (2.20, 7.17)	5.40 (2.46, 11.47)	
Non-Hispanic White	69.96 (62.54, 76.46)	63.05 (55.32, 70.16)	74.51 (67.07, 80.75)	69.26 (56.99, 79.30)	
Non-Hispanic Black	10.79 (9.14, 12.70)	16.07 (13.64, 18.84)	7.38 (5.95, 9.13)	10.74 (6.71, 16.76)	
Other Race	6.12 (4.62, 8.05)	6.82 (4.92, 9.37)	5.82 (4.24, 7.94)	4.69 (2.39, 9.01)	
Education, n (%)					<0.0001
Less than 12th grade	16.10 (14.40, 17.96)	17.51 (16.00, 19.14)	14.69 (12.63, 17.03)	20.56 (14.80, 27.82)	
High school graduate or equivalent	22.70 (20.35, 25.24)	26.33 (22.86, 30.12)	19.86 (17.27, 22.74)	27.25 (20.66, 35.00)	
Some college or above	61.20 (58.05, 64.26)	56.16 (52.97, 59.29)	65.44 (61.30, 69.36)	52.20 (43.40, 60.86)	
PIR	3.09 (3.00, 3.18)	2.92 (2.80, 3.04)	3.23 (3.12, 3.33)	2.88 (2.62, 3.13)	<0.0001
Alcohol status (Yes), n (%)	80.51 (78.06, 82.74)	80.02 (78.00, 81.90)	81.33 (78.27, 84.04)	75.93 (69.90, 81.08)	0.0311
Hypertension, n (%)	26.07 (23.89, 28.38)	29.84 (26.43, 33.48)	24.36 (20.86, 28.23)	19.45 (14.91, 24.96)	0.0084

(Continued)

TABLE 1 (Continued)

Characteristics	All participants (*n* = 3,904)	Short sleep (< 7 h) (*n* = 1,595)	Normal sleep (7–8 h) (*n* = 2046)	Long sleep (≥ 9 h) (*n* = 263)	*P*-value
Diabetes, *n* (%)					0.1390
Yes	7.20 (6.13, 8.45)	8.80 (6.72, 11.44)	6.23 (5.24, 7.39)	6.68 (4.21, 10.46)	
No	91.01 (89.83, 92.07)	89.35 (86.86, 91.41)	92.06 (90.76, 93.20)	91.24 (87.18, 94.10)	
Borderline	1.79 (1.36, 2.35)	1.85 (1.23, 2.78)	1.71 (0.97, 3.00)	2.08 (1.12, 3.84)	
Sleep disorders, *n* (%)	25.89 (23.02, 28.98)	35.75 (32.01, 39.67)	20.01 (17.17, 23.20)	21.35 (12.99, 33.03)	<0.0001
Smoking status (self-reported), *n* (%)					<0.0001
Never smoking	55.74 (51.78, 59.63)	50.53 (46.63, 54.42)	59.47 (54.43, 64.32)	52.44 (41.46, 63.20)	
Former smoker	22.46 (19.34, 25.92)	21.84 (19.24, 24.70)	23.47 (19.27, 28.26)	16.81 (12.23, 22.66)	
Current smoking	21.80 (20.09, 23.61)	27.63 (24.95, 30.47)	17.06 (14.96, 19.38)	30.75 (21.22, 42.25)	

PIR, poverty-to-income ratio; BMI, body mass index. For continuous variables: survey-weighted mean (95% CI), *P*-value was by survey-weighted linear regression (svyglm); For categorical variables: survey-weighted percentage (95% CI), *P*-value was by survey-weighted Chi-square test (svytable).

TABLE 2 Pain prevalence in different body regions among participants with different sleep durations.

Outcomes	All participants (*n* = 3,904)	Short sleep (< 7 h) (*n* = 1,595)	Normal sleep (7–8 h) (*n* = 2046)	Long sleep (≥ 9 h) (*n* = 263)	*P*-value
Neck pain that had lasted 3 or more months, *n* (%)	7.61 (6.64, 8.71)	10.17 (8.08, 12.73)	5.84 (4.79, 7.09)	8.70 (4.49, 16.17)	0.0020
Upper back pain that had lasted 3 or more months, *n* (%)	4.38 (3.73, 5.15)	6.33 (5.05, 7.90)	2.92 (2.01, 4.23)	6.32 (3.10, 12.43)	0.0011
Mid back pain that had lasted 3 or more months, *n* (%)	4.24 (3.54, 5.06)	6.32 (4.88, 8.14)	2.89 (2.06, 4.05)	4.20 (1.61, 10.53)	0.0018
Low back pain that had lasted 3 or more months, *n* (%)	14.23 (12.92, 15.64)	18.50 (16.06, 21.22)	10.94 (10.09, 11.86)	18.96 (12.52, 27.67)	<0.0001
Buttocks pain that had lasted 3 or more months, *n* (%)	6.71 (5.60, 8.01)	9.21 (6.81, 12.35)	5.22 (4.25, 6.41)	5.50 (3.14, 9.47)	0.0005
Hip pain that had lasted 3 or more months, *n* (%)	3.37 (2.73, 4.15)	4.54 (3.49, 5.87)	2.53 (1.77, 3.62)	4.10 (2.30, 7.20)	0.0048
Rib cage pain that had lasted 3 or more months, *n* (%)	0.83 (0.55, 1.26)	0.98 (0.58, 1.65)	0.69 (0.31, 1.55)	1.28 (0.42, 3.89)	0.5859
Chronic musculoskeletal pain, *n* (%)	21.57 (19.41, 23.90)	28.31 (24.99, 31.88)	16.70 (15.00, 18.55)	26.38 (18.08, 36.78)	<0.0001

For categorical variables: survey-weighted percentage (95% CI), *P*-value was by survey-weighted Chi-square test (svytable).

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TABLE 3 Results of multiple logistic regressions on the association between sleep duration and pain outcomes.

Outcomes	Non-adjusted Model		Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Chronic musculoskeletal pain								
Sleep duration	0.806 (0.758, 0.858)	<0.001	0.809 (0.759, 0.863)	<0.001	0.884 (0.829, 0.942)	0.009	0.883 (0.829, 0.942)	0.009
Hours of Sleep								
Short sleep (<7 h)	1.970 (1.648, 2.354)	<0.001	1.984 (1.651, 2.383)	<0.001	1.624 (1.349, 1.955)	0.002	1.611 (1.224, 2.120)	0.005
Normal sleep (7-8 h)	Ref		Ref		Ref		Ref	
Long sleep (≥9 h)	1.797 (1.201, 2.690)	0.013	1.822 (1.186, 2.801)	0.0181	1.774 (1.140, 2.761)	0.044	1.751 (0.923, 3.321)	0.059
Low back pain								
Sleep duration	0.819 (0.755, 0.888)	<0.001	0.823 (0.758, 0.893)	<0.001	0.913 (0.825, 1.010)	0.059	0.911 (0.823, 1.008)	0.057
Hours of Sleep								
Short sleep (<7 h)	1.844 (1.527, 2.228)	<0.001	1.843 (1.527, 2.224)	<0.001	1.447 (1.136, 1.843)	0.008	1.428 (1.085, 1.879)	0.015
Normal sleep (7-8 h)	Ref		Ref		Ref		Ref	
Long sleep (≥9 h)	1.911 (1.233, 2.963)	0.012	1.930 (1.219, 3.056)	0.0160	1.853 (0.972, 3.532)	0.049	1.818 (0.883, 3.741)	0.069

Model I: Adjust for sex, age, race. Model II: Adjust for the variables in Model I plus BMI, alcohol status, smoking status, diabetes and sleep disorders. Model III: Adjust for the variables in Model II plus poverty-to-income ratio.

TABLE 4 Threshold effect analysis of sleep duration on chronic musculoskeletal pain and low back pain.

Outcomes	Non-adjusted Model		Model 1		Model 2	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Chronic musculoskeletal pain (Yes/No)						
Sleep (≤7 h)	0.671 (0.621, 0.725)	<0.001	0.766 (0.716, 0.819)	<0.001	0.772 (0.717, 0.833)	0.002
Sleep (>7 h)	1.431 (1.153, 1.777)	0.006	1.395 (1.113, 1.750)	0.034	1.389 (1.103, 1.749)	0.049
Low back pain (Yes/No)						
Sleep (≤7 h)	0.657 (0.597, 0.722)	<0.001	0.766 (0.673, 0.872)	0.002	0.776 (0.663, 0.906)	0.006
Sleep (>7 h)	1.470 (1.157, 1.869)	0.007	1.430 (0.973, 2.102)	0.049	1.419 (0.904, 2.228)	0.069

Model I: Adjust for sex, age, race. Model II: Adjusted for sex, age, race, poverty-to-Income Ratio, BMI, alcohol status, smoking status, diabetes and sleep disorder.

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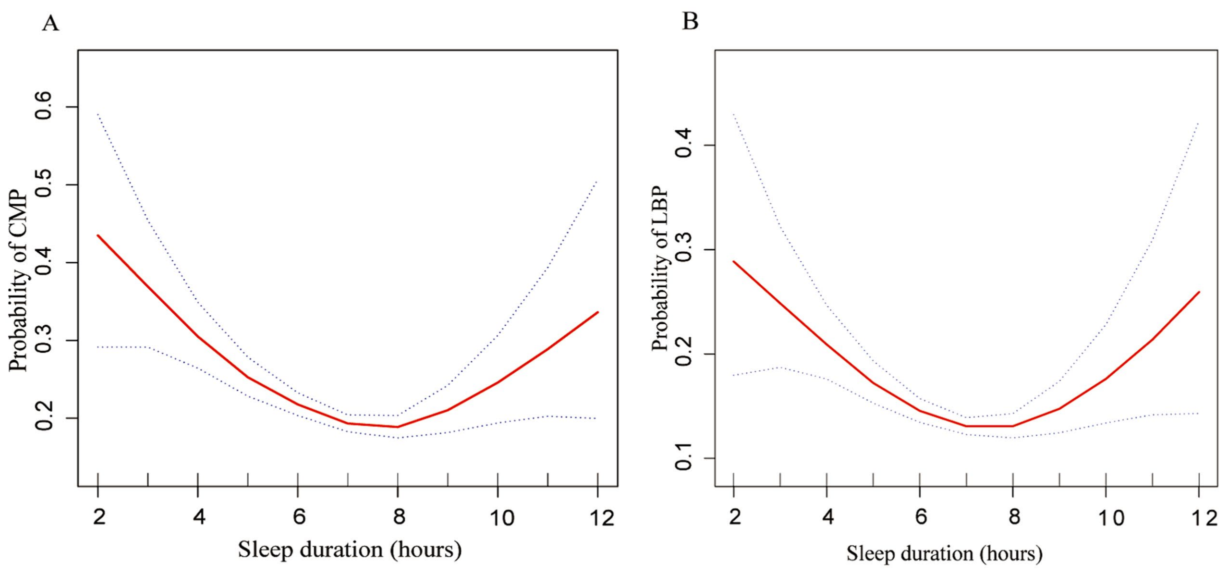

FIGURE 1
Multivariate-adjusted spline curves for relationship of sleep duration with chronic musculoskeletal pain and low back pain. **(A)** Probability of CMP and **(B)** probability of LBP. The solid line represents the estimated probability of CMP and LBP, and the dotted lines show point-wise 95% confidence intervals. These estimates are adjusted for sex, age, race, PIR, BMI, alcohol consumption, smoking habits, diabetes and sleep disorders. CMP, chronic musculoskeletal pain; LBP, low back pain; PIR, Poverty-to-Income Ratio.

Prior research has primarily focused on the adverse effects of insufficient sleep, with less attention given to the dangers linked with excessive sleep. Nevertheless, recent studies, including this one, have identified a U-shaped association between sleep duration and various health outcomes, including chest pain (21) and chronic musculoskeletal pain (22). This study's results align with prior research, highlighting that both insufficient and excessive sleep are associated with higher odds of pain.

In our study, we observed a U-shaped relationship between sleep duration and the prevalence of CMP, with 7 h of sleep being associated with the lowest odds. This finding is consistent with other research demonstrating that deviations from the optimal sleep duration of 7 h are linked to various adverse health outcomes. For example, studies have shown that both insufficient and excessive sleep are associated with increased all-cause mortality (2) and accelerated phenotypic aging (23). These findings suggest that maintaining an optimal sleep duration is crucial not only for reducing the prevalence of chronic pain but also for overall health and longevity.

It is reported that the relationship between pain and sleep is complex and bidirectional: pain can disrupt sleep, while insufficient or interrupted sleep can lower pain thresholds and increase spontaneous pain levels (14). The underlying neurochemical mechanisms involved in this two-way relationship may encompass various components of the opioid, monoaminergic, orexinergic, immune, melatonin, and endocannabinoid systems. Additionally, the hypothalamic–pituitary–adrenal axis, adenosinergic signaling, and nitric oxide pathways are also thought to be implicated (14). Musculoskeletal pain is more prevalent and prone to chronicity compared to headaches or abdominal pain. Previous research has indicated that short-term sleep deprivation disrupts the internal redox balance of the body (24). Furthermore, sleep is thought to not only conserve energy but also facilitate the removal of toxic proteins and metabolic byproducts through different pathways (25). Sleep deprivation leads to oxidative stress in glial mitochondria and lipid droplet accumulation, necessitating overnight sleep for the induction of glial cell and neuronal mitochondrial autophagy. Sleep disruption has been associated with a reduction in N3 sleep while studies have indicated that partial night sleep deprivation can trigger inflammation in the body (26). The responsible mechanisms of the association among excessive sleep and musculoskeletal pain remain to be explored. But the present study demonstrates that individuals sleeping less than 7 h and 9 h or more have elevated levels of CRP and neutrophil count, indicating increased inflammation (Unpublished data). Previous research has demonstrated that CMP can lead to cognitive impairment and accelerated aging in the hippocampal region (27), supporting the rationale for investigating the association between sleep duration and CMP prevalence.

The study identified findings of borderline significance regarding the association between long sleep duration and musculoskeletal pain. Although the p-value of 0.059 is close to the conventional threshold for statistical significance, it suggests that further research is needed to substantiate this finding. Given the potential implications for public health and clinical practice, we recommend that future studies should consider larger sample sizes and longer follow-up periods.

Our research uncovered a more pronounced influence of sleep disturbances on pain perception in women compared to men. The underlying mechanisms behind how sleep affects pain perception, particularly in females, remain unclear. One hypothesis is that there may be biological distinctions in the way pain is regulated, driven by factors such as hormones and genetics, leading to divergent functional neurological changes in females compared to males when experiencing sleep issues (28).

The present study found a higher prevalence of musculoskeletal pain in populations with cigarette smoking. Smoking and pain have a complex relationship. Research indicates that smoking can worsen chronic pain conditions. Smokers with chronic pain tend to report

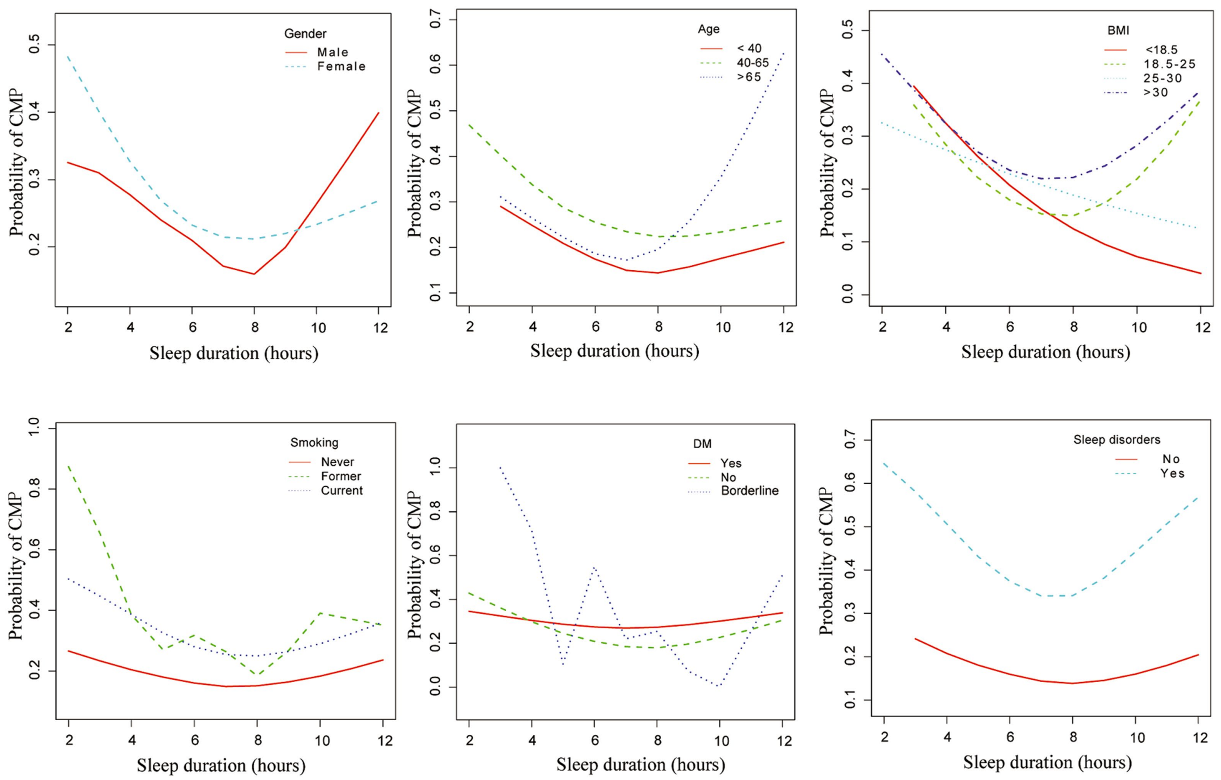

FIGURE 2
Associations between sleep duration and chronic musculoskeletal pain across different subgroups. This figure illustrates the associations between sleep duration and chronic musculoskeletal pain, stratified by gender, age, BMI, smoking status, diabetes, and sleep disorders. Adjusted for age (years), sex, race, PIR, BMI, alcohol consumption, smoking habits, diabetes and sleep disorders. CMP, chronic musculoskeletal pain; PIR, Poverty-to-Income Ratio.

higher pain intensity, functional impairment, and psychological symptoms compared to non-smokers (29). The prevalence of pain was also higher among former smokers compared to never smokers. While nicotine can initially have analgesic effects by stimulating the body's natural pain relief system, chronic exposure to nicotine and tobacco smoke can lead to increased pain sensitivity and the need for more analgesic medication (30, 31). Smoking can impair the body's ability to heal, decrease oxygen delivery, and lead to degenerative diseases that cause chronic pain (32). Additionally, smoking is associated with a higher odds of developing conditions like rheumatoid arthritis, which causes chronic joint pain and stiffness (32).

The present study found a higher prevalence of pain among adults aged 40–65 years compared to those under 40 years and over 65 years of age, excluding prolonged sleep durations. Several factors may contribute to the peak in pain prevalence within this middle-aged group: Many chronic diseases like osteoarthritis and degenerative spinal disease, which can lead to chronic pain, have a higher prevalence during the ages of 40–65 years (33). Adults in this age range often have high occupational stress and decreasing physical activity, predisposing them to musculoskeletal disorders (34). The perimenopausal period in women also falls within this age bracket, and hormone fluctuations may lower pain thresholds (35). Although older adults over 65 years have a high frequency of musculoskeletal conditions, pain thresholds gradually increase and pain perception declines in this elderly population (36).

5 Limitation

Our study boasts certain strengths, such as a relatively large sample size and adjustments for factors closely associated with musculoskeletal pain, such as smoking and alcohol consumption. However, our research also carries limitations. Firstly, the cross-sectional design of our study precludes causal inferences; thus, the directionality between sleep duration and pain requires further investigation through longitudinal or interventional research. Additionally, baseline self-reported sleep quality may be inaccurate, as individuals who self-report sleep disturbances are more likely to inaccurately estimate their sleep onset latency and total sleep time. In the future, both self-reported data and objective measurement methods such as actigraphs or sleep diaries, should be employed concurrently to enhance the accuracy of the data.

Additionally, our study solely focused on sleep duration, overlooking disruptions in sleep quality and patterns, such as fragmentation or shallow sleep, which are closely associated with heightened pain perception. Future research should incorporate monitoring and analyzing sleep patterns to comprehensively understand the relationship between sleep and pain. This study excluded participants with missing covariate data, which may result in a sample that does not fully represent the broader population. Consequently, despite our efforts to control for confounding factors in the analysis, selection bias may still influence the interpretation of our results. The study results are only applicable to the population aged 20–69 with available pain data, indicating that our findings are limited to this specific demographic in the United States.

6 Conclusion

To summarize, the duration of sleep was found to be linked to a higher occurrence of CMP in this study, which utilized data from the NHANES conducted between 2009 and 2010. It was observed that not only insufficient sleep, but also excess sleep, can contribute to a higher prevalence of experiencing pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the ethics review board of the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The protocols for the National Health and Nutrition Examination Survey (NHANES)were approved by the ethics review board of the National Center for Health Statistics, and all participants provided written informed consent.

Author contributions

CL: Methodology, Supervision, Writing – review & editing. HH: Data curation, Formal analysis, Writing – review & editing. QX: Conceptualization, Validation, Writing – original draft. LZ: Data curation, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1461785/full#supplementary-material

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How the arts heal: a review of the neural mechanisms behind the therapeutic effects of creative arts on mental and physical health

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Background: The creative arts have long been known for their therapeutic potential. These modalities, which include dance, painting, and music, among others, appear to be effective in enhancing emotional expression and alleviating adverse physiological and psychological effects. Engagement in creative arts can be pursued as a personal hobby, in a classroom setting, or through a formal therapeutic intervention with a qualified therapist. Engagement can be active (i.e., creating) or passive (i.e., viewing, listening). Regardless of the modality and manner of engagement, the mechanisms explaining the therapeutic efficacy of creative arts remain poorly understood.

Objective: This study aims to systematically review research investigating the neurological mechanisms activated during active or passive engagement in creative arts, with a specific emphasis on the roles of the medial prefrontal cortex (mPFC) and the amygdala in emotional regulation (ER) and creative behaviors. The review seeks to provide preliminary evidence for the possible existence of common neural mechanisms underlying both phenomena, which could inform the development of targeted therapeutic interventions leveraging creative arts for ER.

Methods: A systematic review was conducted following the Cochrane Collaboration guideline and PRISMA standards to identify studies examining the neurological mechanisms underlying creative activities.

Results: A total of six out of 85 records meet the inclusion criteria, with all being basic research studies. Preliminary findings suggest that active and passive engagement with creative arts consistently activate neural circuits implicated in adaptive emotional regulation, including the mPFC and amygdala. These activations mirror the neural pathways engaged in effective ER strategies, suggesting the possible existence of shared mechanisms between creative expression and emotional processing.

Conclusion: The evidence underscores the potential of creative arts as a complementary therapeutic strategy alongside conventional care and other evidence-based mind-body modalities. By elucidating the shared neural mechanisms between creative arts engagement and ER, this review contributes to the theoretical and practical understanding of the role of creative arts in mental health. Future research is recommended to further explore these neural correlations and their implications for therapeutic practice.

KEYWORDS

creative arts, emotional regulation, mind-body modalities, music, art, dance, medial prefrontal cortex (mPFC), amygdala

1 Introduction

1.1 Statement of purpose

At present time, there is limited understanding of how the arts heal. On the other hand, we have a better understanding of the areas of the brain that participate in emotional regulation (ER). Having a clearer picture of the neurological relationship between creative behavior and ER can be of use for advancing mental health interventions.

To address current theoretical limitations and potentially improve clinical practice, this study conducted a systematic review of research that directly investigated the neurological mechanisms activated during engagement in or exposure to creative arts (art, dance, and music), with a particular emphasis on studies highlighting the roles of medial prefrontal cortex (mPFC) and the amygdala.

The approach taken in this study is grounded in the hypothesis that engagement in or exposure to creative activities and ER share a common neuronal mechanism involving the mPFC and the amygdala. More specifically, we seek to show, within the limits of the available evidence, that the mPFC and the amygdala consistently activate during engagement in or exposure to art. By doing so, we provide a strong argument in favor of our hypothesis—engagement in or exposure to creative activities and ER lead to the activation of a common neuronal mechanism which includes the mPFC and the amygdala.

By identifying common neural mechanisms, we achieve two things (1) we provide support for the development of a theoretical framework explaining how art heals and (2) we provide knowledge that informs the development of more targeted therapeutic interventions that leverage the benefits of creative arts for ER. This could lead to the design of intervention protocols that are specifically aimed at engaging these neural pathways to maximize therapeutic outcomes.

We begin with a literature review to highlight the current limitations in our understanding of how the arts contribute to ER at the neurological level.

1.2 Emotions, feelings, and emotional regulation

The American Psychological Association (APA) defines *emotions* as a complex visceral experience, involving experiential, physiological, and behavioral elements (APA, 2018). Under some definitions, feelings represent a phenomenon that is distinct from emotions. More specifically, feelings can be defined as conscious awareness of emotions (Prinz, 2005).

We know from available research that being connected to and in control of our vast emotional spectrum appears to be an important piece of achieving wellbeing and mental and physical health (Consedine, 2008; Alexander et al., 2021; Menefee et al., 2022); however, significantly more studies are necessary for understanding the mechanisms underlying these observations. Being in control is one way of referring to ER—the processes by which individuals influence which emotions they experience, when they experience them, and how they express and respond to these emotions.

Some theories of emotions, such as evolutionary ones, are rooted in the idea that certain emotions have evolved to serve adaptive functions. These classical theories suggest that basic emotions are biologically ingrained and correspond to innate response programs. Jaak Panksepp, for example, proposed seven different neural pathways underlying different emotions: fear, care, lust, panic, seeking, play, and rage (Panksepp, 1986).

The view of specific brain areas as responsible for specific psychological constructs is contradictable by recent literature. For example Rieck et al. (2024), found that the neural representation of emotion spans multiple regions and cannot be summarized by the activation of a single structure; however, the study did find that neuronal signatures can be used as biomarkers for ER. More specifically, the study aimed to identify a neural signature for cognitive reappraisal using machine learning models in a neurotypical population. Participants viewed neutral and negative images with instructions to either look or reappraise and used functional magnetic resonance imaging (fMRI) to measure brain activity. Least absolute shrinkage and selection operator (LASSO) principal component regression and linear discriminant analysis were employed to classify images based on brain patterns. Key brain regions identified included the prefrontal cortex, insula, cerebellum, and occipital lobe.

In the human brain, as well as in other species, the emotional visceral experience originates in the lower primitive brain: the limbic system. For instance, a human and a cat can both experience fear thanks to their amygdala if they hear a loud noise; humans, however, are capable of not letting their fear dominate their behavioral and physical state, i.e., the cat runs away, but the human, although experiencing sensations of fear, may stay in one place, understanding that there is no immediate threat. This difference is due to humans' conscious awareness of emotions and the ability to name and regulate them. This ability appears to be primarily located in the brain's higher advanced cortices, specifically the prefrontal cortex (PFC). These two emotional processing brain centers or neural networks (i.e., the amygdala and the PFC) have been otherwise referred to as the limbic "low road" and the PFC "high road" (Fishbane, 2007).

Under the definition of feelings as conscious awareness of emotions, we can say that ER can occur when we experience feelings. In other words, the distinction between emotions and feelings under this definition is important because it underscores humans' capabilities of engaging in self-regulation, thus altering their physical and behavioral responses to emotions. The more we understand about the mechanisms that participate in ER, the more capable we should be of controlling them.

Does the self-regulated human have a healthier mental and physical response than the cat? Sometimes. ER plays an important role in mental and physical wellbeing, with advances in the understanding of it suggesting that incorporating ER practices can improve existing mental health interventions (Moltrecht et al., 2021); however, processes that make ER possible can also lead to negative outcomes. In other words, not all "high roads" are beneficial to our health, and many can relate to the harmful effects of unprocessed negative emotions. For example, chronic stress has known negative effects on mental and physical health (Mariotti, 2015; Shangkhum and Zikos, 2023). A frequent cause of chronic stress is habitual negative thinking or unhealthy ways of processing emotions, i.e., rumination (Renna et al., 2020).

Alongside standard-of-care approaches to mental health like psychotherapy and medication, mind-body techniques can counteract stress response (Jung et al., 2010; Wolever et al., 2012; Cozzolino et al., 2020; Kim et al., 2013). The body-mind model of art therapy posits that creative expression facilitates the activation, reorganization, growth, and reintegration of the self through integrated body-mind processes (Czamanski-Cohen and Weihs, 2016). The REPAT study, for instance, demonstrated significant improvements in emotion processing among women coping with breast cancer, highlighting the potential of art therapy to modulate emotional responses through creative engagement (Czamanski-Cohen and Weihs, 2023).

Some mind-body modalities (MBM) that have been shown to improve psychological and physical wellbeing are mindfulness, yoga, and meditation (Kwon and Lee, 2022). Although traditional MBM helps regulate the stress response, these techniques do not necessarily get to the root of why internal chronic stress may be there in the first place. Approaches focused on healthily releasing repressed painful emotions are an alternative solution that directly targets the source of stress. For instance, Emotional Awareness and Expression Therapy (EAET) is surfacing as a newer treatment modality, with two randomized control trials (RCT) showing EAET superior to Cognitive Behavioral Therapy (CBT) for chronic pain (Yarns et al., 2020; Lumley et al., 2017).

Other models of therapy applied to artistic engagement include the expressive arts therapy model (Malchiodi, 2003) and narrative therapy (Rice, 2015). The arts therapy model posits that engaging in different forms of creative expression can help individuals explore and process emotions, leading to improved mental health and wellbeing. Narrative therapy is based on the assumption that creating and analyzing personal narratives through writing or other creative means allows reframing experiences and developing more empowering perspectives.

1.3 Creative arts and art therapy in ER

1.3.1 The relationship between ER and creativity

ER can be either adaptive, creating a direct benefit, or maladaptive, creating dysfunction in our mind and body (Gordon and Mendes, 2021). ER mechanisms that are maladaptive (i.e., rumination, suppression) and adaptive (i.e., reappraisal) have been correlated with their consequential deleterious and positive health benefits, respectively. Long-term use of maladaptive mechanisms is correlated with poor mental health and somatic symptoms (Gordon and Mendes, 2021; Salazar Kämpf et al., 2023; Ouhmad et al., 2023; Centers for Disease Control Prevention, 2020; Cavicchioli et al., 2021). fMRI studies have shown that different regions of the brain are dedicated to adaptive and maladaptive emotional processing. For instance, within the prefrontal cortex, the frontal (ventro) medial gyri are involved with adaptive emotional processing mechanisms (Murakami et al., 2015; Hermann et al., 2014; Cutuli, 2014; Gross and John, 2003).

Adaptive ER like reappraisal, which is re-interpreting a negative scenario in a more positive light, has been shown to access neural circuitry on a different "high road" and a different amount of "low road" amygdala activation than maladaptive mechanisms like emotional suppression (Gross and John, 2003). Specifically, reappraisal, mindfulness, and expression of negative emotions have been shown to use the mPFC neural "high road" in conjunction with primal emotional brain centers like the amygdala. Emotional suppression, on the other hand, uses the dorsal PFC (dPFC) "high road" with decreased amygdala activity (Murakami et al., 2015; Hermann et al., 2014; Cutuli, 2014; Ahmed et al., 2015; Etkin et al., 2011; Chen et al., 2017). Depression severity has also been linked to blunted amygdala activity (Ferri et al., 2017). Therefore, adaptive emotional processing has been shown to engage the amygdala more than unhealthy mechanisms like chronic emotional suppression. This may mean subjects are not allowing themselves to access suppressed feelings like fear, which over the long term can have health consequences including all-cause mortality (Murakami et al., 2015; Chen et al., 2017; Chapman et al., 2013).

The activation of the ventromedial prefrontal cortex (vmPFC) with limbic regions is important for healthy ER, stress resilience, and moral judgment (Hänsel and von Känel, 2008; Suzuki and Tanaka, 2021; Hu and Jiang, 2014) and using adaptive emotional high roads i.e., problems solving, positively affects the nervous system, cortisol levels (hypothalamic-pituitary-adrenal axis), and mental and physical health compared to the negative effects of maladaptive high roads, i.e., disengagement (Ahmed et al., 2015; Kop et al., 2011; Gilbert et al., 2017; Patel and Patel, 2019). For instance, one study showed improved regulation of negative emotion with higher vmPFC and improved diurnal rhythm of circulating free cortisol (Urry et al., 2006). Another study showed that vmPFC activation correlates with the activation of the parasympathetic nervous system, improves health outcomes, and plays a pivotal role in biopsychosocial processes of disease (Hänsel and von Känel, 2008).

The evidence above suggests that (1) ER plays an important role in wellbeing defined as positive outcomes in physical and mental health and (2) at least in part, art works by enhancing ER. The clinical relevance of the relationship between ER and art warrants a further investigation of the neuronal mechanisms participating in creative behavior under the assumption of common neuronal mechanisms underlying both phenomena.

1.3.2 Arts in everyday activities and therapeutic settings

Creative arts encompass a broad range of activities including painting, music, dance, and writing, pursued primarily for personal expression, enjoyment, and cultural engagement. These activities are often self-directed and can be undertaken by anyone regardless of their skill level, with the primary goal being creative expression and personal satisfaction (Stuckey and Nobel, 2010).

Personal engagement with creative arts refers to activities pursued as hobbies or for educational purposes in settings such as classes or community groups. This type of engagement is typically self-directed, with individuals choosing activities based on personal interests and goals. Personal engagement can occur individually or in groups. We do not have knowledge of any study which has compared the psychological effects of individual vs. group engagement in creative arts in clinical or non-clinical settings.

There are two modes of art engagement: active participation and passive reception. Active participation consists of creating art and passive reception involves experiencing art created by others. To the best of our knowledge, there are no studies which have investigated whether the clinical effects associated with each engagement modality are explained by the same or different mechanisms or whether the effects in questions are comparable qualitatively and/or quantitatively.

Creative arts have been a vehicle for expression and healing across cultures since ancient times. For example, Egypt's oldest dance, the Zar, was performed for the sole purpose of healing (El Guindy and Schmais, 1994). Engaging in activities such as painting, writing, dancing is embraced not only for personal fulfillment but also for their capacity to modulate emotions. More specifically, evidence suggests that these practices influence mood, promote self-compassion, and enhance overall psychological wellbeing, impacting health at immediate, mid-term, and long-term levels (Stuckey and Nobel, 2010; Fancourt et al., 2019; Graham-Pole, 2000; Ebert et al., 2015; Morris et al., 2005; Šimić et al., 2021; Verger et al., 2022; Mastandrea et al., 2019). For instance, daily creative activities have been shown to improve health markers including cortisol diurnal patterns, autonomic balance, and overall quality of life across various demographic ranges (Stuckey and Nobel, 2010; Kaimal et al., 2016; Bolwerk, 1990; Okada et al., 2009; McCrary and Altenmüller, 2021).

In therapy, creative arts are integrated within different psychotherapeutic modalities to address specific psychological or physiological issues. Examples include art therapy, music therapy, and dance-movement therapy. A recent theoretical development in this field is the body-mind model of art therapy (Corsetti, 2021), which focuses on how art therapy facilitates activation, reorganization, growth, and reintegration of the self through body mind processes. The body-mind model encourages empirical research to explore and validate the key mechanisms posited to underlie the therapeutic effects of art therapy.

Creativity appears to be supported by complex, interconnected brain networks rather than isolated brain regions (Beaty et al., 2014). Engaging in creative tasks may stimulate similar integrative neural processes. For example, there appears to be a link between creative ability to the expression of genes associated with synaptic plasticity (Orwig et al., 2021). These genes are involved in synaptic assembly and signaling, underscoring that the ability to generate novel ideas is related to the brain's capacity to form and reorganize synaptic connections. In therapeutic settings, this suggests that creative arts might foster neural adaptability, potentially aiding recovery or development in clinical populations by promoting neural plasticity. Interventions that enhance synaptic plasticity might be particularly beneficial in rehabilitation settings, where recovery of cognitive functions requires neural reorganization. This assumption is supported by one study with adult art students documenting structural changes like the modification of white matter in response to learning and practicing art, which correlates with increased creative output (Regev and Cohen-Yatziv, 2018).

Clinical studies also support the effectiveness of different creative modalities in improving specific clinical outcomes when integrated within psychotherapy. Here are some examples:

- **Art therapy:** Research suggests that art therapy can improve symptoms in clinical populations. For example, one paper reported that engaging in art making and creative writing improved lab values in dialysis and HIV patients (Stuckey and Nobel, 2010). Art has been shown to significantly reduce cortisol levels irrespective of an individual's prior skill in healthy subjects (Kaimal et al., 2016). Systematic reviews suggest art therapy has clinical effects on mental disorders including anxiety, depression, Alzheimer's, and autism (Hu et al., 2021; Schlegel et al., 2015).
- **Music therapy:** Music therapy has been shown to be effective in improving vital signs, myocardial oxygen demand, and reducing anxiety after acute myocardial infarctions (Bolwerk, 1990). Music therapy can enhance parasympathetic tone and reduce catecholamines and cytokine levels in elderly patients with cardiovascular diseases and dementia (Okada et al., 2009). Reviews and meta-analyses indicate that music therapy significantly reduces stress-related biomarkers across various patient populations (McCrary and Altenmüller, 2021; Salamon et al., 2003; De Witte et al., 2022; Toyoshima et al., 2011).
- **Dance therapy:** Dance movement therapy (DMT) appears to be an effective intervention for decreasing depression and anxiety while increasing quality of life, interpersonal skills, and cognitive functions. Effects have been reported to remain stable or even improve at a 22-week follow-up (Koch et al., 2019).

1.3.3 The mPFC and amygdala as central components of a neural circuitry underlying both creativity and ER

Creativity is not merely a singular cognitive function but a complex interplay of multiple cognitive processes such as cognitive flexibility, working memory updating, and inhibitory control. These processes are supported by structural and functional networks within the brain, including the PFC, which plays a crucial role in creative ideation and problem-solving. Dopaminergic (DA), noradrenergic (NE), and serotonergic (5-HT) systems—modulate these cognitive functions. For instance, DA pathways are linked to both the enhancement of creative drives and the modulation of cognitive flexibility, essential for novel idea generation. In contrast, NE and 5-HT systems play roles in regulating mood states and motivational aspects of creativity, influencing how environmental and internal stimuli are processed creatively (Khalil et al., 2019).

Studies show that creative activities modulate and regulate emotions, increase empathy and tolerance, influence our moods, and affect our mental and physical health (Fancourt et al., 2019; Fancourt and Ali, 2019); however, understanding how they regulate emotions is still a work in progress. There may be a surfacing neuroscientific model to explain this.

With creativity being such an integral part of our humanity, it arguably makes sense that our brain has wiring dedicated to the creative process. Is this wiring limited to the theorized partition of the right creative vs. left logical brain? Interestingly, no. Creativity is much more expansive across neural networks, using more gray and white matter than once thought.

Along with limbic structures like the amygdala (Chan et al., 2023), there are three neural networks utilized during the creative process: the imaginative or Default Mode Network (DMN), the Central Executive Network (CEN), which engages the conscious brain to think and maintain attention, and the Salience Network (SN), which switches between the DMN and CEN (Raichle, 2015; Beaty et al., 2018a,b; Bressler and Menon, 2010; Bolwerk et al., 2014).

Research suggests the existence of dysfunctional interactions within and between the brain's core neurocognitive networks. For example, Menon's triple network model proposes that disruptions in the DMN, SN, and CEN are critical in the manifestation of psychopathological symptoms across a broad spectrum of disorders (Menon, 2011). In this model, the SN plays a key role in detecting and responding to salient stimuli. Dysfunction in this network can lead to inappropriate salience attribution, which is evident in conditions like schizophrenia where it may contribute to the emergence of hallucinations or delusions. In anxiety disorders, hyperactivity in the SN may lead to exaggerated threat perception and worry. Alterations in the DMN, which is involved in self-referential thought processes, have been implicated in a variety of conditions. For example, hyperconnectivity within the DMN is observed in depression, correlating with rumination and negative self-focus. Conversely, disruptions in the DMN connectivity are noted in Alzheimer's disease, reflecting difficulties with memory and self-referential cognition. The CEN supports higher cognitive functions such as working memory and executive control. Dysfunctions in this network often manifest in cognitive deficits across many psychopathologies, including attention deficit hyperactivity disorder (ADHD) and schizophrenia, where there may be a breakdown in cognitive control and attention regulation. The positive clinical effects on creative arts may be at least partly explained by the effects on the mentioned neurocognitive networks.

If creativity has been shown clinically to improve ER, could there be a common neuronal mechanism underlying both processes? Emotions and creativity appear to be tightly linked and that the neural mechanisms underlying creativity may depend on emotional states (McPherson et al., 2016). Two prominent regions seen to participate in both creativity and adaptive emotional processing are the mPFC, which is part of the DMN, and the amygdala.

1.3.3.1 mPFC in emotional processing and creativity

Both imagination and creativity have been shown to highly engage the DMN, including the mPFC (Abraham, 2016). For instance, a study on the neural substrates of spontaneous musical performance showed that improvisation in music suppresses the "inner critic" or dorsal PFC while activating the mPFC (Limb and Braun, 2008; López-González and Limb, 2012). The mPFC activity in the DMN may play a role not only in spontaneous thoughts and self-referential mental activity but also foster a sense of personal identity and lay the foundation for long-term goal pursuit (Fox and Christoff, 2018). Another relevant study argues that free-flowing complex music results from internally generated self-expression (via the mPFC) and attenuation of activity in the dlPFC (López-González and Limb, 2012). Yet another study on musical creativity concluded that the DMN and intensity of emotional experience may coordinate the drive to create music (Bashwiner et al., 2016). Additional research shows that the DMN or imagination phase of creativity engages the mPFC, and this engagement is related to openness to experience, increased resilience, and increased emotional awareness (Beaty et al., 2018b; Bolwerk et al., 2014; Wei et al., 2014; van Leeuwen et al., 2022; Vaisvaser, 2021).

fMRI studies have shown that healthy emotional processing utilizes the mPFC (Li et al., 2014). This anatomical correlation may suggest that creativity improves emotional wellbeing by utilizing similar "high road" neural networks involving the mPFC of the DMN. One study supports this hypothesis by showing less mPFC activity when using maladaptive discharge to process negative emotions in males, and more mPFC activity when women used an adaptive diversion mechanism to distract from negative emotions (Carlson et al., 2015). In short, being creative helps to process difficult and negative emotions in a healthy way, potentially by activating adaptive emotional neural networks involving the mPFC. Further research in this area could advance a theoretical model that would inform practices underlying the assumption that creative arts can improve emotional, mental, and physical health by improving ER.

Exposure to artistic creations also engages the mPFC. For instance, neuroimaging evidence indicates that activity in the mPFC is linked to viewing aesthetically pleasing images (Cattaneo et al., 2020; Kreplin and Fairclough, 2013) and listening to music (Carlson et al., 2015). This acknowledgment warrants the need to explore the neuronal correlates of both creative engagement and artistic exposure in order to elucidate the role of the mPFC in emotional processing following active or passive exposure to art. Understanding the role of the mPFC in emotional processing during both active and passive engagement would be a step toward elucidating whether the clinical effects associated with each engagement modality are explained by the same or different mechanisms.

Given that engagement in and exposure to creative activities activates the mPFC, we can speculate that creative arts may enhance emotional wellbeing by utilizing adaptive emotional networks. Understanding this connection could lead to more effective interventions for emotional and cognitive disorders.

1.3.3.2 "High road" and "low road" activations in creativity

Creativity activates the limbic "low road" regions of the brain, including the amygdala, which is the seat of primary emotions like fear and joy (Šimić et al., 2021; Bashwiner et al., 2016). Adaptive emotional processing has been shown to engage the amygdala more than unhealthy mechanisms like chronic emotional suppression (Murakami et al., 2015; Chen et al., 2017). Given the activation role of creativity, one can speculate that engaging in creative behaviors may help to engage the amygdala in emotional processing and improve emotional wellbeing, perhaps more so for those who have blunted activity or engage in chronic suppression.

The roles of the mPFC and the amygdala in regulating emotions through creative arts can be understood as complementary yet distinct, based on their involvement in adaptive and maladaptive emotional processing mechanisms. The mPFC appears to be primarily engaged in adaptive ER strategies such as reappraisal, where it facilitates positive reinterpretation of negative experiences by accessing "high road" neural circuits. In creative arts, the mPFC may play a role in processes where individuals manage emotions and foster resilience by processing emotions through self-expression and reflection.

On the other hand, the amygdala, part of the "lower road," appears to be more directly involved in the immediate emotional response, particularly emotions like fear and joy. Creativity activates the amygdala, which can help individuals access and process these primal emotions, leading to improved emotional wellbeing. In contrast, maladaptive ER strategies, such as suppression, involve reduced mPFC and amygdala activity, potentially leading to poorer mental health outcomes. Therefore, in the context of creative arts, the mPFC may help in reappraising and cognitively managing emotions, while the amygdala contributes to the visceral, emotional experience of the creative process.

By systematically exploring the neural correlates of creative engagement and emotional processing, we can determine whether the activations of the mPFC and amygdala during ER are indeed the same as those activated during passive or active creative engagement. This assessment could help us better understand the relationship between creativity and ER at the neuronal level and potentially inform the development of targeted interventions that leverage creative arts for enhancing emotional wellbeing.

2 Methodology

2.1 Protocol

The review process was conducted following the guidelines established by the Cochrane Collaboration, which include steps for identifying and selecting studies, extracting data, evaluating the quality of the data, and analyzing the findings (Deeks et al., 2023). Additionally, the reporting of the review adhered to the PRISMA Guidelines (Page et al., 2021).

2.2 Eligibility

1. Inclusion criteria:

- Peer-reviewed studies.
- Research presenting empirical data on the neurological mechanisms that participate in (1) ER and (2) creative arts.

2. Exclusion criteria:

- Studies not involving neuroimaging techniques.
- Studies in languages other than English.
- Studies not focused on mPFC or the amygdala.
- Non-human studies.

Our criteria were selected to directly support our aim of assessing whether the mPFC and the amygdala are activated during active or passive creative arts engagement. As such, we excluded studies not involving the brain structures nor neuroimaging techniques of interest.

2.3 Search strategy

The literature search was conducted across multiple electronic databases, namely PubMed, PsycINFO, and Google Scholar. The following search queries were entered using Boolean operators (AND, OR) to combine the keywords:

- **Creative arts:** ("art therapy" OR "dance therapy" OR "music therapy" OR "creative arts" OR 'creative writing").
- **ER:** ("ER" OR "affect regulation").
- **Neuroimaging/neurological pathways:** ("neuroimaging" OR "fMRI" OR "PET scan" OR "EEG" OR "medial prefrontal cortex" OR "MPFC" OR "amygdala" OR "neural pathways").

The search was conducted by combining these groups of keywords using Boolean operators as follows:

- ("art therapy" OR "dance therapy" OR "music therapy" OR "creative arts" OR "creative writing") AND ("ER" OR "affect regulation") AND ("neuroimaging" OR "fMRI" OR "PET scan" OR "EEG" OR "medial prefrontal cortex" OR "MPFC" OR "amygdala" OR "neural pathways").

Filters were applied to limit the search results to peer-reviewed articles, English language, and human studies.

2.4 Data collection and quality assessment

- Initial Screening: Titles and abstracts of studies retrieved using the search strategy were screened by one reviewer to identify studies that potentially meet the inclusion criteria.
- Full-text Review: Full texts of the selected studies were obtained and independently assessed for eligibility by one reviewer.

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials (Deeks et al., 2023). The risk of bias for each study was assessed by the reviewer using the Cochrane Collaboration's tool for assessing risk of bias (Deeks et al., 2023). This assessment covered various domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was judged as "low," "high," or "unclear" risk.

3 Results

3.1 Overview

Three databases were consulted, yielding a total of 85 records. Prior to screening, no records were removed for reasons such as duplication or ineligibility as indicated by automation tools. Consequently, 85 records underwent a screening process. Of these, 79 records were excluded for not meeting the inclusion/exclusion criteria, leaving six reports that were sought for retrieval. All six retrieved reports were then assessed for eligibility, and none were excluded from this stage (Figure 1).

We included studies that investigated the effects of creative arts on ER during both engagement in and exposure to creative arts (Table 1). Three of the studies included were focused on the ER effects of various creative art forms, including drawing, visual art viewing, and music listening. One study did not discuss creative arts but the effects of exposure to music. This study was included on the assumption that exposure to music may at least partly replicate the effects observed during actively listening to music or even music-making. One study examined the neural mechanisms of creativity during creative improvisation but not as part of art therapy. This study was included on the consideration that during therapeutic arts, the client goes on a creative journey following prompts from the therapist. Similarly, in this study, the musician was given the prompt to express himself freely on the piano, which may mean the activation of similar neural mechanisms.

The studies employed either functional near-infrared spectroscopy (fNIRS) or fMRI to investigate the neural correlates of ER through art creation or exposure to artistic creation (Table 2). None of the studies included took place in a psychotherapeutic or other clinical setting. Key findings revealed both shared and distinct neural mechanisms involved in processing emotions through creative activities. However, limitations such as sample size, demographic diversity, and the specificity of the observation periods were noted across the studies.

A bias risk assessment across the studies indicated various levels of uncertainty in selection, performance, detection, attrition, and reporting biases (Table 3). Some studies showed a high risk in certain areas, while others maintained low-risk profiles. The overall assessment suggests a need for caution in interpreting the studies' findings due to these potential biases.

3.2 Main findings

The study conducted by Zhang et al. (2023) using functional near-infrared spectroscopy (fNIRS) investigated the ER effects of drawing, comparing venting (expressing emotions) and distraction (drawing neutral objects) strategies in 44 college students. After inducing fear through a video, participants were asked to draw based on their emotional experience (venting group) or draw a house (distraction group), followed by a relaxation period.

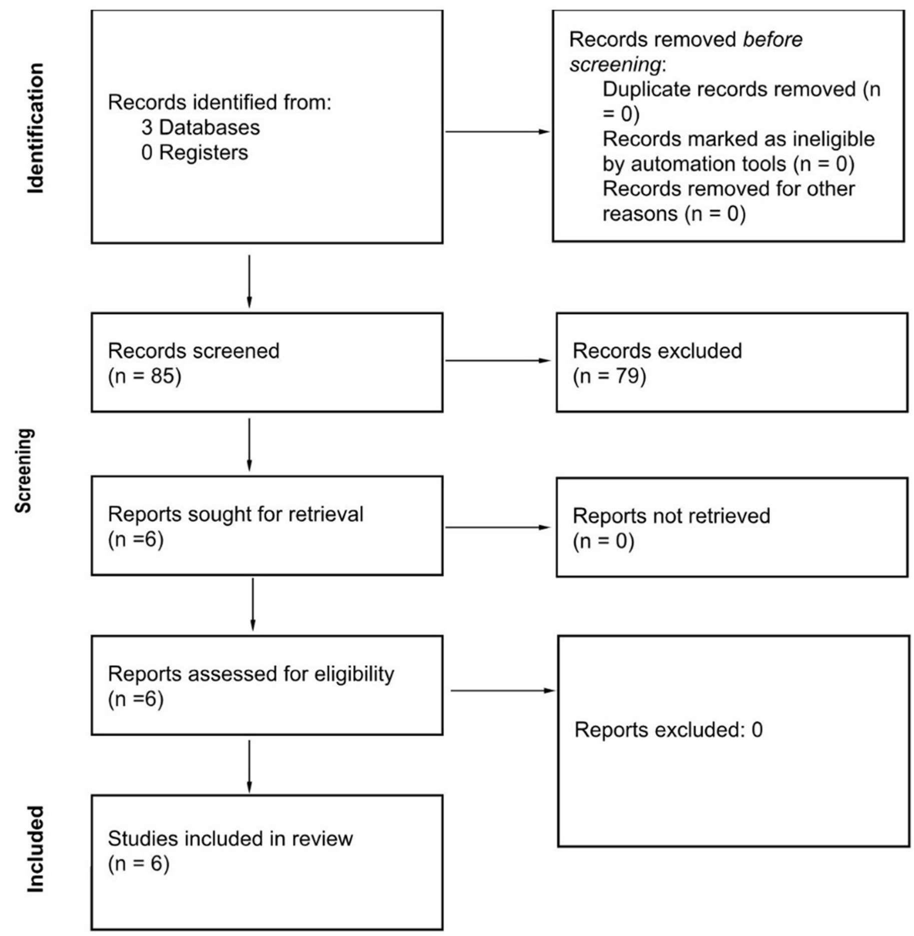

FIGURE 1
Study selection process.

TABLE 1 Summary of studies.

References	Study focus	Creative arts discussed	ER outcome
Zhang et al. (2023)	Investigate the ER effects of drawing, comparing venting vs. distraction strategies	Drawing	Emotional states modulated by drawing.
Kreplin and Fairclough (2013)	Examining rPFC activation using fNIRS during viewing of art intended to induce emotions	Viewing visual art	Emotional responses to visual stimuli
Carlson et al. (2015)	Investigates emotion regulation through music and neural responses in the mPFC	Music listening	Discharge strategy
McPherson et al. (2016)	Examines the influence of emotional cues on creativity during piano improvisation	Piano improvisation	Emotionally targeted musical improvisation
Bolwerk et al. (2014)	Investigates effects of visual art production vs. cognitive art evaluation on brain connectivity and resilience	Visual art production and evaluation	Self-awareness and emotional control
Limb and Braun (2008)	Investigated the neural substrates that underlie spontaneous musical performance	Jazz improvisation	Deactivation of limbic structures involved in regulating motivation and emotional tone

TABLE 2 Neuroimaging technique, key findings, and limitations.

References	Neuroimaging techniques used	Key findings	Limitations
Zhang et al. (2023)	fNIRS	Distraction drawing resulted in a higher valence immediately after the activity compared to venting drawing. During relaxation, venting drawing showed greater improvement in valence. Higher PFC was associated with distraction drawing	Limited observation period; lack of consensus on brain activation interpretations
Kreplin and Fairclough (2013)	fNIRS	Increase in rPFC oxygenated blood during positive image viewing	Viewing conditions not manipulated to investigate the gateway hypothesis
Carlson et al. (2015)	fMRI	Discharge strategy related to decreased mPFC activity in males and increased anxiety and Neuroticism. Diversion strategy related to increased mPFC activity in females	No explicit measures of non-musical mood regulation behavior; potential Type I errors
McPherson et al. (2016)	fMRI	Emotional cues modulate neural activity in PFC and limbic areas during improvisation. Positive improvisation associated with greater deactivation of the dlPFC and increased activation in the left amygdala. Negative improvisation linked to increased connectivity between the insula and substantia nigra	Limited sample size; only male participants
Bolwerk et al. (2014)	fMRI	Visual art production enhances functional connectivity between the PCC/preCUN and the frontal cortex (most notably the mPFC), linked to increased self-awareness, emotional control, and psychological resilience	The study only included post-retirement adults
Limb and Braun (2008)	fMRI	Spontaneous musical improvisation leads to a dissociated pattern of activity in the PFC, extensive deactivation of dorsolateral and lateral orbital regions, with focal activation of the mPFC cortex. Changes in PFC activity were accompanied by widespread activation of neocortical sensorimotor areas and deactivation of limbic structures	Study limited to six highly trained jazz musicians

The study aimed to explore the potential differences in ER between venting and distraction strategies through drawing. Using fNIRS, the researchers measured prefrontal cortex activity, correlating it with self-reported emotional states before and after the drawing activity and a subsequent relaxation period. Initially, the distraction group showed higher emotional valence compared to the venting group immediately after the drawing activity, indicating a quicker recovery from the induced negative emotion. However, no significant difference in emotional valence between the two groups was observed after the relaxation period. During the drawing period, increased activation in BA10 (mPFC) and BA46 (dlPFC) was associated with lower valence (lower emotional improvement). During the relaxation period, decreased activation in these channels was associated with higher valence, suggesting that reduced cognitive control facilitated better emotional recovery.

The study reported a significant difference in mPFC activation between the venting and distraction groups, with the venting group showing a 1.2 μM increase in oxygenated hemoglobin compared to a 0.8 μM increase in the distraction group ($p < 0.05$). The correlation between mPFC activation and emotional valence was $r = -0.45$ ($p < 0.05$), indicating a moderate negative relationship.

The findings suggest that while distraction strategies may offer a quick fix in emotion regulation, venting strategies might lead to a more profound and lasting emotional recovery, evidenced

TABLE 3 Risk of bias.

References	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Zhang et al. (2023)	Unclear	High	Unclear	Unclear	Unclear
Kreplin and Fairclough (2013)	Unclear	Low	Low	Unclear	Unclear
Carlson et al. (2015)	Medium	Low	Low	Unclear	Low
McPherson et al. (2016)	Low	Unclear	Low	Unclear	Low
Bolwerk et al. (2014)	Unclear	Low	Low	Unclear	Low
Limb and Braun (2008)	Low	Low	Low	Unclear	Low

by the changes in emotional valence post-relaxation. The study's findings suggest that expressive art activities engage neural networks involved in adaptive ER where the mPFC and the amygdala play a significant role. The authors noted limitations such as the short duration of the observation period post-drawing activity and the potential for the experimental manipulation (i.e., instructions for drawing tasks) not fully capturing the participants' actual engagement in venting or distraction strategies. Future research is suggested to extend the observation period and explore the underlying mechanisms common to both strategies that facilitate ER.

Bolwerk et al. (2014) investigated the impact of engaging in visual art activities on the brain's functional connectivity, particularly focusing on the DMN, an area which, as discussed earlier, includes the PFC and the amygdala. Utilizing fMRI, the research explores how visual art production (actively creating art) and cognitive art evaluation (cognitively analyzing art) influence psychological resilience and neural connectivity in a non-clinical sample of 28 post-retirement adults. Participants were randomly assigned to either a visual art production group where they actively created art, or a cognitive art evaluation group where they engaged in the cognitive evaluation of artworks at a museum. The DMN's connectivity was analyzed using fMRI before and after the participants attended weekly art sessions for 10 weeks. Psychological resilience was also assessed using the brief German version of the Resilience Scale (RS-11).

The visual art production group showed significant improvement in functional connectivity of the DMN, particularly between the PCC/preCUN and the frontal cortices (BA 8, 9, 10, 46). There was enhanced connectivity from the left and right PCC/preCUN to areas including the premotor cortex (BA 6), prefrontal cortex (BA 8, 9, 10, 46), superior and inferior parietal lobules (SPL, BA 7; IPL, BA 39, 40), and superior and middle temporal gyri (MTG, BA 21; STG, BA 22) at T1 compared to T0.

The cognitive art evaluation group showed weaker improvements in DMN connectivity, with significant connectivity from the right PCC/preCUN to the SPL (BA 7) and PCC (BA 31), and no significant changes for the left PCC/preCUN at T1 compared to T0.

The increases in connectivity were quantified using z-scores, with the most substantial improvements observed in the left PCC to left SPL connectivity ($z = 3.28$, $p < 0.001$). The art production group also showed a significant increase in resilience scores (measured by the RS-11 scale), with an average increase of 2.15 points ($p < 0.01$).

This increased connectivity in the art production group was associated with psychological resilience, suggesting that creating visual art may bolster psychological resilience in adulthood. The cognitive art evaluation group did not show significant changes in the DMN's connectivity, highlighting a specific impact of active art production on brain function. Additionally, the visual art production group demonstrated increased specificity and differentiation in the sensorimotor cortex (S1/M1) at rest, suggesting improved brain function in regions involved in motor and sensory processing.

The findings suggest that engaging in visual art production can lead to enhancements in the functional connectivity of the brain, particularly within the mPFC and amygdala of the DMN, which is associated with cognitive processes like introspection and self-awareness. It is important to note that the study's findings are based on a small, non-clinical sample of post-retirement adults, limiting the generalizability of the results.

The observation that visual art production leads to increased functional connectivity within the DMN, especially between PCC, preCUN, and frontal and parietal cortices, supports the idea that engaging in creative activities can alter brain function in ways that may enhance ER. Since the DMN is associated with self-referential thought processes, an enhancement in its connectivity could facilitate more effective emotional processing and regulation.

Kreplin and Fairclough (2013) explored how the medial rostral prefrontal cortex (mrPFC; BA10) is activated during the viewing of visual arts that evoke positive and negative emotions. Thirty right-handed participants without formal art training were recruited to ensure that the study results were not biased by professional familiarity with visual art. The experimental setup involved viewing 16 pre-rated images (eight positive, eight negative) under two conditions: emotional introspection (EI) and spot-the-difference (SD), serving as a task for external object identification. The use of fNIRS allowed for the monitoring of brain activity, specifically changes in oxygenated and deoxygenated hemoglobin, as indicators of neural activation. The mean increase in oxygenated hemoglobin in the rPFC was 0.5 μM for positive images, compared to 0.2 μM for negative images ($p < 0.05$). The effect size for the difference between positive and negative images was Cohen's $d = 0.65$, indicating a moderate to large effect.

The findings revealed a significant increase in oxygenated blood in the medial rPFC when participants viewed positive images compared to negative ones, indicating a differential brain response based on the emotional valence of the artwork. Notably, there was no significant difference in brain activation between the two viewing conditions (EI and SD), suggesting that the emotional impact of the art was consistent regardless of the focus on internal feelings or external stimulus properties. One limitation noted is the potential confounding effect of having the art stimulus present during both conditions, possibly affecting the purity of internal vs. external attentional focus.

The study suggests that the mrPFC plays a significant role in the emotional evaluation of art, particularly in response to positive imagery. This neural activation pattern suggests a fundamental neural basis for the aesthetic appreciation of art that transcends the mere cognitive analysis of visual properties. The involvement of the medial rPFC in processing positive art evaluations and its role in ER provides neural evidence supporting the hypothesis that engagement in creative arts (like viewing art) may activate similar brain networks involved in adaptive ER.

Carlson et al. (2015) conducted a study on the behavioral and neural correlates of adaptive and maladaptive emotion regulation strategies through music in males and females. A total of 123 participants underwent psychological assessments to evaluate depression, anxiety, Neuroticism, and their uses of music for mood regulation (MMR). Of these, a subset of 56 participants also participated in an fMRI study to examine neural responses to music in the mPFC.

The study reported a significant gender difference in the neural response to music, with females showing a stronger correlation between mPFC activation and positive mood regulation ($r = 0.55$, $p < 0.01$). The effect size for the difference in mPFC activation between discharge and diversion strategies was Cohen's $d = 0.78$, indicating a large effect.

Behavioral results highlighted a positive correlation between the use of music as a discharge mechanism (expressing negative emotions through music) and increased levels of anxiety and Neuroticism, especially in males. This correlation suggests that employing music as a discharge strategy might be linked to maladaptive patterns of emotion regulation. Conversely, the diversion strategy (using music to distract from negative emotions) was associated with more adaptive regulation patterns, indicated by increased mPFC activity during music listening in females. This finding suggests gender-specific differences in how music listening strategies are employed and their neural underpinnings.

The study posits that while music has the potential to be a powerful tool for emotion regulation, the manner in which it is used can have significant implications for mental health. Specifically, the discharge strategy, particularly prevalent among males, may reinforce negative emotional states rather than alleviate them, potentially exacerbating issues like anxiety and Neuroticism. On the other hand, the diversion strategy, more common among females, appears to activate neural mechanisms that could contribute to more effective emotion regulation. Several limitations are acknowledged, such as the lack of measures for non-musical mood regulation behaviors and a focus solely on the mPFC, potentially providing an incomplete picture of the neural processes involved in music-induced emotion regulation. Additionally, the generalizability of the findings may be limited by the sample's cultural and age homogeneity.

The study's acknowledgments that different music listening strategies can activate the mPFC in gender-specific ways are especially relevant. These results contribute to our understanding of how the mPFC, a crucial area for emotion regulation, is involved in the emotional responses elicited by music listening. The gender differences observed in the neural responses to music listening strategies may inform further inquiries into how individual differences affect the engagement with creative arts for ER.

Limb and Braun (2008) conducted an fMRI study to explore the neural substrates of spontaneous musical performance, specifically examining jazz improvisation in professional pianists. The study identified a unique pattern of brain activity associated with the creative process of improvisation, characterized by a dissociated pattern of activity in the prefrontal cortex. This included deactivation of dmPFC (BA 8,9) medial dlPFC (BA 46), lateral dlPFC (BA9), superior dlPFC (BA8), ventral lateral orbitofrontal (lOFC) (BA 11, 47), and Mid lOFC (BA11) alongside focal activation of the mPFC (BA 10).

The study reported a 1.3% increase in BOLD signal in the mPFC during improvisation compared to the control task ($p < 0.05$). This activation was accompanied by a broader network activation including the sensorimotor cortices, with significant increases in BOLD signal observed in the precentral gyrus (BA 6, $z = 3.12$, $p < 0.001$).

Such a pattern suggests a combination of psychological processes necessary for spontaneous improvisation, highlighting a shift away from self-monitoring and conscious control toward a more free-flowing creative state. Furthermore, improvisation was associated with widespread activation of neocortical sensorimotor areas and deactivation of limbic structures, indicating a complex interplay between cognitive control, emotional regulation, and motor execution during creative musical expression. The study's findings highlight the significant neurobiological underpinnings of spontaneous creativity, emphasizing the role of specific prefrontal cortex regions in facilitating a state conducive to creative output. The research, however, was limited by its small sample size, focusing on six highly trained jazz musicians, which may not generalize across broader populations or different musical genres.

Finally, McPherson et al. (2016) investigated the interaction between the neural systems involved in creativity and those involved in emotion through an fMRI study of 12 professional jazz pianists. Participants were shown photographs of an actress depicting positive, ambiguous, and negative emotions. For each photograph, participants received visual and auditory cues instructing them to engage in one of three tasks: view the image, play a chromatic scale, or improvise music. The improvisation task required participants to create music on a custom-built, non-ferromagnetic piano keyboard that they felt represented the emotion in the photograph. This experimental design aimed to examine whether emotional intent influences the neural substrates of creativity.

BA 45 was activated in all emotion conditions (positive, negative, and ambiguous), while the Supplementary Motor Area (SMA) (BA 6) was activated for ambiguous and negative improvisation. Conversely, deactivations were observed in the Bilateral Angular Gyrus (AG), (BA 40), Middle Precuneus (BA 7), Medial and Lateral Frontopolar Prefrontal Cortex (BA 10), and dlPFC across all emotion conditions. Emotion-specific activations included the right superior temporal lobe and temporal pole (BA 22 and BA 21) during ambiguous improvisation, and more widespread deactivation in the dlPFC, AG, and precuneus during positive improvisation compared to negative and ambiguous conditions.

Between-emotion contrasts revealed heightened activity in the right insula (BA 13 and 47), right anterior cingulate cortex (BA 32), right parietal cortex (BA 40), bilateral middle temporal lobes (BA 22), and bilateral middle frontopolar prefrontal cortex (BA 10) during positive vs. negative and ambiguous improvisation. Positive improvisation also showed increased cerebellar activity and more activity in the left hippocampus, amygdala, and right parahippocampal gyrus.

The study observed a main effect of emotion on note densities [$F_{(1,3)} = 31.88$, $p < 0.001$], with positive emotions being expressed through higher note densities (mean note density: positive = 3.61 notes/s, negative = 2.09 notes/s, ambiguous = 2.56 notes/s). Significant differences in connectivity were found using PPI analysis between the left insula and various regions, depending on the emotional context. For instance, the left insula showed significantly higher connectivity with the superior medial gyrus during positive improvisation compared to negative improvisation ($p < 0.001$).

The study found that emotional context significantly modulates brain activity in areas associated with creativity. Notably, the mPFC and limbic regions such as the amygdala and insula showed varying levels of activity and functional connectivity depending on the emotional intent behind the improvisation. Positive emotions elicited more extensive deactivation in the dlPFC, suggesting a deeper state of creative flow. Conversely, negative emotions were associated with heightened connectivity between the amygdala and areas involved in emotional processing and reward, indicating a different pathway of emotional influence on creativity. Musical improvisation, irrespective of emotional context, engaged brain regions known to be involved in language processing, motor planning, and sensory-motor feedback.

The study's findings underscore the tight integration between emotion and creativity, showing that the creative process in music is not just a cognitive task but also emotional. The findings suggest a dynamic neural model of creativity that is sensitive to emotional context. The differential activation and connectivity patterns observed highlight the role of the mPFC and limbic system in mediating the creative process under the influence of emotions. The study's limitations include its focus on a specific form of music creativity (musical improvisation) and its small sample size, which consisted of male participants.

The observed modulation of creativity-related brain networks by emotional intent, and the specific roles of the mPFC and limbic structures in this process, support the hypothesis of a shared neural mechanism between artistic creativity and ER.

4 Discussion

4.1 The role of the PFC and the amygdala in engagement and exposure to creative arts

This systematic review critically examined the evidence supporting the hypothesis of a common neuronal mechanism for ER and engagement in or exposure to artistic creations, with a focus on the roles played by the mPFC and the amygdala in both contexts. We found non-clinical fMRI and fNIRS studies assessing the neuronal correlates of creative engagement (Bolwerk et al., 2014; McPherson et al., 2016; Limb and Braun, 2008; Zhang et al., 2023), as well as non-clinical fMRI studies investigating the neuronal correlates of exposure to artistic exposure (Kreplin and Fairclough, 2013; Carlson et al., 2015).

While the studies included are diverse in terms of art type and engagement modality (creation vs. exposure), we find a consistent pattern of neural activation involving the prefrontal cortex. Some studies also report the engagement of the amygdala during artistic creation (Zhang et al., 2023) and artistic improvisation tasks (McPherson et al., 2016; Limb and Braun, 2008). These results suggest that the PFC appears to participate in both artistic production and exposure to at least certain art types (visual arts and music).

The findings above are consistent with several assumptions we made based on previous literature. For instance, previous literature has found the PFC (Raichle, 2015) and the amygdala (Chan et al., 2023) participate in creative activities, among other structures that belong to the DMN and CEN (Raichle, 2015; Bolwerk et al., 2014). We found that the mPFC and the amygdala participate in drawing (Zhang et al., 2023) and creative improvisation (McPherson et al., 2016; Limb and Braun, 2008), and the mPFC is also activated during exposure to music (Carlson et al., 2015). We also found that the PFC does not only participate in artistic creation but also in exposure to other creations, with the rPFC being activated during exposure to visual arts (Kreplin and Fairclough, 2013) and mPFC being activated during exposure to music (Carlson et al., 2015).

These findings advance the literature by suggesting that both active and passive engagement with artistic creations activate specific parts of the brain, including the PFC and amygdala. If we assume that activation of these brain regions is associated with improved ER, our results provide a compelling argument that engagement in or exposure to creative arts could offer clinical benefits.

4.2 Creative arts and ER

Our literature review shows that engagement and even exposure to creative arts activates parts of the brain that participate in ER. For instance, we know that the PFC plays an important role in adaptive and maladaptive emotional processing (Murakami et al., 2015; Gross and John, 2003) and we showed that this part of the brain is consistently activated during creative engagement/exposure.

We also know from previous research that adaptive ER strategies, such as reappraisal and mindfulness, engage the mPFC in conjunction with the amygdala (Chen et al., 2017). We also know that the amygdala also participates in the immediate emotional response to stimuli, particularly emotions related to fear or pleasure and its engagement is key for the emotional intensity required in creativity and for the embodied experience of emotions (Chen et al., 2017; Šimić et al., 2021; Bashwiner et al., 2016). We found that creative arts engage both structures simultaneously (McPherson et al., 2016; Zhang et al., 2023) during artistic creation, which suggests artistic creation may contribute to ER by activating structures that participate in it. On the other hand, we also found that improvisation activated the mPFC, but deactivated limbic structures, suggesting a complex interplay between cognitive control, emotional regulation, and motor execution during creative musical expression.

The identification of a common neuronal mechanism underlying engagement with or exposure to creative arts and ER highlights a potential avenue for enhancing clinical practices. Specifically, the findings suggest that creative arts could be a valuable tool in improving ER, thereby enhancing emotional intelligence and resilience. This insight supports the use of creative therapies as an effective approach to improving the quality of life for individuals with low ER capacity, offering a new dimension to mental health interventions.

Furthermore, the observed activation patterns in both the PFC and amygdala during creative engagement and exposure suggest potential biomarkers for evaluating the efficacy of art-based interventions in clinical settings.

4.3 Limitations of the study and future research directions

Our study comes with important limitations, which is to be expected given the lack of research investigating our hypothesis. Very few studies on fMRI studies have explored the relationship between engagement in artistic creation or exposure to artistic creations and ER. As such, our systematic review is limited by the small number of studies that were included. In addition, we also note methodological limitations encountered in the review, including variability in study design and population demographics, which may influence the generalizability of the findings.

Equally important, we need to distinguish between studies conducted in controlled laboratory settings and those in real-world clinical interventions such as randomized controlled trials (RCTs). Laboratory studies focus on specific aspects of the therapeutic process under controlled conditions, aiming to isolate and understand particular mechanisms or effects. In contrast, RCTs and real-world interventions assess the overall efficacy of creative arts therapies within complex, real-life clinical settings, considering various interacting factors. We acknowledge there may be differences in neuronal response between laboratory studies and clinical interventions. We also acknowledge that the effects of engagement might be different depending on whether individuals engage with creative arts by themselves or in a group.

Finally, it's important to note that while creativity is a potential major mechanism underlying the therapeutic effects of engagement with creative arts, other mechanisms may contribute to these benefits and separating the effects of each mechanism is a challenging task, to say the least. In visual art-making, the tactile interaction with art materials (e.g., clay, paint, and textiles) will engage sensory and motor pathways and this sensorial experience may enhance emotional expression and regulation (Wong and Au, 2019). In dance and movement therapy, the physical movement of the body is a central component. This movement can help release pent-up emotions, increase body awareness, and improve mood through the release of endorphins. The aesthetic experience itself, whether through creating or observing art, can evoke powerful emotional responses. This experience can activate the brain's reward system, providing a sense of pleasure and satisfaction (Ritter and Low, 1996). The appreciation of beauty in art can also stimulate cognitive and emotional processes, contributing to enhanced wellbeing.

To address some of these limitations and build upon the current findings, future research should aim to standardize methodologies across studies to facilitate comparability and replication. Hybrid studies that compare outcomes between different conditions can clarify the nature of the potential differences in neuronal responses between laboratory studies and clinical interventions. Longitudinal studies are needed to assess the durability of the neural and psychological changes induced by creative arts interventions.

Studies should also explore how different modalities of creative arts therapies can be tailored to individual needs and conditions, and how these interventions can be integrated with existing therapeutic practices. Finally, future studies should seek to explore the potential differences in clinical effects and neuronal correlates between engagement with and exposure to the creative arts.

5 Conclusion

This systematic review examined the neuroanatomical basis of ER and creative engagement to determine whether they share common underlying neuronal mechanisms. The recognition of a common mechanism highlights the potential of creative arts as a complementary therapy for conditions characterized by low ER. We found consistent activation of the mPFC and amygdala during creative engagement, suggesting that these regions are involved in both adaptive ER and creative processes. These findings support the hypothesis that creative arts may engage similar neural networks as those used in ER, offering a neuroscientific basis for the observed benefits of creative therapies in enhancing emotional intelligence and facilitating emotional processing. However, the study's limitations, including a small number of studies, a lack of clinical trials, and methodological constraints, suggest that further research is needed. Future studies should focus on standardizing methodologies, conducting longitudinal research, and exploring the specific mechanisms through which creative arts contribute to ER, which could inform the development of more effective therapeutic interventions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

KB: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. FV: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The impact of mind–body exercise on the quality of life in older adults: the chain mediation effect of perceived social support and psychological resilience

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Background: With the intensification of the global aging trend, there is a contradiction between the extended lifespan and the decline of physiological functions among the older adult. It has become a global consensus to focus on and improve the quality of life for the older adult. Mind–body exercises (Tai Chi, Ba Duan Jin, Yi Jin Jing) play a crucial role in promoting the quality of life for older adults, but the mechanisms and mediating effects are not yet clear.

Objective: This study examines the impact of mind–body exercises (Tai Chi, Ba Duan Jin, Yi Jin Jing) on the quality of life in older adults, with a particular focus on exploring the chain mediating effects of perceived social support and psychological resilience.

Methods: This study is a cross-sectional study that surveyed 1,087 older adults participating in mind–body exercises (Tai Chi, Ba Duan Jin, Yi Jin Jing) in 13 districts of Beijing, China, from March 25 to May 3, 2024. The Physical Activity Rating Scale (PARS-3), the World Health Organization Quality of Life Scale (WHOQOL-BREF), the Perceived Social Support Scale (PSSS), and the Connor-Davidson Resilience Scale (CD-RISC) were used to measure mind–body exercise, perceived social support, psychological resilience, and quality of life, respectively. Data were statistically analyzed using SPSS 26.0, and mediation effects were tested and effect analysis was conducted through structural equation modeling (AMOS) and the Bootstrap method.

Results: The study results show that mind–body exercises (Tai Chi, Ba Duan Jin, Yi Jin Jing) are significantly and positively correlated with the quality of life in older adults ($r = 0.549$, $p < 0.01$). The path coefficients for the relationships mind–body exercise → perceived social support ($\beta = 0.46$, $p < 0.001$) → psychological resilience ($\beta = 0.20$, $p < 0.001$) → quality of life in older adults ($\beta = 0.39$, $p < 0.001$) are significant, indicating that perceived social support and psychological resilience have a chain mediating effect between mind–body exercise and the quality of life in older adults.

Conclusion: Mind–body exercises not only improve the quality of life for older adults but also indirectly enhance it by strengthening perceived social support and psychological resilience. This study provides significant reference for developing health intervention strategies targeted at older adults, suggesting that promoting mind–body exercises can improve their sense of perceived social support and psychological resilience, thereby increasing their quality of life.

KEYWORDS

mind–body exercise, perceived social support, psychological resilience, quality of life in older adults, the chain mediation effect

1 Introduction

The issue of global aging is becoming increasingly severe, with old age being a period of decline in the life cycle of an individual. Older adults must face various stressors that are distinct from those experienced by other age groups, such as limitations in daily activities (1), an increase in chronic diseases (2), changes in social roles (3), and a decrease in self-worth (4). These stressors can all potentially threaten the Quality of Life in older adults (5, 6). A decline in the Quality of Life in older adults can subsequently increase family stress and socio-economic burdens, leading to a variety of social issues. Ensuring the Quality of Life in older adults has become a focal point of concern for the public and the health system.

Existing literature indicates that physical exercise is the most effective, green, and scientific method to enhance the quality of life for older adults, and it can have a positive long-term impact on both physical function and psychological state (7, 8). Mind–body exercise, as a form of physical activity that integrates mental concentration, breath control, and physical movement, possesses characteristics of both aerobic and resistance exercises, making it particularly suitable for older adults (9). Regular and rigorous engagement in mind–body exercise is essential. Numerous studies have shown that appropriate mind–body exercise, especially proactive physical activity, can delay degenerative changes and improve the quality of life and health (10, 11). Furthermore, mind–body exercise also significantly enhances individual psychological health. By strengthening emotional regulation capabilities, it can effectively alleviate psychological stress, depression, and loneliness caused by factors such as family, society, and retirement (12), thereby maintaining a good mental state and enhancing their evaluation of overall quality of life.

The influence of mind–body exercises on the quality of life in older adults is not confined to a single dimension but is subject to the mediating effects of multiple factors, thus constituting a multi-tiered and dynamic mechanism of action. Quality of life encompasses multiple dimensions, including material, psychological, and social aspects, among which the state of mental health is a significant component of the overall quality of life (13). A positive mental health status is crucial for the older adult to enjoy a happy later life and promote harmonious social development. Perceived social support is an essential psychological resource for the older adult, which is closely associated with the quality of life (14). Psychological resilience is one of the components of the mental health quality system (15), and high psychological resilience can help the older adult improve their quality of life, even when they may face adversity (16). Previous research results indicate that the level of perceived social support among older adults has an impact on their level of psychological resilience (17). Therefore, to achieve a more comprehensive analysis, this study incorporates perceived social support and psychological resilience, and by constructing a chained mediation model, it thoroughly investigates the complex interrelationships between mind–body exercise, perceived social support, psychological resilience, and the quality of life in older adults, with the aim of offering insights to facilitate healthy aging in this population.

2 Statement of the study

In recent years, with the intensification of the aging population issue, how to enhance the quality of life for older adults has become a focal point of societal concern. Mind–body exercises have a significant positive impact on the quality of life in older adults, while psychological factors, such as perceived social support and psychological resilience, also play a crucial role in fostering a positive lifestyle among older adults. Existing literature mostly focuses on whether older adults' participation in mind–body exercises has a positive impact on their quality of life (18, 19), with more emphasis on the changes in physical functioning that occur after older adults practice mind–body exercises (20, 21). However, there is less exploration of the roles of these mediating variables in the process, especially the chained mediating effects of perceived social support and psychological resilience, which have not been fully validated. Therefore, this study aims to fill this research gap by exploring the indirect impact of mind–body exercise on the quality of life in older adults through perceived social support and psychological resilience. Specifically, this study proposes a chained mediation model, attempting to reveal how mind–body exercise can enhance the perceived social support of older adults, thereby strengthening their psychological resilience and ultimately improving their quality of life.

The theoretical framework of this study is based on Rutter's Developmental Model (RDM), which emphasizes that individuals develop coping abilities through the interaction of external and internal protective factors when facing stress, adversity, or challenges, thereby enhancing adaptive capacity and mental health, and ultimately improving their quality of life (22). Mind–body exercise, as an external protective factor, can not only enhance the physical function of older adults, improve cardiopulmonary function, increase balance ability, and alleviate health issues related to aging and chronic diseases, but it can also directly promote the improvement of the quality of life by regulating emotions and increasing life satisfaction (23). Perceived social support, as another significant external protective factor, refers to an individual's subjective feelings and evaluations of the degree to which they are supported by external sources, including family support, friend support, and other forms of support (24). Perceived social support can provide emotional backing and practical assistance to older adults, alleviating their feelings of loneliness and stress in life, thereby helping to maintain a higher quality of life. Psychological resilience is a key internal protective factor in the RDM, referring to an individual's ability to adapt and recover when facing adversity (25). Psychological resilience helps older adults maintain a good psychological state and enhance life satisfaction by actively adapting to the processes of aging and social isolation. According to the RDM, mind–body exercise can work through both external (perceived social

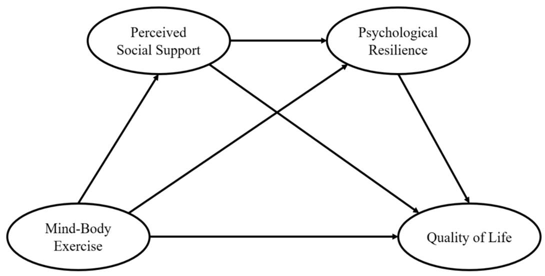

FIGURE 1
A hypothetical model of mind–body exercise affecting quality of life.

support) and internal (psychological resilience) factors to help older adults better cope with life's challenges, thereby improving their quality of life. Thus, this study aims to investigate the mechanism by which physical activity affects the quality of life of older adults, using perceived social support and psychological resilience as mediating variables, and constructs a chain mediation model of the impact of mind–body exercise on the quality of life of older adults. The research conceptual framework (Figure 1) and research hypotheses are both developed based on the RDM.

3 Development of hypotheses

3.1 Relationship between mind–body exercise and quality of life

Mind–body exercise focuses on the integration of mind, body, psychology, and behavior. It involves a series of controlled movements and concentration practices to enhance coordination and awareness (26). Due to its significant health benefits, high safety, lack of special equipment requirements, and ease of learning, mind–body exercise has garnered global attention. In China, common forms of mind–body exercise include Tai Chi, Ba duan jin, and Yi jin jing (27), which have significant effects on improving the health status of older adults. Specifically, by enhancing immunity (28), improving sleep quality (29), increasing balance ability (30), and boosting cardiopulmonary function (31), these exercises can reduce the risk of chronic diseases (32), alleviate clinical symptoms such as limb tremors (33), and decrease the incidence of falls and other accidental injuries (34), thereby improving the quality of life and self-care ability of older adults. Furthermore, participation in mind–body exercises is considered a significant investment in mental health. Through breath regulation and meditation, mind–body exercises help older adults to relax and reduce stress. Research indicates that there is a positive correlation between the duration of participation in mind–body exercises and the level of mental health (35), which also aids in enhancing the ability of older adults to adjust to negative emotions. This enables them to more freely cope with various demands of daily life, thereby enjoying a healthier, more vibrant, and satisfying state of living. Thus, this study selects tai chi, ba duan jin, and yi jin jing as mind–body exercises for older adults, all of which can positively influence their quality of life. Based on the preceding analysis, we propose the following hypothesis:

> *H1:* Mind–body exercise is positively correlated with the quality of life in older adults.

3.2 The mediating of effect perceived social support

Perceived social support plays a crucial effect between mind–body exercise and the quality of life in older adults. Mind–body exercise is a form of physical activity, the essence of which is a type of social interaction, involving not only individuals but also interpersonal communication activities within groups. It is an important way to enhance the level of perceived social support. Research has proven that during the process of participating in physical activities, older adults often gain more longitudinal social support (36). The enhancement of perceived social support can assist older adults in coping with various adverse environments more swiftly. It has a positive buffering effect on individual experiences of anxiety, depression, and distress, preventing the exacerbation of negative emotions and providing continuous regulation for mental health (37). The study results indicate that there is a significant correlation between perceived social support and individual quality of life, and it has a positive predictive effect. The joint action of different types of perceived social support can influence an individual's physical self-worth, sense of happiness, and motivation (38). A survey conducted by Unsar et al. (39) on older adults aged 60 and above showed that perceived social support is significantly positively correlated with the quality of life and enhancing perceived social support can improve the quality of life in later years. In summary, mind–body exercise is closely related to perceived social support, which further influences the quality of life through perceived social support. As a result, the following hypothesis was advanced:

> *H2:* Perceived social support mediates the relationship between mind–body exercise and the quality of life in older adults.

3.3 The mediating effect of psychological resilience

Psychological resilience can help individuals successfully cope with stress and improve mental health, playing a crucial role in maintaining the quality of life in older adults (40). According to the theory of psychological defense mechanisms, psychological resilience is associated with mature defense mechanisms. Individuals with higher psychological resilience possess more mature psychological defense abilities, which they can quickly employ at the initial stage of handling challenging or unexpected events, minimizing the impact (41). Studies have shown that compared to younger individuals, older adults, due to their rich life experiences and coping strategies for adversity, may possess equal or even higher levels of psychological resilience (42). High levels of psychological resilience can reduce physical and mental stress in older adults, mitigate the impact of chronic diseases on daily activities, promote physical health, and enhance the quality of life (43, 44). Existing research has demonstrated that the level of physical activity is an important variable affecting an individual's level of psychological resilience (45). Physical activity contributes to the positive development of psychological resilience, and as physical activity increases, an individual's psychological resilience significantly strengthens. Higher levels of psychological resilience in older adults are associated with greater autonomy in daily activities, physical activity, and overall physical fitness (46). Previous research has demonstrated that participation in mind–body exercises has a significant positive impact on the psychological resilience of older adults (47), improving their emotional state and mental health levels, thereby enhancing their quality of life. In view of this, we proposed the following hypotheses:

> *H3:* Psychological resilience mediates the relationship between mind–body exercise and the quality of life in older adults.

3.4 The chain mediating effect of perceived social support and psychological resilience

According to the Rutter Developmental Model (RDM), individuals enhance their quality of life by establishing new cognitive structures, reducing the negative impact of adverse events, and increasing the utilization of internal and external resources. Psychological resilience emphasizes the development and application of individual internal resources, which not only helps older adults maintain a healthy psychological state amidst stress and setbacks, better cope with life's changes, but also enhances their determination, perseverance, and self-control abilities, promoting the improvement of the quality of life for older adults (48). Perceived social support, as an important external resource, helps to enhance an individual's ability to cope with trauma, thereby promoting the strengthening of psychological resilience. The more social support older adults perceive, the better they can overcome challenges and adversity with a positive attitude, respond to emergencies with an active mindset, and demonstrate a higher level of psychological resilience (49). Existing research has proven that the perceived social support older adults gain from mind–body exercises is an important factor affecting psychological resilience (50). Perceived social support is a protective factor for psychological resilience, and the process through which psychological resilience functions is the result of the interaction between an individual's protective factors and high-risk situations (51). The more perceived social support older adults obtain through participation in mind–body exercises, the stronger their psychological resilience becomes, and consequently, their quality of life is enhanced. Accordingly, the research hypothesis was formulated:

> *H4:* Perceived social support and psychological resilience have a chain mediating effect between mind–body exercise and the quality of life in older adults.

4 Materials and methods

4.1 Research design

In order to obtain the raw data required for the study, researchers designed a self-administered questionnaire based on existing literature and validated data collection tools, focusing on assessing older adults' participation in mind–body exercises, perceived social support, psychological resilience, and quality of life. Since the participants are from the Chinese population, the questionnaire is conducted in Chinese. The tools used in this study are scales that have been scientifically translated and validated, suitable for Chinese older adults, with reliable validity and reliability. Before the final survey, the research team conducted a preliminary assessment (pilot test) with 20 participants to ensure the feasibility of the questionnaire and to test the response rate. Through the pilot study, researchers made adjustments and edits to some of the questions in the questionnaire to maximize the accuracy and comprehensiveness of the responses. From March 25 to May 3, 2024, the research team conducted a questionnaire survey among older adults participating in mind–body exercises (Tai Chi, Ba Duan Jin, Yi Jin Jing) in 13 districts of Beijing, China. The questionnaire included: the Physical Activity Rating Scale (PARS-3), the WHOQOL-BREF scale, the Perceived Social Support Scale (PSSS), and the Chinese version of the Connor-Davidson Resilience Scale (CD-RISC). All data collection was ensured to be conducted under uniform conditions to minimize data bias, with each questionnaire taking approximately 10–20 min to complete. All invitees participated voluntarily, and the project was approved by the Ethics Committee of Beijing Sport University (2024145H).

4.2 Inclusion criteria

Inclusion criteria for participants in this study (1): older adults aged 60 and above (2); older adults with good reading and comprehension abilities who can communicate normally (3); older adults with experience in practicing mind–body exercises (tai chi, ba duan jin, yi jin jing) (4); older adults willing to participate in the survey after fully understanding its purpose. Exclusion criteria (1): Individuals with severe hearing or speech impairments (2); Individuals with abnormal mental states (3); Individuals with severe physical diseases, extreme frailty, or disabilities that prevent them from cooperating with the survey. A total of 1,239 offline questionnaires were collected in this study, and after applying the exclusion and inclusion criteria, 1,087 valid questionnaires were obtained, resulting in an effective recovery rate of 87.73%.

4.3 Measurement tool design and reliability testing

4.3.1 Mind–body exercises level

The level of mind–body exercises was measured using the Physical Activity Rating Scale (PARS-3) developed by Liang et al. (52). The PARS-3 includes three items: exercise intensity, exercise duration, and exercise frequency, each scored using a 5-point Likert scale ranging from 1 to 5. The total score of the scale is calculated using the formula: Frequency score × (Duration score - 1) × Intensity score, with a range of 0 to 100. Higher scores indicate greater exercise intensity, higher frequency, and longer duration. The criteria for exercise volume levels are as follows: 19 points or below indicates mild exercise volume; 20–42 points indicate moderate exercise volume; 43 points or above indicate intense exercise volume. In this study, the Cronbach's α coefficient for the scale was 0.850.

4.3.2 Quality of life scale

The Quality of Life Scale used in this study is the WHOQOL-BREF scale developed by the World Health Organization based on its definition of quality of life (53). This scale consists of 26 items that can be categorized into four domains: physical health (8 items), psychological health (6 items), social relationships (3 items), and environment (9 items). Each item is scored on a Likert 5-point scale, ranging from "never" to "always," with higher scores indicating a higher level of quality of life. The Cronbach's α coefficient for this study is 0.970.

4.3.3 Perceived social support scale

The Perceived Social Support Scale (PSSS) was developed by Zimet et al. in 1988 (54). This scale consists of 12 items, encompassing three dimensions: family support (4 items), friend support (4 items), and other support (4 items). It measures the degree of perceived support from family, friends, and others, with the total score reflecting the overall level of perceived social support. The items are scored on a 7-point Likert scale, ranging from "strongly disagree" to "strongly agree." Total scores between 12 and 36 indicate low support; scores between 37 and 60 indicate moderate support; scores between 61 and 84 indicate high support. Higher total scores indicate higher levels of perceived social support. The Cronbach's α coefficient for this study is 0.950.

4.3.4 Psychological resilience scale

The Psychological Resilience Scale used in this study is the Chinese version of the Connor-Davidson Resilience Scale (CD-RISC), translated by Yu and Zhang (55). This scale consists of 25 items, covering three dimensions: tenacity (13 items), strength (8 items), and optimism (4 items). Each item is scored on a Likert 5-point scale, ranging from "never" to "always," with higher scores indicating higher levels of psychological resilience. The Cronbach's α coefficient for this study is 0.950.

4.3.5 The covariates of the study

In this study, the independent variable is mind–body exercise, the dependent variable is the quality of life in older adults, and the mediator variables are perceived social support and psychological resilience. Research findings on quality of life have indicated that the gender and age of the subjects have become variables that scholars need to control in their studies (56). In addition, quality of life is significantly associated with education level (57), income status (58), and baseline health conditions (59). Therefore, these variables were used as control variables in the study, adjusted during data analysis to minimize their impact on the main results, ensuring that the research focus is on the effects of mind–body exercise on older adults' perceived social support, psychological resilience, and quality of life. This study refers to Sun Wen's age classification (60), Zhang Wen's education classification (61), and the classification of monthly income in the China Longitudinal Aging Social Survey (62).

4.3.6 Statistical analysis

After organizing the valid questionnaire data, the data was analyzed using SPSS 26.0 software. Correlation analysis, linear regression analysis, and other methods were used to examine the impact of mind–body exercise, perceived social support, and psychological resilience on the quality of life in older adults. The Amos 24.0 software package was used to validate the model and test the construct validity of the scales. Currently, the Bootstrap method is commonly used to test mediation effects. This method involves resampling from the original sample and using a 95% confidence interval to test the significance of the mediation effect coefficients. Therefore, this study used the Bootstrap method to test whether perceived social support and psychological resilience mediate the relationship between mind–body exercise and the quality of life in older adults, as well as whether there is a chain mediation effect of perceived social support and psychological resilience in the relationship between mind–body exercise and the quality of life in older adults.

5 Results

5.1 Reliability and validity testing

The scales used in this study were adapted from previous research questionnaires, so it is necessary to verify their reliability and validity. To further test the convergent validity and reliability of the scales, Average Variance Extracted (AVE) and Construct Reliability (CR) were used as evaluation parameters. As shown in Table 1, the AVE values for all factors are greater than 0.5, indicating good model convergence; the CR values for all factors are greater than 0.7, indicating that the items in each scale consistently explain the latent variables, demonstrating good construct reliability. In summary, the questionnaire used in this study has high reliability and validity.

5.2 Common method bias testing

To avoid common method bias, an anonymous coded evaluation method was used during the testing process to control the sources of

TABLE 1 Validity and reliability test of the questionnaires.

Variable	CR	AVE
QOL	0.931	0.771
MBE	0.854	0.662
PSS	0.842	0.643
PR	0.807	0.585

CR, composite reliability; AVE, average variance extracted; QOL, quality of life scale; MBE, mind–body exercise; PSS, perceived social support; PR, psychological resilience.

common method bias from the procedure. Additionally, SPSS 26.0 was used to conduct an exploratory factor analysis on all test items using Harman's single-factor test. The results showed that there were nine factors with eigenvalues greater than 1, and the variance explained by the first factor was 36.44%, which is below the critical standard of 40%, indicating that there is no serious common method bias in this study.

5.3 Descriptive statistics and correlation analysis

Table 2 indicates that the study participants numbered 1,087, with a majority consisting of older adults with chronic diseases, totaling 694 individuals (63.8%), while those without chronic diseases accounted for 393 (36.1%). The gender distribution was balanced, with 548 males (50.4%) and 539 females (49.6%). The age distribution varied across different age groups, notably with 60–64 years old participants making up 35%, followed by 65–69 years old (34.1%), 70–74 years old (22%), 75–79 years old (4.1%), and those aged 80 and above representing 4.8%. The educational background of the participants was diverse, with the highest level of education being undergraduate and above (32.29%), followed by college and higher vocational education (23.82%), high school or technical secondary school (18.67%), middle school (17.01%), and elementary school and below (8.18%). In terms of income levels, the highest percentage was for those earning above 5,001 (40.66%), followed by 3,501–5,000 (35.97%), 1,501–3,500 (18.67%), and below 1,500 (4.69%).

This study focuses on examining the overall scores of the model indicators, without delving into the sub-dimensions of each indicator. Pearson correlation analysis was conducted using the average scores of each variable. The descriptive statistics and correlation analysis results for the four variables: mind–body exercise, perceived social support, psychological resilience, and the quality of life in older adults, are shown in Table 3. The results indicate significant positive correlations between each pair of the four variables. Additionally, the correlation analysis revealed that mind–body exercise and quality of life in older adults are significantly correlated ($r = 0.549$, $p < 0.01$); mind–body exercise and perceived social support are significantly positively correlated ($r = 0.402$,

TABLE 2 Participant demographics.

Demographic category	Frequency	Percent%
Gender		
Male	548	50.4
Female	539	49.6
Age		
60–64	380	35
65–69	371	34.1
70–74	239	22
75–79	45	4.1
80 years and above	52	4.8
Education level		
Elementary school and below	89	8.18
Middle school	185	17.01
High school or technical secondary school	203	18.67
Junior college or higher vocational education	259	23.82
Undergraduate and above	351	32.29
Monthly income		
Below 1,500	51	4.69
1,501–3,500	203	18.67
3,501–5,000	391	35.97
Above 5,001	442	40.66

TABLE 3 Descriptive statistics and correlations for primary variables.

Variable	*M*	S.D.	MBE	PSS	PR	QOL
MBE	9.80	2.81	1			
PSS	53.69	13.88	0.402**	1		
PR	82.99	18.14	0.393**	0.281**	1	
QOL	83.73	21.92	0.549**	0.474**	0.527**	1

$n = 1,078$; M, mean; S.D., standard deviation. *$p < 0.05$; **$p < 0.01$; QOL, quality of life scale; MBE, mind–body exercise; PSS, perceived social support; PR, psychological resilience.

$p < 0.01$); mind–body exercise and psychological resilience are significantly correlated ($r = 0.393$, $p < 0.01$); perceived social support and quality of life in older adults are significantly correlated ($r = 0.474$, $p < 0.01$); psychological resilience and quality of life in older adults are significantly correlated ($r = 0.527$, $p < 0.01$); perceived social support and psychological resilience are significantly correlated ($r = 0.281$, $p < 0.01$). In summary, the significant correlations among the variables provide preliminary evidence for the hypotheses proposed in this study.

This study employed univariate analysis of variance (ANOVA) to examine the differential impact of varying levels of physical activity on the quality of life among older adults. As can be seen from Table 4, there is a significant difference in quality of life across samples with different amounts of physical activity ($p < 0.05$), indicating a variability in the quality of life among these samples. The level of physical activity shows a significant effect on quality of life at the 0.01 level ($F = 148.400$, $p = 0.000$). Comparative differences reveal that participation in moderate to Intense exercise is more conducive to enhancing the quality of life for older adults.

5.4 Analysis of mediation effects

To verify the chain mediating effect of perceived social support and psychological resilience in the relationship between mind–body exercise and the quality of life in older adults, AMOS 24.0 software was used to perform a fit analysis of the conceptual framework chain mediation model. Following the mediation effect testing process proposed by Marsh et al. (63), Table 5 shows the standard results of the fit indices: $\chi2/df < 5$, $GFI > 0.9$, RMSEA <0.10, $CFI > 0.9$, $NFI > 0.9$, $TLI > 0.9$. The model parameters meet the fit requirements, indicating that the mediation model of mind–body exercise and the quality of life in older adults is reasonable.

Furthermore, the standardized path coefficient model of the impact of mind–body exercise on the quality of life in older adults is shown in Figure 2, which indicates that the standardized path coefficient for mind–body exercise → quality of life in older adults is significant ($\beta = 0.32$, $p < 0.001$), indicating a significant positive effect of mind–body exercise on the quality of life in older adults, supporting hypothesis 1. The path

TABLE 4 Anova results of the effects of physical exercise mind–body exercise on the quality of life in older adults.

Variable	Exercise amount (M + S.D.)			*F*	*p*
	Intense exercise (n = 195)	Moderate exercise (n = 483)	Mild exercise (n = 409)		
The quality of life	88.733 ± 18.499	94.494 ± 21.708	72.590 ± 17.709	148.4	0.000**

*$p < 0.05$; **$p < 0.01$.

TABLE 5 Questionnaire model fitting indicators.

	X^2	df	χ^2/df	RMSEA	CFI	GFI	NFI	TLI	IFI
Model	234.304	59	3.971	0.052	0.968	0.968	0.973	0.973	0.98

RMSEA, root mean square error of approximation; CFI, comparative fit index; GFI, goodness-of-fit index; NFI, normed fit index; TLI, Tucker-Lewis index. IFI, increased fit index.

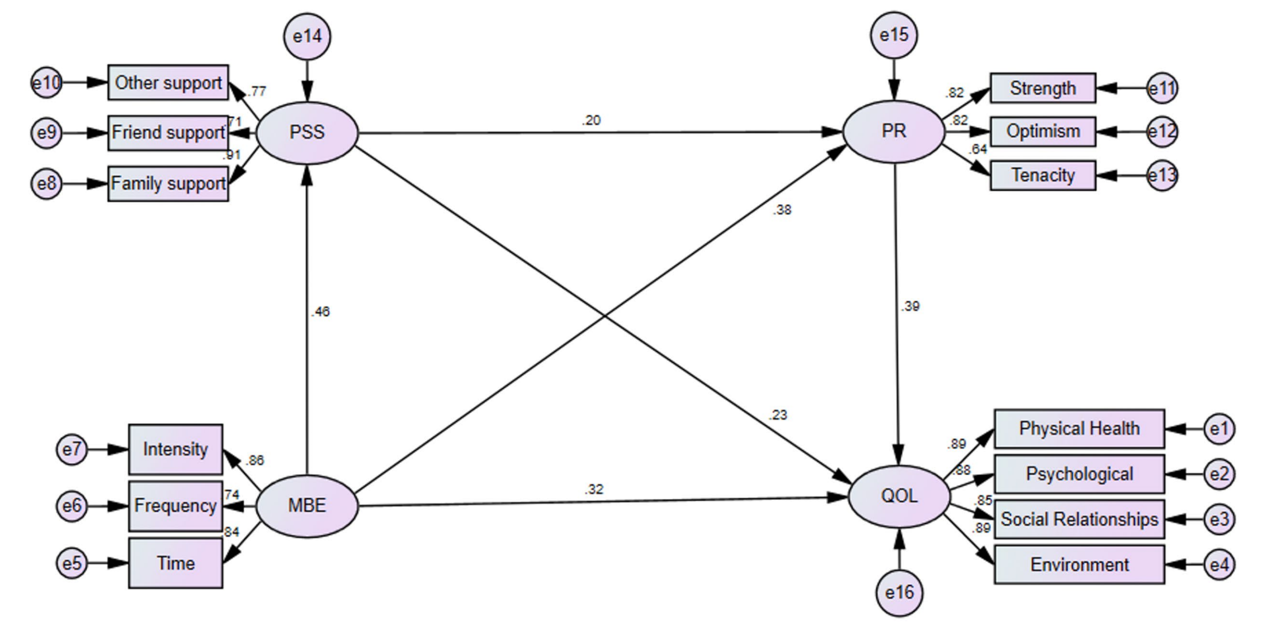

FIGURE 2
Intermediary model diagram. QOL, quality of life scale; MBE, mind–body exercise; PSS, perceived social support; PR, psychological resilience.

coefficients for mind–body exercise → perceived social support ($\beta = 0.46$, $p < 0.001$) → quality of life in older adults ($\beta = 0.23$, $p < 0.001$) are significant, indicating that perceived social support mediates the relationship between mind–body exercise and the quality of life in older adults, supporting hypothesis 2. The path coefficients for mind–body exercise → psychological resilience ($\beta = 0.38$, $p < 0.001$) → quality of life in older adults ($\beta = 0.39$, $p < 0.001$) are significant, indicating that psychological resilience mediates the relationship between mind–body exercise and the quality of life in older adults, supporting hypothesis 3. The path coefficients for mind–body exercise → perceived social support ($\beta = 0.46$, $p < 0.001$) → psychological resilience ($\beta = 0.20$, $p < 0.001$) → quality of life in older adults ($\beta = 0.39$, $p < 0.001$) are significant, indicating that perceived social support and psychological resilience have a chain mediating effect between mind–body exercise and the quality of life in older adults, supporting hypothesis 4.

The bias-corrected non-parametric percentile Bootstrap method was used to evaluate the significance of individual mediation effects to confirm the mediating effect of perceived social support and psychological resilience. Hayes recommends that the number of resamples for Bootstrap mediation effect testing should be at least 1,000 for the original sample (64). Bootstrap mediation effect test results show that if the Bootstrap test CI does not include 0, the indirect effect is considered established (65). In this study, 5,000 Bootstrap samples were used to test the mediation effect, determining a 95% confidence interval (CI). As shown in Table 6, the direct effect of mind–body exercise on the quality of life in older adults is significant (direct effect = 2.173, 95% CI [1.697, 2.703]). The indirect effects include three significant mediation pathways: mind–body exercise → perceived social support → quality of life (indirect effect = 0.733, 95% CI [0.500, 0.980]); mind–body exercise → psychological resilience → quality of life (indirect effect = 1.062, 95% CI [0.832, 1.299]); mind–body exercise → perceived social support → psychological resilience → quality of life (indirect effect = 0.245, 95% CI [0.141, 0.375]). In summary, the 95% confidence intervals for the three mediation paths do not include 0, indicating that the path coefficients in this model are significant. This demonstrates that perceived social support and psychological resilience mediate the relationship between mind–body exercise and the quality of life in older adults, and that perceived social support and psychological resilience play a chain mediation effect.

In order to explore the mediating effect of perceived social support from various sources on the relationship between mind–body exercise and the quality of life in older adults, family support, friend support, and other support were used as independent variables, while quality of life was considered as the dependent variable for linear regression analysis. Table 7 indicates that the model equation is: Quality of Life = 44.387 + 1.130*Family Support +0.611*Friend Support +0.466*Other Support, with an R-squared value of 0.228, suggesting that family support, friend support, and other support can influence the enhancement of quality of life. The model passes the *F-test* ($F = 106.821$, $p < 0.05$), indicating that at least one of the factors—family support, friend support, or other support—has a significant impact on the quality of life. Additionally, the examination of multicollinearity in the model revealed that all VIF values were less than 5, indicating the absence of multicollinearity issues. Furthermore, the Durbin-Watson (D-W) value was around 2, suggesting that there is no autocorrelation in the model, and the sample data do not exhibit any interrelationships, indicating a good model fit. A detailed analysis showed that the regression coefficient for family support was 1.130 ($t = 6.676$,

TABLE 6 Test results of mediation effects.

Effect	Parameter	Estimate	BootSE	Bootstrap LLCI	Bootstrap ULCI
Direct effect	MBE → QOL	2.173	0.254	1.697	2.703
Indirect effect	MBE → PSS → QOL	0.733	0.125	0.5	0.98
	MBE → PR → QOL	1.062	0.166	0.832	1.299
	MBE → PSS → PR → QOL	0.245	0.061	0.141	0.375
Total effect	MBE → PSS → PR → QOL	4.212	0.241	3.728	4.67

The Bootstrap sample size is set at 5000.

TABLE 7 Linear regression analysis results ($n = 1,087$).

	Unstandardized coefficients		Standardized coefficients	*t*	*p*	Collinearity diagnostics	
	B	Standard error	*Beta*			VIF	Tolerance
Constant	44.387	2.37	–	18.73	0.000**	–	–
Family support	1.13	0.169	0.281	6.676	0.000**	2.494	0.401
Friend support	0.611	0.148	0.146	4.128	0.000**	1.752	0.571
Other support	0.466	0.159	0.112	2.94	0.003**	2.047	0.489
R^2	0.228						
Adjusted R^2	0.226						
F	$F(3,1,083) = 106.821$, $p = 0.000$						
D-W值	2.071						

*$p < 0.05$; **$p < 0.01$.

$p < 0.01$), which means that family support has a significant positive impact on the quality of life. Friend support has a regression coefficient value of 0.611 ($t = 4.128$, $p < 0.01$), indicating that friend support significantly and positively influences the quality of life. Other support has a regression coefficient value of 0.466 ($t = 2.940$, $p < 0.01$), indicating that other support also significantly and positively affects the quality of life. In summary, both family support, friend support, and other support significantly and positively impact the quality of life. The magnitude of the standardized coefficients suggests a ranking of their relative influence as family support > friend support > other support.

6 Discussion

This study explored the impact of mind–body exercise on the quality of life in older adults, with a particular focus on the serial mediating roles of perceived social support and psychological resilience. The findings confirm a significant positive correlation between mind–body exercise and the quality of life in older adults. This is consistent with previous research findings (66, 67). Mind–body exercise focuses on enhancing physical strength, flexibility, and balance, thereby avoiding potential injuries associated with high-intensity exercise. Through movement, breathing, and meditation, it alleviates psychological stress and achieves overall coordination and balance of the body and mind, demonstrating significant effectiveness in improving both physical and mental health (68). Consequently, it can effectively enhance the quality of life in older adults. The study further found that participation in moderate to high-intensity mind–body exercise is more conducive to enhancing the quality of life for older adults. This improvement is not only reflected in the enhancement of physical function but also manifested in various aspects of the daily lives of older adults. Engaging in such exercise can foster the habit of maintaining a long-term exercise routine, thereby continuously preserving a state of good health, boosting the confidence of older adults, and promoting emotional stability. Consequently, this leads to an overall increase in life satisfaction and well-being, resulting in a significant enhancement in the quality of life for older adults.

Mind–body exercise not only directly affects the quality of life in older adults but also indirectly influences it by positively impacting perceived social support. Mind–body exercise has a beneficial effect on the level of perceived social support, and the amount of exercise is significantly positively correlated with perceived social support (69). Regular participation in mind–body exercise by older adults not only helps them communicate with others, establish interpersonal relationships, and emotional connections during the exercise process, but also promotes or improves the structure of their social networks (70). Through these social interactions, older adults can enhance their sense of social connection, gain more support from family, friends, and other social sources, which helps alleviate their feelings of loneliness and increase their sense of social belonging. This, in turn, further improves their quality of life, consistent with previous research findings (71). Additionally, this study also found that perceived social support from different sources can have varying impacts on the quality of life in older adults, with family support having the greatest influence on quality of life. This may be related to the concept of filial piety in Chinese culture, where the family (especially spouses and children) plays a significant role in providing emotional support and practical assistance to older adults, particularly in alleviating negative emotions.

At the same time, mind–body exercise can also indirectly affect the quality of life in older adults by having a positive impact on psychological resilience. Mind–body exercise is a protective factor that promotes the development of individual psychological resilience and has a significant predictive role in psychological resilience (72). During the participation in mind–body activities, older adults may fulfil their basic needs for self-competence and intimate relationships, and the satisfaction of these basic needs can promote the natural development of efficacy and autonomy in individuals. This helps to alleviate perceived stress and emotional suppression, leading to better psychological performance in coping with adversity and challenges (73). As the level of psychological resilience increases, the quality of life for older adults also increases. Psychological resilience has a significant positive predictive effect on the quality of life, which is consistent with existing research findings (74). Individuals with high psychological resilience often maintain a more positive attitude when facing life pressures. Relevant surveys indicate that older adults with high psychological resilience continue to enhance their perceived value through various social activities even after retirement, pursuing higher goals, which in turn improves their quality of life (75).

There is a relatively stable systemic association between perceived social support and psychological resilience in older adults (76). The more social support individuals perceive, the more they experience respect, support, and understanding emotionally, the higher their level of inner satisfaction, and the stronger their ability to resist adversity, resulting in a higher level of psychological resilience (77). Therefore, individuals with high perceived social support tend to have higher levels of psychological resilience. Older adults with higher levels of psychological resilience have greater coping abilities in life, thereby achieving a higher quality of life, which is consistent with previous research findings (78). The enhancing effect of mind–body exercise on the quality of life for older adults is multidimensional, as it promotes the well-being of older adults from both external and internal perspectives. From the external environmental factors, older adults can gain positive social support, including mental and material assistance, during their participation in mind–body exercise. This not only meets their living needs but also helps in developing certain psychological resilience traits as internal factors (79). These internal and external factors interact with each other to comprehensively promote the improvement of the quality of life for older adults. The results of this study further demonstrate that mind–body exercise can collectively influence the quality of life in older adults through the serial mediating effects of perceived social support and psychological resilience.

7 Conclusion

This study reveals the impact of mind–body exercise on the quality of life in older adults and provides an in-depth analysis through the serial mediating effects of perceived social support and psychological resilience. The results indicate that mind–body exercise has a positive influence on the quality of life for older adults, with those who regularly participate in such activities not only demonstrating higher levels of quality of life but also showing significant improvements in perceived social support and psychological resilience. The study found that perceived social support, as an external protective resource, has a significant mediating effect between mind–body exercise and quality of life in older adults, with family support playing a particularly important role in promoting the quality of life in older adults. Additionally, psychological resilience, as an internal protective resource, serves as an important mediating variable. When facing challenges such as aging, illness, and social isolation, it helps older adults maintain a positive attitude toward life through active emotional regulation and coping strategies, thereby promoting the improvement of quality of life. This study is the first to validate the chain mediating effect of perceived social support and psychological resilience between mind–body exercise and the quality of life in older adults. Mind–body exercise not only improves the quality of life for older adults but also enhances their life satisfaction and sense of well-being through the elevation of perceived social support and psychological resilience. By effectively utilizing perceived social support and strengthening psychological resilience, older adults can better cope with life's challenges, maintain a positive attitude toward life, and thereby achieve a comprehensive improvement in the quality of life. The chain mediating model proposed in this study integrates the relationship between perceived social support, psychological resilience, and the quality of life in older adults, providing a new perspective for us to more comprehensively understand how mind–body exercise affects the quality of life in older adults through internal mechanisms. This finding not only enriches the existing literature but also provides a theoretical basis for the application of mind–body exercise in the field of health promotion for older adults.

8 Implications and limitations

8.1 Implications

This study explores the mechanism by which mind–body exercise impacts the quality of life in older adults, introducing perceived social support and psychological resilience as mediating variables, thus expanding the existing research on the impact of mind–body exercise on individual quality of life. Mind–body exercise plays a crucial role in improving physical and mental health, effectively helping older adults gain necessary social connections and emotional support, while also reducing negative emotions such as loneliness, anxiety, and depression. By accumulating more social capital, it improves overall quality of life. The study of the chain mediating effect of perceived social support and psychological resilience provides new perspectives and practical approaches for enhancing the quality of life in older adults. Firstly, when aiming to improve the quality of life in older adults, it is essential to adopt more comprehensive intervention measures, taking into account the roles of mind–body exercise, perceived social support, and psychological resilience, to create a positive living environment and healthy lifestyle for older adults (80). Secondly, the community environment should meet the psychological and social needs of older adults, enhancing their social support network with systems composed of family members, friends, and community volunteers. Educating older adults on how to effectively perceive and utilize social support can enhance their positive emotional experiences and further improve their psychological health and life satisfaction. Lastly, attention should be paid to the mechanisms of psychological resilience formation in older adults, with regular, broad-ranging health education and psychological counseling to promote more comprehensive psychological and social growth. This will increase positive emotions and encourage them to have greater confidence in their daily lives.

8.2 Limitations

Despite providing strong evidence of the positive impact of mind–body exercise, perceived social support, and psychological resilience on improving the quality of life in older adults, this study has several limitations. First, the study only explored three types of mind–body exercises: tai chi, ba duan jin, and yi jin jing, while neglecting others such as yoga, Pilates, and meditation. The different types may have varying effects on older adults, this study did not fully consider these differences, suggesting that future research should refine the study design to control for the variables of different exercise types. Second, this study employed a cross-sectional design to explore the mechanism of how mind–body exercise affects the quality of life in older adults, which can only reveal correlations and not causations. Future research could use longitudinal tracking designs to further test and confirm the findings of this study. Finally, the research sample was limited to a specific area in Beijing, China, which may not fully represent all older adults. Differences in understanding and manifestations of these variables across regions could affect the generalizability of the results. Future research should consider expanding the sample collection area to improve the study's conclusions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Sport University (2024145H). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QY: Conceptualization, Data curation, Formal analysis, Writing – original draft. YZ: Investigation, Methodology, Project administration, Writing – original draft. SL: Funding acquisition, Supervision, Writing – review & editing, Project administration, Resources, Visualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Activity-based mindfulness: large-scale assessment of an online program on perceived stress and mindfulness

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Background and objective: Mindfulness has emerged as key construct in mental health over past decades. While current mindfulness-based interventions (MBIs) are usually rooted in Asian contemplative traditions, mindfulness practices can equally be found in other knowledge systems, including integrative medicine systems such as anthroposophic medicine (AM). The *Activity-Based Stress Release* (ABSR) program incorporates the latter as part of an 8-week-long online intervention combining mindfulness exercises, behavioral self-observation, and mindful movement practices derived from this integrative medicine frame. The program could offer additional means for cultivating mindfulness, thereby addressing the necessity for diverse approaches in conjunction with individual differences, diverse clinical demands, or restricted capacities to perform certain mindfulness practices. Using an observational repeated-measures design, the current study aimed to assess a large-scale online implementation of this program in terms of its feasibility, assessing perceived stress and mindfulness.

Method: Individuals who enrolled in any of the 37 ABSR program iterations carried out during 2023 and agreed to participate in the study completed online surveys including validated stress and mindfulness scales at the beginning, middle, end, and follow up of the intervention. Linear-mixed models were used for data analysis.

Results: A total of 830 individuals took part in the study, of which 53.5% filled in at least 2 surveys. In line with our expectation, mindfulness scores increased significantly over the course of the intervention, while stress scores decreased significantly in this timeframe. We further found differential effects of self-practice frequency and duration on the outcomes.

Conclusion: This study provides a first indication of stress reduction in conjunction with the online implementation of this novel MBI. The work further suggests that this AM-based intervention indeed targets mindfulness, as do other MBIs, and that it is adaptable to an online format. However, given the observational single-arm design, controlled studies will be necessary to confirm these results. Nonetheless, the study adds a novel contribution to existent MBIs, which is significant in view of the need for diverse approaches to meet the heterogeneity of individual predispositions and clinical requirements. It remains to established by forthcoming research for which groups of individuals or clinical features this approach could be especially beneficial or less suitable.

KEYWORDS

mindfulness-based intervention, mindfulness, stress, integrative medicine, online intervention, anthroposophic medicine, mind–body interventions, activity-based stress reduction

1 Introduction

Mindfulness has emerged as key construct in mental health over past decades (Cullen, 2011; Galante et al., 2021a; Lee et al., 2021). Since the seminal work of Kabat-Zinn (1990) introducing the Buddhist mindfulness concept—a specific, nonjudgmental present-moment awareness – to Western health science, mindfulness-based interventions (MBIs) have exponentially increased and in some variations have become an integral part of so-called third-wave cognitive behavioral therapies (Khoury et al., 2015; Segal et al., 2018; Garland et al., 2012; Kabat-Zinn, 2003a; Hayes and Hofmann, 2021).

Kabat-Zinn's original "Mindfulness-based Stress Reduction" (MBSR, Kabat-Zinn, 2003b) emphasized psychological stress as fundamental target variable based on its critical role in the chronic mobilization and dysregulation of the neurophysiological stress response, which in turn is associated with increased risk for non-communicable diseases and mental illnesses (Lagraauw et al., 2015; Vanitallie, 2002; Karami et al., 2023; Sinha and Jastreboff, 2013; Gold, 2015; Sapolsky, 2007; McEwen and Morrison, 2013). Subsequent adaptations of the MBSR have been focusing on specific mental health or somatic conditions (e.g., depression, chronic headache, chorioretinopathy), and continued to contribute to the accumulating evidence of MBIs' clinical benefits (Kriakous et al., 2021; Yu et al., 2023; Goldsmith et al., 2023; Smithers-Sheedy et al., 2024; Özcan and Karapapak, 2024; Hoge et al., 2023; Fisher et al., 2023; Anheyer et al., 2019).

While the conceptual frame and practices of the original MBSR programs stem from Eastern and particularly Buddhist teachings (traditionally based particularly on the Satipaṭṭhāna Sutta, see Analayo, 2003), which indeed possess exceptional insight regarding mindfulness ("sati") and other mental/psychological processes (for Buddhist psychology see the Abhidhamma; Bodhi, 2012), there is nothing inherently Buddhist about mindfulness itself, as Kabat-Zinn (2003a) and others (Meaden, 2024) pointed out. Rather, mindfulness should be understood as an innate human capacity, which arises spontaneously under certain circumstances and can be cultivated with various means.

Indeed, albeit under different names, many contemplative and traditional medicine systems of the world describe concepts akin to mindfulness and related practices, not limited to Eastern traditions like Yoga/Ayurveda (Salmon et al., 2009; Mamtani and Mamtani, 2005) or Traditional Chinese Medicine (e.g., Qi Gong, Tai Chi) (Fogaça et al., 2021; Atkins, 2018), but also extending to Indigenous knowledge systems, like the Australian Aboriginal concepts of "Dadirri" or "Ngarraanga Giinganay" (Ungunmerr, 2017; Lavrencic et al., 2021), the immediacy of experience principle of the Brazilian-Amazonian Pirahã, and related concepts by the Congolese Mbuti (Meaden, 2024). Indeed, also from an academic viewpoint, there is no clear consensus as to the defining features of mindfulness practices (Sedlmeier, 2023).

Mindfulness-related practices are also an important pillar of anthroposophic medicine (AM), a well-established integrative medicine framework that originally arose in the early nineteen-hundreds in Central Europe (Bartelme, 2020; Büssing et al., 2011) with some degree of Buddhist influence (Dahlin, 2009; Haas, 2017; Steiner, 1932; Steiner and Dietler, 2006). Today AM is integrated in many hospitals and clinics across Europe and over 60 countries around the world. The approach has originally developed from and fully includes modern conventional medicine and other associated clinical sciences, but extends these concepts with therapeutic approaches that focus on the person as a whole and employs a strongly patient-centered approach (Baars et al., 2017; Kloter et al., 2023). As an integrative and multimodal treatment system, AM thus combines methods from conventional biomedicine, psychotherapy/counseling, and nursing, with complementary methods involving herbal medication, art and movement therapies, and massage techniques (Kienle et al., 2013), aiming to account for the integrity of human experience which consists of physical, psychological, social, as well as spiritual aspects. As is characteristic of complementary medicine systems, mental health is thus addressed as part of the integral therapeutic approach, rather than as a segregated discipline.

Within this system, the importance of mindfulness is articulated in a range of therapeutic approaches, including a mindful movement practice labeled eurythmy therapy, which involves movements linked to speech-sounds performed in a state of focused concentration to connect body movements with inner sensation (Kirchner-Bockholt, 1977; Berger et al., 2015), meditative practice, as well as specific task- or activity-based exercises (see section 2.2 for further details) derived from the AM treatise on approaches to counteract mental restlessness ("nervousness"; Steiner, 2009b, Steiner, 2009a, Kirchner-Bockholt, 1977, von Laue and von Laue, 2010).

The current study aimed to assess the online delivery of an MBI that draws from the latter AM concepts. Labeled *Activity-Based Stress Release* (ABSR) program, the intervention was based on the MBSR in structure and was originally developed as an in-person group therapy supporting psychiatric outpatients (Haas and Hundhammer, 2013). The in-person program has been described in a qualitative account (Haas and Hundhammer, 2013) and was evaluated in a small-scale pilot study based on a clinical sample of $N = 20$ patients (depression, anxiety disorders, or burnout diagnoses) with preliminary indications for improvements in calmness and serenity scales, heart rate variability, and in parasympathetic activity, although physiological parameters were assessed only in a small subsample ($n = 4$) (Kloter et al., 2023). The program represents a novel contribution from a well-established complementary medicine framework, which could offer additional means for cultivating mindfulness. This work thereby addresses the necessity for diverse MBIs in view of individual differences, diverse clinical demands, or restricted capacities to perform certain mindfulness practices. Disposing of multiple distinct approaches is of interest given that 'one-size-fits-all' approaches generally fall short of meeting the complexity and heterogeneity characteristically encountered in the mental health field. However, a large-scale assessment of the program has not yet been conducted, and the feasibility of its online implementation remains to be established.

Using an observational repeated-measures design, the objective of the current study was to assess the online implementation of the ABSR program in terms of intended effects and adaptability of the intervention to the online context (see types of feasibility; Bowen et al., 2009) based on a large-scale cross-cultural sample for feasibility testing. More specifically, using a general international sample, the study aimed to assess (a) stress and (b) mindfulness outcomes in conjunction with the online delivery of the ABSR program. By including mindfulness as an outcome we sought to test if this program indeed targets mindfulness, as is the case for other MBIs. We hypothesized that, compared to baseline, there will be a substantial (a) reduction in stress and (b) increase in mindfulness at the end of the intervention and at follow up.

2 Methods

2.1 Study design and setting

The study was conducted by the University of Bern's Institute of Complementary and Integrative Medicine in collaboration with an accredited health provider specializing in the ABSR model.[1] To assess the online implementation of the ABSR program (see section 2.2 for a detailed description of the intervention), we used a longitudinal repeated measures design with four assessment times to explore changes in stress (primary outcome) and mindfulness (secondary outcome). The four measurement times included baseline (t0), midpoint (t1), program completion (t2), and follow-up (t3).

Given full anonymity of participants at all stages of the research (fully encrypted survey via anonymous self-generated codes, no collection of IP- or E-Mail addresses, no collection of identifying participant data), no ethics/IRB approval was necessary according to the responsible Ethics Committee (Swiss Association of Research Ethics Committees) guidelines and the Federal Act on Research involving Human Beings (Human Research Act, 2011). Facilitators of the ABSR program did not have access to the survey data, which were collected by independent researchers (ET, YMK; University of Bern).

2.2 Intervention

The ABSR program consisted of an eight-week-long online intervention aimed to relieve stress via the cultivation of mindfulness using practices from AM. The intervention was based on weekly 90-min-long live online sessions, during which a trained facilitator introduced each of the weekly themes (8 modules in total, see Table 1) and taught participants the corresponding exercises. Table 1 shows the exercises per module, structured into mindful movement practice exercises (Eurythmy Therapy) and activity-based exercises. The latter label aims to articulate that these types of exercises, although performed with a contemplative attitude, require the active performance of defined tasks involving physical and/or mental operations. Participants were encouraged to practice the exercises over the course of the week (recommendation to practice on a daily basis, at least 15 min per exercise), and during the subsequent online session had the opportunity to discuss experiences from the preceding week, as well as address questions. Together with the closing session the program thus involved 9 online sessions (i.e., a total of 13.5 h of live sessions) and an individually varying amount of self-practice across 8 weeks. Audiovisual material and a forum for exchange outside the live sessions were available on the web portal, and in case participants missed a live session they could also access the recording there.

Data collection took place between September 2023 and March 2024. During this time period, the 8-weeks-long ABSR program was carried out a total of 37 times. Each of these were held by a certified ABSR facilitator, in groups of varying sizes (size being determined based on number of registrations, 2–264 registrations/group) and languages (English, German, Russian, Ukrainian, Slovenian, Dutch, Finnish, Chinese, and Spanish). All facilitators had undergone a standardized comprehensive ABSR certification training imparted by an accredited health provider (see footnote 1) prior to their involvement in this study. The training included four components, namely extensive self-experience with the ABSR practices and the program as a whole as a participant, attending a sequence of training lectures, completing a practicum in which trainees had to teach ABSR-related exercises in a group setting, as well as a final assessment by means of a written report or presentation. Certification was contingent upon successful completion of all four components. ABSR enrolment

1 ABSR International (Eurythmy4you).

TABLE 1 ABSR modules, themes, and mindfulness exercises.

Module	Aspects of mental restlessness/stress[a]	Activity-based exercises	Eurythmy therapy
1	Forgetfulness due to inattention	Conscious misplacement of objects	A (breathing)
2	Nervousness and anxiety	Deliberate modification of handwriting	O (warming)
3	Self-doubt and worry	Reverse order thinking exercises	I (nourishing)
4/5	Restlessness and loss of control	Self-observation; changing habits	E (in−/excreting)
6	Dependencies	Non-reaction to small desires	Ei (maintaining)
7	Compulsions and indecision	Conscious decision-making exercises	Au (growing)
8	Rumination and obsessive thinking	Non-reaction to self−/criticism	U (generating)

[a]Originally termed "aspects of nervousness" in STEINER (2009b).

was fee-based, but rates were kept at the necessary minimum and subsidized spaces were available for those lacking the required means.

2.3 Participants and procedure

The online program and the study were advertised on the health provider's website, in health magazines and newsletters, clinics also offering AM services, physicians', psychiatrists', and psychotherapists' practices, as well as on social media. All individuals who enrolled in any of the 37 ABSR program iterations held between September and December 2023 were invited to participate in the study. They were thoroughly informed about the study and the voluntary nature of participation and provided implied informed consent by completing the survey (opt-in). Individuals who agreed to participate and completed at least one survey were included in the study. Those who were below 18 years of age or participated in more than one cycle of the program were excluded from the study. To assess the outcomes and descriptive items (see section 2.4 for a detailed description of measures) participants were given a survey link upon registration (up to 3 days before program start; t0), again 4 weeks later (t1) at the program's midpoint, again another 4 weeks later (t2) at program completion, and again 8 weeks later (t3) at follow up (i.e., 16 weeks after baseline). Data collection ended when the last program cycle's t3 measures were completed (March 2024).

2.4 Survey

The online survey was constructed by means of the *SoSci Survey* software (Leiner, 2023) and was made available in six languages (English, German, Chinese, Spanish, Russian, and Ukrainian). Aside from anonymized basic demographic information, it involved the following measures:

2.4.1 Stress

The Perceived Stress Scale (PSS-10; Cohen et al., 1983, official validated translations from Mapi Research Trust 2022 © Copyright) is a 10-item instrument designed to assess experienced stress during the past month. Each item is rated on a five-point Likert scale from 1 (*never*) to 5 (*very often*), with higher scores indicating greater perceived stress (total sum scores: 0–40).

2.4.2 Mindfulness

We employed the Mindful Attention Awareness Scale (MAAS; original English: Brown and Ryan, 2003, validated Chinese, German, Spanish, and Russian versions: Chen et al., 2012, Michalak et al., 2008, Barajas and Garra, 2014, Golubev, 2012), which is commonly used in clinical research to assess mindfulness (MacKillop and Anderson, 2007; Carlson and Brown, 2005). The instrument's 15 items are rated on a six-point scale from 1 (*almost always*) to 6 (*almost never*), with higher MAAS scores corresponding to higher levels of mindfulness.

2.4.3 Self-practice time and online participation frequency

To assess the frequency with which participants engaged in self-practice between sessions, they were asked how many days per week they had practiced the exercises in the weeks since the last assessment (possible answers: *0–1 days*, *2–3 days*, *4–5 days*, *6–7 days*) and, to assess the practice duration, how much time they had spent on the exercises per day (options: *not done*, *1–10 min*, *11–20 min*, *21–30 min*, *more than 30 min*).

2.5 Data analysis

All statistical analyses were performed using *R* version 4.4.0 (R Core Team, 2024). We used descriptive statistics to report sample characteristics and additional descriptive items. For all inferential analyses the significance level was set at $\alpha < 0.05$. Surveys that were filled in outside the predefined time windows (i.e., less than 2 weeks apart from each other for t0-t2, more than 7 weeks between t0 and t1, or less than 4 weeks between t2 and t3) were excluded from the analysis. We opted for relatively broad time windows to avoid extensive data loss, but additionally performed all analysis also with a more narrow time window (at least 3 weeks and maximally 6 weeks), which however did not yield any different results.

All analyses were based on the data from all participants, non-completers included. We performed Linear Mixed-Effect Models (LMM) for each outcome variable in order to test whether there were significant changes in participants' stress or mindfulness levels over time, assessing differences between the various measurement points. We opted for LMM because of the method's suitability for analyzing repeated-measures data and for describing variations of the target variable across time, and importantly also due to the method's capacity to calculate unbiased model estimates even in the face of extensive missing data, which is a notorious challenge in longitudinal studies in general, and particularly when conducted online (Krueger and Tian, 2004; Gabrio et al., 2022). For the LMM calculations we used the *R* packages *lme4* (Bates et al., 2015) and *nlme* (Pinheiro et al., 2023). All models were adjusted for age and sex, as well as survey language as a proxy for culture, as covariates.

Finally, we performed a series of one-way ANOVAs to test if the frequency and duration of self-practice had an impact on the outcomes. In other words, we tested if individuals who practiced for longer or more frequent intervals vs. those with shorter or less frequent self-practice showed significant differences in their stress or mindfulness levels at subsequent time points. We opted for one-way ANOVAs to test this due to the method's capacity to compare differences between various group means (Mishra et al., 2019). The ANOVAs that involved practice frequency as predictor compared 4 groups (namely, the groups of individuals who practiced 0–1, 2–3, 4–5, or 6–7 days per week) whereas for the ANOVAs in which practice duration was the predictor, the comparison involved 5 groups (i.e., individuals who reported 0, 1–10, 11–20, 21–30, or >30 min of practice per reported practice day).

3 Results

3.1 Sample characteristics

Overall 1,155 individuals registered in the 37 implementations of the program (English-language implementations had $n = 130$

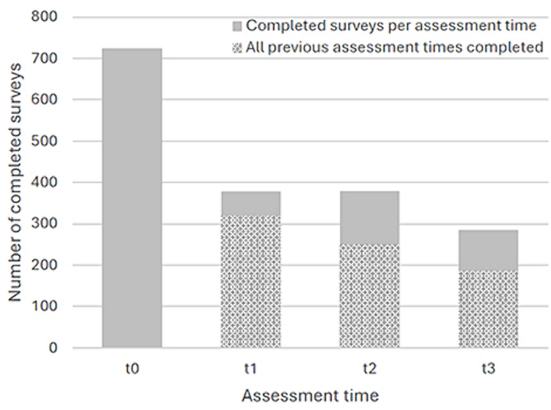

FIGURE 1
Number of completed surveys per assessment time.

TABLE 2 Sample characteristics.

		n	%
Age distribution (years)			
	18–31	32	3.9
	31–40	162	19.5
	41–50	263	31.7
	51–60	203	24.5
	61–70	132	15.9
	>70	32	3.9
	NA	6	0.7
Mean age (SD)		49.79 (11.72)	
Gender			
	Female	730	88
	Male	96	11.5
	Diverse	0	0
	NA	4	0.5
Survey language			
	English	177	21.3
	German	203	24.5
	Chinese	197	23.7
	Spanish	19	2.3
	Russian	149	18
	Ukrainian	85	10.2

NA, not available.

registrations, German: $n = 259$, Chinese: $n = 264$, Russian: $n = 183$, Ukrainian: $n = 200$, Spanish: $n = 19$, Finnish: $n = 33$, Dutch: $n = 17$, and Slovenian: $n = 50$) of whom 830 agreed to participate in the study and filled in the minimally required survey, as per inclusion criteria. Of the full sample ($N = 830$), 444 (53.5%) filled in at least two surveys and 186 (22.4%) filled in all four surveys (see Figure 1 for completed surveys per assessment time). Table 2 shows the full sample's demographic characteristics and language in which the surveys were filled in. The majority of participants were middle aged, female, and of a European context. Table 3 shows the sample's baseline levels of stress and mindfulness. The sample's PSS-10 baseline score was indicative of moderate stress levels (Adamson et al., 2020) and above the norms for healthy adults (Cohen, 1988), whereas the baseline MAAS score was somewhat below normative general population samples (Carlson and Brown, 2005; Brown and Kasser, 2005).

3.2 Outcome measures

Table 3 also shows descriptive statistics of the outcome variables on all assessment times.

3.2.1 Self-reported stress

Model estimates for changes in self-reported stress over the course of the study, controlled for age, sex, and survey language, can be found in Figure 2. PSS-10 scores showed a significant decrease in self-reported stress in conjunction with the intervention ($F(3, 902) = 123.969$, $p < 0.001$; effect size $\eta_p^2 = 0.28$). As visible in Figure 2, stress scores decreased continuously from t0 to t2 and showed a non-significant small increase again at follow up. All estimates (t1, t2, t3) were significant relative to t0 at $p < 0.001$.

Mean frequencies and durations of self-practice per time lapse are provided in Table 4. Both had a significant effect on perceived stress as per ANOVA: PSS-10 scores were significantly lower if activity-based mindfulness exercises had been practiced on more days of the weeks preceding the assessment at t1 ($F(3, 361) = 8.357$, $p < 0.001$), t2 ($F(3, 365) = 9.702$, $p < 0.001$), and t3 ($F(3, 275) = 4.651$, $p = 0.003$), and likewise for longer self-practice durations in the weeks preceding t1 ($F(4, 360) = 6.479$, $p < 0.001$) and t2 assessment ($F(4, 364) = 3.949$, $p = 0.004$). The same held true for eurythmy exercises, with significantly lower stress scores in relation to more frequent self-practice during the weeks before t1 ($F(3, 361) = 5.567$, $p < 0.001$), t2 ($F(3, 365) = 10.18$, $p < 0.001$), and t3 assessment ($F(3, 275) = 4.261$, $p = 0.006$), and similarly for longer practice durations in the weeks prior to t1 ($F(4, 360) = 5.297$, $p < 0.001$) and t2 assessment ($F(4, 364) = 3.03$, $p = 0.018$).

3.2.2 Mindfulness

Figure 3 shows model estimates for changes in mindfulness over the course of the study, again controlled for age, sex, and survey language. There was a significant increase in mindfulness in conjunction with the intervention ($F(3, 871) = 82.530$, $p < 0.001$; effect size $\eta_p^2 = 0.22$), with scores steadily increasing from t0 to t3. All estimates (t1, t2, t3) were significant relative to t0 at $p < 0.001$.

One-way ANOVA yielded significant effects of frequency and duration of self-practice on mindfulness for activity-based mindfulness exercises, pointing to a significant increase in MAAS scores for participants that had practiced more frequently during the weeks preceding t2 ($F(3, 341) = 7.629$, $p < 0.001$) and t3 ($F(3,

TABLE 3 Self-reported stress and mindfulness per assessment time.

	t0		t1		t2		t3	
	n	*M* (SD)	*n*	*M* (SD)	*n*	*M* (SD)	*n*	*M* (SD)
PSS-10	702	20.21 (6.00)	367	16.86 (5.58)	370	15.85 (5.67)	280	16.29 (6.07)
MAAS	621	3.78 (0.83)	355	4.05 (0.75)	345	4.20 (0.84)	270	4.22 (0.86)

PSS-10 = Perceived Stress Scale (Cohen et al., 1983), score range 0–40; MAAS = Mindful Attention Awareness Scale (Brown and Ryan, 2003), score range 1–6: t0 = 0 weeks (baseline), t1 = 4 weeks (mid-intervention), t2 = 8 weeks (completion), t3 = 16 weeks (follow-up).

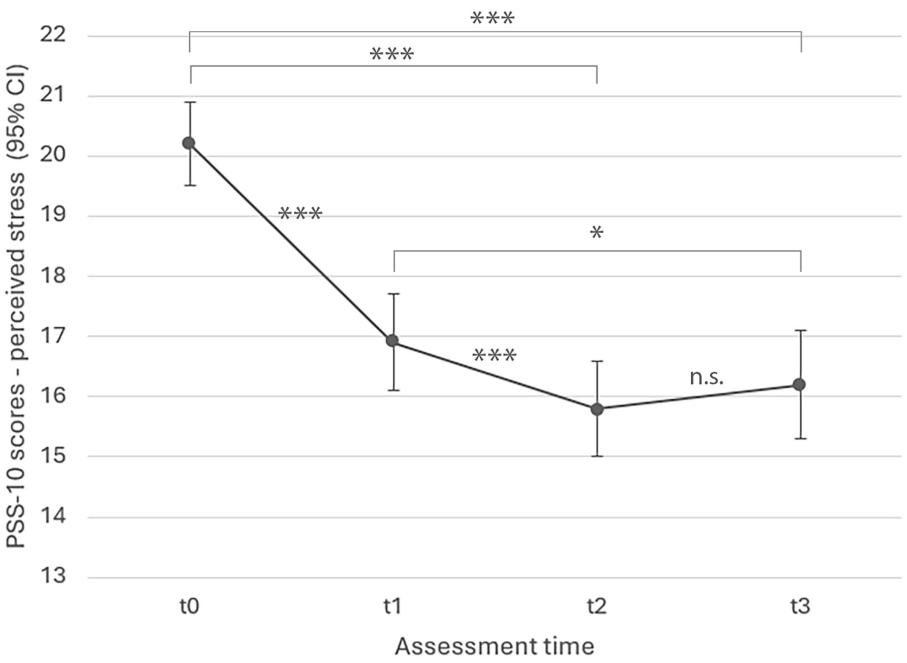

FIGURE 2
LMM model estimated marginal means for perceived stress over time ($p < 0.001$). PSS-10 = Perceived Stress Scale (Cohen et al., 1983); t0 = 0 weeks (baseline), t1 = 4 weeks (mid-intervention), t2 = 8 weeks (completion), t3 = 16 weeks (follow-up). All estimates (t1, t2, t3) were significant relative to t0 at $p < 0.001$; ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

265) = 3.952, $p = 0.009$), and for longer durations in the weeks preceding t2 ($F(4, 340) = 4.395$, $p = 0.002$). Similarly, more frequent self-practice of eurythmy exercises was followed by higher MAAS scores at t2 ($F(3, 341) = 10.600$, $p < 0.001$), and t3 ($F(3, 265) = 5.033$, $p = 0.002$), as were longer self-practice durations in the weeks prior to t2 ($F(4, 340) = 5.35$, $p < 0.001$) and t3 assessment ($F(4, 265) = 2.883$, $p = 0.023$).

4 Discussion

The current study assessed an eight-week-long online MBI incorporating mindfulness-related practices from AM, using an observational repeated measures design and large-scale sample of healthy adults ($N = 830$). In line with our expectation, self-reported stress decreased significantly over the course of the intervention, with the most pronounced improvement occurring between baseline and week four, and the lower stress level maintained until 8 weeks post program completion. The reduction in stress is in line with research on the MBSR and other MBIs addressing stress in healthy adults (Khoury et al., 2015; Chiesa and Serretti, 2009). Furthermore, also in line with our expectation, our results showed a significant increase in mindfulness in conjunction with the intervention, MAAS scores increasing steadily from baseline through to the end of the intervention, with a small but non-significant further increase at follow up 8 weeks later. As such, our findings confirm that, akin to classical MBIs, the intervention indeed targets and cultivates mindfulness (Lamothe et al., 2016; Lampe and Müller-Hilke, 2021; Nyklíček and Kuijpers, 2008), albeit with different means.

We found large effect sizes for both increases in mindfulness and stress (Norouzian and Plonsky, 2018; Richardson, 2011). Studies using the PSS-10 and MAAS to evaluate MBSR showed comparable improvements in degree and effect size (Shapiro et al., 2005; Shapiro et al., 2011; Juul et al., 2018; Jensen et al., 2023; Birnie et al., 2010), although the interpretability of LMM effect sizes across studies is still being debated (Norouzian and Plonsky, 2018, Richardson, 2011).

We found improvements in stress and mindfulness to be maintained after 8 weeks, while MBI studies assessing longer follow-up intervals found positive effects to persist after 1 and even 3 years (Galante et al., 2021b; Beblo et al., 2024). In the current work a slight increase in stress scores was evident at follow up, which was however not significant, but could indicate that some degree of continued self-practice could

TABLE 4 Self-practice times: mean frequency and duration.

	t1 *M* (SD)		t2 *M* (SD)		t3 *M* (SD)	
Exercises	Frequency	Duration	Frequency	Duration	Frequency	Duration
Activity-based	2.31 (0.89)	2.58 (0.88)	2.24 (0.89)	2.51 (0.82)	1.78 (0.83)	1.93 (0.89)
Eurythmy-based	2.34 (0.99)	2.68 (0.85)	2.30 (0.96)	2.58 (0.83)	1.84 (0.93)	2.10 (0.94)

Frequency (in days): 1 = 0–1, 2 = 2–3, 3 = 4–5, 4 = 6–7; duration (in minutes): 1 = 0, 2 = 1–10, 3 = 11–20, 4 = 21–30, 5 = more than 30; t0 = 0 weeks (baseline), t1 = 4 weeks (mid-intervention), t2 = 8 weeks (completion), t3 = 16 weeks (follow-up).

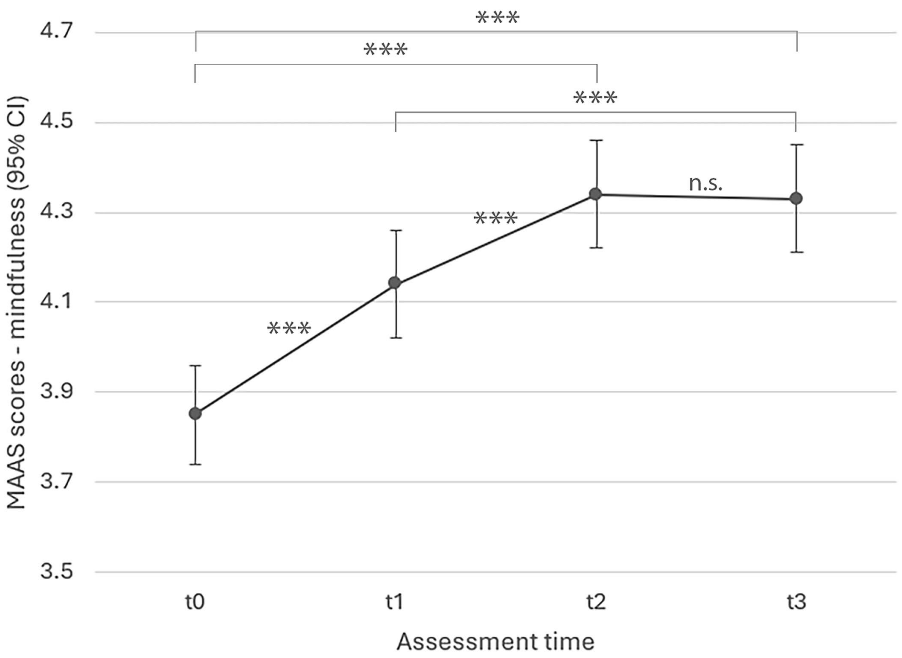

FIGURE 3
LMM model estimated marginal means for mindfulness over time ($p < 0.001$). MAAS = Mindful Attention Awareness Scale (Brown and Ryan, 2003); t0 = 0 weeks (baseline), t1 = 4 weeks (mid-intervention), t2 = 8 weeks (completion), t3 = 16 weeks (follow-up). All estimates (t1, t2, t3) were significant relative to t0 at $p < 0.001$; $***p < 0.001$, $**p < 0.01$, $*p < 0.05$.

be recommendable to sustain beneficial effects in the longer term. Indeed, according to our findings, frequency and duration of self-practice significantly impacted the outcomes, with more frequent and longer self-practice generally associated with larger beneficial changes in stress and mindfulness outcomes. This is consistent with findings from other MBIs, in which the extent of home practice was positively correlated with intervention outcomes (Parsons et al., 2017), but data on practice times are rarely reported in MBI studies (Jacobsen et al., 2022). A recent review reported only seven studies that assessed practice times, of which four found longer durations to lead to larger improvements in clinical outcomes (Lloyd et al., 2018).

This study had several limitations, including the observational single-arm design, which is however the norm for initial phases of feasibility testing of an intervention (Bowen et al., 2009). Future research should assess outcomes of the ABSR program using a randomized-controlled design and include longer follow-up intervals (e.g., 3, 6, 12, and 36 months). The survey completion rate in our study showed a rather high decrease across time, which is however a common finding of online studies with voluntary, anonymous, and uncompensated participation (Rostaminezhad et al., 2013; Bawa, 2016; Fish et al., 2016). Thus, despite the many advantages of online research, the non-committing format and perhaps also the technical demands may have presented a barrier impacting response rates (Gravesande et al., 2023). Further, due to resource constraints we were able to provide only 6 survey languages although the intervention was held in 9 languages, which may have contributed to a lowered response rate. The majority of non-completers left the study in the initial stages (after the first assessment), which is a typical pattern for online interventions in general and also in the context of MBSR studies specifically (De Paepe et al., 2018; Dobkin et al., 2012). Future studies should incorporate strategies to improve completion rate, which may include offering incentives for participation, as well as sending personally tailored email reminders to increase adherence over time (Meyerowitz-Katz et al., 2020), which would however require a non-anonymous study design.

This work had several strengths. It provides first indications for feasibility and beneficial outcomes regarding the online implementation of a novel MBI variant based on concepts and practices from AM, a well-established integrative medicine frame, thereby increasing plurality and diversity of options in the emerging field of MBIs. The current work demonstrated the intervention's adaptability to an online format, which has the advantage of broader accessibility and affordability, as is the case for other MBIs delivered online (Spijkerman et al., 2016; Jayawardene et al., 2017; Sommers-Spijkerman et al., 2021; Mrazek et al., 2019; Gravesande et al., 2023; Teo et al., 2024).

Future studies should examine if this alternative MBI could be particularly supportive for certain subgroups of individuals. Although benefits of MBIs have been extensively documented (Davis and Hayes, 2011; Khoury et al., 2013; Enkema et al., 2020, Baer, 2003), not all types of mindfulness practices seem to be equally well suited for all types of people and purposes (Sedlmeier, 2023). Dobkin et al. (2012) for instance reviewed the literature for reasons for attrition, contraindications, and adverse events in classical MBIs, pointing out that individuals with severe chronic pain tend to be less likely to complete the program. Furthermore, they concluded that classical sitting meditation demands special care in the context of certain predispositions and psychopathologies, such as post-traumatic stress disorder, and is considered contraindicated for individuals with psychotic disorders (Dobkin et al., 2012). Indeed, also meta-analytic evidence suggested a lesser benefit of MBIs involving sitting meditation for individuals with pronounced fear symptoms (de Abreu Costa et al., 2019). Furthermore, specific age groups (Petersen and la Cour, 2016; Sedlmeier, 2023), as well as certain personality features (e.g., neuroticism, narcissism), appear to interact with the kind of mindfulness practice that is preferred or more beneficial for an individual (Sedlmeier, 2023; Tang and Braver, 2020). Although research in this context is only beginning to emerge (Dobkin et al., 2012), the advantage of being able to offer a plurality and diversity of mindfulness approaches and practices is evident given the distinctive needs and corresponding fit, or lack thereof. Further research examining a broader range of outcomes and clinical populations will be necessary to determine for which groups of people this specific mindfulness approach based on AM would be especially suitable. For example, it is conceivable that the activity-based exercises of the ABSR could be supportive for individuals for whom sitting quietly while focusing attention on their inner world is associated with high levels of anxiety or impossible for other reasons. Importantly, future research should consider to assess mental health status and diagnoses of participants to find out who demonstrates most benefits, and conversely, if there are individuals for whom the intervention is less suitable or contraindicated.

5 Conclusion

While the current research provides promising preliminary indications regarding the online implementation of this novel MBI based on practices from AM, these findings need to be confirmed in randomized-controlled studies given the limitations of the current work, in particular its observational single-arm design and completion rate. Nonetheless, the study adds a unique contribution to existent MBIs, which is significant in view of the need for diverse approaches to meet the heterogeneity of individual predispositions and clinical needs. It remains to established by forthcoming research for which subgroups of individuals or clinical features this approach could be especially beneficial, or less suitable.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans given full anonymity of participants at all stages of the research (fully encrypted survey via anonymous self-generated codes, no collection of IP or E-Mail addresses, no collection of identifying participant data). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because participants were thoroughly informed in written form about the study and the voluntary nature of participation; they provided implied informed consent by completing the online survey (opt-in).

Author contributions

ET: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Project administration. YK: Data curation, Writing – review & editing. TH: Writing – review & editing, Conceptualization, Funding acquisition. IB: Writing – original draft, Writing – review & editing. UW: Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Supervision.

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Conflict of interest

TH was employed by company Eurythmy4you.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The relationship between BMI and depression: a cross-sectional study

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Introduction: Mental health problems, especially depressive symptoms, are becoming increasingly prominent, posing a significant risk to public health. Changes in the body mass index (BMI) may impact an individual's mental health, however, the relationship between BMI and depressive symptoms is unclear. The purpose of this study was to investigate the association between BMI and depressive symptoms.

Methods: Using a multi-stage sampling method, 10,686 adults in Longgang District, Shenzhen City, Guangdong Province, China, were selected for participation in this study. Surveys were distributed in 2020 and 2021 to measure participant demographic data and health. Binary logistic regression, restricted cubic spline regression, and subgroup analyses were performed to explore the relationship between BMI and depressive symptoms.

Results: The results showed a U-shaped relationship between BMI and depression. Both obesity and underweight increased the risk of depression among the participants, especially in subgroups of participants who were young, highly educated, single and employed.

Conclusion: These findings suggest that adults should try to maintain a normal body weight as a way to prevent depression and maintain their physical and mental health.

KEYWORDS

depression, body mass index, relationship, restricted cubic spline, subgroup analysis, risk factor

1 Introduction

Depressive disorder is a pervasive mental disorder characterized by a prolonged and constant sense of melancholy or diminished interest in activities. It is closely associated with suicidal behaviours (1). Globally, an estimated 280 million individuals suffer from depression (2), with more than 50 million in China (3). However, China lacks mental health resources, and the prevalence of depression among Chinese adults is currently about 6.9%, higher than the global prevalence (about 5%) (2, 4). Depression is the tenth leading cause of all-cause disability-adjusted life years (DALYs) in China (5), but its complex pathogenesis has not yet been clarified and many risk factors remain to be explored.

To date, several studies have suggested that there may be an association between overweight (or obesity) and depression (6–10). This is supported by mechanism studies. For example, obesity-related inflammatory processes can affect the occurrence and development of depression (11, 12). There is also evidence indicating that weight perceptions influence mental well-being (13). The prevalence of obesity has doubled globally in the past 30 years, with over 2.5 billion adults being classified as overweight in 2022, including 890 million who were considered obese, while 390 million individuals were considered to be underweight (14). According to Chinese standards, between 2015 and 2019, 34.3% of individuals were considered overweight, while the rate of obesity was 16.4% (15). Given the increasing prevalence of abnormal weight, it is particularly important to explore the relationship between body mass index (BMI) and depression. However, the majority of existing research that has examined the association between weight and depression has focused on overweight (or obesity) and depression, with a predominant emphasis on specific demographic groups such as women, children and the elderly, rather than the broader general population.

Shenzhen, a mega-city in China, is one of the pilot cities for the development of a Psychosocial Service System. Accordingly, there is significant concern about the mental health of the general public in this city. A cross-sectional survey found that the prevalence of all types of mental illness among adults in Shenzhen was as high as 21.87% (16). Further, the prevalence of depressive disorders was 7.74% (17), which is higher than the national level. This indicates that Shenzhen faces a significant challenge in preventing and intervening in depression.

Therefore, the aim of this study was to explore the association between BMI and depression among adults in Shenzhen, with the goal of identifying key subgroups that necessitate focused attention. The ultimate goal of this study was to establish a scientific foundation for future prevention and control strategies for depression, and enhanced the treatment and management approaches for affected patients.

2 Materials and methods

2.1 Sample and sampling

A cross-sectional study in 2005 showed that the prevalence of depression among adults in Shenzhen was 7.74% (17). However, this estimate was established 15 years ago, and rapid social change may have brought about a general increase in psychological pressure and stress (18). Further, the current study was conducted during the COVID-19 pandemic, where there was undoubtedly an exacerbation of psychological pressure. Thus, we decided to take 10% as an estimate of the prevalence of depression. Estimation of the required sample size for this study was performed using the Exact (Clopper-Pearson) Formula for Calculating Confidence Intervals for One Proportion in PASS 2021 software. The significance level α was set at 0.01 and the quantity δ for permissible error was set at 0.01. The required sample size was calculated to be 6071. Assuming a sample loss of 20%, the estimated required sample size was 7589.

Sampling for this study was conducted in 2020 and 2021 using a multi-stage sampling strategy. In the first stage, the Longgang District of Shenzhen was chosen as the sampling area based on the accessibility of this district. In stage two, two sub-districts were selected from among the 11 sub-districts in Longgang district using the simple random sampling method. In stage three, within each of the selected sub-districts, four communities were selected using the population size ranking systematic sampling method (eight communities were selected in total). In stage four, in each selected community, four resident groups were selected by the simple random sampling method (a total of 32 resident groups were selected). In stage five, within each of the selected resident groups, 240 households were selected using the simple random sampling method; all usual residents aged 18 years and above in the selected households were investigated (a total of 7,680 households were selected). The inclusion criteria for participation were: aged 18 years or above; has resided continuously in Shenzhen City for more than six months; is able to complete the survey independently or with assistance from others. A total of 10,686 surveys were distributed. Surveys with missing or abnormal values for height and weight, and those with excessively short response times, incomplete data and obvious logical errors, were excluded. Finally, a total of 9,995 surveys were analysed from adult residents in Shenzhen City. All participants provided informed consent before participation. This study was performed in accordance with the Declaration of Helsinki.

2.2 Methods

A self-administered survey was used to collect information about the participants, including age, gender, education, marital status, economic status, employment status, height, weight, smoking and drinking. Further, the severity of depressive symptoms was assessed by the Chinese version of the Patient Health Questionnaire-9 (PHQ-9). The items in the scale cover nine symptom criteria for the diagnosis of clinical depression according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and have shown good reliability and validity (19). In a cross-sectional study of depression in China, the PHQ-9 demonstrated good reliability and validity. The Cronbach α coefficient of the PHQ-9 was 0.839. Taking the results of the Mini-International Neuropsychiatric Interview as the gold standard, the area under the receiver operating characteristic (ROC) curve of the PHQ-9 results for all subjects was 0.898 (20). Each item in the PHQ-9 is scored as follows:

0 = not at all, 1 = several days, 2 = more than half the days, and 3 = nearly every day. The total score ranges from 0 to 27, with a higher score indicating more severe depressive symptoms. Total scores of 0-4, 5-9, 10-14, 15-19 and 20-27 indicate no, mild, moderate, moderately severe and severe depression, respectively. In this study, a score ≥ 5 was considered to indicate the presence of depression (21). BMI was calculated according to the guidelines for the prevention and control of overweight and obesity in Chinese adults, with BMI < 18.5 kg/m^2, 18.5-24.0 kg/m^2, 24.0-28.0 kg/m^2 and ≥ 28.0 kg/m^2 defined as underweight, normal weight, overweight, and obesity, respectively (15).

2.3 Quality control

Quality control before the study. Consult with relevant experts to design the electronic questionnaire. Reminders were set up in the survey to ensure that the participants submitted the complete questionnaire. Centralized and unified training was provided for the investigators.

Quality control during the survey. The investigators had to adopt uniform investigation standards, carefully check the surveys obtained, record the study procedures, and treat the participants politely.

Quality control after survey. Convert the electronic questionnaire into a data format. The data were double-checked to remove participants who completed the survey in too little time and who had obvious logical errors.

2.4 Statistical analysis

Statistical analysis and visualization were performed using R 4.3.2 software. Statistical significance was set at 0.05. Normally distributed data were described by $\bar{x} \pm s$, and differences between groups were examined by ANOVA. Non-normally distributed data were described by M (Q_1, Q_3), and differences between groups were examined using the rank sum test. Categorical data were described by frequencies (constitutive ratios), and differences between groups were examined by the χ^2 test. The association between BMI and depressive symptoms was analysed using a binary logistic regression model. The dose-response relationship between BMI and depressive symptoms was explored using the restricted cubic spline (RCS) model. Subgroup analyses were also performed to investigate the association between BMI and depressive symptoms.

3 Results

3.1 Demographic data

The average age of the participants was 34.0 (29.0, 44.0) years, among which, the average age of individuals with depressive symptoms was 32.0 (27.0, 40.0) years. The percentage of participants with depressive symptoms was 11.8% (1,176). Overall, 62.4% (6,240) of participants were female, and 49.4% (4,942) had an education level of college or higher. The average BMI of the sample was 22.10(20.08, 24.22) kg/m^3.

There were statistically significant differences in the prevalence of depression among residents grouped by age, education, marital

TABLE 1 Demographic information of participants.

	Overall	Depression	*P*
Age [M (Q1, Q3)]	34.00 (29.00, 44.00)	32.00 (27.00, 40.00)	<0.001*
BMI level [M (Q1, Q3)]	22.10 (20.08, 24.22)	21.85 (19.57, 24.22)	0.002*
Gender (%)			0.882
Male	3755 (37.57%)	439(11.69%)	
Female	6240 (62.43%)	737(11.81%)	
Education (%)			<0.001*
Junior high school and below	2477 (24.78%)	230(9.29%)	
High school	2576 (25.77%)	269(10.44%)	
College and above	4942 (49.44%)	677(13.70%)	
Marital status (%)			<0.001*
Married	8182 (81.86%)	754(9.22%)	
Unmarried/ divorced/widowed	1813 (18.14%)	422(23.28%)	
Family economic status (%)			<0.001*
Better	1172 (11.73%)	139(11.86%)	
Ordinary	8031 (80.35%)	814(10.14%)	
Poor	792 (7.92%)	223(28.16%)	
Employment status (%)			<0.001*
Be in employment	8370 (83.74%)	966(11.54%)	
Unemployed/retired	1625 (16.26%)	210(12.92%)	
Smoking (%)			<0.001*
Yes	1451 (14.52%)	249(17.16%)	
No	8544 (85.48%)	927(10.85%)	
Drinking (%)			<0.001*
Yes	1362 (13.63%)	256(18.80%)	
No	8633 (86.37%)	920(10.66%)	
BMI subgroups (%)			<0.001*
Low weight	930 (9.30%)	167(17.96%)	
Normal	6225 (62.28%)	690(11.08%)	
Overweight	2373 (23.74%)	252(10.62%)	
Obese	467 (4.67%)	67(14.35%)	
Total (%)	9995 (100.00%)	1176(11.77%)	

*Statistically significant.

status, family economic status, employment status, smoking, drinking, and BMI subgroups, as shown in Table 1.

3.2 Binary logistic regression

After adjusting for age, sex, education, marital status, economic status, employment status, smoking, and drinking, binary logistic regression showed a no linear association between BMI and the risk of depressive symptoms ($P > 0.05$). Compared with the normal BMI group, the obese and underweight groups had higher risks of depressive symptoms ($P < 0.05$) (Table 2).

3.3 RCS analysis

The RCS analysis revealed a non-linear relationship between BMI and depressive symptoms. That is, a U-shaped association was observed, where the depression OR was the lowest when BMI was 21.3 kg/m^3. A U-shaped relationship was also observed for the various investigated subgroups, including those under the age of 45, and males and females, respectively, where the lowest ORs for depressive symptoms corresponded to a BMI of 22.6 kg/m^3, 24.0 kg/m^{3}and 20.5 kg/m^3, respectively. However, these nonlinear associations were not observed in people aged 45 years and older (Figure 1).

3.4 Subgroup analysis

Normal BMI was used as a reference, and both underweight and obesity were associated with the risk of depression. Underweight increased the risk of depression in people below the age of 45, in females, in individuals with a junior high school and below education, in individuals with a college and above education, in unmarried/divorced/widowed individuals, in individuals with an ordinary economic status, in employed individuals, and in non-smokers and non-drinkers. Obesity increased the risk of depression in people below the age of 45 years, those with a college and above education, those who were unmarried/divorced/widowed, and those who were employed (Table 3, Figure 2).

4 Discussion

This large-scale mental illness-related research project organized by the Longgang District of Shenzhen, found that 11.77% of adults in Shenzhen suffer from depression. This estimate is much higher than the global prevalence of depression among adults (approximately 5%) (2). Thus, mental health issues should be given more attention in this population. In particular, the prevalence of depressive symptoms was higher among those who were unmarried/divorced/widowed, unemployed/retired, smoked cigarettes and drank alcohol.

This study found a U-shaped association between BMI and the prevalence of depressive symptoms in adults. This suggests that being underweight or overweight increases the risk of depression, similar to the findings of previous studies (22–25). The mechanisms by which an unhealthy weight leads to depression are diverse. Many studies have shown that obese people have a higher risk of depression, and this may be related to increased inflammatory response (26), leptin resistance (27, 28), cortisol-binding receptor damage (29), and disordered intestinal flora (30). On the other hand, obesity and underweight, as unhealthy physical characteristics, may have negative effects through social interaction, body image and self-esteem, thus increasing the risk of depression (31, 32).

In contrast to the current findings, some studies have found a significant positive association between BMI and depression (33, 34). For example, a German cross-sectional study found that obese adults had a significantly higher risk of depression than non-obese individuals (35). It is possible that the non-obese subgroups (i.e., underweight, normal, and overweight subgroups) masked the effect of underweight on depression. In the above study, mediation analysis showed that the association between BMI and depressive symptoms was mediated by physical health status. Thus, the authors reported that the likely reason for the high prevalence of depression in obese individuals is that obesity causes changes in health status which, in turn, mediate the development of depression (35).

Similarly, in contrast to the current study, some studies have found an inverse association BMI and depression (36, 37). This may be because these studies targeted specific populations (only middle-

TABLE 2 Binary logistic regression of BMI and depressive symptoms.

	Model1[*OR(95%CI)*]	Model2[*OR(95%CI)*]	Model3[*OR(95%CI)*]
BMI subgroups			
Low weight	1.756 (1.459~2.113)*	1.577 (1.305~1.905)*	1.350 (1.107~1.647)*
Normal	1	1	1
Overweight	0.953 (0.818~1.110)	1.016 (0.870~1.187)	1.048 (0.893~1.230)
Obese	1.344 (1.025~1.761)*	1.384 (1.055~1.817)*	1.343 (1.013~1.782)*
BMI level	0.976 (0.957~0.996)*	0.994 (0.974~1.015)	1.005 (0.984~1.026)

*Statistically significant.
Model 1: no covariates were adjusted.
Model 2: adjust for: age (smooth); gender.
Model 3: adjust for: age (smooth); gender; education; marital status; economic status; employ-ment status; smoking; drinking.

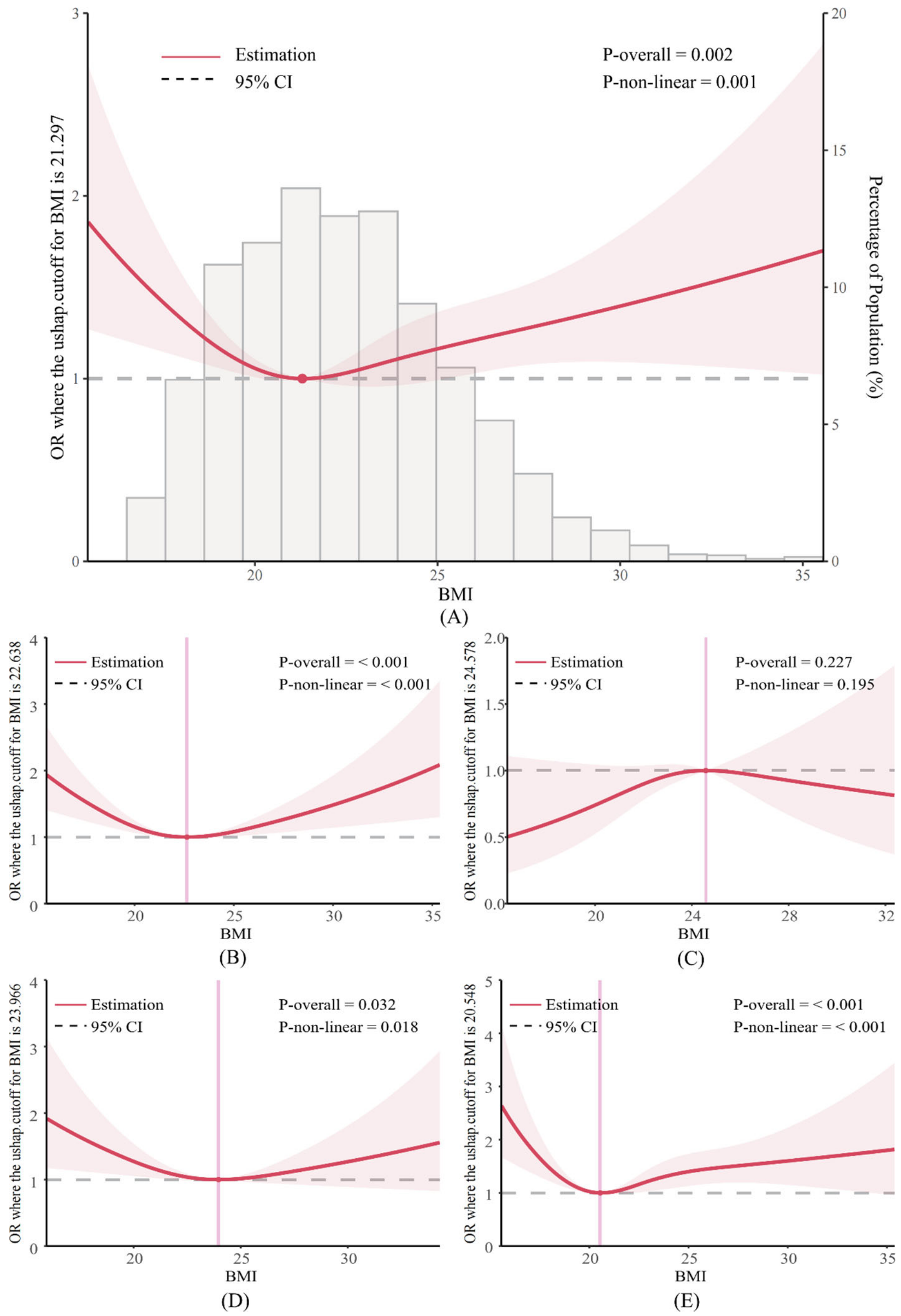

FIGURE 1
RCS curve of BMI levels and risk of prevalence of depression. **(A)** in total study population; **(B)** in <45 years old; **(C)** in ≥45 years old; **(D)** in male; **(E)** in female.

aged and older adults), while our study targeted adults (including middle-aged and older adults). The "jolly fat" hypothesis (fatter people are happier) could be used to explain the results of a cross-sectional study of Chinese middle-aged and older adults, where a negative association between BMI and depression in middle-aged and older adults was observed (36, 38). This hypothesis may also explain why as BMI decreases, the risk of depression increases. That is, psychological stress caused by rapid weight loss, such as diet control, may also increase the risk of depression (36, 38).

The results of the RCS in our study revealed that the relationship between BMI and the prevalence of depressive symptoms was U-shaped association across the adult population. The lowest OR for depression was observed at a BMI of 21.3 kg/m^2, which corresponds to the normal BMI range. Similarly, RCS

TABLE 3 Binary logistic regression analysis of BMI and depression in different demographic subgroups.

Group	Low weight [*OR*(95%*CI*)]	Normal	Overweight [*OR*(95%*CI*)]	Obese [*OR*(95%*CI*)]
Age				
<45	1.490 (1.210~1.822)*	1	0.993 (0.820~1.198)	1.470 (1.062~1.994)*
≥ 45	0.452 (0.109~1.252)	1	1.080 (0.795~1.461)	0.829 (0.394~1.572)
Gender				
Male	1.400 (0.915~2.079)	1	0.823 (0.641~1.050)	1.250 (0.809~1.864)
Female	1.440 (1.143~1.815)*	1	1.200 (0.966~1.475)	1.390 (0.930~2.026)
Education				
Junior high school and below	0.457 (0.186~0.956)*	1	1.230 (0.895~1.688)	1.070 (0.599~1.800)
High school	1.280 (0.807~1.966)	1	0.924 (0.665~1.271)	1.230 (0.620~2.249)
College and above	1.690 (1.326~2.135)*	1	0.960 (0.761~1.205)	1.540 (1.030~2.261)*
Marriage				
Married/coupled	1.150 (0.856~1.512)	1	1.090 (0.908~1.307)	1.150 (0.807~1.596)
Unmarried/divorced/widowed	1.730 (1.289~2.313)*	1	0.890 (0.633~1.236)	2.030 (1.161~3.474)*
Economic status				
Better	1.070 (0.599~1.850)	1	0.995 (0.612~1.580)	1.270 (0.527~2.712)
Ordinary	1.440 (1.142~1.808)*	1	1.090 (0.899~1.308)	1.320 (0.920~1.861)
Poor	1.280 (0.724~2.241)	1	0.927 (0.618~1.377)	1.370 (0.739~2.466)
Employment status				
Be in employment	1.400 (1.126~1.734)*	1	0.995 (0.829~1.190)	1.400 (1.021~1.900)*
Unemployed/retired	1.110 (0.661~1.825)	1	1.250 (0.875~1.784)	0.989 (0.460~1.926)
Smoking				
Yes	1.050 (0.600~1.804)	1	1.180 (0.834~1.649)	1.330 (0.718~2.342)
No	1.410 (1.134~1.742)*	1	0.987 (0.820~1.183)	1.320 (0.942~1.803)
Drinking				
Yes	1.260 (0.746~2.088)	1	1.130 (0.794~1.600)	1.330 (0.730~2.314)
No	1.380 (1.105~1.708)*	1	1.020 (0.850~1.220)	1.380 (0.986~1.891)

*Statistically significant.

analysis of different age subgroups showed a U-shaped relationship between BMI and the risk of depressive symptoms in young people, but not in middle-aged and older adults. This suggests that BMI is more strongly associated with depressive symptoms in younger populations. This is a novel finding. The U-shaped association was also observed in the gender subgroups. However, we observed something even more interesting. Specifically, the lowest risk of depression was found in males and females with BMI values of 24.0 kg/m^2 and 20.5 kg/m^2, respectively. Combined with the RCS curve morphology and trends in men and women it appears that the risk of depression in women is more likely to be affected by changes in BMI than in men, possibly because obesity or underweight causes an increased psychological burden in women. A study based on the 2005-2018 NHANES data showed that at the lowest risk of depression, women had a lower optimal BMI value (21.1 kg/m^2) than men (25.2 kg/m^2), which is consistent with our speculation (22).

Further subgroup analyses revealed that among those who were employed, both underweight and obesity increased the risk of depression. This may be due to the presence of more work and life stressors, and thus, an unhealthy BMI may pose a greater mental burden (39). Further, among those who were unmarried/divorced/widowed, both underweight and obesity increased the risk of depressive symptoms. This may be related to the experience of loneliness among this population, which can increase the risk of mental illness (40). Unexpectedly, among smokers and drinkers, abnormal BMI was not associated with depressive symptoms. This may be because smoking and drinking increase a

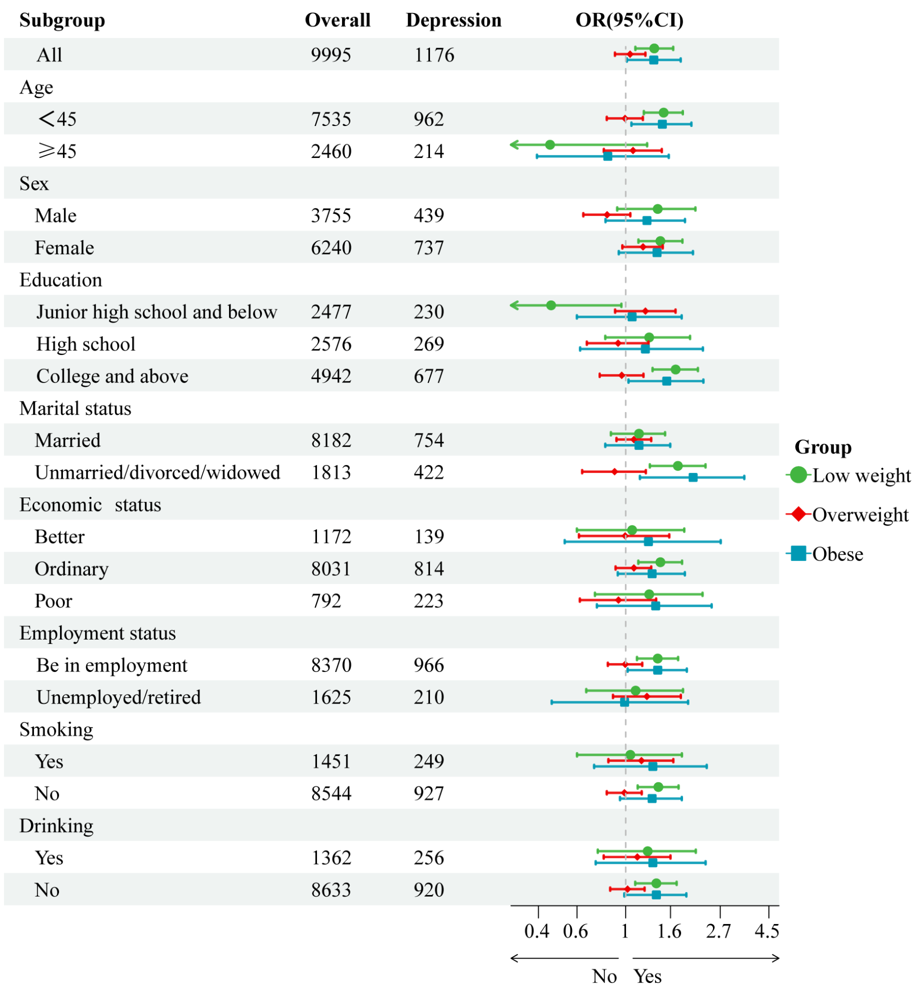

FIGURE 2
Forest plot of association between BMI and depressive symptoms in different demographic subgroups.

sense of pleasure and reduce mental stress, thus alleviating the onset of depressive symptoms (41).

The strengths of this study include the large sample size and examination of the adult population in general, as compared to studies that only included the elderly or young people. Thus, this study offers more a comprehensive insight into the association between BMI and depression among adults. Further, RCS analysis was conducted to explore the relationship between BMI and the risk of depression in the total sample as well as in different subgroups, which is rarely performed in the available literature. Nonetheless, this study still has some limitations. First, this was a cross-sectional study and as such, causal inferences cannot be made. Cohort studies are needed to investigate these causal relationships in the future. Second, the data in this study were based on self-report. Thus, inaccuracies and information bias cannot be excluded. In addition, important influencing factors, such as physical fitness, activity status and diet, were not adjusted for in this study and may have confounded the results. Future mediation studies of the relationship between BMI and depression may help to elucidate the potential causal mechanisms.

5 Conclusions

These findings reveal a U-shaped association between BMI and the risk of developing depression. That is, being underweight or obese was found to increase the risk of developing depression in adults. Importantly, a U-shaped association between BMI and depression was observed in the younger subgroup but not in the middle-aged and older subgroups. The risk of depression in the female population was more likely to be associated with a change in the BMI, as compared to male population. Moreover, high rates of depression were observed among smokers and drinkers, but an unhealthy BMI was not associated with an increased risk of depression in these groups.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Shenzhen Longgang Center for Chronic Disease Control. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HC: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. YX: Writing – review & editing, Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. CW: Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition. JY: Writing – review & editing, Visualization, Methodology, Data curation. WZ: Writing – original draft, Visualization, Supervision, Formal analysis, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Depression among keratoconus patients: a systematic review and meta-analysis

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Background: Keratoconus (KC) is a chronic corneal disease that typically presents in early adulthood, and may potentially result in poor mental health in affected individuals. The evidence regarding the association of depression with KC is controversial. Hence, we investigated the association between depression and KC via a systematic review and meta-analysis.

Methods: Five electronic medical databases (PubMed, Scopus, PsycINFO, Web of Science, and CINAHL Complete) were systematically queried for English-language records from their inception to January 8, 2024. We include observational studies that measured the risk of depression or compared depression scores in KC patients in comparison to healthy ones. The Newcastle–Ottawa Quality Assessment Scale was utilized to assess bias risk in the included studies. Random-effect modeling was applied for meta-analysis (STATA-17).

Results: Out of the 159 documents retrieved, seven articles were deemed relevant after screening. An analysis involving 83 KC patients and 3,186 controls indicated that KC participants had significantly higher depression scores [SMD: 0.71 [0.31, 1.11]; $p < 0.01$, I^2: 52.7%]. However, a meta-analysis of four studies comparing depression rates in KC patients ($n = 23,838$) to control groups ($n = 73,482$) found no increased risk of depression among KC patients compared to controls [OR: 1.13 [0.66, 1.94]; $p = 0.65$, I^2: 95.35%].

Conclusion: While KC patients exhibit significantly higher depression scores compared to controls, a meta-analysis indicates no increased overall risk of depression among KC patients. These findings highlight the complexity of the relationship between keratoconus and mental health, warranting further investigation.

Systematic review registration: PROSPERO, identifier, CRD42024502247, available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024502247.

KEYWORDS

keratoconus, depression, mental health, systematic review, meta-analysis

1 Introduction

Keratoconus (KC) is a bilateral chronic corneal disease characterized by progressive thinning and steeping of the cornea that changes the normal dome shape of the cornea into a cone-shaped one. This change results in irregular astigmatism and myopia (1). The global prevalence of KC has been reported as 1.38 per 1,000 population (2). However, the Asian population, particularly the Middle Eastern countries, is at significantly higher risk of developing KC (3, 4). The incidence of KC is typically higher among young adults in the third decade of life (5, 6).

Although KC is rare, its chronic nature and typical onset in young adulthood have raised a concern about its potential psychological impact (7). Adolescence and young adulthood are key stages in which individuals undergo physical and psychosocial changes, seek their goals, and shape their future (8). Hence, a chronic progressive eye disorder in early adulthood, which can lead to significant vision loss, may profoundly affect patients in terms of psychosocial problems, quality of life, and treatment adherence (9, 10).

Studies reported higher psychiatric disorders and lower quality of life among KC patients (11, 12). In a study in Saudi Arabia, the prevalence of anxiety and depression was 63.2 and 56.1% respectively among KC patients (12). Also, in a study in Turkey, the rate of psychiatric diagnosis and moderate-severe depression was 37.2 and 13.8%, respectively (11). However, studies assessing depression in KC patients compared to control have yielded conflicting results. Lin et al. (13) in a population-based study, reported depression as a protective factor against developing KC. In contrast, some studies suggest a significant association between KC and depression (14, 15), while other studies have reported no significant association (16, 17).

Individuals suffering from depression are at greater risk of life-threatening situations like suicide and tend to have a lower quality of life (18, 19). So, the potential link between depression and KC has raised concern about the potential psychological consequences of KC.

This systematic review and meta-analysis aim to comprehensively assess the prevalence and risk of depression among individuals diagnosed with KC compared to healthy controls.

2 Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 (20). The registration number in PROSPERO is CRD42024502247. The PRISMA checklist is included in Supplementary material 1.

2.1 Search strategy

Five electronic databases (PubMed (Medline), PsycINFO, Scopus, Web of Science, and CINAHL Complete) were systematically searched for English-language records from their inception to January 8, 2024. The searches included keyword combinations such as “Keratoconus” AND “Depression” (Supplementary material 2). Additionally, the references of the included studies and Google Scholar were screened to identify potentially eligible articles.

2.2 Eligibility criteria

We included observational studies to evaluate the risk of depression and compare depression scores between KC patients and healthy individuals. Our inclusion criteria, based on the PECO framework (Population, Exposure, Comparison, Outcomes), were as follows:

Population and Exposure: Confirmed KC patients.

Comparison: General population.

Outcomes: Depression scores (measured using validated tools) or prevalence of depression.

We excluded studies that met any of the following criteria: (1) Replication of secondary data from other studies, (2) Studies classified as reviews, editorials, conference papers, case series/reports, secondary analyses, or animal studies, and (3) Studies utilizing qualitative research methods.

2.3 Study selection

Two authors (AA and RM), independently reviewed the titles and abstracts of potentially eligible studies using Rayyan (21). For studies that seem potentially eligible, authors independently assessed the full texts. Any conflicts concerning study design or methods, as well as the ultimate decision on whether to include studies, were resolved through a consensus meeting with the senior author (HM).

2.4 Data extraction

Two authors (AA and RM), independently extracted information from the included articles and all discrepancies were resolved through additional discussions. The following general characteristics were gathered: author name and publication year, study location, study design, sample size, residence of participants including urban and rural, ethnicity, male-to-female ratio, depression tool, the time which has passed from KC diagnosis, primary findings of the included studies, and risk of bias (Table 1).

2.5 Quality assessment

We utilized the Newcastle–Ottawa Quality Assessment Scale to assess bias risk in the cohort, case-control, and cross-sectional studies included in our analysis. Studies were categorized as having either a low (≥7 stars), moderate (5–6 stars), or high risk of bias (≤4 stars), with an overall quality score of nine stars.

2.6 Quantitative analysis

We use two types of data for analysis. First, we use, standard mean differences (SMDs) were employed to account for variations in depression measurement methods across diverse studies. In our research, we utilized SMDs along with a 95% confidence interval (CI) to evaluate the disparities in depression scores between KC and control groups. Second, to obtain the comparison of the risk of depression between KC and control groups, odds ratio (OR) and standard error (SE) statistics were used. A random effects model (restricted maximum–likelihood model) was used

TABLE 1 General characteristics of all included studies.

References	Country	Design	Participants (KC, control)	Male/female	Age (SD)	Urban/rural	Depression tool	Time from KC diagnosis; year (SD)	Findings	Limitation	Risk of bias
Xu et al. (23)	China	Population-based cross-sectional study	27; 3,139	4/23, 1,370/1,769	64.2 (11.3), 64.2 (9.7)	7/20, 1,665/1,474	Interview with standardized questions	N/A	Positive significant association in univariate analysis; non-significant association in multivariate analysis.	Unclear definition of depression	Low risk of bias
Woodward et al. (16)	US	Population-based study-case-control study	16,053; 16,053	9,456/6,597; 9,456/6,597	40.4 (13.0); 40.4 (13.0)	14,660/1,263; 14,213/1,730	Data registration	4.7 (2.9)	Non-significant association	Only individuals with health insurance included	Low risk of bias
Moschos et al. (14)	Greece	Case-control study	56; 47	34/22; 30/17	41 (7); 42 (9)	N/A	Zung SDS-PHQ9	N/A	Positive significant association	Unknown duration of KC	Low risk of bias
Bak-Nielsen et al. (22)	Denmark	Nationwide population-based study-case-control study	2,679; 26,790	1,791/888; 17,910/8,880	38.2 (15.9); 38.2 (15.9)	N/A	Data Registration	N/A	Positive significant association after considering the time from diagnosis (108% higher odds of depression compared to controls)	The duration of KC was not precisely clarified; although it is considered in the analysis	Low risk of bias
Lin et al. (13)	Taiwan	Nationwide population-based study-case-control study	5,055; 20,220	2,991/2,064; 11,964/8,256	29.76 (12.02); 29.76 (12.02)	1,717/1,566; 5,846/7,538	Data registration	9.85 (4.75)	Negative significant association	Diagnosis of KC was not confirmed with health records	Low risk of bias
Aslan et al. (15)	Turkey	Case-control study	59; 65	41/18; 40/25	23.98 (5.7); 25.82 (5.4)	N/A	BDI-21	N/A*1	Positive significant association	Being the majority of KC patients in the early stages	Low risk of bias
Marx-Gross et al. (17)	German	Prospective population-based cohort study	51; 10,368	28/23; 5,352/5,067	40–80*2	1	PHQ-9	N/A*3	Non-significant association	Unknown duration of KC; Exclusion of mentally ill persons who were unable to participate in the study	Low risk of bias

*1Majority of KC patients were in Stages I and II (relatively earlier stages).
*2All participants' age span.
*3All participants are above 40 years old at baseline; Thus, it can be assumed that all subjects with keratoconus had already developed the disease at the start of the cohort.
KC, keratoconus; BDI-21, Beck Depression Inventory-21; PHQ-9, Patient Health Questionnaire-9; N/A, Not Available; SDS, Zung Self-Rating Depression Scale; CDVA, Corrected distance visual acuity; CXL, corneal cross-linking.

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to pool the extracted OR. Heterogeneity between the studies was evaluated by using the chi-square test and I square statistic. Publication bias was assessed by using the Begg and Egger tests. A meta-regression analysis was conducted to assess the impact of the publication year, total population, average age, and percentage of males. A sensitivity analysis was also carried out to test the robustness of the pooled effect size. All analyses were performed in Stata software (version 17, Stata Corporation, College Station, Texas, USA). *P*-values < 0.05 were considered statistically significant.

3 Results

3.1 Selection of studies

Initially, the search criteria generated 159 articles. After eliminating 69 duplicates using EndNote, we excluded 90 articles following title and abstract screening. Subsequently, based on the eligibility criteria, we identified 14 articles as potentially relevant to our systematic review. Following a thorough evaluation of the full texts, seven (13–17, 22, 23) articles were excluded, resulting in seven articles remaining (Figure 1).

3.2 Study characteristics

Seven studies (13–17, 22, 23) involving 100,487 participants including 23,921 KC patients, were included. All studies were published in 2012 or later. The mean age of participants ranged from 24 to 80. Five of these studies were large population-based studies conducted in the US (16), Denmark (22), Taiwan (13), China (23), and Germany (17). Also, two case-control studies with sample sizes of 103 and 124, were conducted in Greece (14) and Turkey (15), respectively. International Classification of Diseases (ICD) diagnosis codes (13, 16, 23), PHQ-9 (14, 17), BDI (15), and interview (23) were used for depression assessment.

Overall, three studies found a significant association between depression and KC (14, 15, 22). Conversely, Lin et al. (13) reported that depression is a protective factor against developing KC, showing a 42% reduced odds ratio of KC. Also, Xu et al. (23) and Woodward et al. (16) found no significant association between KC and depression.

The main limitation of the studies was the lack of consideration for the index time, which refers to the date of initial KC diagnosis. Only two studies reported the index time (13, 16). Also, in the Bak-Nielsen et al. (22) study, although the index time was not specified, subsequent analysis revealed 108% higher odds of depression compared to controls when accounting for the index time.

3.3 ROB

All studies showed low ROB score (Table 1).

3.4 Synthesis of results

3.4.1 Risk of depression

To evaluate the risk of depression in individuals with KC compared to control groups, four studies (13, 16, 17, 22) were included in the analysis. A total of 23,838 KC participants and 73,482 controls were analyzed, revealing no significant increase in the risk of depression among KC participants compared to the control group [OR: 1.13 [0.66, 1.94]; I^2: 95.35%; Figure 2]. We performed a sensitivity analysis to assess the individual impact of each study on the odds ratio (OR), which is the primary outcome in our statistical model. This analysis involved systematically removing one study at a time. The exclusion of the study by Bak-Nielsen et al. (22) had a notably greater effect on the overall effect size estimation compared to the other studies [OR = 0.89 [0.42, 1.35], $p < 0.001$].

The funnel plot exhibited an asymmetric distribution of the data, suggesting a potential presence of publication bias. However, this finding was inconsistent with the results of Egger's and Begg's tests, which indicated a low risk of publication bias ($p = 0.019$ and $p > 0.99$, respectively), as shown in Figure 3. Consequently, we applied the trim-and-fill method, which provided evidence of publication bias with the addition of one more study [OR: 1.036 [0.473, 1.599]].

A meta-regression analysis was performed to evaluate the overall influence of the publication year, total population, average age, and percentage of males on the pooled effect size, none of which were found to be significant (Table 2).

3.4.2 Depressive score

To compare the depression score between KC and control participants two studies (14, 23) were included. In total 83 KC and 3,186 control from these two studies were included in the analysis that showed higher depression scores in KC participants [SMD [95% CI]: 0.71 [0.31, 1.11]; $p < 0.01$; I^2: 52.7%; Figure 4].

4 Discussion

Depression significantly influences treatment adherence and outcomes in patients with chronic diseases (24), thereby potentially hindering the course of KC progression and compromising the effectiveness of treatment modalities. In our systematic review and meta-analysis, we found a higher prevalence of depression among KC patients; however, this association was not statistically significant. Furthermore, we observed higher depression scores in patients with KC, indicating a more notable psychological burden within this group of patients.

Several studies have investigated the association between depression and KC and indicated a non-significant association between depression and KC (14, 15, 17, 22). A study by Alfardan et al. (12) showed that patients with KC tend to experience more psychiatric issues, particularly depression, with 56.1% of the 57 patients diagnosed with depression. Al-Dairi et al. (25) discovered that depression is significantly prevalent among KC patients, with a prevalence rate of 40.6%. Notably, this link persists regardless of disease severity or socio-demographic factors.

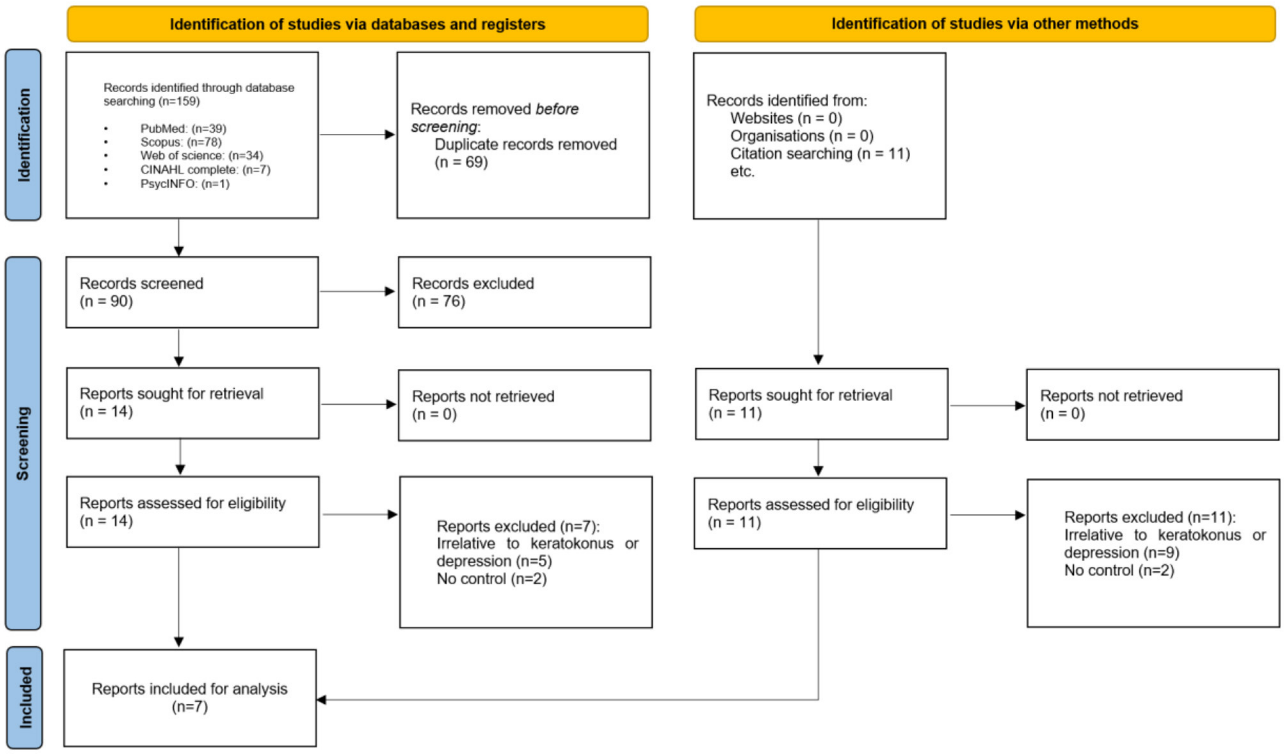

FIGURE 1
PRISMA of all included studies.

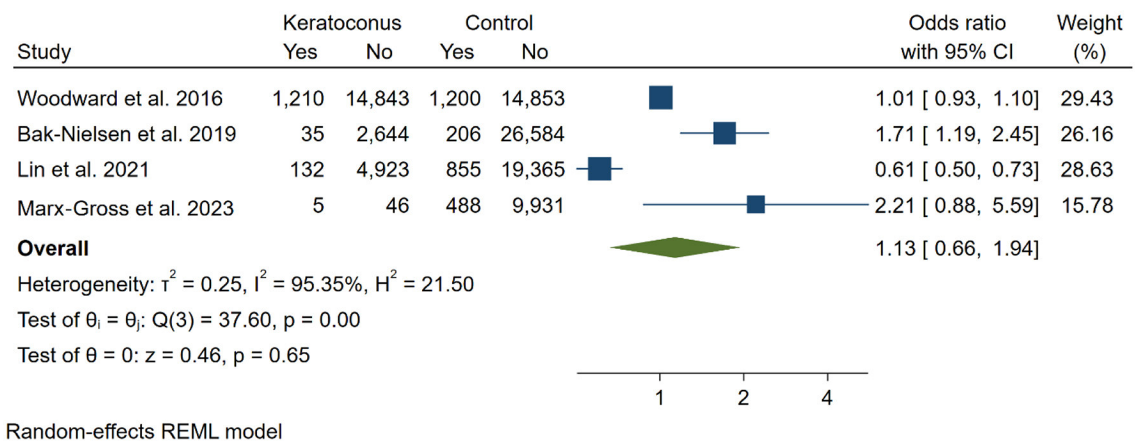

FIGURE 2
Meta-analysis for the prevalence of depression in all included studies.

The assertion that patients with depression demonstrate a protective effect against KC is not adequately supported, as only one study by Lin et al. (13) has explored this association. Lin et al. findings contradict previous studies in the literature due to their reliance on health records without direct verification, potentially leading to diagnosis inaccuracies. Moreover, the study's methodology raises doubts about whether depression genuinely confers protection against KC. Important factors such as eye rubbing and family medical history were not thoroughly examined, and the focus on older patients overlooks potential risk factors in younger individuals. Additionally, cultural stigma in some Asian communities often leads to underreporting of depressive symptoms, which may influence the observed association between depression and KC (26). Consequently, while the study hints at a connection between depression and KC, further research is necessary to confirm this link, by considering these methodological limitations.

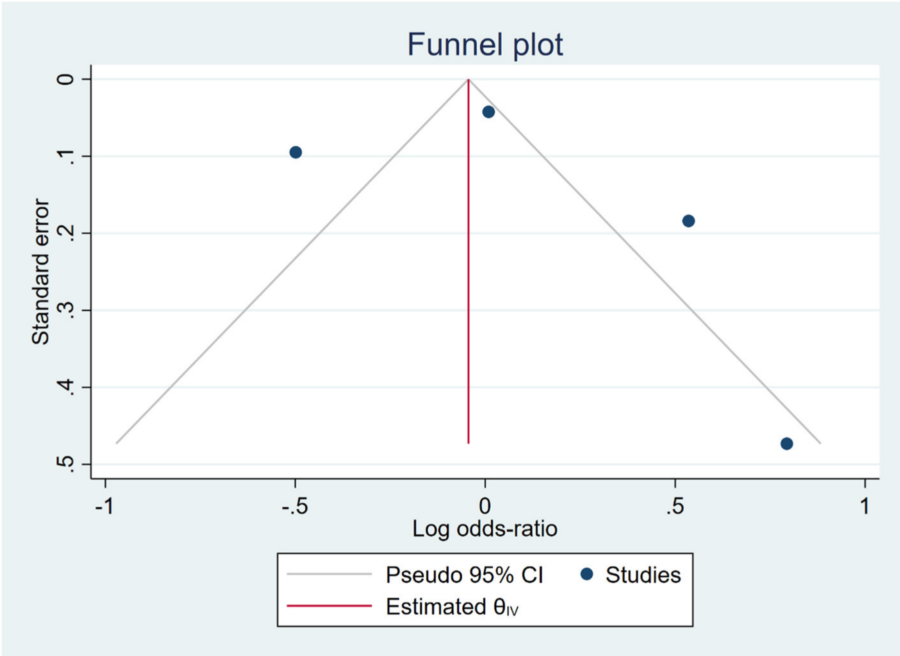

FIGURE 3
Funnel plot of all included studies for the prevalence of depression.

Several studies found no significant link between depression and KC (16, 23). In a study by Bak-Nielsen et al. (22), there was no significant difference in the depression prevalence observed between KC patients and the control group. However, after the index time, the prevalence of depression was estimated to be higher among KC patients. Additionally, due to potential misclassification of KC and associated conditions, challenges in differentiating KC from post-refractive surgery ectasia, incomplete coverage of ophthalmological healthcare data in the registry, and delays in diagnosis, their findings may not accurately reflect the expected outcomes. In another study, Jonas et al. (26) found no significant association between several ocular diseases such as KC, and depression prevalence; however, this association was marginally significant in patients with lower visual acuity (VA).

The diversity in depression prevalence among individuals with KC can be attributed to differences in sample sizes, study designs, depression tools, chronicity of KC and methodologies. Smaller sample sizes or less robust study designs may overlook certain aspects of depression prevalence or fail to capture its full extent. Genetic and environmental factors in KC development indirectly influence depression prevalence, as indicated by Gordon-Shaag et al. (27). Genetic predispositions and environmental stressors linked to KC may contribute to mental health challenges, including depression. Sociodemographic factors like age, gender, and location significantly affect KC prevalence and characteristics (22). Furthermore, cultural disparities and healthcare access might influence how depression is expressed and reported among KC patients in different regions or demographic groups. Additionally, diverse diagnostic criteria and tools utilized for KC identification, such as corneal pachymetry, tomography, and topography, can influence reported prevalence rates and associated risk factors (28).

Moreover, differences in KC chronicity and severity may be another source of variation in depression scores. Al-dairy et al. (25) found a significant association between depression and KC regardless KC severity. Bak-Nielsen et al. (22) in Danish national registries, found 108% higher odds of depression compared to controls after the consideration of index time as the time of first KC diagnosis for the KC group and time of matching for the control group; whereas the relationship of KC and depression was significant before index time consideration. This result highlighted the impact of the chronicity of KC on depression. In contrast, another study by Alfardan et al. (12) investigated the chronology of psychiatric illness and KC. They found that 51% of psychiatric illnesses had been diagnosed before KC development, suggesting higher susceptibility of individuals with psychiatric illnesses to KC rather than a causal relationship between them. Further prospective studies with more vigorous methodologies are required to help us understand the relationship of psychiatric illnesses and KC.

The scores obtained in depression assessments among KC patients can vary. In our systematic review and meta-analysis, we found higher depression scores in KC patients. In another study by Moschos et al. (14), 12.5% of KC patients did not suffer from depression according to the PHQ-9 score, while 46.4% encountered mild, 28.6% moderate, and 12.5% severe depressive symptoms. These varying scores reflect the spectrum of depressive symptoms observed in KC patients and the importance of using validated assessment tools to evaluate depression in this population. Based on Durakovic et al.'s (7) research, deteriorating mental health scores were associated with reduced visual acuity in both the better and worse eyes, heightened ocular asymmetry, and worsening disease severity. Mental health effects were frequently found to exceed those related to changes in visual acuity. However,

TABLE 2 Meta regression based on desired variables.

Variables	Coefficient	Standard error	95% confidence interval	*P*-value
Published year	0.036	0.135	−0.228, 0.301	0.788
Total population	−0.029	0.020	−0.069, 0.011	0.150
Mean age	0.067	0.060	−0.051, 0.183	0.265
Male (%)	−0.768	0.464	−1.677, 0.140	0.097

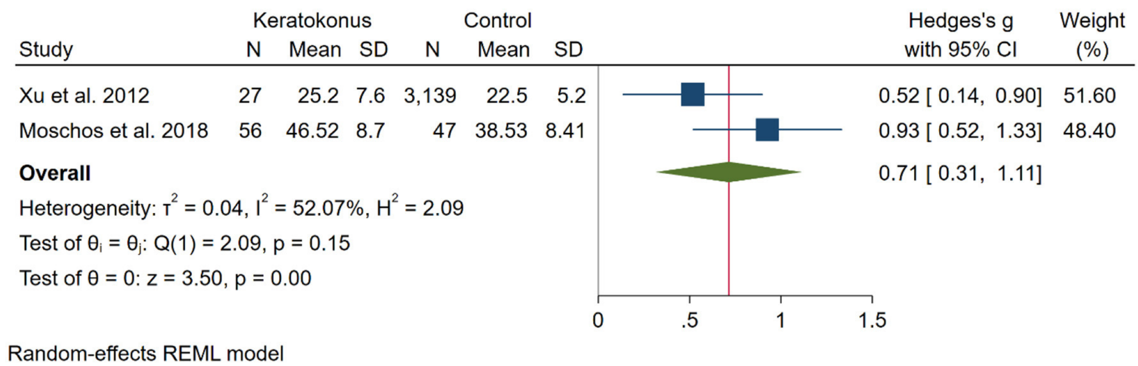

FIGURE 4
Meta-analysis for depression score of all included studies.

with time, mental wellbeing tended to improve, indicating a potential stabilization of the disease and increased acceptance by patients (29).

We believe that the variation in depression scores among individuals with KC arises from several factors. The severity of the condition, varying from mild to severe, significantly influences the emotional distress experienced by the individual, particularly if their vision impairment is notable (30). The coping mechanisms employed and the level of support received from social circles and family networks also exert a substantial impact. Those with effective stress management techniques and robust support networks typically exhibit lower levels of depression, whereas those lacking support may experience heightened distress (31). Socioeconomic factors such as financial limitations and differences in mental health service access could exacerbate levels of depression (32). Additionally, the presence of concurrent health issues or past adverse experiences can contribute to the complexity of depression management (33). Recognizing these various effects is crucial for developing effective strategies to address depression in individuals with KC.

The bidirectional relationship between depression and KC suggests a complex interplay where each condition may influence the other's development or progression; however, this interaction has not been well-studied. Individuals with depression may exhibit behaviors or habits, such as eye rubbing or neglecting eye care, that could potentially exacerbate KC or contribute to its progression (34). Additionally, the stress and emotional burden associated with depression may compromise immune function or exacerbate inflammation, which is believed to play a role in the pathogenesis of KC (35). KC can potentially impact the quality of life related to vision, with social and physical impairments. Fan et al. conducted a qualitative study and revealed that patients with KC, reported that the visual symptoms they experienced had a profound effect on their education and early career. Consequently, it resulted in their disengagement in school and restricted career opportunities. Moreover, the ability to relish life was also a factor, as they had to reduce their participation in activities and hobbies and experienced emotional distress from lost confidence and the restrictions imposed on their travel. The vision and emotional state of the individuals, along with financial problems, had a negative impact on their relationships and driving contributing to frustration and susceptibility to depression (36). Similarly, another qualitative study by Fournie et al. showed that KC patients, report sense of fear, worry and anxiety due to their condition, such as concerns for visual disturbance, car accidents due to impaired sight, and anxiety about potential eye surgery (37).

In another study, Steinberg et al. revealed that anxiety about the uncertain future effects of vision loss can significantly impact a patient's mental health (38). Consequently, longitudinal studies that investigate the onset of ocular disease and the development of depression as a consequence are crucial for understanding the bidirectional association between ocular disease and mental wellbeing and developing particular strategies to improve psychological outcomes in these patients (39).

We hypothesize that the physical manifestations and visual impairment linked to KC can significantly impact an individual's psychological wellbeing, potentially leading to or worsening depressive symptoms. Visual challenges, including difficulty in daily activities, social interactions, and occupational tasks, may contribute to feelings of frustration, isolation, and low self-esteem, all characteristic of depression. Additionally, the chronic nature of both depression and KC can create a cycle where each condition exacerbates the other. For instance, stress and anxiety resulting from KC progression may worsen depressive symptoms, while individuals with depression may struggle to adhere to KC treatment, impacting their eye health and potentially worsening KC symptoms (29, 39). Recognizing the bidirectional relationship between depression and KC is essential for providing comprehensive care to affected individuals. By addressing both the physical and psychological aspects of these conditions, healthcare providers can potentially enhance patient support and improve overall wellbeing.

A notable strength of our study lies in its innovative nature as it is the first systematic review performed in this particular field. Using a meta-analysis methodology, we synthesized data from several high-quality studies to offer a precise overview of the correlation between ocular disease and mental health. Including comprehensive studies improves the reliability and validity of our findings and enhances the robustness of our conclusions.

The study has several limitations. First, the inclusion of studies with retrospective designs, may introduce biases that compromise the reliability of our findings. Secondly, limited sample sizes in several studies restrict the generalizability of our findings to larger populations. Thirdly, the absence of all ethnic groups in the included studies may limit the applicability of the findings to diverse populations. Moreover, the high heterogeneity among studies could influence pooled results and affect result interpretation. Despite our meta-regression analysis not identifying any significant determinants of heterogeneity, several potential sources may be contributing to this variability. These include differences in study design, participants' characteristics, study quality, and publication bias. Addressing the issue of heterogeneity is a multi-faceted task, which involves the investigation of new variables, as well as the improvement of study methodologies. Lastly, potential publication bias underscores the need for precise interpretation, as it may lead to an incorrect estimation of depression prevalence rates.

Future research should focus on larger-scale studies and across diverse settings and populations to improve precision in elucidating the mechanisms underlying the relationship between KC onset and depression. Moreover, they should be directed at recognizing and controlling possible heterogeneity sources to improve the strength and applicability of meta-analytic results. Prospective cohort studies are recommended for capturing longitudinal data and identifying causal relationships. Additionally, evaluating interventions to mitigate the impact of ocular disease on mental wellbeing is essential for informing targeted strategies.

5 Conclusion

In conclusion, while the analysis of depression scores suggested significantly higher levels in KC patients compared to controls, the meta-analysis of depression rates found no increased risk of depression in KC patients. These contradictory findings highlight the need for further research to clarify the relationship between keratoconus and depression. Larger, well-designed studies with standardized assessment methods are necessary to provide a more definitive conclusion. Nonetheless, the review underscores the importance of considering mental health in the management of KC patients to ensure comprehensive and holistic care.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

RM: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. AA: Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. NS: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. GM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. HM: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1477411/full#supplementary-material

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Effects of high intensity interval training and moderate intensity continuous training on enjoyment and affective responses in overweight or obese people: a meta-analysis

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Background: High-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) have demonstrated significant potential for enhancing physical and mental health. However, their respective effects on enjoyment and affective responses remain contentious.

Objective: The objective of this meta-analysis is to evaluate and compare the effectiveness of HIIT and MICT on enjoyment and affective responses in overweight or obese people, and to find the most appropriate exercise mode for overweight or obese people.

Materials and methods: This study was conducted following PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. A comprehensive search was performed across databases including Cochrane, EMBASE, PubMed, and Web of Science, with a cutoff date of August 2024. Data extraction and organization were carried out using Excel, and Review manager was used to evaluate the quality of the literature and to analyze and process the data. The Stata was used to test publication bias.

Results: A total of 16 articles were included in the literature, and a total of 537 participants met the inclusion criteria, including 213 participants in HIIT, 183 participants in MICT, 84 participants in alternating HIIT and MICT, and 57 participants in other forms of intervention (self-selected intensity exercise, very-high-intensity interval exercise, repetitive sprint training, and blank control). All study participants were between the ages of 18–70 years old, and the duration of the intervention ranged from 1 to 16 weeks. Enjoyment and affective effects of HIIT and MICT were analyzed using the Physical Activity Enjoyment Scale, Feeling Scale and Felt Arousal Scale.

Conclusion: Both HIIT and MICT can bring about similar enjoyable and positive affective responses in overweight and obese people, HIIT caused participants to experience higher enjoyment and similar affect responses compared to MICT.

KEYWORDS

affect, enjoyment, overweight, obese, high intensity interval training, moderate intensity continuous training

1 Introduction

Overweight and obesity have emerged as a global "epidemic." By 2022, it was estimated that 43% of adults aged 18 and older were classified as overweight, with 16% classified as obese (1). The average body mass index (BMI) of the global population is gradually increasing. With the average body mass index of the global population gradually increasing, overweight and obesity have become a public health crisis. It has placed a huge burden on the healthcare and economic systems of both developed and developing countries (2). According to the World Obesity Alliance (2024), the fight against obesity requires significant financial investment, and by 2035, high BMI will result in a reduction of more than $4 trillion in the global economy, nearly 3% of global GDP (Gross Domestic Product) (3). Overweight and obesity also bring poor physical and mental health to patients, they not only increase the risk of type 2 diabetes and heart disease, affect bone health and reproductive system, but also may raise the risk of certain cancers (4). In addition, people who are overweight and obese show poorer mental health outcomes (5). Extensive epidemiological research has established a link between high body weight and deteriorating mental health, particularly concerning depression and subclinical depressive symptoms (6). Psychological stress induced by weight stigma and discrimination can lead to psychological distress and may, in turn, impede weight management efforts (7).

The main treatments available for overweight or obesity are nonoperative management and bariatric surgery, with nonoperative management being a multimodal approach that includes dietary changes, increased physical activity, behavioral changes, and medications (8). Among them physical activity is an effective means of weight loss and health management with fewer side effects and adapted to most populations., it can prevent weight gain, reduce weight loss, minimize weight regain after weight loss, and reduce the chances of developing chronic diseases (9). Research shows that exercise requires long-term persistence, and affective responses may be predictors of exercise adherence (10). Feelings of pleasure and enjoyment are key factors in adherence to an exercise program, and an increase or decrease in pleasure may contribute to the likelihood of forming positive or negative exercise memory traces. This in turn affects their subsequent decisions to participate in, persist with, or withdraw from exercise (11). William et al. also mentioned in his study that the core potency response (i.e., pleasure/displeasure) experienced during exercise has been identified as a key determinant of future physical activity behavior, especially for overweight or sedentary adults, who are most in need of interventions to enhance adherence to exercise programs (12). Some obese and overweight people may have difficulty maintaining long-term adherence due to weight stigma, self-rejection, or low - and moderate-intensity exercise that is monotonous and non-stimulating, and thus stop exercising after a period of exercise because they cannot stick to it (13, 14). This led us to consider the relationship between obesity and emotional response to exercise. What kind of exercise can give obese and overweight people a good sense of enjoyment and affective response, so that they can keep exercising?

When it comes to physical activity modality choices, there is a wealth of research that proves that high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) are effective modalities of exercise for improving body composition (15, 16). They are effective in improving health and fitness parameters (17, 18). For example, one mate-analysis showed that low-volume HIIT (LV-HIIT; i.e., ≤5 min high-intensity exercise within a ≤ 15 min session) can have similar effects on cardiometabolic health and body composition as MICT and high-volume HIIT, such as in terms of blood pressure, fat mass and waist circumferences (19). It is also proved that HIIT once a week, even with low weekly activity, can improve cardiorespiratory fitness, body composition, and blood pressure in overweight or obese adults (20). However, the research on assessing affective or pleasurable responses to HIIT and MICT has been largely ambiguous, no matter what kind of population they are in (21). For example, study by Niven et al. concluded that compared to MICT, HIIT is experienced less positively but post-exercise is reported to be more enjoyable (22). While study by Oliveira et al. (23) suggested that HIIT may garner equal or more positive psychological responses than MICT (23). In present review we attempted to update more precisely describe participants' affective responses to HIIT and MICT. At the same time, HIIT leads to similar or better physiological and biochemical effects than MICT, but takes less time (20, 24, 25). This provides a new direction and a new way of thinking about the barriers to physical activity in overweight or obese patients, i.e., insufficient time to maintain physical activity levels, and is a good prescription for a "short and fast" way to promote physical activity (26).

Some previous systematic reviews and meta-analysis investigated affective and enjoyment responses to HIIT and MICT have not distinguished obese and overweight people from the general population. Thus, the purpose of this study is to try to find which type of exercise brings better emotional and pleasurable experiences to obese and overweight people and whether HIIT is a better form of exercise for obese people than MICT. Through a systematic review and meta-analysis of the existing literature, to provide new ideas for the selection of exercise prescription for weight loss.

2 Materials and methods

2.1 Literature retrieval

The study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA Statement for Systematic Evaluation (27). Four electronic literature databases were searched to identify included studies: Cochrane, EMBASE, PubMed and Web of Science. Search terms included combinations of subject and free words for interventions, outcome indicators, and study subjects (see Table 1).

2.2 Eligibility criteria

The following inclusion criteria were used to select studies: (1) overweight or obese adults aged ≥18 years; (2) comparison of the HIIT with the MICT; (3) reported measures of affect, pleasure, and intention and (4) overweight or obese who participated in HIIT and MICT. All the studies are randomized controlled trials.

2.3 Literature quality evaluation

In this study, 2 evaluators (YL and JSZ) independently assessed the quality of the included literature by using Cochrane Collaboration's tool for assessing risk of bias. The quality of the literature was systematically evaluated in the following 7 areas: (1) description of the randomization method; (2) concealment of the allocation scheme; (3) double-blind principle; (4) blinding principle for outcome evaluation; (5) data completeness; (6) selective reporting of outcome results; and (7) assessment of the presence of other biases (Figure 1).

2.4 Data extraction

Data extraction and literature quality assessment were conducted independently by 2 evaluators (YL and JSZ) who extracted data from the included studies into an electronic data extraction form. When there is disagreement, a third reviewer will reevaluate it. Extracted data included literature general study information, study participant information (number, age, BMI), intervention characteristics (intensity, duration), and data on outcome indicators. When situations existed where data were unavailable, but graphical displays were available, we extracted data using a freely available web-based data extraction tool (Engauge Digitizer version 12.1) (28–31).

Data extraction and literature quality assessment were compared between two evaluators, with any disagreements being resolved by a third evaluator.

2.5 Publication bias

A visual analysis of funnel plot and the Egger's and Begg's test were performed to assess the publication bias across studies. At the same time, we used trim-and-fill process to assess the publication bias. This method involves examining the correlation between effect sizes and standard errors of effect sizes to determine if there is a significant association between study effect size and study precision.

2.6 Statistical analysis

Effect sizes were determined by calculating the standardized mean difference (SMD). Heterogeneity was tested using I^2. I^2 for 0–50% is low heterogeneity and 50–100% is high heterogeneity (32). Due to the heterogeneity of the Meta-analysis, a random effects model was chosen to integrate the combined data across the text. Review Manager 5.4.1 was used to perform three statistical analyses with confidence intervals (CI) of 95% for the three

TABLE 1 Systematic review search terms.

Interventions (linked by or)	Outcome indicators (linked by or)	Study subjects (linked by or)
High intensity interval training	Affective	Overweight
High-intensity interval trainings	Enjoyment	Obese
Interval training, high-intensity	Pleasure	
Interval trainings, high-intensity	Mood	
Training, high-intensity interval	Happiness	
Trainings, high-intensity interval		
High-intensity Intermittent exercise		
Exercise, high-intensity intermittent		
Exercises, high-intensity intermittent		
High-intensity Intermittent exercises		
Sprint interval training		
Sprint interval trainings		

Interventions, outcome indicators and study subjects are linked by 'AND'.

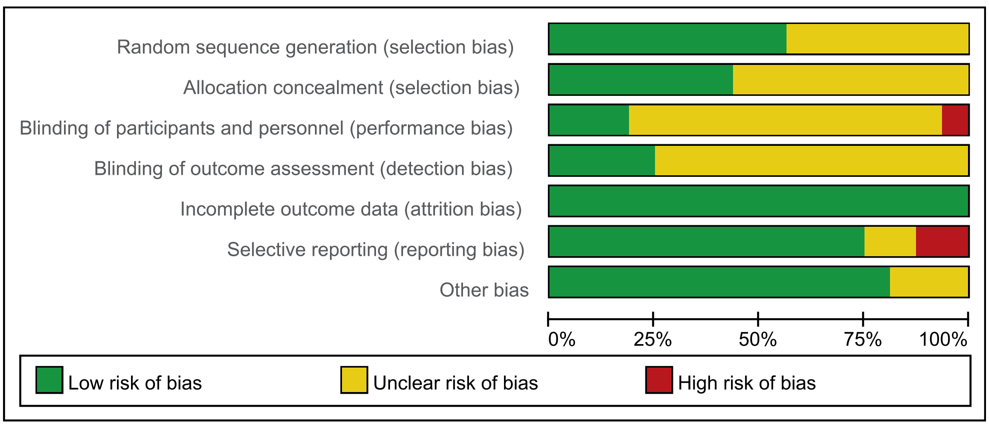

FIGURE 1
The bias risk assessment included in the literature. Green represents low risk and red represents high risk; yellow represents uncertainty.

outcomes (Physical Activity Enjoyment Scale, Feeling Scale and Felt Arousal Scale) of this study.

3 Results

3.1 Literature screening results

The initial review yielded 73 studies, and after excluding 10 duplicates, 11 studies that were not relevant to the topic, 21 studies that did not compared HIIT and MICT, 5 review studies, 2studies that had the same data and could not be analyzed based on the titles and abstracts, 2 other language studies, 1 chronic study, 2paediatric studies and 3 other studies, there were still 16 studies that needed to be evaluated in full text. Figure 2 illustrates the PRISMA process for study selection.

A total of 537 participants met the inclusion criteria in 16 studies, including 213 participants in HIIT, 183 participants in MICT, 84 participants in alternating HIIT and MICT, and 57 participants in other forms of intervention (self-selected intensity exercise, very high-intensity interval exercise, repetitive sprint training, and blank control). All participants were between the ages of 18–70 years, had

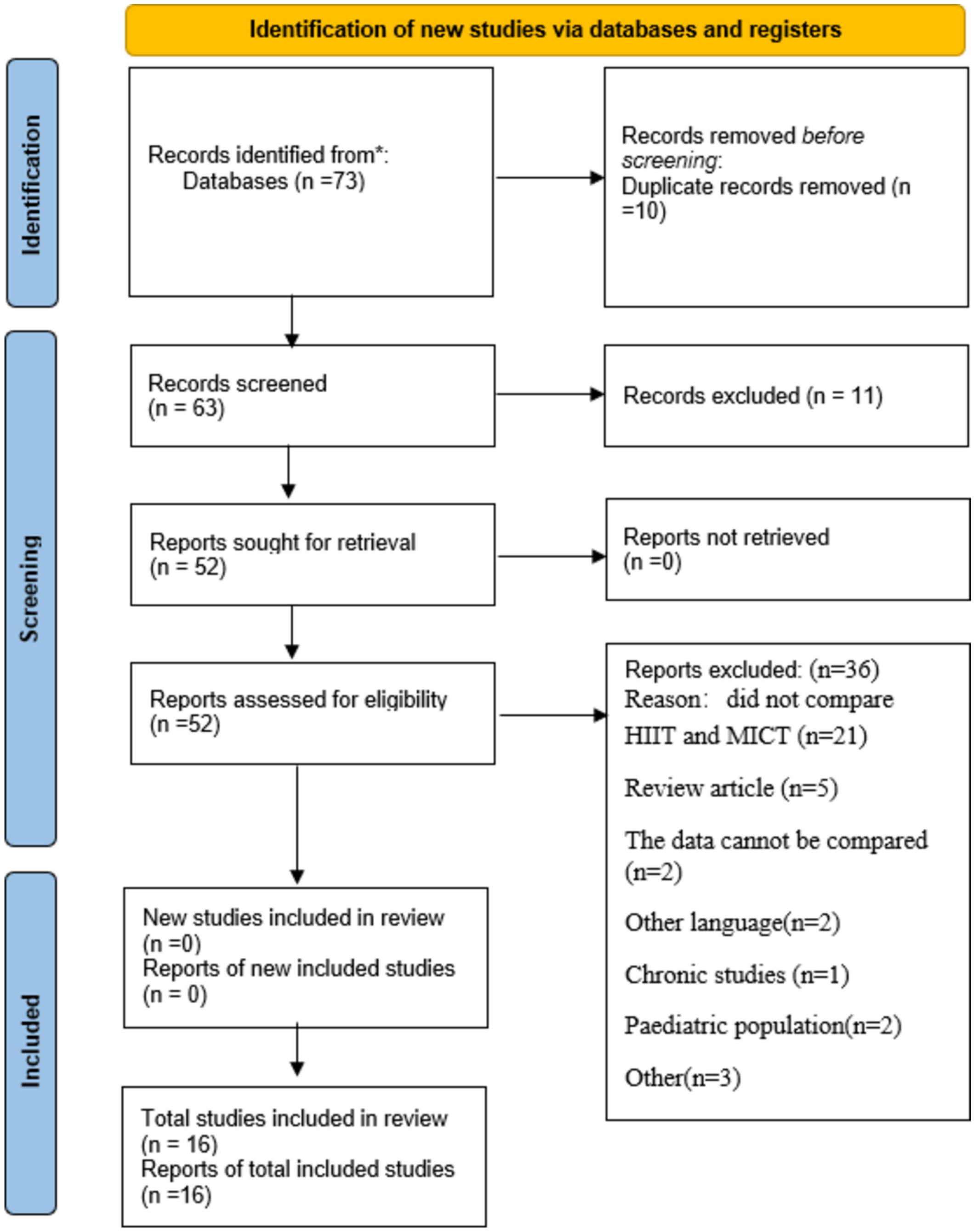

FIGURE 2
The flow chart of literature inclusion screening.

an intervention duration of 1–16 weeks, and had a BMI of 25 or higher. Five studies crossed over two exercises with the same group of participants. Eleven studies had participants under the age of 40 years, three between the ages of 40–60 years, and two over the age of 60 years.

3.2 Quality evaluation included in the study

Nine studies described the use of randomized grouping methods, such as the random number table method or computer generated randomization (21, 29, 31, 33–38), they were therefore assessed as having a low risk of bias. Seven studies were assessed as having an unclear risk of bias due to the lack of description of the randomization method (28, 30, 39–43).

Seven studies described a method of allocation concealment in which sealed opaque envelopes were employed or allocated by a third people (31, 33, 36–40), thus were assessed as having a low risk of bias. The remaining 10 studies did not describe the allocation hiding method, thus indicating an unclear risk of bias (21, 28–30, 34, 35, 41–43).

One study showed that participants were not blinded (21), it was therefore assessed as having a high risk of performance bias. Three studies have a low risk of bias due to the description of the double-blind method (34, 40, 43). The rest 12 studies did not describe the use of blinding of participates and personnel (28–31, 33, 35–39, 41, 42), thus indicating an unclear risk of bias.

In four studies, detection bias was judged to be low risk because they provided detailed information on the assessment of blinded outcomes (21, 28, 35, 41). The other 12 studies were judged to have uncertain risk because there was no description of blind outcome assessment (29–31, 33, 34, 36–40, 42, 43).

All 16 studies, reported complete outcome data, thus were assessed as having a low risk of bias.

Two studies did not report all pre-specified primary outcome (30, 34), thus were judged to be high reporting risk. Two studies had insufficient information to determine whether there was a risk of selective reporting of results (39, 41), thus were judged to be unclear reporting risk bias. The other 12 studies were judged to have low risk because all needed outcomes have been reported (21, 28, 29, 31, 33, 35–38, 40, 42, 43).

3.3 Publication bias and sensitivity analysis

Meta-analysis showed high heterogeneity of PACES and FS, and exclusion of the studies failed to reduce the level of heterogeneity, indicating a stable overall outcome. However, after excluding two studies (31, 34) the heterogeneity of PACES was significantly reduced to a relatively low level (I^2 = 46%). All two studies had an intervention duration of 12 weeks, three times per week, to further investigate the possibility of high heterogeneity, we performed subgroup analyses for age, form of exercise, and duration of exercise, but the significance of the results did not change significantly.

We used funnel plot and trim and fill process to assess publication bias. Based on visual observations, we found that the funnel plot for PACES and FS, there is no significant asymmetry (Figures 3, 4), which suggests that the included studies may not be significantly affected by publication bias, so the results of the meta-analysis may be relatively reliable. Further quantitative tests showed that there was no significant publication bias across studies (Begg's test, p = 0.100; Egger's test, p = 0.152, Supplementary Figure 1; The estimated effect size is 1.160 with a 95% confidence interval of 0.147 to 2.173, Supplementary Figure 2.

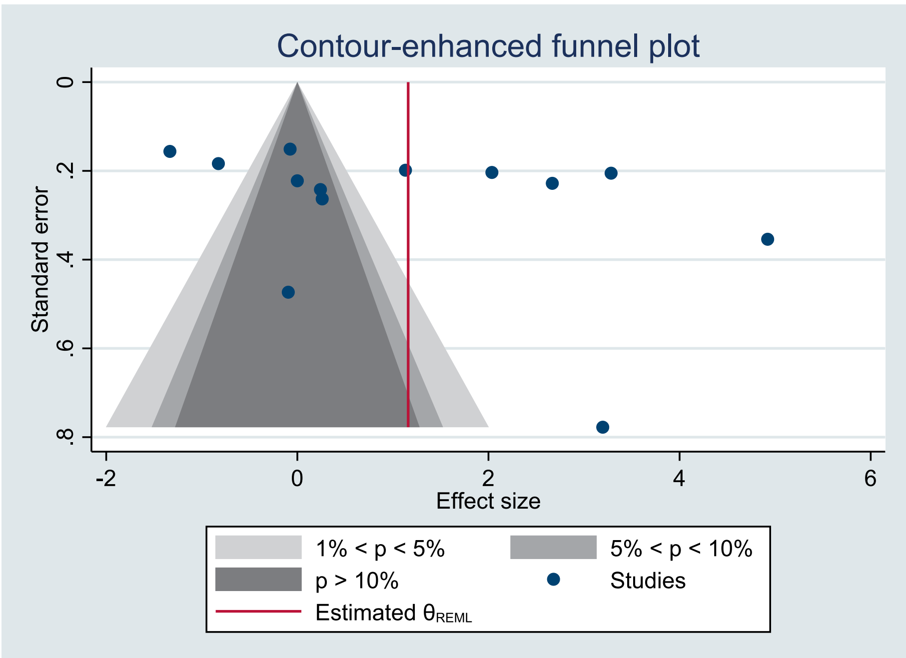

FIGURE 3
Funnel plot for PACES meta-analysis.

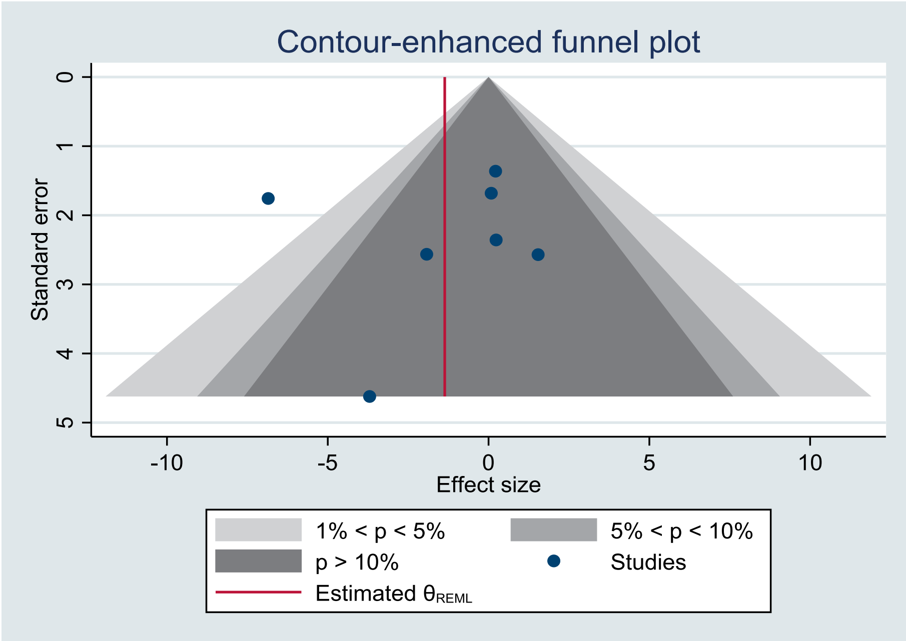

FIGURE 4
Funnel plot for FS meta-analysis.

Begg's test, $p = 0.368$; Egger's test, $p = 0.867$, Supplementary Figure 3; The estimated effect size is −1.362 with a 95% confidence interval of −3.787 to 1.063, Supplementary Figure 4). The analysis revealed no studies to be supplemented, indicating that there was no significant publication bias in the current dataset, or that the effect of publication bias was not large enough to be corrected by trim and fill process.

3.4 Meta-analysis

Study characteristics are summarized in Table 2.

3.4.1 Enjoyment response analysis

A total of 11 studies have measured the enjoyment response to HIIT and MICT (Table 2) in a manner that was measured using the Physical Activity Enjoyment Scale (PACES; (44)) at the end of training. Two of the studies were measured once after 8 and 16 weeks of training, so these two studies were chronic studies (33, 38) and the rest were acute studies. A high level of heterogeneity was observed in the combined results ($I^2 = 69\%$), so a random-effects model was used. Meta-analysis showed that the overall effect of the pleasure response (SMD = 0.47; 95% CI = 0.12 ~ 081; $p < 0.05$) was statistically significant, indicating that the difference in the rate of outcome events between the two groups was statistically significant (Figure 5).

However, it is still difficult to evaluate what the clinical consequences of this heterogeneity may be for future settings. So a prediction interval is reported in the study to illustrate which range of true effects can be expected in future settings. The resulting $SD_{PI} = 0.566$, 95% prediction interval ranging from −0.758 to 1.688. This suggests that the true effect size in similar future studies may be in this range, or may even be opposite to summary point estimate of the meta-analysis, or have greater effect uncertainty (45).

3.4.1.1 Subgroup analysis of acute and chronic studies

A subgroup analysis was performed to investigate the difference between acute and chronic studies. As shown in Figure 6, nine acute studies (SMD = 0.51; 95% CI = 0.12 to 0.90; $p < 0.05$) showed beneficial overall effects of HIIT on enjoyment, indicating that HIIT exercise may contribute to obtaining psychological responses that are equal to or more positive than MICT sessions in short period. In contrast, two chronic studies (SMD =0.23; 95% CI = −0.35 to 0.82; $p > 0.05$) did not show a significant effect.

3.4.2 Affective response analysis

A total of seven studies have measured affective responses to HIIT and MICT using the Feeling Scale (FS; (46)) before, during and after exercise (Table 3), all of them are acute studies. For studies where multiple measures of affective responses (pre-, mid-, and post-exercise) were present, we calculated mean and standard deviation values, reducing the data for each exercise condition to only one value. A high level of heterogeneity was observed in the combined outcome Feeling Scale ($I^2 = 82\%$), so a random-effects model was used. Meta-analysis showed that the overall effect of Feeling Scale (SMD = −0.47; 95% CI = −1.17 ~ 0.23; $p > 0.05$) was not statistically significant, indicating that the difference in the rates of outcome events between the two groups was not statistically significant (Figure 7). The resulting $SD_{PI} = 0.920$, 95% prediction interval ranging from −2.721 to 1.781. This suggests that although the current effect estimates are negative, near zero or slightly positive effects may be expected in future studies.

3.4.3 Arousal analysis

Two of these studies also used the Felt Arousal Scale (47) measured before and after exercise (Table 3). A low level of heterogeneity was observed in the combined outcome Felt Arousal

TABLE 2 Enjoyment and affective data of the selected studies.

Inclusion research	Country	Participant information		Intervention time	Exercise conditions		PACES scores		FS scores	
		HIIT	MICT		HIIT	MICT	HIIT	MICT	HIIT	MICT
Farias-Junior et al. (39)	Brazil	Number:20 Age: 28.9 (5.0) BMI: 28.9 (4.98)	Number:20 Age: 28.9 (5.0) BMI: 28.9 (4.98)	once	10* 1 min high-intensity-exercise at 75–80% HRR, interspersed with 10* 1 min rest at 35–40% HRR	20 min of continuous exercise at 55–59% HRR	106 (16.5)	96 (14.5)	−3.1 (1.8)	0.8 (1.8)
Santos et al. (36)	Canada	Number:47 Age: 51.8 (8.80) BMI: 31.4 (6.6)	Number:52 Age: 50.0 (9.90) BMI: 31.4 (5.9)	2 weeks	4–10 *1 min at ~77–95% of max heart rate interspersed with 1 min at 60% of HRmax	20 to 50 min exercise at 64–76% of HRmax	102.52 (17.5)	101.53 (20.3)	*NM*	*NM*
Patten et al. (34)	Australia	Number:15 Age: 29.7 (4.8) BMI: 35.5 (6.8)	Number:14 Age: 32.5 (6.2) BMI: 38.4 (9.3)	12 weeks	2*(12 * 1 min interval sat 90–100% %HR peak, interspersed with 1 min of active recovery) + 1*(8 * 4 min intervals at 90–95%HRpeak, interspersed with a 2 min light load)	45 min of continuous moderate-intensity cycling at 60–75%HRpeak.	101.8 (7.6)	87.9 (7.6)	*NM*	*NM*
Poon et al. (33)	Canada	Number:12 Age: 49.6 (7.8) BMI: 26.1 (1.6)	Number: 12 Age: 46.5 (3.6) BMI: 25.6 (3.1)	8 weeks	10 * 1 min bouts of running at 80–90% HRmax interspersed with 1 min active recovery	50 min continuous jogging/ brisk walking at 65–70% HRmax	111.4 (9.4)	105.7 (14.7)	*NM*	*NM*
Dupuit et al. (37)	France	HIIT 1 Number:12 Age: 59.5 (5.8) BMI: 28.9 (3.9)	Number:12 Age: 59.5 (5.8) BMI: 28.9 (3.9)	once	60 cycles of sprinting/speeding for 8 s interspersed with slow pedaling (20–30 rpm) for 12 s	cycling for 35 min at 60–65% HRmax	90.8 (17)	91.3 (15.4)	*NM*	*NM*
		HIIT 2 Number: 12 Age: 59.5 (5.8) BMI: 28.9 (3.9)		once	10*1 min bouts at 80–90% HRmax, interspersed with 10*1 min recovery bouts (ie, slow pedaling at 20–30 rpm).		86.8 (10.9)		*NM*	*NM*
Vella et al. (28)	America	Number:8 Age: 23.1 (6.6) BMI: 29.9 (3.3)	Number:9 Age: 28.9 (8.1) BMI: 33.1 (6.0)	5 weeks	10*1 min bouts of high-intensity exercise at 75–80% HRR, interspersed with 10*1 min recovery bouts at 35–40% HRR.	20 min of continuous exercise at 55–59% HRR	100.1 (4.3)	100.3 (4.4)	*NM*	*NM*
Poon et al. (38)	France	Number:11 Age: 40.5 (7.1) BMI: 26.3 (2.4)	Number:10 Age: 40.1 (3.6) BMI: 26.7 (2.6)	16 weeks	12*1 min running bouts at 80e90% HRmax interspersed with 1 min active recovery at 50% HRmax	40 min brisk walk at 65e70% HRmax	109.1 (11.1)	109.1 (9.5)	*NM*	*NM*

(Continued)

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TABLE 2 (Continued)

Inclusion research	Country	Participant information		Intervention time	Exercise conditions		PACES scores		FS scores	
		HIIT	MICT		HIIT	MICT	HIIT	MICT	HIIT	MICT
Hu et al. (31)	China	HIIT Number:15 Age: 21.5 (1.7) BMI: 25.5 (2.4)	Number:15 Age: 20.9 (1.4) BMI: 25.8 (2.6)	12 weeks	4 min cycling bouts at 90% VO_2peak and interspersed with 3 min passive recovery bouts until the targeted mechanical work was achieved.	continuous cycling at a workload of 60% VO_2peak until the targeted mechanical work was fulfilled.	99.99 (4.78)	95.88 (1.4)	*NM*	*NM*
		SSIT Number:15 Age: 21.4 (1.0) BMI: 25.6 (2.3)		12 weeks	80 repetitions of 6 s cycling sprints interspersed with 9 s passive recoveries (20 min/session).		101.79 (5.73)		*NM*	*NM*
Sim et al. (41)	Australia	Number:17 Age: 30 (8) BMI: 27.7 (1.6)	Number:17 Age: 30 (8) BMI: 27.7 (1.6)	once	1:4 (60s at 100% VO_2peak: 240 s at 50% VO_2peak)	30 min continuous exercise performed at moderate intensity (60% VO_2peak)	86 (11)	85 (13)	*NM*	*NM*
Li et al. (30)	China	HIIT120 Number:14 Age: 19.9 (1.7) BMI: > 23	Number:14 Age: 19.7 (1.0) BMI: > 23	12 weeks	1 min effort at 120% VO_2peak for 19 ± 2 min	60% VO_2peak for 57 ± 8 min	92.5 (11.4)	80.8 (11.8)	*NM*	*NM*
		HIIT90 Number:14 Age: 20.7 (2.2) BMI: > 23		12 weeks	4 min effort at 90% VO_2peak for 26 ± 3 min		96.8 (13.9)		*NM*	*NM*
Decker & Ekkekakis (35)	America	Number:24 Age: 39.25 (11.23) BMI: 34.96 (4.46)	Number:24 Age: 39.25 (11.23) BMI: 34.96 (4.46)	once	4* 3 min intervals of recumbent cycling at 115% of Watts	25 min of recumbent cycling at 90% of Watts	82.25 (21.76)	90.79 (22.6)	1.25 (1.47)	2 (1.22)
Oliveira, et al. (29)	Brazil	Number:12 Age: 27.92 (7.98) BMI: 28.65 (3.85)	Number:13 Age: 32.46 (7.60) BMI: 27.90 (3.90)	12 weeks	10 *1 min high-intensity bouts (brisk walking or jogging or running) at RPE 15–17 (i.e., “hard to very hard”) interspersed with 1 min of active recovery walking slowly (20 min exercise).	30 min at PRE13	*NM*	*NM*	0.51 (0.55)	1.31 (0.53)
Marillier et al. (22)	France	Number:10 Age: 48.5 (7.6) BMI: 31.9 (5.7)	Number:10 Age: 47.8 (9.7) BMI: 33.5 (11.4)	8 weeks	1 min bouts of cycling at 100% WR peak interspaced by 1 min of passive recovery.	50% peak work rate (WR peak) for 45 min	*NM*	*NM*	3.22 (1.09)	3.06 (2.05)

(Continued)

TABLE 2 (Continued)

Inclusion research	Country	Participant information		Intervention time	Exercise conditions		PACES scores		FS scores	
		HIIT	MICT		HIIT	MICT	HIIT	MICT	HIIT	MICT
Ram et al. (21)	Australia	Number:16 Age: 30 (6) BMI: 28.1 (4.1)	Number:12 Age: 20 (8) BMI: 27.4 (4.0)	6 weeks	10 × 1 min intervals at ~90% HRpeak interspersed with 1 min active recovery intervals at a low workload (15%WRpeak)	30 min at 65–75% HRpeak	*NM*	*NM*	2.69 (0.9)	2.09 (1.1)
Boukabous et al. (42)	Canada	Number:9 Age: 66.0 (3.4) BMI: 30.1 (4.9)	Number:9 Age: 64.2 (3.7) BMI: 31.7 (3.5)	8 weeks	6* 1 min intervals at 90% HRR interspersed by 2 min of active recovery at 40% HRR, and a 2 min cool down at 40% HRR	45 min of exercise at 55% HRR	*NM*	*NM*	4.2 (0.9)	4.1 (0.9)
Kong et al. (43)	China	Number:15 Age: 20.8 (2.7) BMI: 25.5 (3.1)	Number:13 Age: 21.5 (3.1) BMI: 24.9 (1.9)	4 weeks	10 sets of 6 s all-out cycling interspersed with 9 s of rest	30 min cycling at 50–60% of peak oxygen consumption, VO_2peak	*NM*	*NM*	1.33 (1.57)	1.28 (1.57)

HRR, heart rate reserve; HRpeak, peak heart rate; HRmax, maximal heart rate; VO_2max, maximal oxygen uptake; VO_2peak, peak oxygen consumption; WRpeak, peak work rate; RPE, Rating of perceived exertion; NM, Not measured. Data are expressed as mean (SD).

Scale (I^2 = 0%), and therefore a fixed-effects model was used. Meta-analysis showed that the overall effect of Felt Arousal Scale (SMD = −0.29; 95% CI = −0.86 ~ 0.28; $p > 0.05$) was not statistically significant, indicating that the difference in the rate of outcome events between the two groups was not statistically significant (Figure 8).

4 Discussion

The objective of this meta-analysis is to evaluate and compare the effectiveness of HIIT and MICT on enjoyment and affective responses in overweight or obese people, and to explore the most appropriate exercise mode for overweight or obese people.

4.1 Enjoyment response of HIIT compared with MICT

While affect is a conscious response to an emotional direction (positive, neutral, or negative), enjoyment is a more specific feeling (48). Traditional concept suggests that high-intensity exercise above the ventilation threshold can cause unpleasant feelings about exercise (49). Although HIIT is a form of high-intensity exercise, it is characterized by brief, repeated intervals of rest or low-intensity exercise (50). There are multiple "recovery" cycles, which can lead to a psychological "rebound effect" in exercisers. Jung suggests that during recovery intervals there may be a "rebound effect" whereby participants may feel a more positive emotional response during the recovery period, as the intervals may contribute to a repeated boost in confidence during a single workout, allowing participants to know that they are approaching a "comfort zone" for recovery, and thus mobilizing their own positive emotions (51), Participants' confidence and mobilization of positive emotions can thus be continuously enhanced. However, the "rebound effect" seems to occur only on the post-exercise scale, because participants have more time to cushion and recover after exercise, and the use of the scale during exercise may not be a good explanation for this effect, because participants will still feel tired during short intervals of exercise. Therefore, the overall effect of HIIT on the PACES scale measured after exercise will be better than MICT.

In addition, exercise preference is one of the factors that influence people's choice of different types of exercise. Hedonistic theories of behavior suggest that people are intrinsically predisposed to behaviors that bring them pleasure and stay away from those that bring them displeasure (52). It has been suggested that HIIT may be preferred for achieving personal health goals better than MICT, which may cause participants to become frustrated and give up more easily because it may take more time (53).

It is worth noting that it involves both acute and chronic studies on enjoyment response. The result of subgroup analysis of acute and chronic studies shows that HIIT may contribute to obtaining psychological responses that are equal to or more positive than MICT in short period. The reason why it is feasible to include both acute and chronic is because we are looking at an overall effect. Acute effects may disappear over time, or adaptive changes may occur over a long period of time. By combining acute and chronic studies, we can reveal more complex time-dependent effects. The overall effect shows beneficial effects of HIIT on enjoyment indicating that overweight or obese

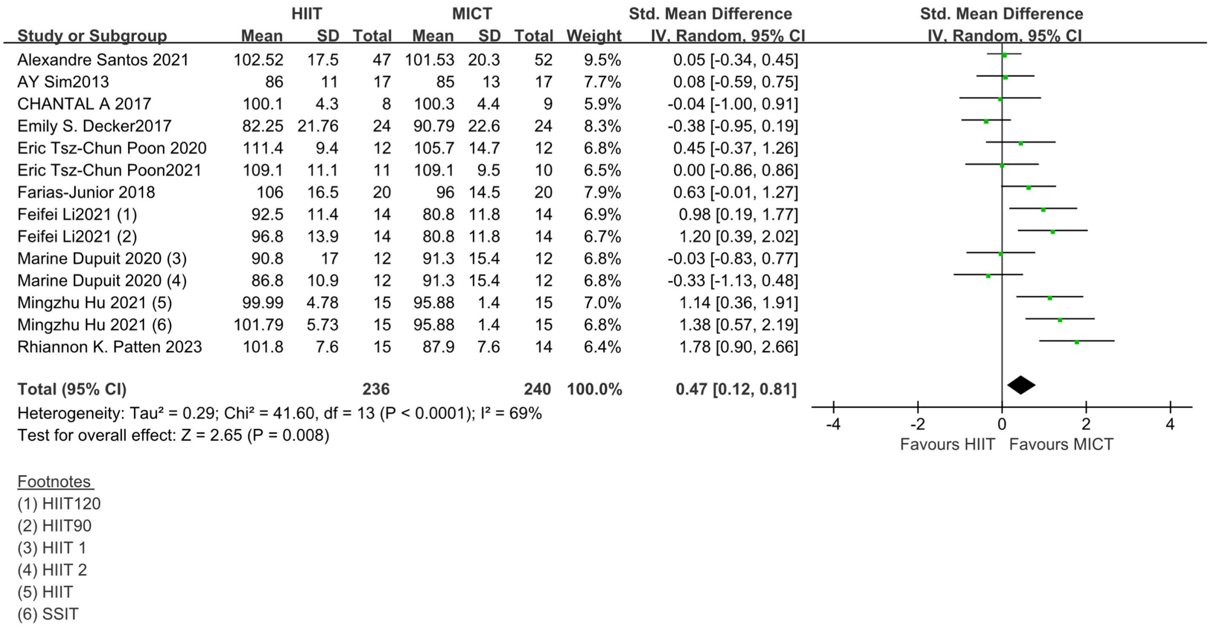

FIGURE 5
Standardized mean difference of physical activity enjoyment scale between HIIT and MICT conditions. CI, confidence interval; HIIT, high intensity interval training; MICT, moderate intensity continuous training.

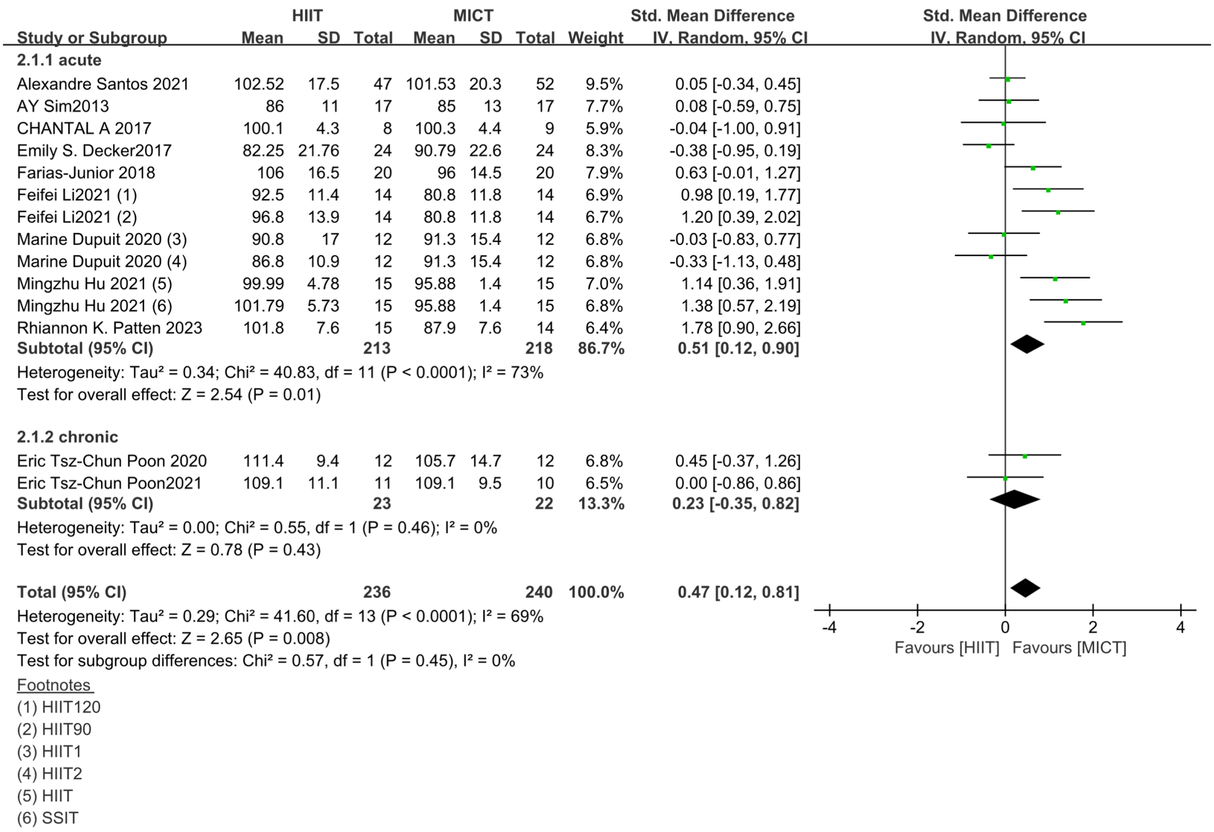

FIGURE 6
Results of subgroup analysis of acute and chronic studies; CI, confidence interval; HIIT, high intensity interval training; MICT, moderate intensity continuous training.

TABLE 3 Arousal data of the selected studies.

Inclusion research	Country	Participant information		Exercise conditions		Scores	
		HIIT	MICT	HIIT	MICT	HIIT	MICT
Marillier et al. (22)	France	Number:10 Age: 48.5 (7.6) BMI: 31.9 (5.7)	Number:10 Age: 47.8 (9.7) BMI: 33.5 (11.4)	1 min bouts of cycling at 100% WRpeak interspaced by 1 min of passive recovery.	50% peak work rate (WRpeak) for 45 min	3.1 (1.53)	3.48 (1.13)
Kong et al. (43)	China	Number:15 Age: 20.8 (2.7) BMI: 25.5 (3.1)	Number:13 Age: 21.5 (3.1) BMI: 24.9 (1.9)	10 sets of 6 s all-out cycling interspersed with 9 s of rest	30 min cycling at 50–60% of peak oxygen consumption, VO_2peak	3.83 (0.96)	4.1 (0.78)

WRpeak, peak work rate; VO_2peak, peak oxygen consumption. Data are expressed as mean (SD).

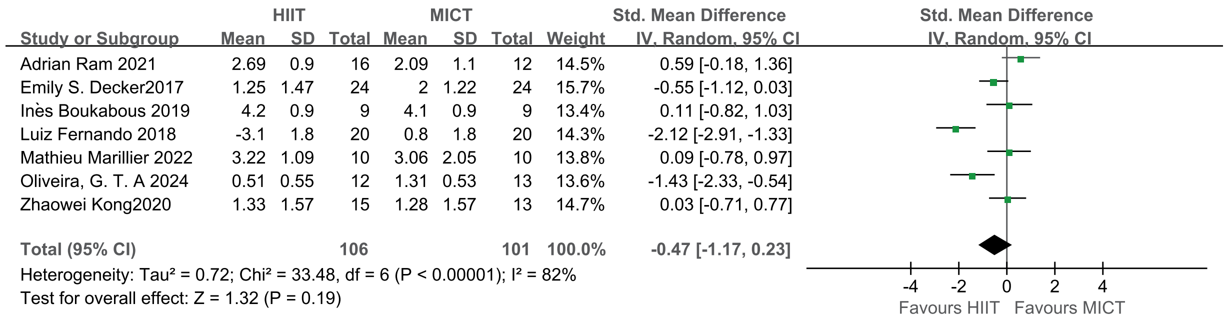

FIGURE 7
Standardized mean difference of Feeling Scale between HIIT and MICT conditions. CI, confidence interval; HIIT, high intensity interval training; MICT, moderate intensity continuous training.

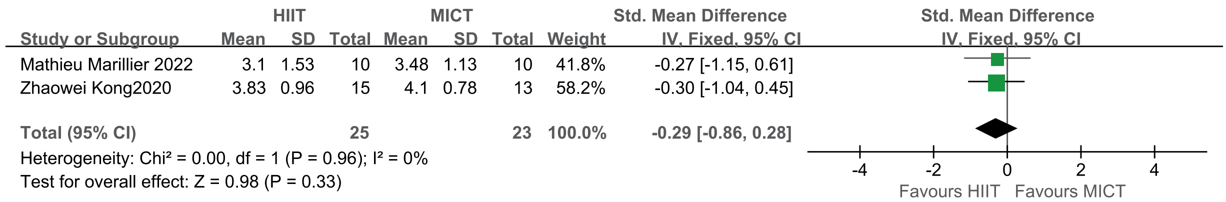

FIGURE 8
Standardized mean difference of Felt Arousal Scale between HIIT and MICT conditions. CI, confidence interval; HIIT, high intensity interval training; MICT, moderate intensity continuous training.

people may more willing to try HIIT due to hedonistic theories of behavior.

4.2 Affective response of HIIT compared with MICT

Results show that the difference in the rates of outcome events between the two groups was not statistically significant. It might because HIIT is performed using multiple sets of stimulus/recovery combinations, and variations in the ratio of stimulus to recovery time will affect the emotional experience of participants, which will likely have an impact on affective responses (43). In the experimental design of Oliveira et al. (29), the affective responses to HIIT were lower than those of MICT in a pattern of 1 min of exercise with 1 min of active recovery as a group (29). However, in the experimental design of Ram et al. the affective responses to HIIT were higher than those of MICT in a pattern of 10 * 1 min intervals at 90% peak heart rate with 1 min active recovery intervals at a low workload (15% WRpeak) (21), suggesting that by rationalizing the ratio of stimulation to recovery time in high-intensity exercise and improving the affective responses resulting from influencing it, it might be a good prescription for the overweight and obese groups.

4.3 Arousal of HIIT compared with MICT

Two studies reported data on the assessment of Arousal during exercise using Felt Arousal Scale (47). Due to the small number of literatures and the different measurement times of FAS scale in the two studies, the average score was calculated for analysis. The results showed that both HIIT and MICT could bring positive emotional activation responses to participants, but there was no significant difference between groups (SMD = −0.29; 95% CI = −0.86 ~ 0.28; $p > 0.05$). Due to the limited amount of literature, it may not be possible to fully understand the research status and development trend of this field. In addition, the lack of sufficient information may also limit the in-depth discussion of certain specific issues. However, studies have shown that emotional activation depends on the intensity of the activity (e.g., light or moderate intensity) or the different moments of the session (e.g., warm up, cool down) (54). Thus, the results should be treated with caution.

In conclusion, this review showed that HIIT can bring better pleasure response than MICT in overweight or obese people, but there is no significant difference in emotional response. It is possible that the inconsistency between this conclusion and the results of existing studies may also be due to differences in the interventions, such as the relative intensity, duration, and total number of work sessions completed (34, 39); and heterogeneity in the backgrounds of the participants, such as age, activity level, and obesity (29, 35, 42). Since the study population of the present meta-analysis was exclusively obese and overweight patients, whereas previous meta-analyses have had a much broader study population (22, 23), BMI may be one of the factors influencing the discrepancy between the results of the present study and those of previous studies. It has been shown that obese women experience lower levels of pleasure and energy compared to non-obese women, which may partially explain their significantly lower levels of participation in physical activity (55), and therefore this may make a smaller difference in the emotional responses of the obese group to the two types of exercise.

5 Limitations

Regarding the risk of bias, the FS and PACES analyses showed heterogeneity of the data, a fact that should be considered in the interpretation of the present study. The following reasons for the significant level of heterogeneity in this study may exist: first, the diversity of exercise styles. Different training methods may have different effects on pleasurable and affective responses, leading to instability in the results (e.g., different stimulus to recovery ratios). Second, we must recognize the inherent limitations associated with Meta-analysis. For example, the possibility of publication bias cannot be completely ruled out, i.e., studies with significant results are more likely to be published, which may bias our results. Third, due to limitations in the available literature, we may not have access to all relevant data, which may affect our statistical analysis. Fourth, there may have been inappropriate controls or unconsidered variables in the studies, further contributing to heterogeneity. Although our main results attempted to reduce heterogeneity to a large extent, heterogeneity was not completely eliminated. Therefore, future studies may consider focusing on a particular type with a better study design to cope with the problem when more relevant studies become available. Fifth, some literature data only provided figures without specific values, so Engauge Digitizer was used to estimate and extract the data, which may have some differences with the original data and may lead to inaccurate analysis results.

6 Conclusion

We conducted a meta-analysis to compare which exercise modality, HIIT or MICT, brings better enjoyment and affective responses in overweight or obese individuals. We found that HIIT caused participants to experience higher enjoyment and similar affect responses compared to MICT, implying that time-efficient training modalities such as HIIT seem to have a place in the choice of exercise prescription for overweight and obese individuals. We therefore conclude that HIIT exercise may be a viable strategy for improving health.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YL: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. JZ: Conceptualization, Supervision, Writing – review & editing. HJ: Conceptualization, Methodology, Writing – review & editing. XM: Conceptualization, Supervision, Writing – review & editing. JH: Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1487789/full#supplementary-material

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Expectations of doctoral students in the field of medicine and health sciences towards a graduate school: an online cross-sectional survey in Germany

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The doctoral thesis in medicine is a special case, as it is usually started during the course of study and the students have no experience of scientific work. This lack of scientific training is often criticized, and the quality of doctoral theses in medicine is considered low. In order to increase the quality of doctoral theses and the successful completion rate, a structured doctoral programme can provide the appropriate support. A cross-sectional survey of doctoral students in the field of medicine and health sciences was conducted to assess their expectations of a structured programme offered by a graduate school planned for doctoral studies in complementary and integrative medicine (CIM). Among other questions concerning experiences in their doctorate, the participants were asked to indicate their expectations in two free text answers and 24 pre-defined answers (5-point Likert scale). In addition, participants were asked how supervision should be organized in the curriculum. The majority of the participants expected individual personal support and advice in the graduate school, while financial support was not very important for them. In addition to the scientific training, networking and support among the participants of the graduate school was considered important. The non-medical participants were interested in personality development in science and networking with other doctoral students, whereas the medical doctoral students were more interested in scientific guidance. Doctoral students with a CIM topic expected a predicate and a better final grade by participating in such a graduate school. These results provide important information on how the curriculum in the graduate school should be designed. The next steps will be to evaluate the preliminary curriculum in order to develop a curriculum following the six-step approach of Kern.

KEYWORDS

scientific education, dissertation, PhD, medical doctor, faculty development, complementary and integrative medicine and health

1 Introduction

Worldwide 1.1% of the population on average in OECD countries have a doctorate, with the number of medical doctorates far outstripping those in other disciplines. From all doctorate holders Slovenia has the highest rate, followed by Sweden, with Germany in sixth place. The report from 2019 notice that doctoral graduates cannot only pursue an academic career, but are also in demand in industry and other sectors of the economy. Finding a successful and safe career in academia is difficult in all countries and leads many doctoral graduates to seek career opportunities outside of academic research (1).

In general, the doctorate is not part of the basic qualification for the professions, but is an academic degree added to the master's/diploma degree. A large proportion of university research is carried out in the context of doctoral studies, which contribute significantly to the reputation of universities (2). Despite this great importance for the universities, the supervision and guidance of doctoral research is not part of a structured programme, but is the responsibility of the scientific standards of the individual research groups (3). Doctorates, or their supervision, are recorded as achievement of universities and their successful completion is considered as another indicator of academic qualification and value in the nationwide university ranking (2). In addition, doctorates are also used as an indicator for the calculation of performance-related funding and are considered, for example, as criteria for the evaluation of research funding programmes (4). Therefore, the successful completion of doctoral graduation is a central and mandatory duty of academic institutions. Faculty and administrators should prevent attrition of doctoral students by developing mechanisms for topic selection, emphasizing sequential planning, addressing motivation, providing regular faculty guidance, and encouraging peer support like dissertation groups (5–7).

Given the importance of higher education, many students still drop out during their studies for several reasons (8–10). Numbers of discontinued doctoral thesis are not easy to find and there is a high number of unreported cases as some doctoral students quit in an early stage (11). Reliable, generalizable information on success and drop-out rates for doctorates in Germany is still not available (11, 12). There are a number of factors contributing to doctoral attrition. As far as dropping out is concerned, doctoral students without funding have the highest drop-out rate, while students with selective research grants have the lowest (13). Lack of supervision, inadequate training of both students and supervisors, methodological problems and personal differences are important reasons for attrition (14–16). These challenges can be exacerbated by a lack of statistical support (14, 17) as well as the feeling of being exploited by the supervisor during the doctoral period (14) or not supported due to internal rivalries of research groups (18). Both the positive and negative aspects and the influence of supervisors need to be recognized by themselves (19) as the emotional wellbeing of doctoral students are connected to the supervisor (20). A high workload and psychological stress are common challenges with doctoral students reporting burnout (21), higher levels of depression, anxiety and stress (22). A meaningful research project, supportive relationship between supervisor and doctoral student, a sense of progress and limited suffering are crucial factors in whether students complete or drop out of their doctoral thesis (23–26).

Until a few years ago, medical students pursuing a doctorate in medicine lacked solid basic science training. Many scientific organizations have therefore called for quality-improving changes in recent years (27, 28). The scientific level of the doctoral theses accompanying the studies has been repeatedly criticized by the German Council of Science and Humanities, among others, and in a European comparison the German medical doctorate is not regarded as proof of independent research (28). Moreover, it is repeatedly criticized for its lack of quality not only in Germany (29, 30). Although very few medical graduates work in research after their studies in Germany, the doctorate rate for human medicine and health sciences graduates remains high with about 60, and 52% for veterinary medicine graduates (3).

Research projects and critical thinking skills are crucial for medical students and physicians to improve their professional competence and contribute to the advancement of medical knowledge (31). Moreover the indirect and implicit benefit of a doctorate can be seen in the fact that doctoral graduates have developed personally as a result of their doctoral thesis and feel more academically competent for their future career as physicians (32).

The doctorate in medicine (Dr. med.) is a special case in Germany compared to other doctorates, as it can usually be started during the actual medical studies and no official degree is required, e.g., in the form of a Master's thesis for admission to a doctorate. However, the doctoral thesis may only be submitted after the license to practise medicine has been granted. Most of medical doctoral students (85%) are doing their doctorate because it is common for physicians and 75% believe that a doctorate improves their job opportunities (32). In the field of health sciences academic careers are more in the focus of the doctoral candidates but still there is a lack of career options in universities (33). In Germany, different titles are possible at the end of a doctorate. In the field of medicine and health sciences, which is an interdisciplinary field, students without a specific medical degree can also study for a doctorate at medical faculties, but will receive doctoral degrees such as Dr. rer. medic or Dr. hum. biol. e.g., (34).

Complementary and integrative therapies continue to be very popular among the population in Europe (35, 36) with no predictive factors for why patients visit a therapist specializing in CIM (37). Latest numbers for Germany indicate that 70% of the respondents reported that they had used CIM at some time during their lives (38). Although there is increasing evidence of positive effects on health in several areas for example in the treatment of nausea and vomiting during pregnancy (39) or in the treatment of patients in oncology (40), these authors conclude that quality and number of studies included in the reviews were poor and more studies are needed. The lack of studies in the field of CIM in Germany is related to the very small number of faculties with the expertise and willingness to conduct research on CIM topics. In addition to facilities, finances are a limiting factor too (41). As CIM research projects often are conducted within the scope of doctoral theses there is a great need for a thorough training and guidance for doctoral students in science. One successful opportunity was demonstrated by the cooperation between two faculties that taught CIM students in scientific training programmes as part of a mentoring programme (42).

Another option to improve scientific training is to implement a structured doctoral programme for doctoral students with a CIM topic. The figures for the number of doctoral students in structured doctoral programmes at German universities still vary widely between 19 and 42% depending on the data source and study used. Referring to the numbers of the latest report in Germany, around 40% of doctoral students in medicine and health sciences took part in structured doctoral programmes in 2019 (43). In Germany, structured doctoral programmes are usually offered in Graduate Schools, which tend to be thematically focused. A structured doctorate is characterized by official enrollment in a doctoral programme, regular supervision by several university lecturers and a compulsory range of courses (44). The number of courses and how many have to be attended, the thematic focus, whether colloquia or scientific lessons and the frequency can vary (45).

Several faculties in Germany have established medical research schools as structured doctoral programmes. So far, there is no such programme for CIM. Since CIM is constantly under great scrutiny due to the lack of high quality studies and evidence, a structured doctoral programme is needed to improve the quality of dissertations and promote young researchers. At the Witten/Herdecke University, an inter-professional and inter-faculty graduate school was to be established for all doctoral students interested in complementary and integrative medicine (CIM). In advance, this survey was designed to provide detailed information on the needs of potential participants in order to start developing a curriculum.

1.1 Aim of this study

This study was conducted to analyze

1. what benefits doctoral students expect from a structured doctoral programme in a graduate school,
2. what suggestions they have for the content and timing of the curriculum,
3. whether doctoral students with a topic in the field of CIM differ from those with a Non-CIM topic regarding the expectations,
4. whether there are differences between medical and non-medical doctoral students regarding the expectations.

2 Materials and methods

A cross sectional online survey was conducted among doctoral students via LimeSurvey (LimeSurvey GmbH, n.d.) from October 1, 2020 to December 31, 2020. Students from the health sector - mainly medical students - in Germany were invited to participate. Inclusion criteria for the study were that participants were currently pursuing or had completed a doctoral degree. The questionnaire explicitly addressed doctoral students with a topic in CIM. Recruiting was carried out through email distribution lists of the medical departments and faculties in Germany, German medical education association GMA and the *Forum universitärer Arbeitsgruppen* - an association of working groups at medical faculties specialized on *Complementary and Integrative Medicine* (CIM). Mail recipients were asked to forward the request for participation in the survey to their doctoral student mailing lists. As the latter group of recipients is known for research in the field of CIM, the target group of CIM doctoral students were reached via this mailing list to answer the questionnaire.

The questionnaire was self developed through a systematic process including literature review, expert knowledge gained from existing medical research schools, pre-testing (think-aloud-method) with medical students and revision after the pretest. The pre-test was used to check the comprehensibility of the questions, which were then linguistically adapted. In order to identify the needs of doctoral students for good supervision in the graduate school, questions have been compiled on skills that are considered fundamental to scientific work. These include skills such as academic writing, literature research and administration, and the use of software programmes. On the other hand, questions were formulated that are cited in the literature as reasons for dropping out of a doctoral programme and that may be helpful in the context of a graduate school: Finances, support both within the team and from a statistician, career opportunities, e.g., the questionnaire consisted of 35 questions divided into the following main topics: 1. Experiences of doctoral students working on their theses, 2. Identifying and describing difficulties and factors for doctoral success, 3. Expectations of structured supervision in a CIM-focused graduate school.

For this piece of work, results of the third field in the questionnaire, consisting of six questions, were analyzed (Supplementary Material 1). A pre-defined list of 24 general expectations and scientific competencies that can be achieved in graduate school was given, supplemented by spaces for free text responses. The competencies listed are in the following areas: research methodology, software training, epistemological and health theory approaches, the various therapy approaches, literature research and managing, personal abilities like communication skills and conflict management as well as promotion of personality development in science. In addition, the following expectations could be stated: Finding a professional perspective and/or career in science, individual guidance for scientific work, personal support by a statistician, networking and interdisciplinary cooperation with other doctoral students, mutual support and motivation in the doctoral team to write and keep going, support in case of arising questions or problems, quality improvement of the doctoral thesis and a better final degree grade, covering costs (all or travel expenses or material costs) related to the curriculum of the graduate school, a scholarship programme of its own as well as receiving a predicate due to participation.

Participants could rate these predefined skills in the list on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). Descriptive statistics were carried out (SPSS 27.0). Chi-square tests were calculated to compare two independent groups with regard to the distribution of a categorial variable. The resulting *p*-values were interpreted as strictly descriptive.

TABLE 1 Frequencies of CIM areas in doctorates for the total sample and the subgroup of medical students (multiple entries possible).

Topic of the doctorate belongs to the following area:	Total sample	Medical doctoral students
Naturopathy	18	9
Anthroposophic medicine	17	14
Phytotherapy	10	7
Relaxation techniques	8	3
TCM	5	4
Yoga	5	3

3 Results

3.1 Study collective

In all, 246 participants saved their answers in the online tool. 162 data sets were completed and used for the evaluation of the study. Most participants were female (64.8%, *n* = 105), about one-third were male (33.9%, *n* = 55), two (1.2%) did not provide gender information. On average, participants were 36 years old (22–66 years, median 32). Stated disciplines were assigned to six fields of study. Most participants, 54.3%, studied medicine (*n* = 88) including dentistry (*n* = 5) and veterinary medicine (*n* = 3), 18.5% (*n* = 30) studied health sciences, and 12.3% (*n* = 20) natural sciences. Only 6.2% of the participants studied nursing sciences (*n* = 10), 4.3% psychology (*n* = 7) and 4.3% CIM (*n* = 7). Most participants - 62.3% (*n* = 101) - reported that they were studying for a doctorate at the time of the survey, 35.8% (*n* = 58) had already completed their thesis, two intended to do a doctorate and one canceled. 162 participants answered the question about their professional situation. 29.6% participants (*n* = 48) stated that they were employed full-time during their doctorate. 21.0% (*n* = 34) reported being employed by the institution they are doing their doctorate. Another 21.0% (*n* = 34) participants were following their doctorate parallel with their studies. 16.0% (*n* = 26) were employed part-time during their doctorate, 10.5% (*n* = 17) were released from work to do their doctorate. 131 participants answered how much time they spend on their doctoral studies. The average was 20.3 h per week (1–60 h, median 16). 37.6% (*n* = 61) participants were working on a doctorate with a topic from the CIM area, while 62.3% (*n* = 101) were working on a topic that cannot be assigned to CIM (Non-CIM). Topics from CIM were assigned to the following areas (Table 1). Multiple entries were possible.

3.2 Expectations toward a graduate school (total sample)

In all, between 148 and 153 participants answered the single questions of the predefined list. The percentages listed below refer to the combined answers "strongly agree" and "agree." The majority (90.2%, *n* = 138) expected a support among the participants of the graduate school, when questions and problems are arising, 77.8% (*n* = 119) were hoping for networking with other doctoral students and 79.1% (*n* = 121) for an interdisciplinary exchange in the group. Beside these demands for a support within the group of the doctoral students, 78.1% of the participants (*n* = 118) wished to have an introduction into research methodology. 77.0% (*n* = 117) hoped to receive support in the graduate school in the form of individual guidance for scientific work and a statistician as a personal contact (63.6%, *n* = 96). The graduate school should also provide competencies like software trainings (65.8%, *n* = 100) and support in finding (58.3%, *n* = 88) and managing literature (66.4%, *n* = 101). Only 32.0% (*n* = 49) expected to find a professional perspective being attendee in the graduate school whereas 61.4% (*n* = 94) expect finding a career in science. To receive a predicate as being an attendee was only important for 29.0% of the participants (*n* = 43) and for 38.0% getting a coverage of the costs (*n* = 57). Further results shown in Figure 1.

In order to get an idea of how the curriculum of the graduate school should be structured from the participants' point of view, the participants were asked to indicate, at which location, how often and in what form they would participate in education events/colloquia. A third of the participants (35.0%, *n* = 55) expected the curriculum of the graduate school taking place at different university locations. The question about the frequency and type of events showed that the participants would prefer on average four face-to-face conferences (1–54, Median 4), six video conferences (0–52, Median 6) and two face-to-face events at other universities per year (0–27, Median 2). The majority (79.6%, *n* = 125) expected individual personal support and consultation in the graduate school. 28.0% (*n* = 44) of participants expected the curriculum and supervision to be primarily group-based. For 37.5% (*n* = 59), it was important to include units that serve personality development, such as modules on stress management or biography work.

3.3 Different expectations of medical doctoral students with CIM and non-CIM topics

We investigated whether the choice of topic made a difference in the expectations within the group of medical doctoral students (*n* = 88). 44.3% (*n* = 39) of them worked on a topic assigned to CIM and 55.6% (*n* = 49) not related to a CIM topic. As group size was small we condensed the 5 point Likert scale to three categories (agree, partly and not agree) for the comparison. 81.3% doctoral students with a Non-CIM topic (*n* = 39) asked for more individual guidance for scientific work than CIMs (75.7%, *n* = 28) ($p = 0.024$). An individual guidance from a statistician was also more important for 81.3% Non-CIMs (*n* = 39) and only for 56.8% of the CIMs (n = 21) ($p = 0.028$). A better final grade and receiving a predicate being member in the graduate school was less important for the Non-CIMs [not agree: 38.3% (*n* = 18) and 58.7% (*n* = 27)] than for the CIMs [not agree: 22.2% (*n* = 8) and 37.8% (*n* = 14)] ($p = 0.04$, $p = 0.024$) (Figure 2 and Table 2).

3.4 Different expectations of medical and non-medical doctoral students

As medical students may request different support than students from other disciplines, participants were subdivided in

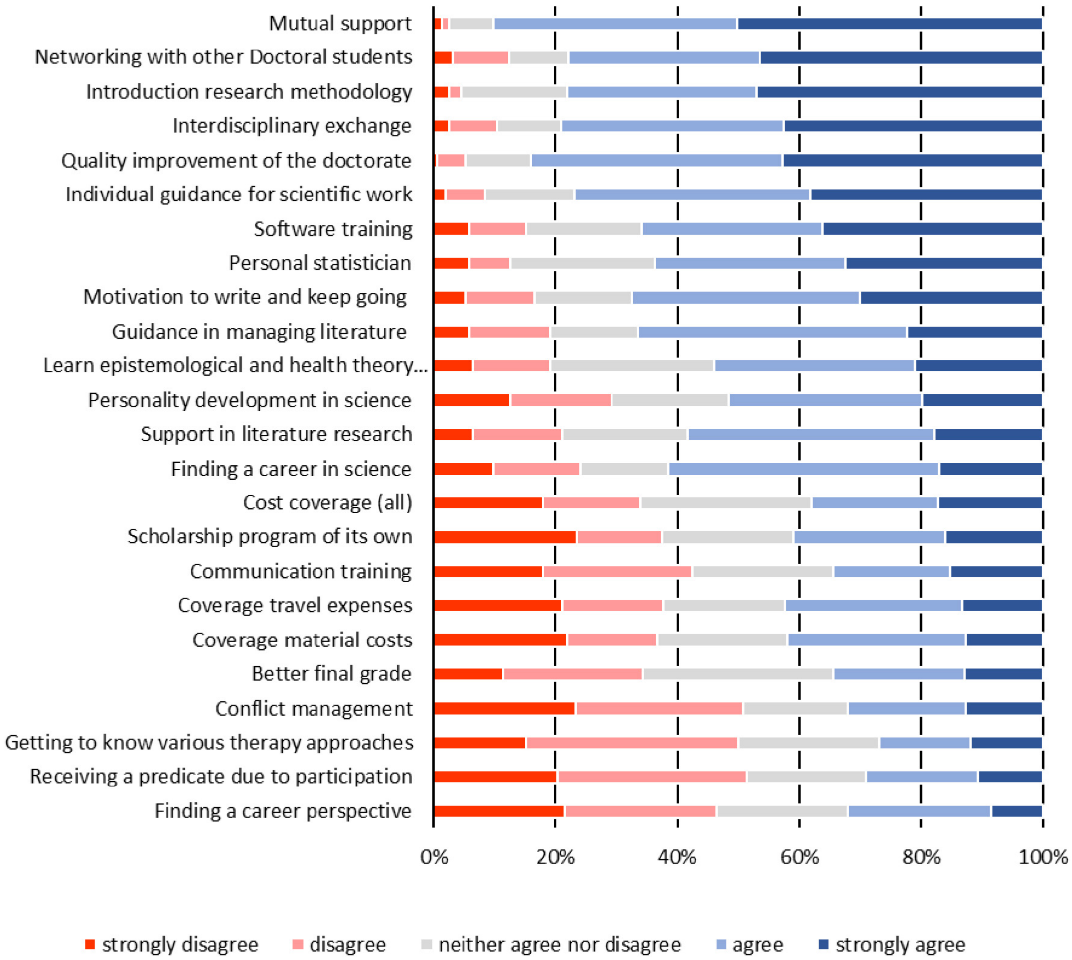

FIGURE 1
Expectations of a graduate school (5-point-Likert scales "strongly disagree" to "strongly agree") - total sample.

two groups: The following compares 88 medical doctoral students (*Medicals*) and 74 non-medical (*Non-Medicals*).

The main differences between the two groups are that Medicals expect more support in terms of methodology and software training: 67.9% of Medicals (n = 57) wanted help in researching for literature unlike 46.3% of Non-Medicals (n = 31) (p < 0.001). 78.8% Medicals (n = 67) need support for managing the literature and only 50.7% of Non-Medicals (n = 34) (p < 0.001). Software training is needed by 74.1% Medicals (n = 63) and 55.2% Non-Medicals (n = 37) (p = 0.028). 91.7% of the Medical Doctoral students (n = 77) expect by training and supervision in the graduate school a quality improvement of the doctoral thesis whereas 74.2% of the Non-Medicals do so (n = 49) (p = 0.027).

Non-Medicals have a greater need for networking in the group and personality development in science through graduate school: 38.8% Medicals (n = 33) did not see a great need for the support of the development of personality in science in contrast to 62.1% of the Non-Medicals (n = 41) who consider it very important (p = 0.021). 89.7% Non-Medicals (n = 61) see networking with other doctoral students as important, while only 68.2% Medicals (n = 58) indicated this (p = 0.002). 88.2% of the Non-Medicals (n = 60) also rate interdisciplinary cooperation very important whereas less Medicals do so (71.8%, n = 61) (p = 0.052) (Figure 3 and Table 3).

3.5 Further comments in the free text sections

In addition, the participants had the opportunity to document in free text what else they expected from the graduate school. They expressed the wish for an independent contact person outside their own research group, who could also mediate between doctoral students and supervisors. The opportunity to think outside the box was mentioned several times, as well as the desire for peer learning, the provision of contacts to other research institutions, support in applying for research funding and ethics grants, and an alumni programme. Comments are listed in (Supplementary Table 2).

4 Discussion

In a cross-sectional survey of doctoral students in Germany, participants were asked to comment on structured doctoral

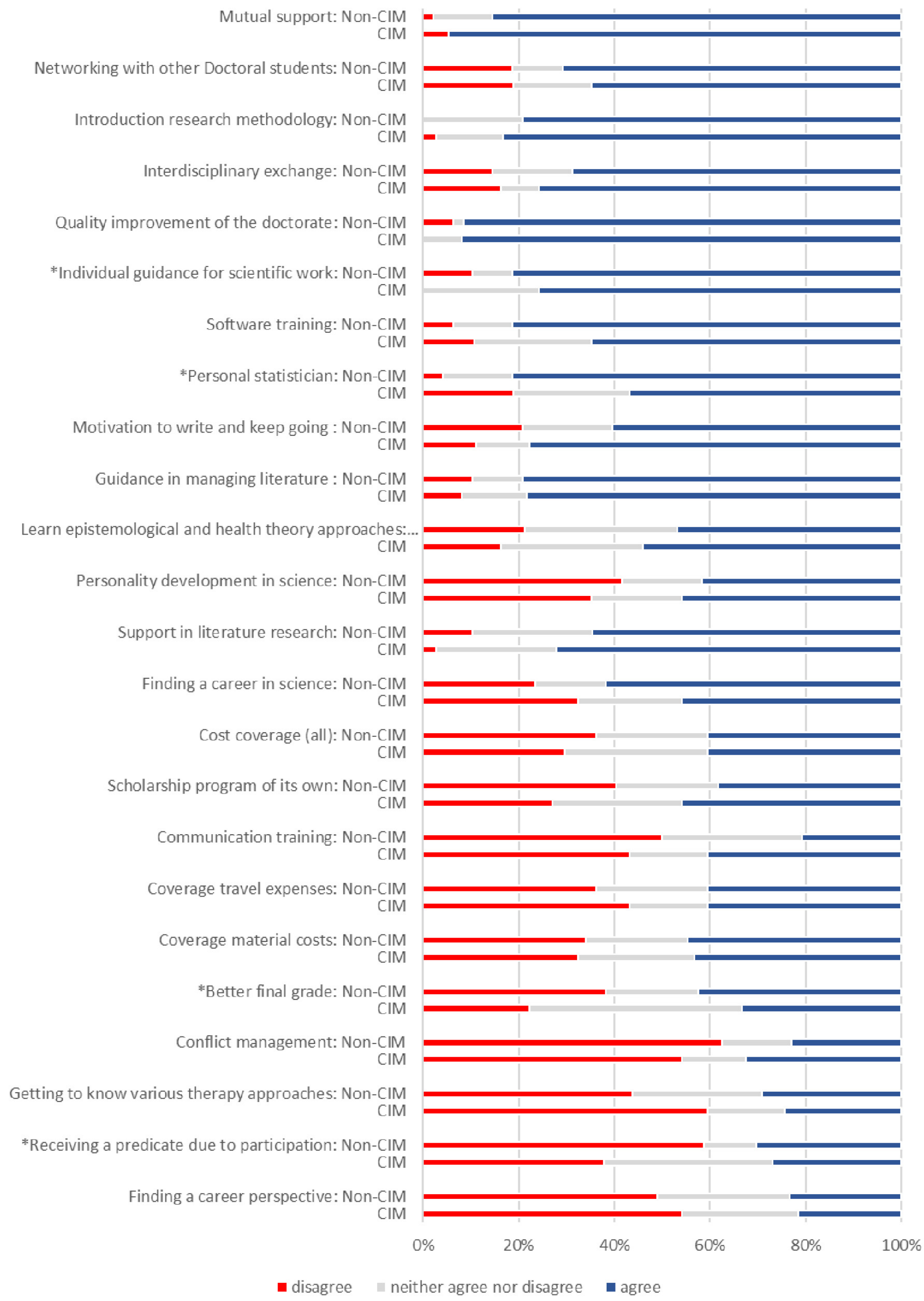

FIGURE 2
Expectations of a graduate school (5-point-Likert scales "strongly disagree" to "strongly agree") - comparison of medical doctoral students with CIM and Non-CIM topic. For this figure the categories "strongly disagree" and "disagree" were combined into "disagree," "strongly agree" and "agree" were combined to "agree." *Indicates group differences ($p \leq 0.05$).

programmes and to formulate their recommendations for a curriculum in a graduate school with a focus on CIM. The majority of the study participants expected a mutual support in the graduate school for questions and problems and more than two-thirds hoped for networking with other doctoral students and an interdisciplinary exchange within the group. The personal exchange and regular meetings of the members in a cross-faculty framework were desired. Regular face-to-face meetings, in addition to video calls, were considered important for the timing and structure of the curriculum. While the medical students attached more importance to courses with specific content on scientific skills, the non-medical students stated that they preferred the exchange with others. Doctoral students with a CIM topic hoped for a better final grade and a predicate for attending a graduate school, while the non-CIM doctoral students hoped for more individual guidance for scientific work and a perspective for a research career.

TABLE 2 Expectations of a graduate school (frequencies and test statistics) - medical doctoral students with CIM and non-CIM topic.

Expectation	Group	Disagree *n* (%)	Neither agree nor disagree *n* (%)	Agree *n* (%)	$\chi^2(2)$	*p*
Finding a career perspective	CIM	20 (54.1)	9 (24.3)	8 (21.6)	0.223	0.895
	Non-CIM	23 (48.9)	13 (27.7)	11 (23.4)		
Finding a career in science	CIM	12 (32.4)	8 (21.6)	17 (45.9)	2.080	0.354
	Non-CIM	11 (23.4)	7 (14.9)	29 (61.7)		
Individual guidance for scientific work	CIM	0 (0)	9 (24.3)	28 (75.7)	7.430	0.024
	Non-CIM	5 (10.4)	4 (8.3)	39 (81.3)		
Support in literature research	CIM	1 (2.8)	9 (25)	26 (72.2)	1.857	0.395
	Non-CIM	5 (10.4)	12 (25)	31 (64.6)		
Guidance in managing literature	CIM	3 (8.1)	5 (13.5)	29 (78.4)	0.290	0.865
	Non-CIM	5 (10.4)	5 (10.4)	38 (79.2)		
Introduction research methodology	CIM	1 (2.8)	5 (13.9)	30 (83.3)	1.933	0.380
	Non-CIM	0 (0)	10 (20.8)	38 (79.2)		
Software training	CIM	4 (10.8)	9 (24.3)	24 (64.9)	2.940	0.230
	Non-CIM	3 (6.3)	6 (12.5)	39 (81.3)		
Communication training	CIM	16 (43.2)	6 (16.2)	15 (40.5)	4.451	0.108
	Non-CIM	24 (50)	14 (29.2)	10 (20.8)		
Conflict management	CIM	20 (54.1)	5 (13.5)	12 (32.4)	0.970	0.616
	Non-CIM	30 (62.5)	7 (14.6)	11 (22.9)		
Personality development in science	CIM	13 (35.1)	7 (18.9)	17 (45.9)	0.378	0.828
	Non-CIM	20 (41.7)	8 (16.7)	20 (41.7)		
Getting to know various therapy approaches	CIM	22 (59.5)	6 (16.2)	9 (24.3)	2.304	0.310
	Non-CIM	21 (43.8)	13 (27.1)	14 (29.2)		
Networking with other Doctoral students	CIM	7 (18.9)	6 (16.2)	24 (64.9)	0.652	0.722
	Non-CIM	9 (18.8)	5 (10.4)	34 (70.8)		
Mutual support	CIM	2 (5.4)	0 (0)	35 (94.6)	5.475	0.065
	Non-CIM	1 (2.1)	6 (12.5)	41 (85.4)		
Interdisciplinary exchange	CIM	6 (16.2)	3 (8.1)	28 (75.7)	1.359	0.507
	Non-CIM	7 (14.6)	8 (16.7)	33 (68.8)		
Learn epistemological and health theory approaches	CIM	6 (16.2)	11 (29.7)	20 (54.1)	0.528	0.768
	Non-CIM	10 (21.3)	15 (31.9)	22 (46.8)		
Motivation to write and keep going	CIM	4 (11.1)	4 (11.1)	28 (77.8)	2.856	0.240
	Non-CIM	10 (20.8)	9 (18.8)	29 (60.4)		
Personal statistician	CIM	7 (18.9)	9 (24.3)	21 (56.8)	7.124	0.028
	Non-CIM	2 (4.2)	7 (14.6)	39 (81.3)		
Quality improvement of the doctorate	CIM	0 (0)	3 (8.1)	34 (91.9)	3.917	0.141
	Non-CIM	3 (6.4)	1 (2.1)	43 (91.5)		
Better final grade	CIM	8 (22.2)	16 (44.4)	12 (33.3)	6.462	0.040
	Non-CIM	18 (38.3)	9 (19.1)	20 (42.6)		
Receiving a predicate due to participation	CIM	14 (37.8)	13 (35.1)	10 (27)	7.456	0.024
	Non-CIM	27 (58.7)	5 (10.9)	14 (30.4)		
Cost coverage (all)	CIM	11 (29.7)	11 (29.7)	15 (40.5)	0.574	0.751

(Continued)

TABLE 2 (Continued)

Expectation	Group	Disagree *n* (%)	Neither agree nor disagree *n* (%)	Agree *n* (%)	$\chi^2(2)$	*p*
	Non-CIM	17 (36.2)	11 (23.4)	19 (40.4)		
Coverage material costs	CIM	12 (32.4)	9 (24.3)	16 (43.2)	0.111	0.946
	Non-CIM	16 (34)	10 (21.3)	21 (44.7)		
Coverage travel expenses	CIM	16 (43.2)	6 (16.2)	15 (40.5)	0.792	0.673
	Non-CIM	17 (36.2)	11 (23.4)	19 (40.4)		
Scholarship program of its own	CIM	10 (27)	10 (27)	17 (45.9)	1.655	0.437
	Non-CIM	19 (40.4)	10 (21.3)	18 (38.3)		

The categories "strongly disagree" and "disagree" were combined into "disagree," "strongly agree" and "agree" were combined to "agree." $\chi^2(2)$ = test statistic of Chisquare test, p = *p*-value of Chisquare test.

4.1 Strengths and limitations

The response rate (65.8%) was quite high due to a convenient distribution point, although the questionnaire appeared to be too long as many participants did not complete all parts of the whole questionnaire. The normal online survey response rate is 44.1% (46). The method of an online survey implies the problem of uncontrolled distribution and that people participate who are not part of the focus group in the first place (47). Initially, we intended to address only medical students or other health professions working on a topic in CIM for their doctorate. It turned out that other professions and doctoral students without a topic in CIM participated as well. This allowed us to compare subgroups in the second place.

The survey was scheduled for a short period of 3 months from October to December. A longer period might have resulted in a higher response rate and brought in further aspects from other participants. The sample is therefore not representative, but is intended to give an initial impression of what students might expect from a graduate school.

There is already a great deal of research on doctoral training in programmes and their various orientations: from interdisciplinarity to international courses (34). However, to date there have been no surveys on the wishes and expectations of doctoral students themselves with regard to structured doctoral supervision.

4.2 Improvement of quality in a structured doctoral programme

The quality of doctoral programmes is being discussed in many countries and efforts have already been made to improve doctoral training in such a programme in accordance with the respective doctoral regulations of the individual countries (34). In this study, more than 80% of the participants expect an improvement in the quality of the doctorate supervised in a graduate school. This is a high motivation for the participants to join a structured programme or an inter-faculty graduate school. In order to meet this expectation and to achieve the goal, the curriculum has to meet the needs.

To ensure the scientific training of students, there is no template for the curriculum, but mandatory things for a successful training are an adequate supervision, a sufficient time schedule and enough autonomy (48). These statements are in line with our results. In addition to course units that teach, mainly the medical students, the basic skills of scientific work, there must also be room for mutual exchange and individual support. This needs to be considered when designing the first curriculum as well as meeting the different needs of an interprofessional group. The non-medical doctoral students in this study emphasized the importance of being encouraged in graduate school to develop their personalities in order to find their career in academia.

4.3 Forms of support depending on topic (CIM or non-CIM) and disciplines

In this study, participants working on a non-CIM topic in particular wanted individual support from a graduate school by a statistician to better understand their own data. This is in line with the results of Can et al., according to which the majority of students lack statistical support (15). When considering the methods used in the doctoral projects with a CIM topic in this study, mainly literature searches and qualitative methods were reported, only a few studies were clinical or quantitative and required appropriate statistical analysis. This could be the reason why this group does not require intensive statistical support. Clinical studies, especially in the field of CIM, are difficult to carry out as part of a medical thesis, as they require not only an experienced research team, but also the appropriate inpatient or outpatient involvement and financial support. In Germany, there are only a few centers with large hospitals (Berlin, Tübingen, Essen, Witten e.g.,) where students can work in such a clinical environment with thematically experienced professional support. For those doctoral students who worked on a topic in CIM, a better final grade and the award of the predicate "member of the graduate school" were more important than the supervision itself.

Whereas the non-medical participants hope, that the graduate school will facilitate good interdisciplinary exchange, medical doctoral students hope for a good guidance in preparing their theses. This is not surprising, as the non-medical students have usually already written two theses (Bachelor's and Master's) in

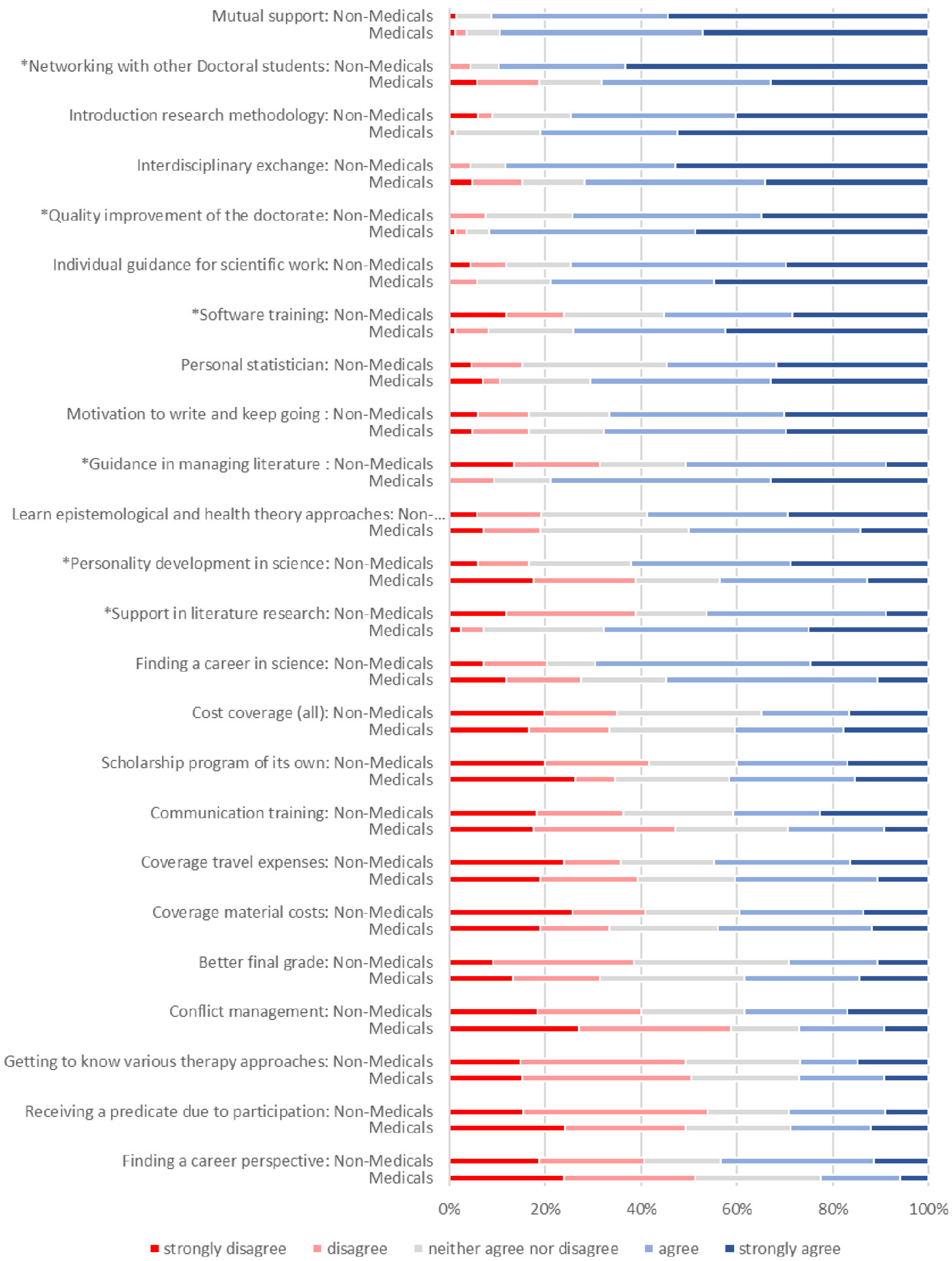

FIGURE 3
Expectations of a graduate school (5-point-Likert scales "strongly disagree" to "strongly agree") - comparison of medical and non-medical doctoral students. *Indicates group differences ($p \leq 0.05$).

preparation for their doctoral thesis and have therefore already gained experience in scientific work.

4.4 Finances

Financial issues are one of the most challenging factors for doctoral students and are responsible for high dropout rates during doctoral studies (13, 23). Research assistants could benefit most from integration into such a structured doctoral programme, as their doctoral topic is often integrated into their work and at least partly paid for. External attendees whose job is not connected to the project have time problems in particular and feel more burdened by participating in such a programme (44). In this study, less than 20% participants wanted financial support in form of a scholarship. A cost coverage of expenses is expected by about

TABLE 3 Expectations of a graduate school (frequencies and test statistics) - medical and non-medical doctoral students.

Expectation	Group	Strongly disagree *n* (%)	Disagree *n* (%)	Neither agree nor disagree *n* (%)	Agree *n* (%)	Strongly agree *n* (%)	χ^2 (4)	*p*
Finding a career perspective	Medicals	20 (23.8)	23 (27.4)	22 (26.2)	14 (16.7)	5 (6)	7.911	0.095
	Non-medicals	13 (18.8)	15 (21.7)	11 (15.9)	22 (31.9)	8 (11.6)		
Finding a career in science	Medicals	10 (11.9)	13 (15.5)	15 (17.9)	37 (44)	9 (10.7)	6.890	0.142
	Non-medicals	5 (7.2)	9 (13)	7 (10.1)	31 (44.9)	17 (24.6)		
Individual guidance for scientific work	Medicals	0 (0)	5 (5.9)	13 (15.3)	29 (34.1)	38 (44.7)	7.301	0.121
	Non-medicals	3 (4.5)	5 (7.5)	9 (13.4)	30 (44.8)	20 (29.9)		
Support in literature research	Medicals	2 (2.4)	4 (4.8)	21 (25)	36 (42.9)	21 (25)	25.134	<0.001
	Non-medicals	8 (11.9)	18 (26.9)	10 (14.9)	25 (37.3)	6 (9)		
Guidance in managing literature	Medicals	0 (0)	8 (9.4)	10 (11.8)	39 (45.9)	28 (32.9)	24.231	<0.001
	Non-medicals	9 (13.4)	12 (17.9)	12 (17.9)	28 (41.8)	6 (9)		
Introduction research methodology	Medicals	0 (0)	1 (1.2)	15 (17.9)	24 (28.6)	44 (52.4)	7.218	0.125
	Non-medicals	4 (6)	2 (3)	11 (16.4)	23 (34.3)	27 (40.3)		
Software training	Medicals	1 (1.2)	6 (7.1)	15 (17.6)	27 (31.8)	36 (42.4)	10.840	0.028
	Non-medicals	8 (11.9)	8 (11.9)	14 (20.9)	18 (26.9)	19 (28.4)		
Communication training	Medicals	15 (17.6)	25 (29.4)	20 (23.5)	17 (20)	8 (9.4)	6.317	0.177
	Non-medicals	12 (18.2)	12 (18.2)	15 (22.7)	12 (18.2)	15 (22.7)		
Conflict management	Medicals	23 (27.1)	27 (31.8)	12 (14.1)	15 (17.6)	8 (9.4)	5.675	0.225
	Non-medicals	12 (18.5)	14 (21.5)	14 (21.5)	14 (21.5)	11 (16.9)		
Personality development in science	Medicals	15 (17.6)	18 (21.2)	15 (17.6)	26 (30.6)	11 (12.9)	11.501	0.021
	Non-medicals	4 (6.1)	7 (10.6)	14 (21.2)	22 (33.3)	19 (28.8)		
Getting to know various therapy approaches	Medicals	13 (15.3)	30 (35.3)	19 (22.4)	15 (17.6)	8 (9.4)	1.820	0.769
	Non-medicals	10 (14.9)	23 (34.3)	16 (23.9)	8 (11.9)	10 (14.9)		
Networking with other doctoral students	Medicals	5 (5.9)	11 (12.9)	11 (12.9)	30 (35.3)	28 (32.9)	17.332	0.002
	Non-medicals	0 (0)	3 (4.4)	4 (5.9)	18 (26.5)	43 (63.2)		
Mutual support	Medicals	1 (1.2)	2 (2.4)	6 (7.1)	36 (42.4)	40 (47.1)	2.331	0.675
	Non-medicals	1 (1.5)	0 (0)	5 (7.4)	25 (36.8)	37 (54.4)		
Interdisciplinary exchange	Medicals	4 (4.7)	9 (10.6)	11 (12.9)	32 (37.6)	29 (34.1)	9.374	0.052
	Non-medicals	0 (0)	3 (4.4)	5 (7.4)	24 (35.3)	36 (52.9)		
Learn epistemological and health theory approaches	Medicals	6 (7.1)	10 (11.9)	26 (31)	30 (35.7)	12 (14.3)	5.784	0.216
	Non-medicals	4 (5.9)	9 (13.2)	15 (22.1)	20 (29.4)	20 (29.4)		
Motivation to write and keep going	Medicals	4 (4.8)	10 (11.9)	13 (15.5)	32 (38.1)	25 (29.8)	0.238	0.993
	Non-medicals	4 (6.1)	7 (10.6)	11 (16.7)	24 (36.4)	20 (30.3)		
Personal statistician	Medicals	6 (7.1)	3 (3.5)	16 (18.8)	32 (37.6)	28 (32.9)	7.928	0.094
	Non-medicals	3 (4.5)	7 (10.6)	20 (30.3)	15 (22.7)	21 (31.8)		
Quality improvement of the doctorate	Medicals	1 (1.2)	2 (2.4)	4 (4.8)	36 (42.9)	41 (48.8)	10.959	0.027
	Non-medicals	0 (0)	5 (7.6)	12 (18.2)	26 (39.4)	23 (34.8)		

(Continued)

TABLE 3 (Continued)

Expectation	Group	Strongly disagree *n* (%)	Disagree *n* (%)	Neither agree nor disagree *n* (%)	Agree *n* (%)	Strongly agree *n* (%)	χ^2 (4)	*p*
Better final grade	Medicals	11 (13.3)	15 (18.1)	25 (30.1)	20 (24.1)	12 (14.5)	3.467	0.483
	Non-medicals	6 (9.2)	19 (29.2)	21 (32.3)	12 (18.5)	7 (10.8)		
Receiving a predicate due to participation	Medicals	20 (24.1)	21 (25.3)	18 (21.7)	14 (16.9)	10 (12)	4.282	0.369
	Non-medicals	10 (15.4)	25 (38.5)	11 (16.9)	13 (20)	6 (9.2)		
Cost coverage (all)	Medicals	14 (16.7)	14 (16.7)	22 (26.2)	19 (22.6)	15 (17.9)	0.847	0.932
	Non-medicals	13 (19.7)	10 (15.2)	20 (30.3)	12 (18.2)	11 (16.7)		
Coverage material costs	Medicals	16 (19)	12 (14.3)	19 (22.6)	27 (32.1)	10 (11.9)	1.524	0.822
	Non-medicals	17 (25.8)	10 (15.2)	13 (19.7)	17 (25.8)	9 (13.6)		
Coverage travel expenses	Medicals	16 (19)	17 (20.2)	17 (20.2)	25 (29.8)	9 (10.7)	2.915	0.572
	Non-medicals	16 (23.9)	8 (11.9)	13 (19.4)	19 (28.4)	11 (16.4)		
Scholarship program of its own	Medicals	22 (26.2)	7 (8.3)	20 (23.8)	22 (26.2)	13 (15.5)	5.810	0.214
	Non-medicals	13 (20)	14 (21.5)	12 (18.5)	15 (23.1)	11 (16.9)		

$\chi^2(4)$ = test statistic of Chisquare test, p = *p*-value of Chisquare test.

40% of the participants in this study either medical or non-medical.

4.5 Structured doctoral programme in a graduate school

Participating in a structured doctoral programme provides an improvement of quality, increasing of the completion rate (49), and facilitate academic career paths within and outside universities (3).

As a result of this study, running the programme in a graduate school offers the opportunity to build a network by bringing together young researchers at different levels of knowledge. Collaboration within the graduate school and networking with the scientific community are not the only important aspects. Attendees of the graduate school expect to develop skills that go beyond pure scientific training, such as conflict management or personal development. The opportunity for interdisciplinary exchange and the idea of networking in a graduate school was more important for the non-medical participants in this study than for the medical students. Medical doctoral students focused on the need to improve their scientific work as defined in the course content. This is in accordance to earlier investigations (50, 51) and needs be incorporated into the curriculum.

With regard to the interprofessional orientation of the curriculum, the expectations and needs of both non-medical and medical professionals need to be taken into account when designing the curriculum as well as the perspective of the supervisors. The supervisors' assessments differ considerably from those of the doctoral students. While doctoral students more frequently cited difficulties with the research methodology or the dissertation topic in general as reasons for dropping out of the project, the supervisors suspected that the real reasons for dropping out were difficulties with time management and also reported personal differences with the students (15). While this piece of work focuses on the needs of doctoral students, in the next step, the attitudes and wishes of the supervisors are surveyed and analyzed. The input from supervisors will also be used in the development of the Graduate School, as will the regular evaluation of the Graduate School programme. As the process continues, these surveys and analyses will feed into the development of the curriculum. This development will follow Kern's six-step approach (52).

5 Conclusion

The implementation of structured doctoral programmes in universities is a promising factor for improving the quality and completion rate of doctoral students worldwide. This study focused on the requirements for a curriculum, planned to establish a graduate school with expertise in CIM topics and in an interprofessional framework at Witten/Herdecke University. The expectations formulated by the participants themselves provide a good indication of the content and organizational structure of this graduate school. Although the topic of supervised doctoral students should belong to CIM, the general needs of students do not differ much from other topics. A good graduate school curriculum that offers structured guidance in scientific work is a basic prerequisite for the successful completion of a doctoral project. The following factors play a crucial role in the successful implementation of the project in the Graduate School: teaching the basic skills of scientific work, providing space for participants to support and exchange ideas with each other, and supporting participants in their personal development so that they feel equipped for a scientific and professional career. All these factors will be taken into account when creating and developing the curriculum.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving humans was approved by the Ethics Committee of Witten/Herdecke University, Alfred-Herrhausen-Str. 50, 58455 Wiiten/Germany. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants in accordance with the national legislation and institutional requirements.

Author contributions

BS-S: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. SL: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – review and editing.

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Supplementary material

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Association between breakfast consumption frequency and handgrip strength and standing long jump: a systematic review and meta-analysis

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Background and aims: Over the past decade, numerous studies investigating the relationship between breakfast consumption frequency and handgrip strength and standing long jump have produced conflicting evidence, leading to uncertainty regarding this association. This study aimed to provide further clarity on the relationship between breakfast consumption frequency and handgrip strength and standing long jump.

Methods: A comprehensive search of the literature up to September 15, 2023, was conducted on Web of Science, PubMed, Scopus, MEDLINE, and CNKI. Six studies related to grip strength and three studies related to standing long jump performance were included in the meta-analysis. For studies defining breakfast consumption frequency as an ordinal variable, the effect sizes of the lowest and highest frequency groups were analyzed.

Results: No significant differences in handgrip strength were found between the highest and lowest breakfast consumption groups. Furthermore, unlike in men, women with the highest frequency of breakfast consumption showed significantly higher handgrip strength levels than women with the lowest frequency of breakfast consumption. No significant positive associations were found between breakfast intake frequency and standing long jump levels.

Conclusion: These results suggest that while regular breakfast consumption may enhance handgrip strength in women, it does not influence standing long jump performance in both sexes.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, CRD42024547903

KEYWORDS

breakfast consumption frequency, grip strength, standing long jump, meta-analysis, review

1 Introduction

Sustaining optimal muscle strength is crucial for public health (Zhu et al., 2020). Increasing evidence suggests that superior muscle strength in adolescence, adulthood, and old age can help prevent various chronic non-communicable diseases, such as type 2 diabetes(Fraser et al., 2021), hypertension (Oliveira et al., 2023), and cardiovascular diseases (Peralta et al., 2023).

Unfortunately, muscle strength levels as reflected by grip strength or standing long jump have decreased in both the adolescent and general population (Masanovic et al., 2020; Li et al., 2023; Fifth National Physical Fitness Monitoring Communiqué, 2022; Kidokoro et al., 2020; Emeljanovas et al., 2020; Kasović et al., 2021). For example, a systematic review indicated that a substantial majority of studies showed a constant decline in muscle strength (Masanovic et al., 2020). Further, a long-term, large-scale study in China found a significant decline in standing long jump levels over time in a representative sample of adolescents aged 7–18 years between 1985 and 2019 (Li et al., 2023). The muscular strength of adults men in 2020 was found to be significantly lower by 1.9% compared to that of adults men in 1984, however, a significant decline was not observed in women's muscular strength during the same period (Fifth National Physical Fitness Monitoring Communiqué, 2022). Meanwhile, a study in Japan revealed a significant decline in grip strength among college students over the past few decades. Compared to Japanese college students in 1984, the grip strength of Japanese college students in 2016 was significantly lower by 8.1 kg (Kidokoro et al., 2020). Similar patterns of decline in muscle strength were observed in both Asian and Western populations. For instance, Lithuanian children and adolescents (Emeljanovas et al., 2020), as well as Croatian children and adolescents (Kasović et al., 2021) showed a declining trend in grip strength or standing long jump over time. These findings highlight the importance of investigating preventive factors that affect muscle strength, as they can provide valuable insights into the overall health of the population.

Results from epidemiological studies have shown that specific foods or nutrients, including lycopene (Sahni et al., 2021), dairy products(Miyazaki et al., 2023), vegetables and fruits (Yokoyama et al., 2021), fatty fish (Khaing et al., 2024; Xu et al., 2022), nuts (Jun and Shin, 2024), and coffee (Ferreira et al., 2022) are associated with higher muscle strength whereas ultra-processed food intake is associated with lower muscle strength (Zhang et al., 2022). There is also evidence that dietary patterns [e.g., balanced and rice-meat dietary patterns (Liu et al., 2021), plant-based diet (Liu et al., 2021), and plant-poultry-based diet (Shahinfar et al., 2020)] are associated with higher muscle strength. However, researchers have recently focused on breakfast, as breakfast intake can affect an individual's total-day diet quality (Cuadrado-Soto et al., 2020). Breakfast is typically defined as the first meal consumed within 2 h of waking up, ideally before 10 am. It is considered an important meal, contributing approximately 20–35% of the total daily energy consumption (Jabri et al., 2021). Prior study has demonstrated that subjects who habitually skip breakfast exhibit elevated levels of chronic inflammation (Zhu et al., 2021). The evidence indicates that an increase in inflammatory cytokines, including CRP, IL-6, and TNF-α, is associated with a reduction in muscle mass and strength. The decline in inflammatory cytokines has been observed to result in a reduction in anabolic factors, such as insulin and insulin-like growth factor (IGF-1), which can subsequently lead to a down-regulation of muscle protein synthesis (Cervo et al., 2020). It can be reasonably speculated, therefore, that habitual skipping of breakfast may have a deleterious effect on the decline of skeletal muscle strength through the process of elevated systemic inflammation.

Conversely, consuming a regular breakfast is associated with numerous physical and mental health benefits. From a physical perspective, it has been linked to a reduced risk of obesity (Ma et al., 2020), hypertension (Li et al., 2022) and cardiovascular disease (Chen et al., 2020). In terms of mental health, breakfast consumption frequency has been associated with a lower risk of depression (Zahedi et al., 2022) and anxiety (Zahedi et al., 2022). Over the past decade, several studies have investigated the relationship between breakfast consumption frequency and physical function, particularly skeletal muscle strength (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020; Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020). However, there is conflicting evidence regarding the association between breakfast consumption frequency and grip strength. While some studies (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020) have reported a positive association, others (Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020) have not.

To date, existing studies from various countries report a prevalence of irregular breakfast consumption ranging from approximately 8–33% (Yokoro et al., 2021). Breakfast habits, as a modifiable dietary behavior, have significant public health implications in preventing the decline of muscle strength (Khaing et al., 2024). Therefore, our study aimed to systematically review whether a regular breakfast consumption frequency (≥six times/week) is significantly associated with higher skeletal muscle strength in the upper and lower limbs assessed through grip strength and standing long jump.

2 Materials and methods

Following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), this study has been registered at https://www.crd.york.ac.uk/PROSPERO/ (Registration number: CRD42024547903).

2.1 Literature search

A thorough literature search of five databases, including Web of Science, PubMed, Scopus, Medline, and the China National Knowledge Infrastructure (CNKI), was conducted from inception to September 15, 2023 to identify relevant studies that examined the relationship between the frequency of breakfast consumption and handgrip strength and standing long jump. The specific search terms are listed in the Supplementary material. To search for relevant literature, the following search terms were used: ("muscle strength" OR "handgrip strength" OR "grip strength" OR "fitness" OR "physical fitness") AND ("breakfast frequency" OR "breakfast" OR "breakfast skipping" OR "breakfast omission").

2.2 The inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies focusing on human populations; (2) those with observational study designs; (3) those that used breakfast consumption as the exposure variable; and (4) those that used handgrip strength and standing long jump as outcome variables. Studies were excluded if they were animal experiments or review articles, did not examine the relationship between breakfast consumption frequency and handgrip strength and standing long jump, or were published in languages other than English or Chinese.

2.3 Data extraction and quality assessment

Two independent investigators collected the following information by reviewing each included article using a standardized form: author (publication year), country, study population, sex (sample size), age, exposure variable, exposure assessment, outcome variable, outcome assessment, adjusted confounding factors, mean handgrip strength or standing long jump, and measures of variability [standard deviation, standard error, or 95% confidence interval (95% CI)] for each category of breakfast consumption frequency. The mean handgrip strength or standing long jump with the most appropriate adjustment for confounding factors was extracted. Subgroup analyses were performed based on sex (male and female), adjustment for confounders (yes or no), and assessment tools (Japan and others). The study also extracted the effect estimates for the highest and lowest frequency of breakfast consumption after adjusting for confounding factors. The present study did not employ any automated tools during the process of data collection.

The quality of the included studies in this study was assessed using the Newcastle-Ottawa Scale (NOS). The NOS includes three dimensions: participant selection (0–4 points), comparability (0–2 points), and outcome (0–2 points). The scores of all the items within these dimensions were summed to obtain a total quality score. A total score of ≤5 was considered low quality, 6–7 was considered intermediate quality, and 8–9 was considered high quality.

2.4 Statistical analysis

The meta-analysis aimed to assess the association between breakfast consumption frequency and handgrip strength or standing long jump was performed using Stata 17.0. Due to different grip strength measurement tools, we used standardized mean difference (SMD) to express the impact between the highest and lowest categories of breakfast consumption frequency. Conversely, the mean difference (MD) was used to evaluate the standing long jump between the categories with the highest and lowest breakfast consumption frequency.

I^2 statistics was used to examine the heterogeneity of effect estimates among different studies. As per prior studies, I^2 values between 25 and 49% were considered low, 50–74% were considered moderate, and 75–100% were considered high heterogeneity. When there is a high degree of heterogeneity ($I^2 > 50\%$), the random-effect model was employed for meta-analysis. The subgroup analysis was conducted based on geographical region (Asian, or Non-Asian), sex (male or female), age (<18 or ≥ 18 years), measurement tools (same or different), and adjustment for confounders (yes or no). Sensitivity analysis was performed to assess the impact of including or excluding any single study on the heterogeneity of integrated studies. Publication bias was assessed using the funnel plot with Egger's test. For all two-sided tests, statistical significance was set at <0.05.

3 Results

3.1 Literature search and screening

Figure 1 provides a summary of the literature search and screening process. Initially, a total of 398 relevant papers were identified: 195 from Web of Science, 110 from PubMed, 1 from Scopus, 5 from Medline, and 87 from CNKI. Following the exclusion of duplicate based on the titles and abstracts of each article (N = 171), we identified 21 eligible articles. Based on the inclusion criteria, only nine full-text articles were deemed eligible; seven of them were included in the meta-analysis.

3.2 Basic characteristics of the included overall studies

Among all nine studies (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020; Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020; Gioxari et al., 2023; Hu et al., 2020) that adopted cross-sectional study designs, eight examined the association between breakfast consumption frequency and handgrip strength (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020; Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020; Gioxari et al., 2023), while five examined the association between breakfast consumption frequency and standing long jump (Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020; Hu et al., 2020). These studies reported the mean handgrip strength (with SD, SE, or 95% CI) for each category of breakfast consumption frequency. The studies were conducted in various countries: China (n = 3) (Cui et al., 2018; Ding et al., 2020; Hu et al., 2020), Japan (n = 1) (Huang et al., 2014), Korea (n = 1) (Jang et al., 2020), Ghana (n = 1) (Annan et al., 2020), Greece (n = 1) (Gioxari et al., 2023), and European countries (n = 2) (Cuenca-García et al., 2014; Zaqout et al., 2016). These studies included 25,819 participants, whose age ranges from 6 to 83 years old. Handgrip strength was measured using a hand dynamometer, and breakfast consumption frequency was assessed through self-reported 24-h recalls (Cuenca-García et al., 2014), a brief self-administered dietary history questionnaire (Huang et al., 2014), and other self-reported methods (Cui et al., 2018; Ding et al., 2020; Jang et al., 2020; Zaqout et al., 2016; Annan et al., 2020; Gioxari et al., 2023; Hu et al., 2020). In the nine studies, five included both sexes (Ding et al., 2020; Zaqout et al., 2016; Annan et al., 2020; Gioxari et al., 2023; Hu et al., 2020), while four studies analyzed the association separately for males and females (Huang et al., 2014; Cui et al., 2018; Jang et al., 2020; Cuenca-García et al., 2014). Additionally, Huang et al. (2014) recruited employees who worked in the study region, while Cui et al. (2018) and Ding et al. (2020) recruited regional college students and adults, respectively. The remaining six studies included representative samples of children, adolescents, adults, and older adults (Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020; Gioxari et al., 2023; Hu et al., 2020).

The categorization of breakfast consumption frequency varied across different studies. Chinese population-based studies categorized breakfast consumption frequency into three groups: ≤1 time/week, 2–5 times/week, and ≥ 6 times/week (Cui et al., 2018; Ding et al., 2020; Hu et al., 2020). One Japanese study classified breakfast consumption frequency as ≤2 times/week, 3–5 times/week, and ≥ 6 times/week (Huang et al., 2014). One Korea study classified breakfast consumption frequency as skipping breakfast every day, irregular breakfast with snack, irregular breakfast meal, and breakfast meal everyday (Jang et al., 2020). One Greece study classified breakfast consumption frequency as daily, most of the days, sometimes, and no (Gioxari et al., 2023). The remaining three studies did not specify the number of days per week for the categorization of breakfast consumption frequency (Cuenca-García

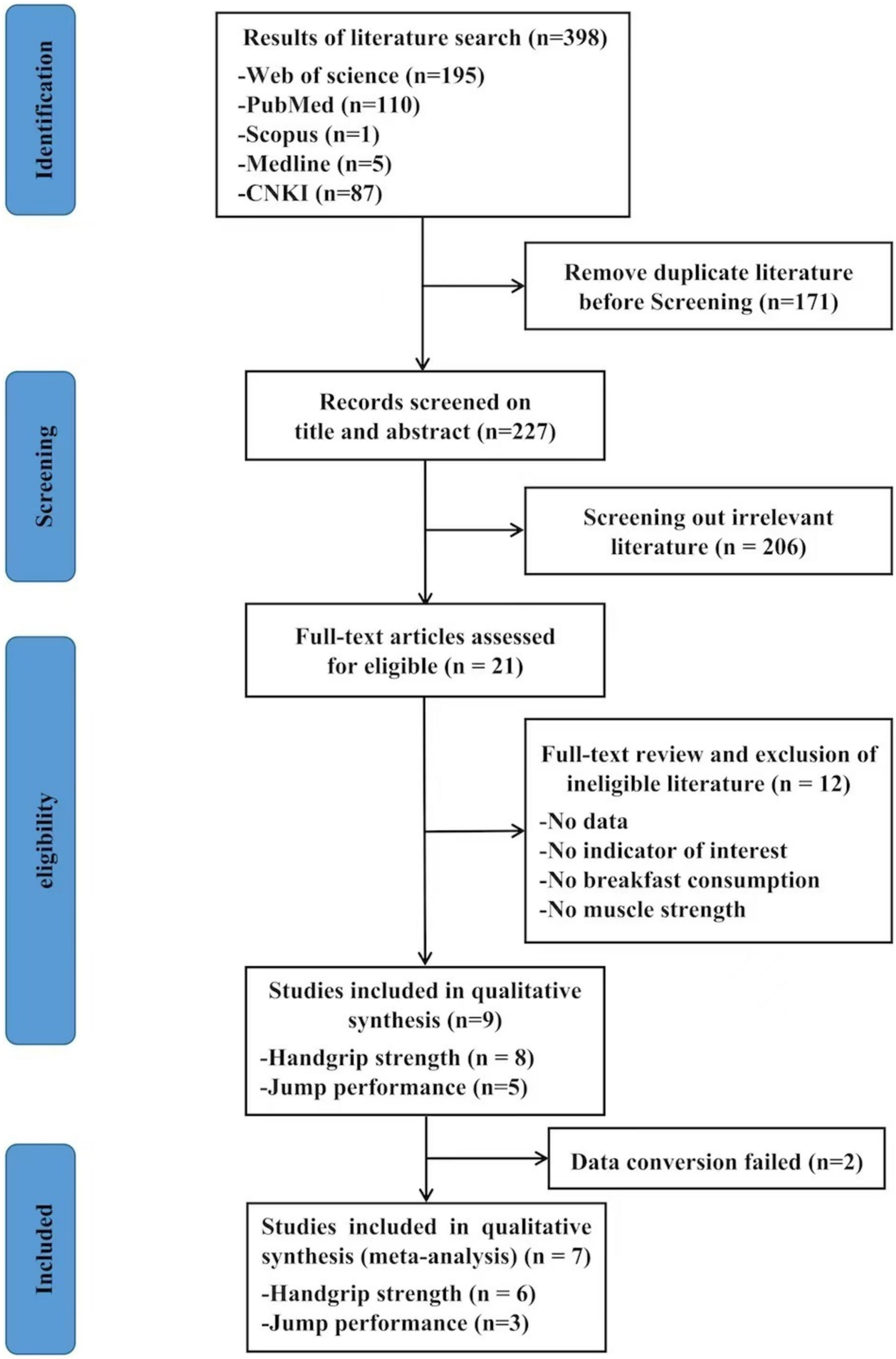

FIGURE 1
Flow diagram of study selection.

et al., 2014; Zaqout et al., 2016; Annan et al., 2020). Regarding the measurement of handgrip strength, all included studies used a dynamometer. Among them, a Takei dynamometer was used in three studies (Huang et al., 2014; Cui et al., 2018; Zaqout et al., 2016), a WCS-100 in one study (Ding et al., 2020), a handheld digital dynamometer in one study (Cuenca-García et al., 2014), a Jamar Plus+ Digital Hand Dynamometer in one study (Gioxari et al., 2023), and other types of dynamometers in three studies (Jang et al., 2020; Annan et al., 2020; Hu et al., 2020). The standing long jump test is evaluated based on the distance between the start line and the heel. Detailed information on the basic characteristics of the included studies are shown in Tables 1, 2.

Regarding the outcome measurement, two studies explained the measurement of grip strength and standing long jump (Zahedi et al., 2022; Huang et al., 2014) and indicated that staff need to undergo training. One study conducted a pre-test for staff (Zahedi et al., 2022). Another study (Huang et al., 2014) indicated that six staff received a 3-day training and conducted a 1-day data collection program. The remaining seven articles (Zhu et al., 2021; Cervo et al., 2020; Ma et al., 2020; Li et al., 2022; Chen et al., 2020; Cui et al., 2018; Jang et al., 2020) did not indicate that staff need to undergo training and pre-experiments to measure grip strength and standing long jump.

Regarding the day/conditions of outcome measurement, one study (Jang et al., 2020) indicated that the measurement of physical fitness was after lunchtime at school; another study (Huang et al., 2014) indicated that measurement was conducted in public primary schools but the time of measurement was not introduced; one study (Zahedi et al., 2022) indicated that the standing long jump was conducted on a smooth and hard surface in primary schools, and one study (Cui et al., 2018) indicated that the measurement site was at the hospital. The remaining studies (Zhu et al., 2021; Cervo et al., 2020; Ma et al., 2020; Li et al., 2022; Chen et al., 2020) did not introduce the day/conditions of outcome measurement.

3.3 Quality assessment

After assessing the quality of studies using the NOS, one, three, four, and one studies had quality scores of 8, 7, 6, and 5, respectively. Detailed results for quality assessment are presented in Table 3.

3.4 Systematic review results

Regarding handgrip strength, there were discrepant findings in the literature. Four studies (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020; Ding et al., 2020) reported a positive association between regular breakfast consumption and higher handgrip strength levels, while four studies (Jang et al., 2020; Cuenca-García et al., 2014; Zaqout et al., 2016; Annan et al., 2020) found no significant association.

Regarding the standing long jump, one study reported a positive association between regular breakfast consumption frequency and higher standing long jump in both adult males and females (Jang et al., 2020). In another study, the results indicate that regular breakfast was positively associated with standing long jump in women but not in men (Hu et al., 2020). There were no significant positive associations found between regular breakfast consumption and higher standing long jump among children (Annan et al., 2020) and adolescents (Cuenca-García et al., 2014). In another study, no significant associations were found between breakfast consumption and standing long jump among children (Zahedi et al., 2022).

3.5 Meta-analysis results

3.5.1 Handgrip strength

Six studies (Huang et al., 2014; Cui et al., 2018; Ding et al., 2020; Jang et al., 2020; Cuenca-García et al., 2014; Annan et al., 2020) reported the outcome of handgrip strength of 21,444 individuals. The meta-analysis result indicated no significant association between regular breakfast consumption frequency and higher handgrip strength (SMD = 0.05, 95% CI = −0.10, 0.20; I^2 = 87.45%; p = 0.51; Figure 2).

3.5.2 Standing long jump

Three studies (Jang et al., 2020; Annan et al., 2020; Hu et al., 2020) reported the outcome of handgrip strength of 5,085 individuals and found that there was no significant difference observed between breakfast consumption frequency and standing long jump (MD = −2.58, 95% CI = −8.40, 3.24; I^2 = 89.67%; p = 0.38; Figure 3).

3.5.3 Subgroup analysis

To identify the source of heterogeneity, we conducted a subgroup analysis based on sex, adjustment for significant confounding factors, and measurement tools. In the sex-based subgroup analysis, unlike in men, women with the highest frequency of breakfast consumption showed significantly higher handgrip strength levels than women with the lowest frequency of breakfast consumption (SMD = 0.89, 95% CI = 0.02, 1.77; I^2 = 67%; p = 0.04). Furthermore, we found that the association between regular breakfast consumption frequency and higher handgrip strength remained significant, whether adjusting for confounding factors (SMD = 0.17, 95% CI = 0.06, 0.28; I^2 = 76%; p = 0.02) or not (SMD = −0.13, 95% CI = −0.22, −0.03; I^2 = 0%; p = 0.01). In terms of the measurement tools used for handgrip strength, our subgroup analysis indicated that there is a significant positive association between breakfast consumption frequency and handgrip strength, whether using the same handgrip (SMD = 0.12, 95% CI = 0.07, 0.16; I^2 = 0%; $p < 0.01$) or different handgrip measures (SMD = −0.12, 95% CI = −0.22, −0.02; I^2 = 0%; p = 0.02). Detailed results of the subgroup analysis are shown in Table 4.

3.6 Sensitivity analysis and publication bias

The sensitivity analysis indicated that there was no substantial change in the positive association when each study was omitted one by one (Figure 4). Figure 5 shows that the visualized funnel plot displayed a fairly even distribution of the individual studies within the range of the combined effect size, indicating a modest publication bias.

4 Discussion

The systematic review and meta-analysis found that, unlike in men, women with regular breakfast consumption frequency have higher grip strength than women with irregular breakfast consumption frequency. However, there is no significant difference observed in standing long jump between the two groups. To the best of our

TABLE 1 Characteristics of studies of a meta-analysis investigating the relationship between breakfast consumption frequency and handgrip strength.

Study ID/year	Country	Population	Study design	Sex/total sample size	Age (mean ± SD)	Exposure variable	Exposure assessment	Outcome variable	Outcome assessment	Adjusted confounding factors	Adjusted mean (SD/SE/95%CI)
Cuenca-García et al. (2014)	European cities	Adolescents	Cross-sectional study	2,148	No	Breakfast consumption frequency	Self-reported 24-h recalls	Handgrip strength (kg/kg)	Handheld digital dynamometer (K 5101;Japan)	Center, age, mother's education, father's education, and family affluence.	Men: Consumer: 0.5 (0.02) Occasional: 0.5 (0.03) Skipper: 0.5 (0.03) Women: Consumer: 0.6 (0.01) Occasional: 0.6 (0.02) Skipper: 0.6 (0.03)
Huang et al. (2014)	Japan	Adults	Cross-sectional study	Men/723 Women/346	43.8 ± 10.5	Breakfast consumption frequency	Brief self-administered dietary history questionnaire	Handgrip strength (kg)	Handheld digital dynamometer (TKK 5401; Japan)	Age, body mass index, daily energy, protein, vitamin C, vitamin D, a-tocopherol intakes, metabolic syndrome, depression symptoms, and high-sensitivity C-reactive protein, education level, occupation, marital status, sleep duration, toothbrushing, smoking status, drinking frequency, and physical activity.	Men: ≤2 times/week: 41.6 (41.0, 42.2) 3–5 times/week: 41.7 (40.8, 42.6) ≥6 times/week: 42.4 (41.9, 42.9) Women: ≤2 times/week: 25.0 (24.1, 26.0) 3–5 times/week: 25.8 (24.7, 26.9) ≥6 times/week: 25.6 (25.0, 26.3)
Huang et al. (2014)	Japan	Adults	Cross-sectional study	Men/723 Women/346	43.8 ± 10.5	Breakfast consumption frequency	Brief self-administered dietary history questionnaire	Handgrip strength (kg/kg)	Handheld digital dynamometer (TKK 5401; Japan)	Age, body mass index, daily energy, protein, vitamin C, vitamin D, a-tocopherol intakes, metabolic syndrome, depression symptoms, and high-sensitivity C-reactive protein, education level, occupation, marital status, sleep duration, toothbrushing, smoking status, drinking frequency, and physical activity.	Men: ≤2 times/week: 0.613 (0.605, 0.621) 3–5 times/week: 0.616 (0.604, 0.629) ≥6 times/week: 0.625 (0.618, 0.633) Women: ≤2 times/week: 0.479 (0.463, 0495) 3–5 times/week: 0.489 (0.471, 0.508) ≥6 times/week: 0.490 (0.478, 0.501)
Cui et al. (2018)	China	College students	Cross-sectional study	Men/2377 Women/3874	No	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Handheld digital dynamometer (TKK 5401; Japan)	Grade, body mass index, race, physical activity, living status, smoking habits, drinking habits, depressive symptoms, and sleep quality.	Men: ≤1 times/week: 41.6 (41.3, 41.9) 2–5 times/week: 42.1 (41.8, 42.4) ≥6 times/week: 42.4 (42.2, 42.7) Women: ≤1 times/week: 25.1 (24.9, 25.4) 2–5 times/week: 25.9 (25.7, 26.2) ≥6 times/week: 26.7 (26.5, 26.9)

(Continued)

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TABLE 1 (Continued)

Study ID/year	Country	Population	Study design	Sex/total sample size	Age (mean ± SD)	Exposure variable	Exposure assessment	Outcome variable	Outcome assessment	Adjusted confounding factors	Adjusted mean (SD/SE/95%CI)
Jang et al. (2020)	Korea	Adults	Cross-sectional study	Men/1662 Women/1136	38.14 ± 12.71	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Dynamometer	No	Men: skipping breakfast everyday: 43.90 (9.64) irregular breakfast with snack: 43.36 (8.20) irregular breakfast meal: 42.61 (8.88) breakfast meal everyday: 42.44 (9.13) Women: skipping breakfast everyday: 24.15 (5.62) irregular breakfast with snack: 25.01 (5.24) irregular breakfast meal: 25.12 (6.55) breakfast meal everyday: 25.24 (5.72)
Jang et al. (2020)	Korea	Older adults	Cross-sectional study	Men/263 Women/362	72.22 ± 5.25	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Dynamometer	No	Men: skipping breakfast everyday: 26.85 (8.88) irregular breakfast with snack: 35.44 (5.20) irregular breakfast meal: 31.83 (7.04) breakfast meal everyday: 32.13 (7.87) Women: skipping breakfast everyday: 21.68 (3.45) irregular breakfast with snack: 20.34 (4.91) irregular breakfast meal: 21.32 (5.36) breakfast meal everyday: 20.34 (5.45)
Annan et al. (2020)	Ghana	Adolescents	Cross-sectional study	Men/213 Women/225	11.1 ± 1.1	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Dynamometer	No	Consumer: 4.4 (2.2) Non-consumer: 4.6 (1.8)
Ding et al. (2020)	China	Adults	Cross-sectional study	Men/1171 Women/838	25–65	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Handheld digital dynamometer (WCS-100; Shanghai, China)	Age, sex, body mass index, hypertension, diabetes, depressive symptoms, physical activity, educational level, occupation, living status, smoking and drinking habits.	≤1 times/week: 35.2 (34.7, 35.8) 2–5 times/week: 36.0 (35.6, 36.4) ≥6 times/week: 36.9 (36.6, 37.3)
Zaqout et al. (2016)	European cities	Children	Cross-sectional study	4,903	6–11	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Dynamometer (TKK 5101 Grip D, Takey)	No	β: −0.002
Gioxari et al. (2023)	Greece	Children	Cross-sectional study	134	6–11	Breakfast consumption frequency	Self-reported	Handgrip strength (kg)	Jamar Plus+ Digital Hand Dynamometer (Patterson Medical, Warrenville, IL, United States)	No	Daily or Most of the Days: 14.5 (5.0) Sometimes/No: 16.2 (3.8)

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TABLE 2 Characteristics of studies of a meta-analysis investigating the relationship between breakfast consumption frequency and standing long jump.

Study ID/year	Country	Population	Study design	Sex/total sample size	Age (mean ± SD)	Exposure variable	Exposure assessment	Outcome variable	Outcome assessment	Adjusted confounding factors	Adjusted mean (SD/SE/95%CI)
Jang et al. (2020)	Korea	Adults	Cross-sectional study	Men/1662 Women/1136	38.14 ± 12.71	Breakfast consumption frequency	Self-reported	Standing long jump (cm)	The distance between the start line and the heel	No	Men: skipping breakfast everyday: 200.28 (32.42) irregular breakfast with snack: 193.81 (29.77) irregular breakfast meal: 200.64 (31.12) breakfast meal everyday: 195.15 (31.65) Women: skipping breakfast everyday: 144.09 (26.39) irregular breakfast with snack: 136.03 (28.68) irregular breakfast meal: 142.22 (25.25) breakfast meal everyday: 137.73 (26.38)
Hu et al. (2020)	China	Adolescents	Cross-sectional study	Men/959 Women/890	15.53 ± 1.80	Breakfast consumption frequency	Self-reported	Standing long jump (cm)	The distance between the start line and the heel	No	Men: Breakfast skippers: 223.89 (22.93) Non-breakfast skippers: 226.25 (22.44) Women: Breakfast skippers: 170.27 (16.16) Non-breakfast skippers: 175.61 (17.08)
Zaqout et al. (2016)	European cities	Children	Cross-sectional and follow-up study	Cross-sectional study: 4893 follow-up study: 2,263	6–11	Breakfast consumption frequency	Self-reported	Standing long jump (cm)	The distance between the start line and the heel	Adjustment for moderate-to-vigorous physical activity	Cross-sectional study: β: −0.002 follow-up study: β: −0.019
Annan et al. (2020)	Ghana	Adolescents	Cross-sectional study	Men/213 Women/225	11.1 ± 1.1	Breakfast consumption frequency	Self-reported	Standing long jump (cm)	The distance between the start line and the heel	No	Consumer: 4.6 (2.1) Non-consumer: 5.0 (1.8)
Cuenca-García et al. (2014)	European cities	Adolescents	Cross-sectional study	2,148	No	Breakfast consumption frequency	Self-reported 24-h recalls	Standing long jump (cm)	The distance between the start line and the heel	Center, age, mother's education, father's education and family affluence.	Men: Consumer: 187.9 (2.54) Occasional: 183.4 (3.11) Skipper: 185.8 (4.09) Women: Consumer: 147.3 (3.64) Occasional: 144.4 (3.97) Skipper: 147.0 (4.53)

TABLE 3 Quality assessment of included studies investigating the relationship between breakfast consumption frequency and handgrip strength and standing long jump.

Cross-sectional studies	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Study control for age	Study control for any additional factor	Assessment of the outcome	Statistical test	Total score of quality
Cuenca-García et al. (2014)	*	*	*	*	*		*	*	7
Huang et al. (2014)	*	*	*	*	*	*	*	*	8
Cui et al. (2018)			*	*	*	*	*	*	6
Jang et al. (2020)	*	*	*	*			*	*	6
Annan et al. (2020)	*	*	*	*			*	*	6
Ding et al. (2020)			*	*	*	*	*	*	6
Zaqout et al. (2016)	*	*	*	*	*		*	*	7
Hu et al. (2020)	*	*	*	*	*		*	*	7
Gioxari et al. (2023)			*	*	*		*	*	5

The studies were classified as having low quality (≤5), intermediate quality (6–7), and high quality (8–9).

knowledge, this study is the first of its kind to examine the relationship between breakfast consumption frequency and handgrip strength and standing long jump.

Although the biological mechanisms underlying the effect of breakfast consumption frequency on handgrip strength remain unclear, several potential mechanisms have been explored. A meta-analysis has shown that breakfast consumers have higher intake of minerals, such as calcium and magnesium, as well as vitamins, such as vitamin D, compared to those who skip breakfast (Giménez-Legarre et al., 2020). An intake of vitamin D and calcium may enhance nerve conduction and transmission at the neuromuscular junction, subsequently leading to enhanced contraction of skeletal muscles. Similarly, magnesium plays a crucial role in muscle function and performance. Mg2+ regulates troponin expression by controlling Ca^{2+} concentration gradients and transport (Rayani et al., 2021). Additionally, Mg2+ plays a role in stabilizing protein structures, including actin. Actin, existing as a globular monomer, interacts with ATP and Mg2+, which are essential for the formation of the chemical structure complex required for cross-bridge formation in the sarcomere (Castiglioni et al., 2024). Muscle contraction relies on the relaxation phase, during which Ca2+ is pumped back into the sarcoplasmic reticulum (SR) of the muscle fiber (Castiglioni et al., 2024). This process relies on specific pumping mechanisms that require both ATP and Mg2+ (Castiglioni et al., 2024). Mg2+ serves as an anchor for cofactors like ATP and activates enzyme reactions (Vishnu et al., 2024). Inflammation alteration is likely to explain this association. In a cross-sectional study investigating the impact of skipping breakfast on inflammation alteration, an inverse relationship was found between regular breakfast consumption frequency and chronic inflammation levels (Zhu et al., 2021). The prevention of change in handgrip strength by the mechanisms underlying breakfast consumption frequency may be attributed to the increase in adrenergic activity and blood pressure levels induced by prolonged fasting, which could accelerate inflammatory responses. Based on these findings, we hypothesize that the significant association between regular breakfast consumption and greater handgrip strength may be influenced by the regulation of inflammation levels.

Additionally, sex differences in hand grip strength could explain the significant association between regular breakfast consumption frequency and higher handgrip strength, which was exclusively observed in females compared to males. We explored several potential explanations for the observed sex difference in the present study; in particular, the significant positive association between breakfast frequency and grip strength observed in women but not in men. According to previous studies, among the Asian population included in this study, women had better breakfast habits compared to men, specifically including those rich in protein (Díaz-Torrente and Quintiliano-Scarpelli, 2020). A placebo-controlled, double-blind, randomized controlled trial (Kim et al., 2021) and animal experiments (Aoyama et al., 2021) examined the effect of different timing of protein intake on muscle function and found that regular and adequate breakfast protein intake plays an important role in maintaining muscle strength and mass, with the effect being more pronounced in women. Furthermore, sex differences exist in the diurnal variations of myogenic differentiation 1 (MyoD) expression, a gene involved in muscle differentiation, and these diurnal variations are regulated by clock genes and significantly influenced by dietary intake (Aoyama et al., 2021). Based on these reasons, we speculate that female protein

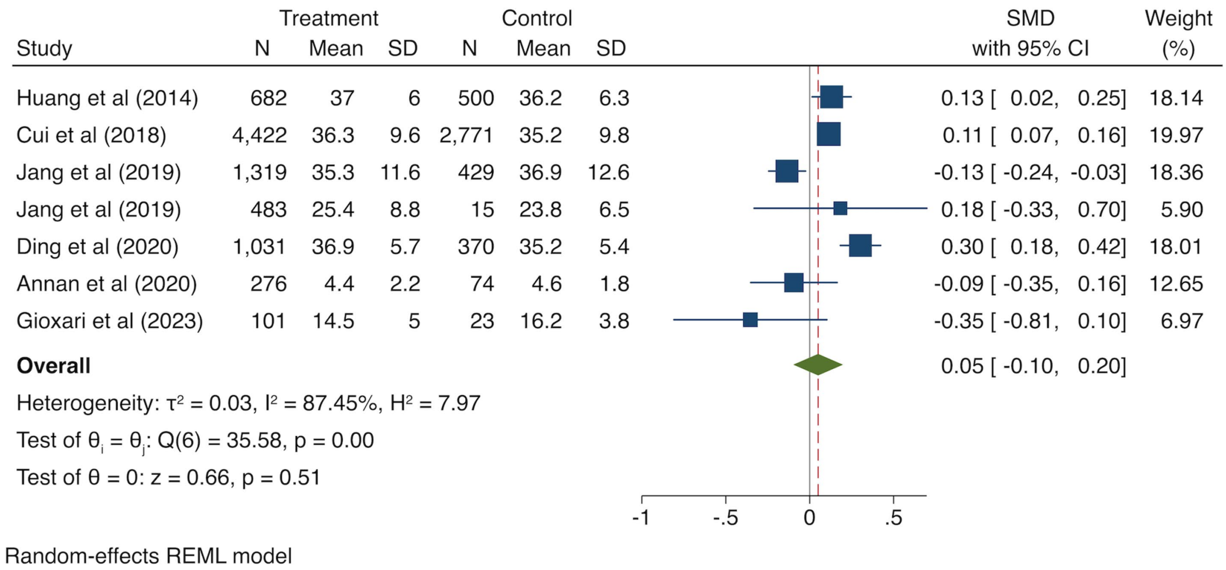

FIGURE 2
Forest plot of handgrip strength in highest versus lowest category of breakfast consumption.

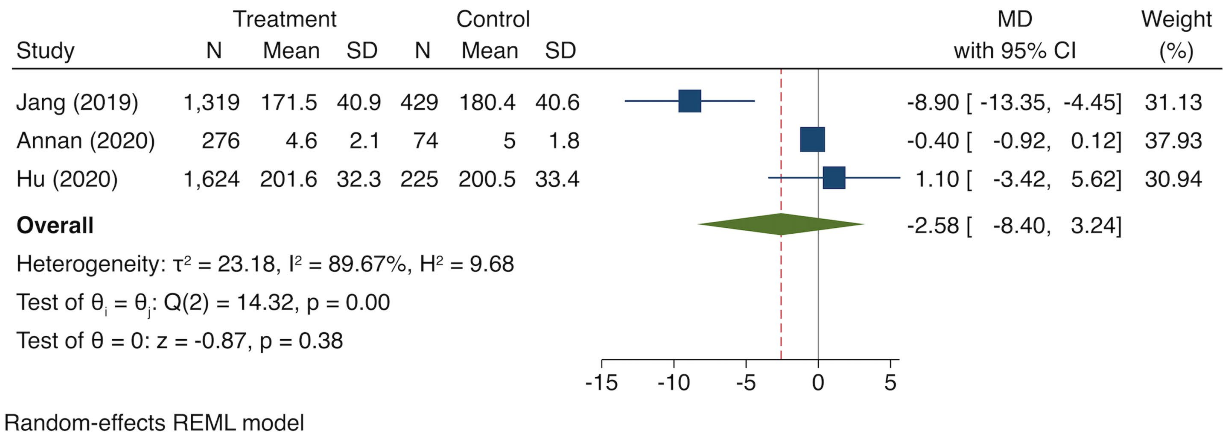

FIGURE 3
Forest plot of standing long jump in highest versus lowest category of breakfast consumption.

intake during breakfast suppresses the decline in muscle regeneration capacity caused by reduced female hormone secretion and also suppresses the weakened muscle regeneration ability resulting from the same decrease in hormone secretion. Both of these mechanisms are achieved through MyoD.

This study found no significant positive association between breakfast consumption frequency and standing long jump, as compared to grip strength. One possible reason could be that the performance of a standing long jump is dependent not only on lower body muscle strength; an arm swing can also contribute by creating an additional downward force on the body when the major hip and knee extensors are in a better position to exert vertical ground reaction force, thereby improving jumping performance (Zhou et al., 2020).

Previous studies on the impact of upper limb strength on lower limb power have focused on the effects of handheld extra weights while jumping and found that handheld extra weights during the jump process allow for greater muscle activation, resulting in proper muscle contractions. Additionally, dynamic features also showed that as the horizontal translation of the center of mass caused by extra hand weights increases, ground reaction forces also increase (Zhou et al., 2020). This also indicates that the upper limb has a significant effect on lower limb strength.

This study had several limitations. First, the cross-sectional design of the study meant that it could not establish a causal relationship between breakfast consumption frequency and handgrip strength. Second, the subgroup analyses conducted to assess sex, measurement tools, and confounding factors helped reduce heterogeneity, indicating their importance as sources of heterogeneity. However, there may be other unmeasured factors influencing the association. Third, self-reporting of breakfast consumption frequency may be prone to recall errors, potentially affecting the accuracy of the assessment. Fourth,

TABLE 4 Subgroup for the association between breakfast consumption frequency and handgrip strength and standing long jump.

Outcomes	Subgroup	Variables	Number of studies	I^2 (%)	Effect model	Effect size (95% CI)	*p*- value	Weight (%)
Handgrip strength	Geographical region	Asian	5	86	Random model	SMD = 0.11 (−0.03, 0.24)	0.13	83.4
		Non-Asian	2	0	Fixed model	SMD = −0.16 (−0.38, 0.07)	0.17	17.6
	Sex	Male	4	76	Random model		0.57	47.9
		Female	4	67	Random model	SMD = 0.89 (0.02, 1.77)	0.04	52.1
						SMD = 0.31 (−0.75, 1.37)		
	Age	<18 years	2	0	Fixed model	SMD = −0.16 (−0.38, 0.07)	0.17	17.6
		≥18 years	5	86	Random model	SMD = 0.11 (−0.03, 0.24)	0.13	83.4
	Measurement tools	Japan, TKK5401	2	0	Fixed model	SMD = 0.12 (0.07, 0.16)	<0.01	38.08
		Others	5	84	Random model	SMD = −0.00 (−0.23, −0.23)	0.98	61.92
	Mixed factors control	Adjustment	3	76	Random model	SMD = 0.17 (0.06, 0.28)	0.02	84.5
		Non-adjustment						
		Korea (20–64 years)	1	–	–	SMD = −0.13 (−0.24, 0.03)	–	77.87
		Korea (> = 65 years)	1	–	–	SMD = 0.18 (−0.33, 0.70)	–	3.51
		Ghana and Greece	2	0	Fixed model	SMD = −0.16 (−0.38, 0.07)	0.17	18.62
		Unadjusted nutrient intake	6	89	Random model	SMD = 0.03 (−0.15, 0.21)	0.76	100
Standing long jump	Sex	Male	2	83	Random model	MD = −1.33 (−8.68, 6.02)	0.72	49.6
		Female	2	93	Random model	MD = −0.43 (−11.89, 11.03)	0.94	50.4

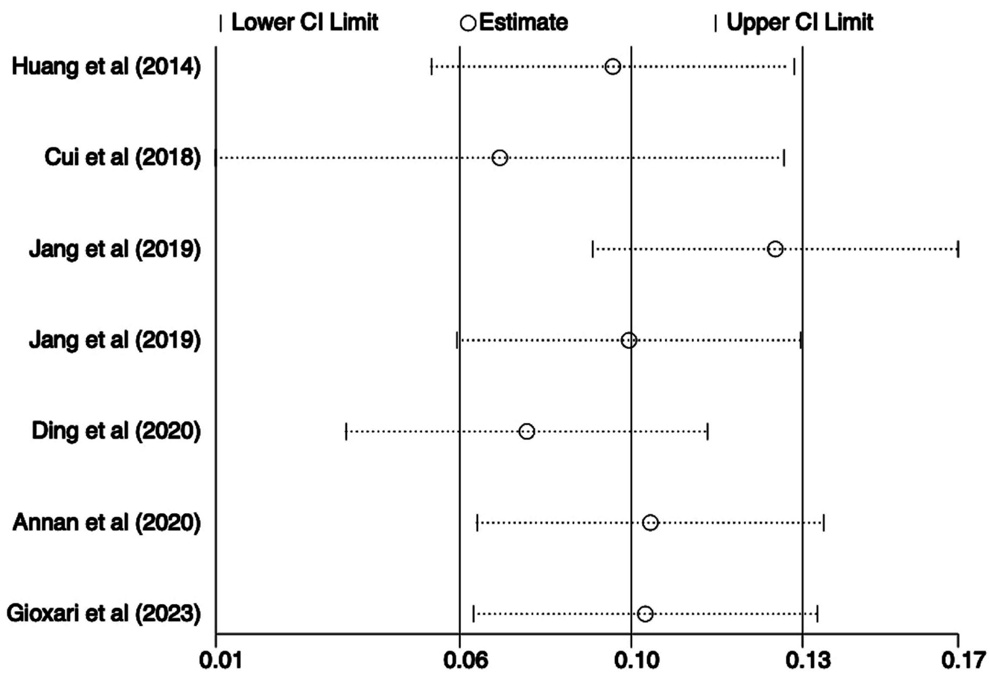

FIGURE 4
Sensitivity analysis results of included studies for handgrip strength in highest versus lowest category of breakfast consumption.

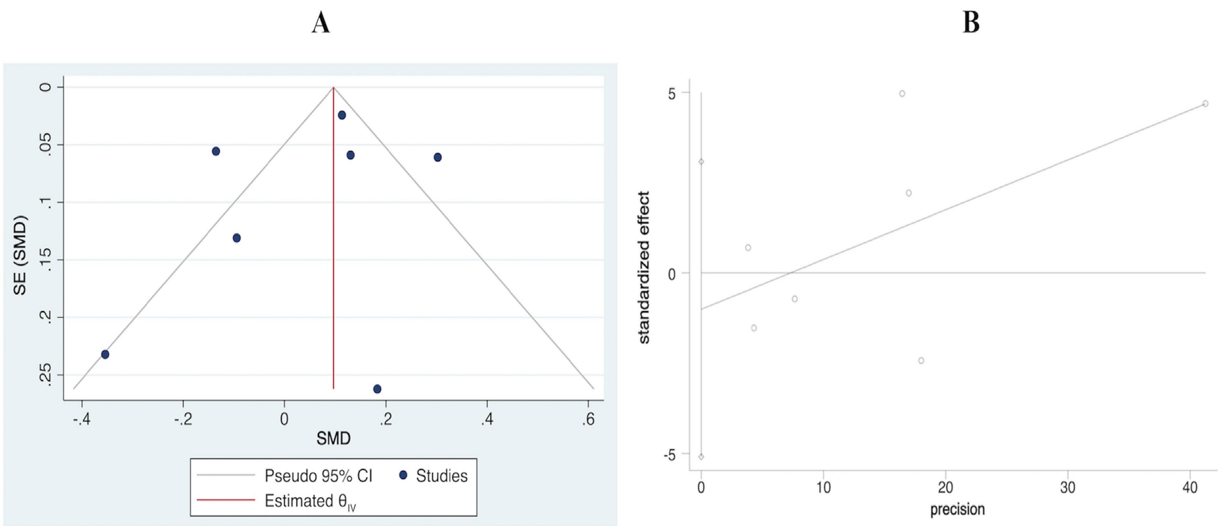

FIGURE 5
Funnel plot with pseudo 95% confidence limits **(A)** and Egger's funnel plot **(B)** of handgrip strength in highest versus lowest category of breakfast consumption.

there were other differences between studies, such as the choice of reference and exposure groups, which could have influenced the true association in a positive or negative way. Fifth, while some studies adjusted for important potential confounders, other unknown factors could have confounded the association between breakfast consumption frequency and handgrip strength. Sixth, regular breakfast consumption frequency might also be associated with total daily nutritional intake. For example, two meta-analyses indicated that individuals who had regular breakfast consumption had a higher intake of minerals (iron, calcium, magnesium, potassium, zinc, and iodine) (Giménez-Legarre et al., 2020), carbohydrates, and fiber, as well as a lower fat intake than breakfast-skippers (Giménez-Legarre et al., 2020). According to Cochrane collaboration commandments, ≥10 studies are needed to obtain clear conclusions on publication bias (Nasser, 2020). Egger's test was used to analyze publication bias of the included studies and the results did not change substantially. However, further research examining the association between breakfast consumption frequency and muscle strength is needed. Seventh, although we have explored the association between breakfast consumption frequency and muscle strength, the type of food and food quantity consumed during breakfast were not specified. However, in previous studies that dairy products were found to be the most common breakfast food (Murakami et al., 2022; Wang et al., 2024), indicating that individuals who regularly consume breakfast tend to have healthier dietary habits, especially those who include protein-rich foods. Eighth, for most studies, the categories of breakfast consumption or breakfast skipping, varied from yes/no to every day/almost every day/3–5 days per week/1–2 days per week/none. However, few studies have provided clear definitions for regular breakfast consumption frequency or skipping breakfast. Finally, a bias derived from methods for collecting data at what timeframe on breakfast consumption frequency could significantly affect the association between regular breakfast consumption frequency and muscle strength. Therefore, these different timeframes make it difficult to draw conclusions about the impact on muscle strength.

5 Implications for clinicians and policy makers

In addition to muscle strength, previous meta-analysis have demonstrated positive and negative associations between breakfast consumption and various chronic non-communicable diseases, including depressive symptoms (Zahedi et al., 2022; Ren et al., 2020), cardiovascular disease (Chen et al., 2020; Morze et al., 2020). Although all current results regarding the association between breakfast consumption frequency and muscle strength are widely based on epidemiologic studies and the mechanism underlying the effect of breakfast consumption frequency on muscle strength is uncertain, the primary purpose of these studies was to provide plausible dietary recommendations to prevent the decline of muscle strength, reinforcing the public health message for a rational breakfast consumption frequency. Considering that breakfast is considered an important meal, contributing approximately 20–35% of the total daily energy consumption and daily micronutrients intake (Wang et al., 2024), further research, particularly intervention studies, is required in order to gain a deeper understanding of the quality of food consumed at breakfast, as well as to inform the development of effective policies to promote regular breakfast consumption among the general population, because they are more likely to identify causal relationships. These studies will also provide evidence regarding appropriate and inappropriate breakfast consumption choices that can be used by physicians and patients with decline of muscle strength, as well as information about certain foods of breakfast consumption that could help lower the risk of recurrent decline of muscle strength attacks. This study proposes that in order to provide optimal guidance on evidence-based dietary recommendations, consideration should be given to a comprehensive approach that encompasses not only the prevention of chronic non-communicable diseases, including physical and mental health conditions, but also the potential impact of dietary habits, including the consumption of breakfast, on the risk of muscle strength decline.

6 Conclusion

Our systematic review and meta-analysis provide an important contribution to the field by identifying sex differences in the association between breakfast consumption frequency and handgrip strength and standing long jump. Unlike in men, women with regular breakfast consumption frequency have higher grip strength than women with irregular breakfast consumption frequency. However, there is no significant difference observed in standing long jump between males and females. Further studies are needed to examine the association between breakfast consumption frequency in terms of food quantity and specific foods and muscle strength in males and females. Understanding how breakfast characteristics (food quantity and specific foods) influence muscle strength will help design more effective tailored sex-specific breakfast programs that prevent muscle strength decline and improve the overall quality of life. Further meta-analyses of prospective cohort studies or interventional studies evaluating the effect of breakfast consumption on muscle strength are also warranted to determine the causal association. These types of studies will provide more robust evidence regarding the association.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

ZR: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. XZ: Writing – original draft, Conceptualization, Investigation, Methodology. YW: Writing – original draft, Conceptualization, Data curation, Investigation, Software. SL: Data curation, Writing – original draft. BC: Conceptualization, Investigation, Project administration, Software, Supervision, Writing – original draft. HW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1451799/full#supplementary-material

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Satiety-enhancing placebo intervention decreases selective attention to food cues

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Background: As placebo interventions could influence appetite and satiety in first studies, they are a promising tool for the future treatment of obesity. Furthermore, individuals with heightened body weight show increased selective attention for food cues. This study aimed to investigate whether placebo induced changes of appetite and satiety can affect attention allocation and to examine correlating factors.

Methods: In a double-blind design, 63 healthy participants were randomized into one of three groups: the enhanced appetite placebo group, the enhanced satiety placebo group, or the control group. Appetite and satiety were induced by administering a placebo capsule along with a group specific expectancy manipulation. One hour later, participants performed a visual probe task to measure attentional bias by comparing reaction times for different conditions. Correlations between reaction times and subjective hunger and satiety ratings, as well as current food craving and plasma ghrelin levels, were explored.

Results: The induction of attentional bias toward non-food stimuli was successful in women in the enhanced satiety placebo group but not in the enhanced appetite placebo group. Women of the enhanced satiety placebo group showed significantly higher reaction times for food cues compared to non-food cues. Across conditions, reaction times were associated with subjective hunger ratings and current food craving in women. No attentional bias was induced in men in either placebo group.

Conclusion: Placebo-induced satiety inhibited attention allocation toward food in healthy women, potentially mediated by reduced hunger and food craving. Placebo effects on satiety could thus be demonstrated on a highly complex cognitive process.

KEYWORDS

placebo effect, expectation, attentional bias, selective attention, appetite, satiety, food craving, visual probe task

1 Introduction

Overweight and obesity are major cardiovascular risk factors and continue to pose a growing global health challenge. As of 2022, 43% of adults worldwide were classified as overweight, and 16% as obese (1). Although increased energy intake and reduced physical activity are primary contributors to elevated body weight (2), recent studies have also focused on the neurobiological and cognitive mechanisms regulating appetite and satiety (3, 4) in search of novel therapeutic strategies. Modifying attention to food cues has emerged as a promising approach for addressing dysregulated attentional processes related to appetite.

Attentional bias arises from various attention-regulation mechanisms that enable the brain to prioritize processing of relevant stimuli, helping meet immediate needs as efficiently as possible (5). Early research on attentional bias primarily focused on threat-related stimuli (6, 7), yet biases have since been observed for a range of stimuli types (8, 9). Food-related stimuli, often perceived positively, may inherently induce attentional bias (10), particularly when addressing an immediate need like hunger (8). For example, in studies using the dot probe task, hungry participants demonstrated heightened attentional bias toward food-related words (e.g., chocolate, honey) over neutral words, as evidenced by faster reaction times (11). Additionally, elevated attentional bias toward food cues has been observed in overweight and obese individuals compared to those of normal weight, suggesting a dysregulated attentional process in obesity similar to that seen in individuals with substance use disorders (12, 13). Functional MRI studies further support this, showing a positive correlation between body mass index (BMI) and activation in brain regions associated with attention when exposed to food cues (14).

Appetite and satiety are closely tied to mental states such as craving (15) and expectations. For instance, studies show that participants preferred Coke more when it was branded (16), and perceived taste ratings for cheese and yogurt were lower when labeled as fat-reduced (17). Expectations also influence physiological appetite regulation, including the release of the appetite-stimulating hormone ghrelin. In a study by Crum and colleagues, participants were given an identical milkshake described as either “high-calorie, indulgent” or “low-calorie, sensible,” and blood ghrelin levels were measured before and after consumption. Participants consuming the “indulgent” milkshake displayed a significantly steeper decline in ghrelin levels, suggesting a stronger sense of satiety compared to the “sensible” milkshake (18). Positive expectations, a major component of the placebo effect, could therefore be harnessed to modulate appetite and satiety. Recent research further shows that beliefs about a hunger-altering placebo intervention influence medial prefrontal cortex activation and even impact later food choices (19). Additional evidence comes from studies demonstrating that when the expected satiety from a previous meal is higher, calorie intake at the next meal is lower (20), underscoring the powerful effect of expectations on eating behavior. Finally, a recent systematic review provides initial evidence suggesting that placebo interventions can promote weight loss in adults (21).

In this study, we integrated insights from placebo and attention research to examine whether placebo-induced changes in appetite and satiety can influence attentional bias toward food cues. Within a larger trial investigating placebo effects on appetite, satiety, and their objective markers, participants were administered a placebo capsule with instructions that it would either stimulate appetite or increase satiety (22). Later, a subgroup of these participants completed a visual probe task, one of the most established paradigms for measuring attentional bias (23). We hypothesized that placebo-induced appetite would heighten attention to food cues, evidenced by faster reaction times for food stimuli relative to neutral stimuli, while placebo-induced satiety would reduce attention to food cues. Additionally, we explored both behavioral and physiological factors that might moderate attentional bias in our analyses.

2 Material and methods

2.1 Participants

Healthy participants aged 18-40 years with normal body weight (BMI 19-25kg/m^2) were included in the main study, within which this substudy was embedded. Exclusion criteria comprised pregnancy or breastfeeding, smoking, alcohol or drug abuse, food allergies, regularly intake of medication (except contraceptives), acute or chronic disease, history of psychiatric disease, surgery within the last four weeks prior to participation, elevated fasting blood glucose levels (>100mg/dl), and clinically relevant anxiety or depression scores [score >7 in at least one subscale of the Hospital Anxiety and Depression Scale (HADS) (24)]. Recruitment was conducted through university mailing lists and flyers. All participants provided written informed consent and received 45€ as compensation.

2.2 Study design

This study was conducted at the Institute of Medical Psychology at Ludwig-Maximilians-University Munich, Germany, and was nested within a larger double-blinded randomized controlled trial investigating the neurobiological mechanisms of placebo interventions on appetite and satiety [for details, see (22)]. In the main study, 90 participants were randomly allocated to one of three groups stratified by sex: enhanced appetite placebo, enhanced satiety placebo, or control. For ethical reasons and to ensure double-blinding, six additional participants were randomly allocated to the enhanced appetite verum and enhanced satiety verum groups (Figure 1). Since this substudy started later than the main study, only 67 out of the 96 study participants from the main study were included. The original study protocol and the amendment describing this substudy were approved by the ethics committee of the Medical Faculty, Ludwig-Maximilians-University Munich, Germany (approval number 650-15).

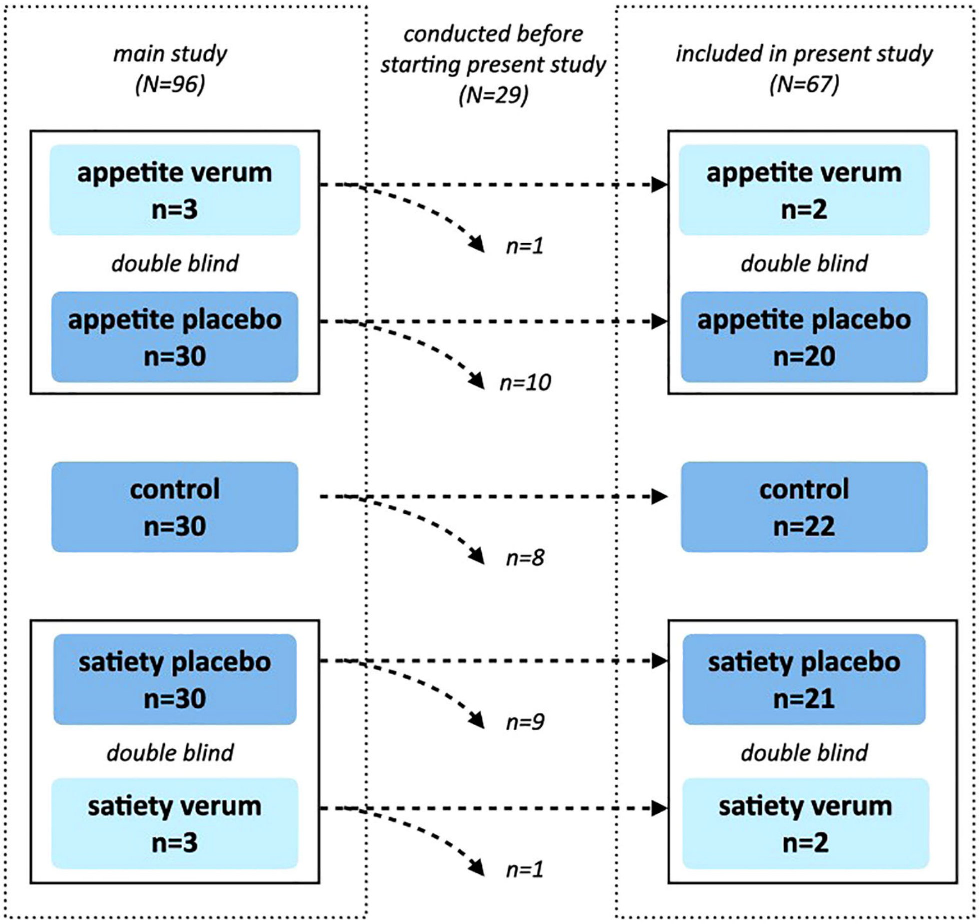

FIGURE 1
Study Design. The main study was designed as a randomized, double-blind, controlled trial, in which 96 participants were randomized into one of five groups (control, appetite placebo, appetite verum, satiety placebo, satiety verum). A total of 29 measurements had already been conducted before the start of this substudy. Verum groups were included only for double-blinding and were not analyzed further. Randomization was maintained, which led to slightly different group sizes within the substudy.

2.3 Randomization and blinding

As detailed in (22), sequentially numbered and sealed envelopes were prepared by a person not directly involved in the experiment, using a computer-generated randomization list. Each envelope contained a capsule along with information about the type of intervention (either appetite-enhancing, satiety-enhancing, or control). To ensure double-blinding, neither the participant nor the experimenter knew whether the capsule in the appetite- or satiety-enhancing intervention contained a placebo or an active ingredient.

2.4 Experimental procedure

The experimental procedure of the main experiment is described in detail in Hoffmann and colleagues (22). In brief, each participant underwent a single experimental session starting at 8 a.m. after fasting for 10 to 12 hours. Finger blood samples to measure blood glucose levels were taken using a BG Star device (Sanofi-Aventis, Hannover, Germany). Blood samples to assess ghrelin levels were repeatedly drawn from a peripheral intravenous catheter flushed with saline. After placing electrodes to monitor the electrocardiogram and the electrogastrogram, participants completed the “Hospital Anxiety and Depression Scale” [HADS (24)] and the “Food Craving Questionnaire - Trait” [FCQ-T (25, 26)], rated their current levels of hunger and satiety on 100 mm visual analogue scales (VAS), and assessed their current food craving using the “Food Craving Questionnaire – State” [FCQ-S (25)]. Thereafter, the first ghrelin blood sample was taken. The experimenter then opened the sealed envelope, performed the verbal expectancy manipulation according to group allocation, and the participant swallowed the provided capsule with 100 ml of mineral water. After each of two consecutive 30 min resting periods, hunger and satiety ratings were assessed, and ghrelin blood samples were collected. Participants were then asked to complete the FCQ-S (25) again. Following a brief instruction on the visual probe task (VPT) by the experimenter, participants performed the VPT while the experimenter left the room to minimize distraction. After completing the VPT, participants in the appetite- and satiety-enhancing intervention groups were asked to guess their allocation to either the verum or placebo group.

2.5 Interventions

Lactose (Heirler Cenovis GmbH, Radolfzell, Germany) was used as the inert ingredient for the control group and placebo groups, while an alginate complex (CM3 Alginat Kapseln, Easyway GmbH, Monheim, Germany) served as the satiety-enhancing active ingredient, and a bitter herb extract (Appetit-Anreger, Zirkulin Naturheilmittel GmbH, Bremen) was used as the appetite-enhancing active ingredient. In the appetite-enhancing and satiety-enhancing intervention groups, participants were informed that they would receive a capsule containing a real treatment or a placebo. Participants in the control group were told they would receive a capsule with an inert substance [for details, see (22)].

2.6 Visual probe task

The VPT was designed using "Visual Studio, Framework.net 4.5.2" in C# and performed on a fast PC. Participants were seated 500 mm from a 400 mm screen. One hundred pictures were paired, with five pairs used for a brief instruction. The remaining 45 pairs included either two pictures of neutral objects (15 pairs) or one picture of appetizing food paired with one neutral object (30 pairs). All pictures were sourced from the "food.pics database" (27) and screened for similar complexion, object size, brightness, and contrast within each pair. Additionally, food pictures were included only if they had a calorie density between 250-500 kcal/100g and total calories greater than 250 kcal per picture, along with high craving and palatability scores in the database's internal ratings. Participants rated the 30 food types depicted in the selected pictures for personal craving prior to the experimental session day. Only the 15 highest-rated food picture pairs were used to create individualized VPTs for each participant, enhancing the internal reliability of the task by selecting the most attractive stimuli (28).

A total of 120 reaction times (RTs) under three different conditions were measured. Each trial began with a fixation cross displayed for 500 ms in the center of the screen. Two hundred and fifty milliseconds after its disappearance, two pictures were displayed for 100 ms each, positioned 60 mm to the left and right of the center, respectively. Immediately after the pictures disappeared, a dot appeared at the former position of one of the pictures. Participants were instructed to detect the dot as quickly as possible and then press a button ("A" for left or "L" for right) to confirm detection. The time between the appearance of the dot and the button press was recorded as RT. After a variable interval of 300 ms to 2000 ms, the next trial started with the display of the fixation cross (29, 30).

The three conditions were defined as congruent (30 trials per participant), incongruent (30 trials per participant), and baseline (60 trials per participant). Trials featuring two neutral objects were classified as baseline, measuring the participant's individual ordinary RT. If one picture was a neutral object and the other a food object, the trial was considered congruent if the dot appeared

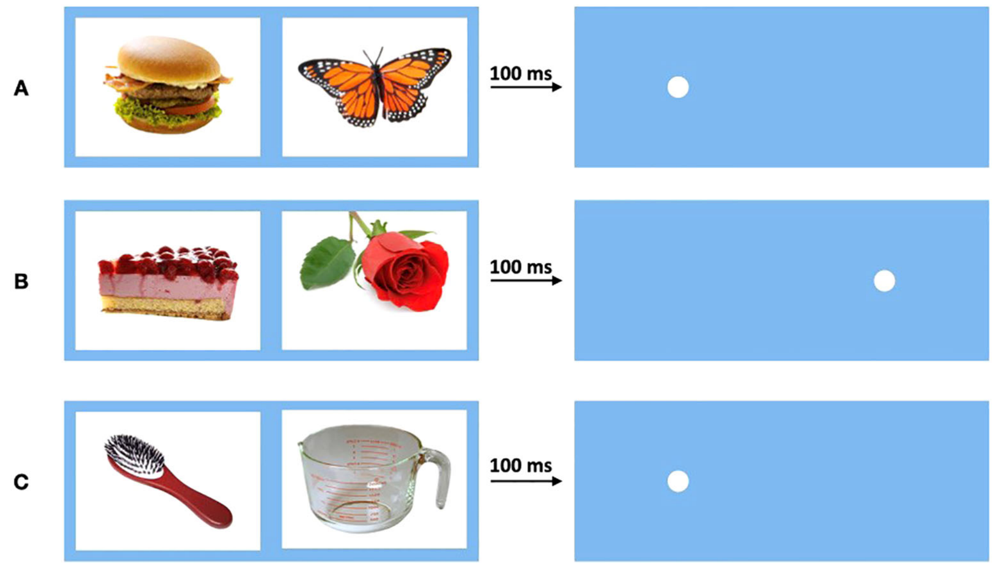

FIGURE 2
Conditions of the visual probe task. Pictures were displayed for 100 ms before disappearing, then dot appears. **(A)** Condition congruent: One neutral and one food picture. Dot appears behind food picture. **(B)** Condition incongruent: One neutral and one food picture. Dot appears behind neutral picture. **(C)** Condition baseline: Two neutral pictures. Dot appears behind one of neutral pictures.

at the location of the food picture and incongruent if it appeared at the location of the neutral picture (Figure 2).

2.7 Outcome parameters

2.7.1 Reaction times of visual probe task

As primary outcome parameters, the mean RTs and standard deviations (SD) for each condition ($M_{baseline}$, $M_{congruent}$, $M_{incongruent}$) were calculated from the 120 measured RTs per participant. Before calculation, outliers were excluded following a previously established three-stage process similar to other outlier exclusion procedures in studies using the VPT (29, 31). First, all trials with errors (e.g., pressing the wrong button) or trials with RTs <100 ms or >2000 ms were removed, as they clearly do not reflect the true RTs. Second, all trials differing by more than 3.5 SD from the participant's condition-specific mean RT were excluded. Third, all trials differing by more than 2.5 SD from the condition-specific mean RT of the entire sample were excluded, as they might reflect atypical situations (e.g., lack of understanding of the test, poor concentration).

In the VPT, lower mean RT for the congruent condition ($M_{congruent}$) compared to the baseline condition ($M_{baseline}$) indicates a higher orienting toward food stimuli, while a higher mean RT for the incongruent condition ($M_{incongruent}$) compared to $M_{baseline}$ indicates delayed disengagement from food stimuli. Conversely, a higher mean RT for the congruent condition ($M_{congruent}$) compared to the baseline condition ($M_{baseline}$) indicates delayed disengagement from non-food stimuli, while a lower mean RT for the incongruent condition ($M_{incongruent}$) compared to $M_{baseline}$ indicates enhanced orienting toward non-food stimuli.

2.7.2 Behavioral parameters

A 100 mm VAS was used for repeated measurements of subjective hunger and satiety ratings, ranging from "not at all hungry/full" to "extremely hungry/full". Additionally, a dichotomous scale was administered to determine whether participants believed they had received a placebo or an active treatment.

2.7.3 Questionnaires

The Food Craving Questionnaire – State (FCQ-S; 25) and the short version of the Food Craving Questionnaire – Trait (FCQ-T; 26) were employed to assess general food craving and to measure current food craving at multiple time points. Both the state and trait measures of food craving have been shown to enhance selective attention to food cues (15). Furthermore, the Hospital Anxiety and Depression Scale (HADS) was utilized to screen for elevated levels of anxiety and depression, following the suggested cut-off values [(24); see above]. Additionally, participants were asked to provide their body weight and height for the calculation of the BMI.

2.7.4 Plasma ghrelin

To measure plasma ghrelin levels, blood samples were taken at three different time points into commercially available EDTA tubes (2.7ml) prepared with 54 µl of 4mM 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) (32). The samples were immediately stored on ice after collection until they were centrifuged within 60 minutes for 10 minutes at 3,000g and 4°C. Two subsamples of 500 µl per blood sample were transferred to Eppendorf tubes prepared with 100 µl of 1 mM HCl and gently mixed before being stored at -70°C until final analyses. Plasma ghrelin levels (pg/ml) were measured in duplicate, following the protocol, using the Human Ghrelin (total) ELISA Kit (Catalogue number EZGRT-89K, Merck Millipore, Darmstadt, Germany).

2.8 Statistical analyses

Before analysis, all data were assessed for normality using skewness, kurtosis, and the Kolmogorov-Smirnov test. All continuous outcome parameters met the normality assumption. To account for individual differences in RTs, a mixed analysis of covariance (ANCOVA) was employed to explore the RTs of the VPT. In this analysis, $M_{baseline}$ served as a covariate, while condition-specific mean RTs ("condition") were treated as a within-subjects factor. The factors "group" (enhanced appetite placebo, enhanced satiety placebo, control) and "sex" were included as between-subjects factors. To directly compare $M_{congruent}$ and $M_{incongruent}$ with $M_{baseline}$, two-tailed t-tests were used. Bonferroni corrections for multiple comparisons were applied where appropriate to control for the increased risk of Type I errors. Dichotomous parameters were analyzed using the chi-square test.

Pearson correlation coefficients were calculated to assess possible relationships between subjective states of hunger, satiety, and food craving, individual RTs, ghrelin levels, and general food craving. Participants from both placebo groups (enhanced appetite placebo and enhanced satiety placebo) and the control group were included, as an association between appetite regulation and RTs was expected in the entire sample. To account for participants' individual ordinary RTs, difference scores (Δ) were calculated and entered into the correlational analyses as follows: for the congruent condition ($\Delta M_{congruent} = M_{congruent} - M_{baseline}$) and for the incongruent condition ($\Delta M_{incongruent} = M_{incongruent} - M_{baseline}$). To account for baseline differences in hunger, satiety, and food craving ratings as well as ghrelin levels, Δ scores were computed and entered into the correlational analyses as follows: for hunger (ΔHunger (VAS) = $VAS_{hunger\ before\ VPT} - VAS_{hunger\ baseline}$), for satiety ($\Delta$Satiety (VAS) = $VAS_{satiety\ before\ VPT} - VAS_{satiety\ baseline}$), for current food craving (ΔFood craving (FCQ-S) = $FCQ\text{-}S_{before\ VPT} - FCQ\text{-}S_{baseline}$), and for ghrelin levels ($\Delta Ghrelin = Ghrelin_{beforeVPT} - Ghrelin_{baseline}$).

All statistical analyses were performed using SPSS (Version 25), and a significance level of $p \le 0.05$ was assumed.

3 Results

3.1 Participants

Out of 240 individuals who responded to the recruitment efforts for the main study, 113 were screened for eligibility. Seventeen participants were excluded before the experimental session (3 did not meet inclusion criteria, 12 did not provide informed consent, and one did not show up). Additionally, one participant was retrospectively excluded due to elevated fasting blood glucose levels and was replaced with a new participant. In total, 96 participants were included and completed the experimental session. Twenty-nine of these were tested before commencing this substudy. Four of the remaining participants received a verum treatment and were therefore excluded from further analyses. Consequently, data from 63 participants (31 men, 32 women) were included in the following analyses (Figure 1).

The study groups were comparable at baseline in terms of demographic, behavioral, and humoral parameters, as well as general food craving scores, and anxiety and depression scores (Table 1). The mean age of participants was 23.6 years (SD = 2.9), and the mean BMI was 21.6 (SD = 1.8).

3.2 Reaction times in visual probe task

In total, 4.3% of the data were removed during the prescribed outlier exclusion process (2.1% in the first step, 0.6% in the second step, and 1.6% in the third step, the latter leading to exclusion of the VPT data of one participant in the enhanced appetite placebo group). The mixed ANCOVA revealed a significant three-way interaction ($F_{\text{condition x group x sex}}(2, 55) = 4.19$, p = 0.020) (Table 2). Bonferroni-corrected two-way ANCOVAs, conducted separately for the placebo groups, showed a significant interaction between "condition" and "sex" in the enhanced satiety placebo group ($F_{\text{condition x sex}}(1, 18) = 6.14$, p = 0.046), but not in the enhanced appetite placebo group ($F_{\text{condition x sex}}(1, 16) = 2.27$, p = 0.304). Further Bonferroni-adjusted *post hoc* tests for the enhanced satiety placebo group revealed $M_{\text{congruent}}$ was significantly higher than $M_{\text{incongruent}}$ in women ($F_{\text{condition}}(1,8) = 8.1$, p = 0.044) (Figure 3), while this was not the case for men ($F_{\text{condition}}(1,9) = 0.004$, p = 1) (Figure 4). To investigate whether this effect in women could be attributed to delayed disengagement from or enhanced orienting toward the food cues, two separate Bonferroni-corrected t-tests comparing $M_{\text{congruent}}$ and $M_{\text{incongruent}}$ with M_{baseline} in female participants from the enhanced satiety placebo group were performed. Neither test was significant ($M_{\text{congruent}}$: $t_{(9)} = -1.236$, p = 0.496, $M_{\text{incongruent}}$: $t_{(9)} = 0.687$, p = 1).

3.3 Correlations between reaction times and hunger, satiety, and food craving ratings

Pearson correlation coefficients were calculated separately for men and women. In women, significant correlations emerged between $\Delta M_{\text{incongruent}}$ and ΔHunger ratings (r = 0.356, p = 0.046) as well as ΔFood craving (r = 0.389, p = 0.028), but not with ΔSatiety ratings (r = -0.334, p = 0.062). In contrast, $\Delta M_{\text{congruent}}$, was not related to ΔHunger ratings, ΔSatiety ratings, or ΔFood craving in women. All analyses were repeated for men, and no significant correlations were found (Table 3).

3.4 Correlations between reaction times and ghrelin levels

Neither $\Delta M_{\text{congruent}}$ nor $\Delta M_{\text{incongruent}}$ correlated with ΔGhrelin in either sex (Table 3).

TABLE 1 Group characteristics at baseline.

	Control (n=22) mean ± SD	Appetite Placebo (n=20) mean ± SD	Satiety Placebo (n=21) mean ± SD	p-value
Sex	12 women 10 men	10 women 10 men	10 women 11 men	
Age (years)	23.2 ± 3	24 ± 2.6	23.6 ± 3.1	0.666
BMI (kg/m^2)	22 ± 1.9	21.5 ± 1.9	21.4 ± 1.6	0.484
Hunger (VAS)	5.4 ± 2.7	5.0 ± 2.8	5.6 ± 2.3	0.731
Satiety (VAS)	2.2 ± 1.9	3.8 ± 3.1	2.4 ± 2.4	0.106
Food Craving State (FCQ-S)	26.1 ± 6.9	23.1 ± 5.6	26.3 ± 5.0	0.144
Blood Glucose (mg/dl)	95.5 ± 6.7	94.6 ± 7.9	97.2 ± 9.7	0.607
Ghrelin Level (pg/ml)	391 ± 119	422 ± 175	368 ± 124	0.510
Food Craving Trait (FCQ-T)	40.3 ± 12.8	34.8 ± 9.7	35.1 ± 10.4	0.196
Anxiety (HADS)	3.0 ± 2.1	3.2 ± 2.5	3.2 ± 1.5	0.909
Depression (HADS)	1.6 ± 1.9	1.4 ± 1.6	1.9 ± 2.1	0.742

SD, Standard Deviation; VAS, Visual Analogue Scale; FCQ-S, Food Craving Questionnaire – State; FCQ-T, Food Craving Questionnaire – Trait; HADS, Hospital Anxiety and Depression Scale. Bold values indicate significant p-values (p<0.05).

TABLE 2 Means of $M_{congruent}$ and $M_{incongruent}$ (controlled for $M_{baseline}$) by group and sex.

	Control		Appetite Placebo		Satiety Placebo	
	Female (n=12) mean ± SE	Male (n=10) mean ± SE	Female (n=10) mean ± SE	Male (n=9) mean ± SE	Female (n=10) mean ± SE	Male (n=11) mean ± SE
$M_{congruent}$ (ms)	431.7 ± 3.8	430.3 ± 4.1	427.7 ± 4.1	434.1 ± 4.4	441.1 ± 4.4	430.9 ± 4.1
$M_{incongruent}$ (ms)	430.8 ± 4.3	432.8 ± 4.7	434.1 ± 4.7	430.8 ± 5.1	429.2 ± 5.1	441.0 ± 4.7

SE, Standard Error.

3.5 Correlations between reaction times and general food craving

Neither $\Delta M_{congruent}$ nor $\Delta M_{incongruent}$ correlated with general food craving (FCQ-T) in either sex (Table 3).

3.6 Treatment guesses

In the satiety placebo group, nine out of 21 participants (42.9%) believed they received an active treatment, while only one out of 20 participants (5%) in the appetite placebo group thought the same. A significant group difference was observed (χ^2 = 7.96, p = 0.005). In total, 4 women (20%) and 6 men (29%) in the placebo groups guessed they had received an active ingredient. There was no significant difference between sexes (χ^2 = 0.41, p = 0.523).

4 Discussion

To our knowledge, this is the first study to investigate attentional bias toward food cues following placebo-induced appetite and satiety in healthy men and women. The results partially confirm our hypothesis that placebo-induced appetite and satiety would affect selective attention to food stimuli. Notably, we demonstrated for the first time that women receiving the placebo intervention to enhance satiety exhibited longer reaction times for food cues compared to neutral stimuli, indicating reduced attention to food cues after expectancy manipulation. Conversely, the placebo intervention to enhance appetite did not affect attention allocation to food cues neither in women nor in men.

Our findings align with several studies demonstrating decreased selective attention to food cues following satiety induction. For example, a study observed a decreased percentage of fixations and reduced viewing time of food pictures in an eye movement paradigm among women with weight concerns after satiety was induced using a placebo pill paired with a verbal suggestion (33). Another study using the VPT revealed an attentional bias toward two different food types in a hungry state. After consumption of one food type until sated, a significant decrease of selective attention to that food was detected, while no such decrease was observed for the uneaten food (34). These

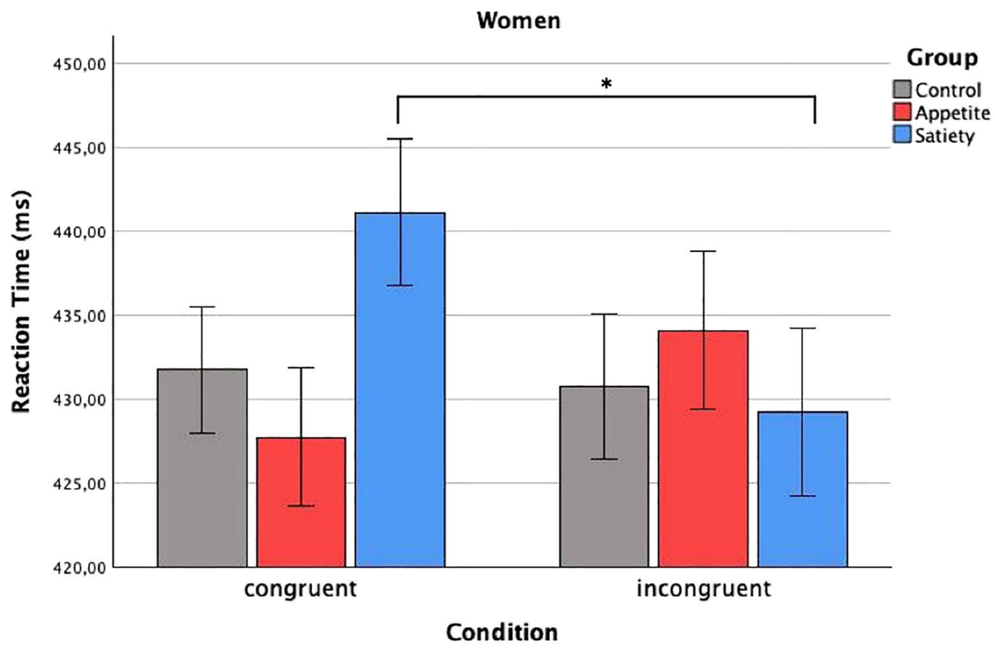

FIGURE 3
Reaction times in women. Baseline-corrected reaction times (ms) in women according to condition and group (estimated means ± SD). Significant difference of reaction time to congruent and incongruent condition in the group placebo-satiety. *p<0.05.

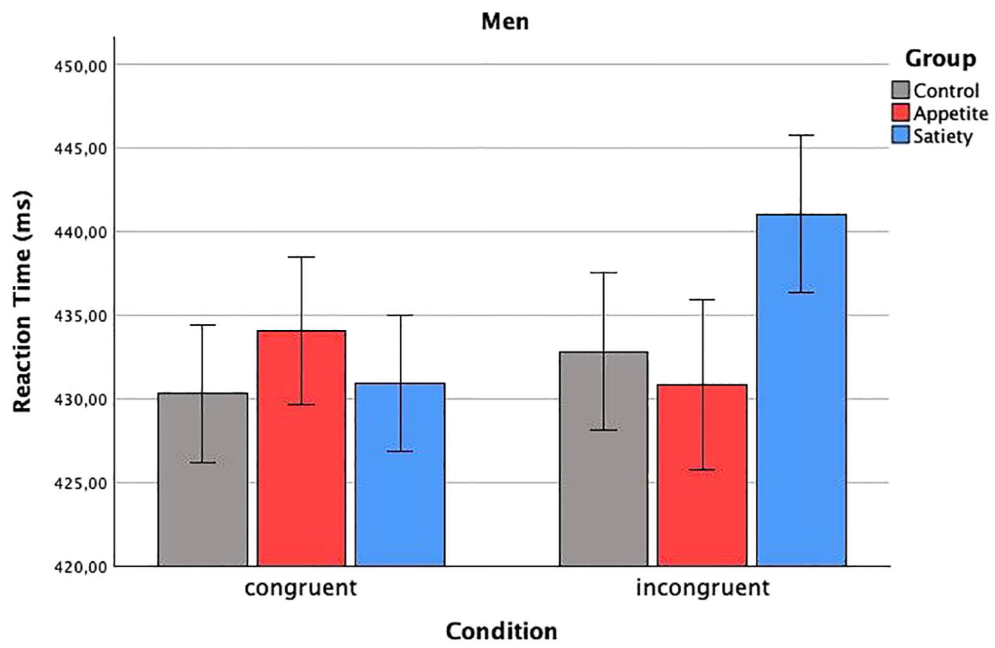

FIGURE 4
Reaction times in men. Baseline-corrected reaction times (ms) in men according to condition and group (estimated means ± SD). No significant difference.

studies, in conjunction with our findings, suggest that selective attention adjusts rapidly and even indicate that attention is drawn away from stimuli addressing satisfied needs.

Interestingly, despite successful satiety induction in both sexes (22), no attentional bias could be detected in men from the enhanced satiety placebo group. Treatment guesses also did not differ between men and women, refuting the idea that men's potentially higher skepticism accounts for this discrepancy. Recent studies suggest that sex significantly influences the relationship between eating behavior and visual attention to food cues; for instance, emotional eating correlates with visual attention only in women (35). Additionally, women tend to focus more on low-calorie, low-fat foods (36, 37) but are more likely to consume sweet snacks when experiencing stress (38), whereas men generally pay more attention to both sweet and savory high-calorie foods (37). In this study, the predominance of high-calorie food images could partly explain the observed gender difference. While placebo-induced satiety may reduce selective attention to high-calorie foods

TABLE 3 Pearson correlation coefficients between $\Delta M_{congruent}$ and $\Delta M_{incongruent}$ (controlled for $M_{baseline}$) and behavioral ratings (ΔHunger, ΔSatiety, ΔFood craving, controlled for baseline levels), humoral measurements (ΔGhrelin, controlled for baseline levels), and general food craving.

	Women		Men	
	$\Delta M_{congruent}$	$\Delta M_{incongruent}$	$\Delta M_{congruent}$	$\Delta M_{incongruent}$
ΔHunger (VAS)	n=32 r = 0.075 p = 0.685	**n=32 r = 0.356 p = 0.046***	n=30 r = -0.136 p = 0.473	n=30 r = -0.262 p = 0.162
ΔSatiety (VAS)	n=32 r = 0.049 p = 0.790	n=32 r = -0.334 p = 0.062	n=30 r = 0.101 p = 0.595	n=30 r = 0.093 p = 0.626
ΔFood craving (FCQ-S)	n=32 r = 0.052 p = 0.778	**n=32 r = 0.389 p = 0.028***	n=30 r = -0.084 p = 0.658	n=30 r = -0.236 p = 0.210
ΔGhrelin (pg/ml)	n=29 r = 0.296 p = 0.119	n=29 r = 0.127 p = 0.510	n=26 r = 0.193 p = 0.344	n=26 r = -0.048 p = 0.817
General food craving (FCQ-T)	n=32 r = 0.196 p = 0.282	n=32 r = 0.052 p = 0.778	n=30 r = 0.020 p = 0.915	n=30 r = -0.225 p = 0.231

VAS, Visual Analogue Scale; FCQ-S, Food Craving Questionnaire – State; FCQ-T, Food Craving Questionnaire – Trait; *p<0.05.
Bold values indicate significant p-values (p<0.05).

in women, it may not counteract men's naturally higher attention toward such foods.

The sex-specific pattern in attentional bias, despite similar reductions in satiety for both sexes, is also consistent with findings from placebo research. While men and women reported comparable placebo effects on visceral pain and nausea, their neurobiological correlates differed (39, 40). Specifically, the insular cortex showed varying activation patterns, with placebo effects in men involving neural down-regulation of the insular cortex and related interoceptive experiences, such as pain or nausea. Conversely, placebo effects in women were more closely associated with prefrontal cortex activity (40). According to a recent functional MRI study, placebo-induced satiety in women may result from altered perceptual attentional filtering, where the perceived tastiness of food becomes less relevant under decreased hunger conditions (19).

Contrary to our expectations and prior studies (11, 29), we did not observe an attentional bias for food cues in the enhanced appetite placebo group. The most likely explanation for this finding is that the appetite-enhancing placebo intervention did not successfully induce increased hunger in our study (22). Notably, significantly more participants believed they had received an active treatment in the satiety-enhancing intervention group, suggesting that the placebo intervention was more credible in this group than in the appetite-enhancing intervention group.

In our female participants, decreased selective attention to food cues was correlated with changes in hunger ratings and current food craving. A recent meta-analysis similarly provided evidence for a positive correlation between selective attention to food cues and both current food craving and subjective hunger (41). Notably, general food craving did not correlate with attentional bias for food cues, neither in previous research (42) nor in our study. In addition, the correlation of hunger and food cravings with $M_{\text{incongruent}}$ but not $M_{\text{congruent}}$ suggests that the altered attentional bias may result from enhanced orienting toward non-food stimuli rather than delayed disengagement from non-food stimuli.

In this study, we used a cue exposure duration of 100 ms, as prior studies on food attentional bias, especially when using the VPT, indicated this duration as beneficial (7, 29). Very short exposure durations (<250 ms) serve as subliminal exposures that appear to engage early attentional processes such as enhanced orienting. Support for this interpretation comes from an eye-tracking study showing that, in a fed state, normal-weight individuals tend to direct their initial gaze to the non-food picture, indicating an initial orienting response to the non-food stimulus (31). Furthermore, Potthoff and colleagues found a higher percentage of fixation on non-food images after placebo-induced satiety, pointing in a similar direction (33).

Contrary to our expectations, no correlation between the appetite-enhancing gut hormone ghrelin and attentional bias was detected. Notably, ghrelin levels remained unchanged in the enhanced satiety placebo group (22). These findings support the conclusion that placebo-induced satiation is not mediated by ghrelin. Rather, verbally induced expectations may lead to a top-down modulation of satiety that operates independently of humoral mechanisms. Further evidence for this interpretation comes from a recent study showing that, although expectations of increased satiety reduced calorie intake in subsequent meals and throughout the day, no effect on ghrelin levels was observed (20). However, further research should examine whether other peptides involved in appetite regulation, such as cholecystokinin, glucagon-like peptide 1, and peptide YY, may play a role in expectation-enhanced satiety (43).

Several limitations of this study should be noted. First, because we analyzed men and women separately, each group size was limited to 10 to 12 participants. Future studies may benefit from reducing the number of intervention groups or increasing the sample size. Second, this study examined only healthy, normal-weight participants. Including overweight or obese individuals would allow for investigation into whether placebo interventions can alter the dysregulated attentional processes associated with obesity (12). Third, we used expectancy manipulation, rather than conditioning, to induce placebo effects on satiety and appetite. Conditioning, which is known to engage unconscious processes and produce longer-lasting placebo responses (44, 45), could be advantageous for addressing long-term outcomes such as body weight.

We propose three key areas for further research. First, the potential of deregulating visual attention as a therapeutic tool should be explored for individuals with overweight and obesity. Ideally, this research would integrate multimodal strategies that combine approaches to achieve rapid and sustainable weight loss, ultimately reducing cardiovascular risk. Second, future longitudinal studies could use conditioning to generate longer-lasting placebo effects. Notably, a recent study using an expectancy-based placebo application demonstrated a decrease in appetite only during the first two days of a seven-day follow-up period (46). Third, the neurobiological mechanisms underlying placebo-induced satiety and the subsequent reduction in selective attention to food cues, as well as potential sex-specific differences, warrant further investigation. In this context, functional MRI could be a promising tool, especially for examining the involvement of the brain's reward system, which plays a crucial role in food-related behaviors and can override physiological appetite control (47).

In conclusion, the results of the present study demonstrate that placebo-induced satiety inhibits attention allocation toward food cues in healthy women, presumably mediated by decreased subjective hunger and food craving. Attention allocation, as a largely unconscious process, verifies the placebo effect on satiety also at an objective level. Our findings align with growing evidence that placebo interventions, particularly those utilizing expectancy effects, can significantly influence food craving and related behaviors. Rodríguez-Martín and colleagues (48) demonstrated that expectancy-based placebo interventions were effective in controlling food craving and intrusive food-related thoughts over time. This suggests that cognitive factors, such as the belief in a treatment's efficacy, may modulate attention to and desire for food independently of physiological hunger signals. In our study, similar top-down processes likely contributed to the observed placebo effects on attentional bias and satiety in women. These findings support the potential of placebo-based cognitive interventions not only in normal-weight individuals but also as a feasible adjunct for managing food craving in overweight and obese populations, offering a promising avenue for further research on placebo-induced modulation of eating behavior.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by ethics committee of the Medical Faculty, Ludwig-Maximilians-University Munich, Germany. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ML: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. VH: Conceptualization, Investigation, Methodology, Writing – review & editing. KM: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Effects of mind–body exercise on physical ability, mental health and quality of life in stroke patients: a systematic review and meta-analysis

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Purpose: To systematically evaluate the effects of mind–body exercise on physical ability, mental health and quality of life in stroke patients.

Methods: According to the PRISMA statement, we searched Web of science, Pubmed, Embase, Sinomed, CNKI, Wanfang, and VIP databases to collect randomized controlled trials on the effects of mind–body exercise on improving balance function, motor capacity, walking function, depression and quality of life in stroke patients. The search was conducted in January 2024. Review Manager5.3 was used for statistical analysis of the data.

Results: A total of 33 randomized controlled trials with a total of 1985 participants were included. The results of meta-analysis showed: Mind–body exercise had a significantly effect on balance ability [MD = 5.64, 95%CI = 4.17, 7.11, $p < 0.00001$], upper limb motor ability [MD = 6.98, 95%CI = 1.96, 12.01, $p = 0.006 < 0.01$], lower limb exercise capacity [MD = 3.55, 95% CI = 0.31, 6.78, $p = 0.03 < 0.05$], exercise capacity [MD = 7.24, 95% CI = 4.36, 10.12, $p < 0.00001$], depression [MD = –3.28, 95%CI = –3.86, –2.69, $p < 0.00001$] and quality of life [MD = 10.62, 95%CI = 5.17, 16.06, $p = 0.0001 < 0.01$]. However, mind–body exercise did not affect walking ability [MD = –1.82, 95%CI = –4.20, 0.57, $p = 0.14 > 0.05$]. The results of subgroup analysis showed: Qigong (Baduanjin) exercise for more than four weeks, 6–10 times a week, 15–40 min each time can significantly improve balance function and quality of life in stroke patients.

Conclusion: Mind–body exercise can be used as a supplement therapy to conventional rehabilitation therapy, which is not only low intensity, high safety, but also because it is not limited to the site, can be accepted by most people and accelerate the rehabilitation process of stroke.

KEYWORDS

mind–body exercise, Tai Chi, Qigong, yoga, balance ability, quality of life, meta

1 Introduction

Stroke, also known as cerebrovascular disease, refers to insufficient blood supply or bleeding in specific areas of the brain. In most cases, it can lead to cell death, functional impairment, and impaired neurological function that reflects the location and size of brain regions (1). It has become a global health challenge. Although there are great geographical differences in the epidemiological statistics of stroke, its significant characteristics include high incidence rate, morbidity, mortality and disability rates, among which the incidence of low - and middle-income countries, especially Eastern Europe and Sub Saharan Africa, is the highest (2). According to the 2019 Global Burden of Disease Study (3), stroke remains the second leading cause of death and the third leading cause of death and disability worldwide. Stroke is often accompanied by hemiplegia, depression, motor disorders, cognitive impairment, and other sequelae, which seriously affect an individual's physical function, mental health, and quality of life.

Aerobic exercise is considered a key component of stroke rehabilitation (4). There is evidence to suggest that aerobic training is a safe intervention that can not only increase the recruitment of exercise units in stroke patients, prevent muscle atrophy, and improve their exercise ability; It can also increase the maximum oxygen uptake level of stroke patients and reduce cardiovascular risk (5, 6). In addition, resistance exercise is also considered a safe and effective tool to support post stroke recovery, which can improve upper and lower limb muscle strength, motor function, and quality of life in stroke patients (7). These exercises are all based on physical training aimed at changing the patient's physical function. However, stroke patients also have psychological health issues, such as anxiety, depression, and sleep problems (8). About one third of patients suffer from depression after stroke, and the incidence rate of PSD in the past 2 years is between 11 and 41% (9). Therefore, we should not only focus on the physical impact of stroke patients, but also emphasize their mental recovery.

Mind–body exercise is a multifaceted form of physical activity that combines exercise sequences, respiratory control, and attention regulation (10). The characteristics of this form of exercise are deliberate slow movements, symmetrical postures, stretching and relaxation of muscles and bones, controlled breathing, and mental focus (11). It is worth noting that Tai Chi, yoga, and qigong are widely recognized as the most popular ways of mind–body exercise (12). The study by Zou et al. (11) showed that mind–body exercise has a significant impact on depression, daily living activities, and mobility in stroke patients, but has no positive impact on sleep quality. Su et al.'s research shows that three mind–body exercises, Tai Chi, Qigong, and yoga, can significantly improve the quality of life of patients. Among them, Tai Chi has shown the most comprehensive improvement in balance, limb movement function, daily life activities, and depression (13). Chen et al.'s research suggests that mind–body exercise can have a beneficial impact on balance ability in the short term (14). The above evidence indicates that mind–body exercise can not only improve the physical function of stroke patients, but also have a certain impact on their mental health.

At present, there are few literature reviews on the impact of mind–body on stroke patients, and there is a lack of recommendations for exercise prescriptions. In this study, Tai Chi, Qigong (Baduanjin) and yoga were included as mind–body exercise interventions. This article will conduct a meta-analysis to consolidate existing evidence and elucidate the rehabilitation effects of mind–body exercise on the physical function, mental health, and daily activities of stroke patients, with the aim of conducting a relatively comprehensive study on its outcome indicators. In addition, by studying the effects of different intervention methods, durations, cycles, and frequencies on patient balance function, relevant exercise prescriptions are formulated to lay a theoretical foundation for enhancing balance function in stroke patients in clinical settings.

2 Research methods

2.1 Literature search strategy

Under the guidance of PRISMA guidelines, the study was conducted using various databases including Web of Science, PubMed, Embase, Cochrane Library, CNKI, Wanfang, and VIP. The search was focused on journal articles, with the search period ending on January 26, 2024. Chinese search terms included "mind–body exercise," "Tai chi," "Qigong," "yoga," "Baduanjin" and "stroke." English search terms include: "mind–body exercise," "Tai Chi," "Taiji," "Qigong," "Baduanjin," "Yoga," "Stroke," "Cerebrovascular Accident," "CVA," "Cerebrovascular Apoplexy," "Brain Vascular Accident," "Cerebrovascular Stroke," "Apoplexy," "Cerebral Stroke," "Acute Stroke," "Acute Cerebrovascular Accident" et al. The language of the included studies were limited to English and Chinese. The search strategies used in this study for Web of Science is presented in Supplementary Table 1.

2.2 Eligibility criteria

2.2.1 Types of studies

In this review, the types of studies included are parallel controls in randomized controlled trials (RCTs). Cross design or other types will be excluded. In addition, the participants, interventions, controls, outcome indicators, etc. of the study must meet the following requirements.

2.2.2 Types of participants

The age of the participants is ≥18 years old, meeting the diagnostic criteria for stroke, and has been confirmed by CT or MRI. In the stage of stroke recovery. The participants were conscious, and had no cognitive dysfunction. Participants with severe sequelae, such as mobility impairments, were excluded.

2.2.3 Types of interventions

In this review, we consider "mind–body exercise" as an intervention method for stroke patients, including Tai Chi, Qigong (Baduanjin), and yoga. The experimental group can only involve one type of mind–body exercise, and mixed exercise will be excluded.

2.2.4 Types of comparators

In this review, we first excluded studies without control groups. In the control group, routine care, traditional rehabilitation training (balance function training, walking ability training, et al) and stretching will be retained. For example, a control group with tai chi or resistance exercise will be excluded.

2.2.5 Types of outcomes measures

The results reported from each embedded RCT included at least one of the following outcomes:

1. Balance ability: Berg Balance Scale (BBS).
2. Motor ability: Motor Function Scale (Fugl-Meyer, FMA).
3. Walking ability: Timed Up-and-go Test (TUGT).
4. Mental health: Hamilton Depression Scale (HAMD).

5. Quality of life: Barthel Index Rating Scale (BI), Modified Barthel Index Rating Scale (MBI).

2.3 Literature management and data extraction

Document management using Endnote X20. Two reviewers (JC and EL) independently screened the titles and abstracts of the citations retrieved from seven electronic databases, removed duplicates, and identified eligible randomized controlled trials based on inclusion criteria. After reading the full text of the above qualified literature, the final included literature can be determined after exclusion. Two reviewers work together to resolve differences. If the discrepancy persists, a third reviewer (JD) will be invited to adjudicate.

The basic data were extracted from the included literature. The contents of literature extraction include: (1) Author and publication year; (2) Gender of subjects and sample size; (3) Age of the subject; (4) Intervention measures in the experimental group (time, frequency and method); and (5) Outcome indicators.

2.4 Literature bias risk assessment

Based on the Cochrane risk Bias assessment tool (15), Review Manager 5.3 software was used to conduct the assessment. The quality of the included literature was evaluated on six indicators, including random allocation scheme, allocation scheme hiding, blind method, outcome data integrity, selective reporting of research results, and other biases. At the same time, PEDro scale (16) was used to evaluate the quality of the included studies, which included 11 items: the first item did not score, and each other item scored 1, a total of 10 points. A score of 3 and below is considered low quality, 4–5 is medium quality, 6–8 is high quality, and 9–10 is very high quality.

2.5 Statistical analysis

In this study, Review Manager5.3 software was used for analysis. Since the outcome indicators of the included literatures were continuous variables with the same measurement unit, mean difference (MD) and 95% confidence interval (CI) were used as the effect scale for analysis. The purpose of the meta-analysis was to derive the average effect size from different studies (17). In statistics, p-values are based on tests of significance, it is the probability that the event will happen by chance if the null hypothesis is true. The p-value is a number between 0 and 1 that the researcher interprets when deciding whether to reject or retain the null hypothesis (18). When $p < 0.01$, the result is highly significant. When $0.01 \le p < 0.05$, there was a significant difference between the experimental group and the control group, and the results of meta-analysis were statistically significant. Q test is often used to evaluate heterogeneity. When $p > 0.1$, it indicates no heterogeneity (19). The variance can be used to describe the extent of variability in effect across studies (19, 20), it ranges from 0 to 100%. The Cochrane Handbook provides a rough yet widely used rule to interpret this measure: $I^2 \le 40\%$ may indicate unimportant heterogeneity, $30\% \le I^2 \le 60\%$ may represent moderate heterogeneity, $50\% \le I^2 \le 90\%$ may represent substantial heterogeneity, and $75\% \le I^2 \le 100\%$ implies considerable heterogeneity (21). When there is heterogeneity among the included studies, in which case, the random effects model was used for meta-analysis, and sensitivity analysis and subgroup analysis were performed to determine the source of heterogeneity. Funnel plot was used to analyze publication bias. This study mainly discusses the rehabilitation effect of different mind–body exercises on stroke patients.

3 Results

3.1 Literature search results

Through the search of various databases, a total of 1799 articles were obtained. After importing the literature management software Endnote 20 to remove duplicate literatures, a total of 958 literatures were included. After reading the titles and abstracts of the literatures, 873 irrelevant literatures were excluded and 85 were left after preliminary screening. After further reading the full text, a total of 32 (22–54) RCT literatures were included in the meta-analysis. Furthermore, an additional literature was acquired through alternative methods, and a total of 33 literatures were ultimately included (Figure 1).

3.2 Basic features of the included literature

The basic characteristics of the included literatures are shown in Tables 1, 2. A total of 33 literatures (22–54) were included, including 1985 stroke patients, including 1,019 patients in the experimental group and 966 patients in the control group. Published from 2009 to 2024. A total of three mind–body exercises are involved, including 16 items of Tai Chi (22, 23, 27, 28, 30–34, 36, 38, 42, 44, 46, 49, 52), 15 items of Qigong (Baduanjin) (24, 25, 35, 37, 39–41, 43, 44, 47, 48, 50, 51, 53, 54) and 2 items of Yoga (26, 29).

There was no statistical difference in the comparison of general data between the experimental group and the control group in each RCTS, which was comparable. There was no statistical difference in the comparison of general data between the experimental group and the control group in each RCTS, which was comparable.

3.3 Quality assessment of included literature

In the analysis of 33 studies (22–54), all studies reported the baseline condition of patients. Among them, 4 studies (22, 29, 46, 48) utilized computer randomization and were evaluated as low risk. Additionally, 16 studies (24, 25, 31, 36, 39–45, 47, 49, 51–54) employed the random number table method and were also evaluated as low risk. One study (23) randomized participants based on discharge order, while another study (33) used randomization according to sex, age, and lesion type. The remaining studies mentioned randomization without specifying the method. Only a study (44) mentioned single blindness. Only one study (48) reported allocation concealment and was evaluated as low risk in this aspect. Similarly, only one study (41) blinded outcome evaluators and was considered low risk in this regard. All studies had complete outcome data, and explanations for any lost follow-up or withdrawals were

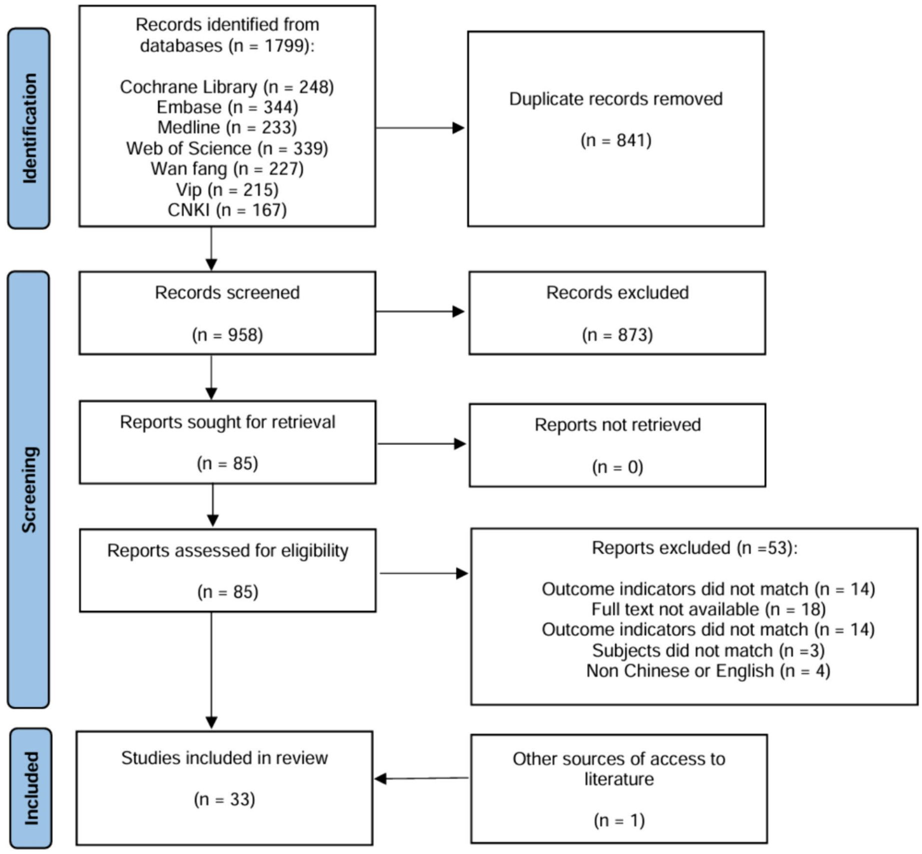

FIGURE 1
Screening diagram of included references.

provided, without impacting the outcomes, leading to them being evaluated as low risk. None of the studies exhibited selective reporting of results (Table 3 and Figure 2).

The PEDro scores of the included studies ranged from 6 to 8 points, indicating that these studies were of high quality.

3.4 Results of meta-analysis

3.4.1 Influence of mind–body exercise on balance ability of stroke patients (BBS index)

Among the included literatures, a total of 21 literatures (22–24, 26–29, 31, 33, 35, 39, 41–45, 47, 48, 52, 53) reported the effects of mind–body exercise on the balance ability of stroke patients, involving a total of 1,267 stroke patients. The results of meta-analysis (Figure 3) showed that the total effect size and 95%CI of the combined study were 5.64 [4.17, 7.11], $p < 0.00001$. The results showed that the balance ability increased significantly after exercise intervention, which was significantly different from the control group. Heterogeneity test ($I^2 = 87\%$), $I^2 > 75\%$ indicated significant heterogeneity. A random effects model was selected for meta-analysis, and the source of heterogeneity was explored.

In order to explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the index of balance ability. The results of meta-analysis showed that there was little difference in heterogeneity among all studies, the exclusion of one article had little impact on the index of balance ability, and the results of meta-analysis were stable. The traditional funnel plot was used to test publication bias, and the funnel plot could form a good left–right symmetric distribution without significant publication bias (Figure 4).

In order to further explore the sources of heterogeneity, subgroup analysis was conducted from four aspects: intervention mode, intervention cycle, intervention frequency, and intervention time (Table 4). In terms of intervention methods, Qigong (Baduanjin) has a significant effect on improving the balance function of stroke patients; In terms of intervention cycle, intervention for >4 weeks had a significant effect on improving the balance function of stroke patients; In terms of intervention time, 15–40 min of intervention has a significant effect on improving the balance function of stroke patients. In terms of intervention frequency, 6–10 interventions per week have a significant effect on improving balance function in stroke patients.

3.4.2 Effects of mind–body exercise on motor ability of stroke patients (FMA index)

Among the included literatures, a total of 16 literatures (21 research reports) (31, 35–38, 41–46, 48–53) reported the impact of mind–body exercise on the motor ability of stroke patients, involving a total of 1,120 stroke patients.

TABLE 1 Summary of the included studies.

Author and year	Country	Total simple	M/F	Age (EG/CG)	Course of disease (EG/CG)
Au-Yeung 2009 (22)	Hong Kong	114	66/48	61.7 ± 10.5/65.9 ± 10.7	>6mon
Liu 2009 (23)	China	48	25/23	52.13 ± 14.13/53.51 ± 12.63	17.65 ± 5.34d/18.73 ± 8.78d
Bai 2011 (24)	China	60	42/18	53.7 ± 4.5/51.3 ± 7.5	43.2 ± 6.53d/38.5 ± 6.12d
Cai 2011 (25)	China	60	43/17	60.27 ± 10.48/61.27 ± 7.42	≥6mon
Schmid 2012 (26)	USA	47	30/28	63.9 ± 8.7/60.2 ± 8.9	>6mon
Yang 2013 (27)	China	100	66/34	54.3 ± 13.8/55.2 ± 14.6	26–63d
Xv 2014 (28)	China	80	38/42	60.14 ± 10.25/48.23 ± 12.32	47.34 ± 22.56d/45.21 ± 25.42d
Immink 2014 (29)	South Australia	22	9/13	56.1 ± 13.6/63.2 ± 17.4	81.6 ± 77.5 m/23.3 ± 12.5 m
Zheng 2015 (30)	China	106	58/48	59 ± 13/60 ± 12	First or multiple
Zhou 2015 (31)	China	22	Unknown	35–70	<6mon
Kim 2015 (32)	Korea	22	13/9	53.45 ± 11.54/55.18 ± 10.20	Unknown
Fu 2016 (33)	China	60	37/23	59.7 ± 7.6/60.3 ± 8.4	≤3mon
Yang 2016 (34)	China	60	41/19	60.71 ± 7.32/58.56 ± 8.52	First
Tian 2017 (35)	China	60	36/24	54.3 ± 4.7/53 ± 4.3	Unknown
Zhao 2017 (36)	China	60	39/21	53.85 ± 11.69/51.38 ± 14.83	First, steady within 1w
Cui 2018 (37)	China	43	27/16	53.67 ± 12.98/55.33 ± 14.32	47.32 ± 16.83d/45.84 ± 14.12d
Li 2018 (38)	China	60	33/27	71.03 ± 8.21/71.06 ± 8.33	110.7 ± 13.69d/102.60 ± 13.8d
Ding 2019 (39)	China	113	64/49	55.37 ± 4.71/56.32 ± 3.17	6.72 ± 2.36w/7.11 ± 1.59w
Wei 2019 (40)	China	80	38/42	56.1 ± 9.2/58.7 ± 10.3	15.4 ± 3.3mon/13.0 ± 2.3mon
Xie 2019 (41)	China	40	25/15	51.10 ± 12.92/53.95 ± 13.00	3.2 ± 1.44mon/3.60 ± 1.57mon
Zhang 2020 (42)	China	60	33/27	68.5 ± 9.4/65.5 ± 10.1	80.3 ± 30.4d/76.6 ± 31.9d
Liu 2021 (43)	China	60	21/39	57.58 ± 5.71/56.85 ± 7.47	15.42 ± 5.65w/15.61 ± 6.11w
Song 2021 (44)	Korea	34	21/13	58.72 ± 17.13/57.18 ± 10.65	7.58 ± 5.98/10.94 ± 8.50
Zhou 2021 (45)	China	70	42/28	69.1 ± 8.5/69.5 ± 8.3	1.91 ± 0.73mon/1.88 ± 0.84mon
He 2022 (46)	China	55	43/12	62.96 ± 8.98/62.50 ± 10.73	Unknown
Ji 2022 (47)	China	90	55/35	69.32 ± 5.94/68.42 ± 6.85	49.36 ± 7.48d/48.92 ± 6.37d
Liu 2022 (48)	China	43	27/16	59.19 ± 4.69/57.73 ± 5.55	8.08 ± 2.99w/9.07 ± 3.61w
Tang 2022 (49)	China	67	41/26	54.9 ± 13.1/56.5 ± 11.2	36.9 ± 12.2d/38.4 ± 10.8d
Chen 2023 (50)	China	80	50/30	62.33 ± 6.58/62.41 ± 6.63	12.28 ± 2.56mon/12.30 ± 2.66mon
Tang 2023 (51)	China	60	35/25	57.18 ± 7.71/57.14 ± 7.68	4.16 ± 1.65mon/4.13 ± 1.32mon
Wang 2023 (52)	China	17	13/4	49.11 ± 11.85/52.88 ± 11.79	67.22 ± 33.55d/52.50 ± 36.50d
Wang 2023 (53)	China	60	40/20	62.96 ± 6.18/62.94 ± 6.17	8.20 ± 3.66w/8.17 ± 3.65w
Chen 2024 (54)	China	42	34/8	52.86 ± 14.84/54.14 ± 12.30	210.57 ± 398.09d/183.67 ± 234.44d

M, Male; F, Female; EG, Experimental group; CG, Control group; d, day; w, week; mon, month.

3.4.2.1 Upper limb motor function (FMA-UE index)

Six studies reported the effects of mind–body exercise on upper limb motor ability in stroke patients. The results of meta-analysis (Figure 5A) showed that the total effect size and 95%CI of the combined study were 6.98 [1.96, 12.01], $p = 0.006 < 0.01$. The results showed that the exercise ability increased significantly after the intervention, and there was a significant difference compared with the control group. Heterogeneity test ($I^2 = 96\%$), $I^2 > 75\%$ indicated significant heterogeneity. A random effects model was selected for meta-analysis, and the source of heterogeneity was explored.

To explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the indicators of motor ability. The study showed that after the article by Cui et al. (37) was excluded, the heterogeneity was significantly reduced ($I^2 = 78\%$), that mean, Cui et al. (37) was the source of heterogeneity of the influence of mind–body exercise on the upper limb motor ability of stroke patients.

3.4.2.2 Lower limb motor function (FMA-LE index)

Among them, 6 studies reported the effects of mind–body exercise on lower limb motor ability of stroke patients. The results of meta-analysis (Figure 5B) showed that the total effect size and 95%CI of the combined study were 3.55 [0.31, 6.78], $p = 0.03 < 0.05$. The results

TABLE 2 Experimental protocols and outcomes of the included studies.

Author and year	N/n	M/F	Intervention measure				Instructor	Location	Outcome index	Mark
			Mode	Cycle	Time	Frequency				
Au-Yeung 2009 (22)	E:59	33/26	Tai Chi	12w	1 h (3 h self-exercise)	1/w	Therapist	Community or Day care centers.	BBS TUGT	7
	C:55	33/22	Breathing and stretching exercises							
Liu 2009 (23)	E:24	14/10	Tai Chi	12w	30 min	7/w	Therapist	Home	BBS	6
	C:24	11/13	Routine rehabilitation training							
Bai 2011 (24)	E:30	20/10	Qigong (Baduanjin)	6w	20 min	14/w	Therapist	Hospital	BBS	7
	C:30	22/8	Balance function training							
Cai 2011 (25)	E:30	20/10	Qigong (Baduanjin)	12w	30 min	4-5/w	Nurse	Community	BI	7
	C:30	23/7	General health guidance							
Schmid 2012 (26)	E:37	20/22	Yoga	8w	1 h	16/w	Therapist	Home	BBS	7
	C:10	10/6	Routine care							
Yang 2013 (27)	E:50	35/15	Tai Chi	4w	45 min	6/w	Therapist	Hospital	BBS BI	7
	C:50	31/19	Balance function training							
Xv 2014 (28)	E:40	22/18	Tai Chi	12w	20 min	14/w	Therapist	Hospital	BBS	7
	C:40	16/24	Balance function training							
Immink 2014 (29)	E:11	6/5	Yoga	10w	90 min × 1 + 40 min × 6	7/w	Yoga teacher	Home	BBS	7
	C:11	3/8	Routine rehabilitation training							
Zheng2015 (30)	E:51	27/24	Tai Chi	48w	30 min	14/w	Therapist	Hospital	HAMD	7
	C:55	31/24	Routine rehabilitation training							
Zhou 2015 (31)	E:11		Tai Chi	4w	1 h	5/w	Therapist	Hospital	BBS FMA	7
	C:11		Routine rehabilitation training							
Kim 2015 (32)	E:11	7/4	Tai Chi	6w	1 h	2/w	Researcher	Hospital	TUGT	7
	C:11	6/5	General physical therapy							
Fu 2016 (33)	E:30	19/11	Tai Chi	8w	40 min	6/w	Therapist	Hospital	BBS	6
	C:30	18/12	Routine rehabilitation training							
Yang 2016 (34)	E:30	20/10	Tai Chi	8w	15 min	1/w	Therapist	Hospital	BI	7
	C:30	21/9	Walking ability training							

(Continued)

TABLE 2 (Continued)

Author and year	N/n	M/F	Intervention measure				Instructor	Location	Outcome index	Mark
			Mode	Cycle	Time	Frequency				
Tian 2017 (35)	E:30	17/13	Qigong (Baduanjin)	14w	30–40 min	2/w	Therapist	Hospital	BBS FMA	7
	C:30	19/11	Conventional treatment							
Zhao 2017 (36)	E:30	20/10	Tai Chi	8w	30 min	5/w	Therapist	Hospital	FMA HAMD BI	7
	C:30	19/11	Conventional treatment							
Cui 2018 (37)	E:24	15/9	Qigong (Baduanjin)	8w	45 min	3/w	Therapist	Hospital	FMA	7
	C:19	12/7	Conventional treatment							
Li 2018 (38)	E:30	17/13	Tai Chi	12w	1 h	7/w	Therapist	Hospital	FMA HAMD	7
	C:30	16/14	Drug therapy							
Ding 2019 (39)	E:57	33/24	Qigong (Baduanjin)	4w	20 min	10/w	Therapist	Hospital	BBS	7
	C:56	31/25	Balance function training							
Wei 2019 (40)	E:40	17/23	Qigong (Baduanjin)	6w	30 min	5/w	Therapist	Hospital	MBI	7
	C:40	21/19	Conventional treatment							
Xie 2019 (41)	E:20	13/7	Qigong (Baduanjin)	3w	50 min	3/w	Therapist	Hospital	BBS FMA BI	8
	C:20	12/8	General physical therapy							
Zhang 2020 (42)	E:30	17/13	Tai Chi	4w	20 min	14/w	Therapist	Hospital	BBS FMA	7
	C:30	16/14	Routine rehabilitation training							
Liu 2021 (43)	E:30	11/19	Qigong (Baduanjin)	4w	45 min	3/w	Therapist	Hospital	BBS FMA HAMD	7
	C:30	10/20	Drug therapy							
Song 2021 (44)	E:18	10/8	Tai Chi	24w	50 min	2/w	Tai chi instructor	Hospital	BBS	7
	C:16	11/5	Symptom management plan							

(Continued)

TABLE 2 (Continued)

Author and year	N/n	M/F	Intervention measure				Instructor	Location	Outcome index	Mark
			Mode	Cycle	Time	Frequency				
Zhou 2021 (45)	E:35	20/15	Qigong (Baduanjin)	12w	30 min	14/w	Therapist	Hospital	BBS FMA	7
	C:35	22/13	Routine rehabilitation training							
He 2022 (46)	E:29	23/6	Tai Chi	4w	40 min	4/w	Therapist	Hospital	BBS FMA	7
	C:26	20/6	Conventional treatment							
Ji 2022 (47)	E:45	26/19	Qigong (Baduanjin)	8w	15 min	6/w	Therapist	Hospital	FMA	7
	C:45	29/16	Routine rehabilitation training							
Liu 2022 (48)	E:21	14/7	Qigong (Baduanjin)	4w	30 min	12/w	Therapist	Hospital	BBS TUGT	8
	C:22	13/9	Conventional treatment							
Tang 2022 (49)	E:33	21/12	Tai Chi	8w	15 min	6/w	Therapist	Hospital	BBS FMA TUGT MBI	7
	C:34	20/14	Conventional treatment							
Chen 2023 (50)	E:40	24/16	Qigong (Baduanjin)	24w	40 min	6-10/w	Therapist	Hospital	FMA MBI	7
	C:40	26/14	Routine rehabilitation training							
Tang 2023 (51)	E:30	17/13	Qigong (Baduanjin)	8w	15 min	6/w	Therapist	Hospital	FMA HAMD	7
	C:30	18/12	Drug therapy							
Wang 2023 (52)	E:9	7/2	Tai Chi	4w	30 min	7/w	Therapist	Hospital	FMA MBI	7
	C:8	6/2	Conventional treatment							
Wang 2023 (53)	E:30	20/10	Qigong (Baduanjin)	4w	20 min	6/w	Therapist	Hospital	BBS FMA	7
	C:30	20/10	Conventional treatment							
Chen 2024 (54)	E:21	17/4	Qigong (Baduanjin)	4w	45 min	6/w	Therapist	Hospital	BBS FMA MBI	7
	C:21	17/4	Routine rehabilitation training							

BBS, Berg Balance Scale; FMA, Fugl-Meyer; TUGT, Timed Up-and-go Test; HAMD, Hamilton Depression Scale; BI, Barthel Index Rating Scale; MBI, Modified Barthel Index Rating Scale.

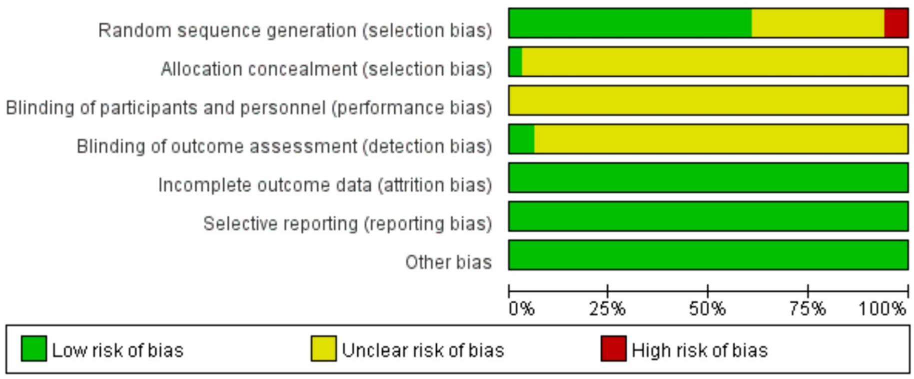

FIGURE 2
Risk shift diagram.

showed that the exercise ability increased after the mind–body exercise intervention, and there was a significant difference compared with the control group. Heterogeneity test (I^2 = 96%), I^2 > 75% indicated significant heterogeneity. A random effects model was selected for meta-analysis, and the source of heterogeneity was explored.

To explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the indicators of motor ability. The study showed that after the article by Cui et al. (32) was excluded, the heterogeneity was reduced (I^2 = 84%), that is, Cui et al. (32) was the source of heterogeneity of the influence of mind–body exercise on lower limb motor ability of stroke patients.

3.4.2.3 Motion function (FMA index)

Among them, 9 studies reported the effect of mind–body exercise on the overall motor ability of stroke patients. The results of meta-analysis (Figure 5C) showed that the total effect size and 95%CI of the combined study were 7.24 [4.36, 10.12], $p < 0.00001$. The results showed that the exercise ability increased significantly after the intervention, and there was a significant difference compared with the control group. Heterogeneity test (I^2 = 91%), I^2 > 75% indicated significant heterogeneity. A random effects model was selected for meta-analysis, and the source of heterogeneity was explored.

To explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the indicators of motor ability. Studies have shown that there is little difference in heterogeneity among different studies, and the exclusion of a certain article has little effect on the overall motor ability of stroke patients.

3.4.3 Influence of mind–body exercise on walking ability of stroke patients (TUGT index)

Among the included literatures, a total of 4 literatures (22, 32, 47, 48) reported the effects of physical and mental exercise on walking ability of stroke patients, involving a total of 248 stroke patients. The results of meta-analysis (Figure 6) showed that the total effect size and 95%CI of the combined study were − 1.82 [−4.20, 0.57], $p = 0.14$. The results showed that the walking ability was improved after exercise intervention, but there was no significant difference compared with the control group. Heterogeneity test (I^2 = 35%), I^2 < 40% indicates that the heterogeneity is small, the fixed effect model was selected for meta-analysis, and the source of heterogeneity was explored.

In order to explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the index of balance ability. Studies have shown that after the article by Liu et al. (47) was excluded, the heterogeneity was significantly reduced (I^2 = 0%), that mean, Liu et al. (47) was the main source of heterogeneity in the impact of mind–body exercise on the walking ability of stroke patients.

3.4.4 Effects of mind–body exercise on depression in stroke patients (HAMD index)

Among the included literatures, a total of 5 literatures (30, 36, 38, 43, 50) reported the effects of mind–body exercise on post-stroke depression, involving a total of 346 stroke patients. The results of meta-analysis (Figure 7) showed that the total effect size and 95%CI of the combined study were −3.28 [−3.86, −2.69], $p < 0.00001$. The results showed that depressive mood improved significantly after exercise intervention, and there was a significant difference compared with the control group. Heterogeneity test (I^2 = 35%), I^2 < 40% indicates that the heterogeneity is small, the fixed effect model was selected for meta-analysis, and the source of heterogeneity was explored.

In order to explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the index of balance ability. The study showed that after removing the article of Zheng et al. (30), the heterogeneity was significantly reduced (I^2 = 0%), that mean, Zheng et al. (30) was the main source of heterogeneity in the influence of mind–body exercise on depression in stroke patients.

3.4.5 Effects of mind–body exercise on quality of life of stroke patients (MBI, BI index)

Among the included studies, a total of 10 articles (25, 27, 34, 36, 40, 41, 48, 49, 51, 53) reported the effects of mind–body exercise on the quality of life of stroke patients. The results of meta-analysis (Figure 8) showed that the total effect size and 95%CI of the combined study were 10.62 [5.17, 16.06], $p = 0.0001 < 0.01$. The results showed that the quality of life increased significantly after the mind–body exercise intervention, and there was a significant difference compared with the control group. Heterogeneity test (I^2 = 98%), I^2 > 75% indicated

TABLE 3 Literature quality evaluation.

Author and year	A	B	C	D	E	F	G
Au-Yeung 2009 (22)	Computer randomization	Unknown	Unknown	Unknown	Low	Low	Low
Liu 2009 (23)	Random according to discharge order	Unknown	Unknown	Unknown	Low	Low	Low
Bai 2011 (24)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Cai 2011 (25)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Schmid 2012 (26)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Yang 2013 (27)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Xv 2014 (28)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Immink 2014 (29)	Computer randomization	Unknown	Unknown	Unknown	Low	Low	Low
Zheng 2015 (30)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Zhou 2015 (31)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Kim 2015 (32)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Fu 2016 (33)	Random according to sex, age and lesion type	Unknown	Unknown	Unknown	Low	Low	Low
Yang 2016 (34)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Tian 2017 (35)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Zhao 2017 (36)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Cui 2018 (37)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Li 2018 (38)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Ding 2019 (39)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Wei 2019 (40)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Xie 2019 (41)	Random number table method	Unknown	Unknown	Blind	Low	Low	Low
Zhang 2020 (42)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Liu 2021 (43)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Song 2021 (44)	Random number table method	Unknown	Single blind	Unknown	Low	Low	Low
Zhou 2021 (45)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
He 2022 (46)	Computer randomization	Unknown	Unknown	Unknown	Low	Low	Low
Ji 2022 (47)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Liu 2022 (48)	Computer randomization	An opaque envelope	Unknown	Unknown	Low	Low	Low
Tang 2022 (49)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Chen 2023 (50)	Random	Unknown	Unknown	Unknown	Low	Low	Low
Tang 2023 (51)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Wang 2023 (52)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Wang 2023 (53)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low
Chen 2024 (54)	Random number table method	Unknown	Unknown	Unknown	Low	Low	Low

A, Random sequence generation; B, Allocation hiding; C, Both subjects and interveners were blinded; D, Blind the outcome evaluators; E, Outcome indicator data integrity; F, Selective reporting of results; G, Other migration sources.

significant heterogeneity. A random effects model was selected for meta-analysis, and the source of heterogeneity was explored.

To explore the sources of heterogeneity, sensitivity analysis was used in the overall study to exclude the included studies one by one and assess the impact of each study on the indicators of motor ability. Studies have shown that there is little difference in heterogeneity among all studies, and the exclusion of a certain article has little impact on the quality of life of stroke patients. The results of meta-analysis are stable, and the traditional funnel plot is used to test publication bias, and the funnel plot can form a good left–right symmetric distribution, and there is no obvious publication bias (Figure 9).

In order to further explore the sources of heterogeneity, subgroup analysis was conducted from four aspects: intervention mode, intervention cycle, intervention frequency, and intervention time (Table 5). In terms of intervention methods, Qigong (Baduanjin) has a significant effect on improving the quality of life of stroke patients; In terms of intervention cycle, intervention for >4 weeks has a significant effect on improving the quality of life of stroke patients; In terms of intervention time, 15–40 min of intervention had a significant effect on improving the quality of life of stroke patients. In terms of intervention frequency, 6–10 interventions per week have a significant effect on improving the quality of life of stroke patients.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Au-Yeung 2009	46.9	5.1	59	45.2	7.2	55	5.5%	1.70 [-0.61, 4.01]
Bai 2011	48.61	5.67	30	35.38	4.82	30	5.3%	13.23 [10.57, 15.89]
Chen 2024	48.95	5.18	21	49.43	5.04	21	5.0%	-0.48 [-3.57, 2.61]
Ding 2019	53.25	5.74	20	47.8	9.77	20	3.7%	5.45 [0.48, 10.42]
Fu 2016	40.44	10.15	30	29.46	9.67	30	3.7%	10.98 [5.96, 16.00]
He 2022	48.17	4.591	29	45.23	6.562	26	5.0%	2.94 [-0.09, 5.97]
Immink 2014	50.7	6.3	11	48.5	8	11	3.1%	2.20 [-3.82, 8.22]
Liu 2009	48.55	8.67	24	34.5	8.55	24	3.8%	14.05 [9.18, 18.92]
Liu 2021	48.31	2.71	30	44.79	3.49	30	6.0%	3.52 [1.94, 5.10]
Liu 2022	22.86	2.78	23	19.32	2.56	23	6.0%	3.54 [2.00, 5.08]
Schmid 2012	46.3	9.1	37	43.8	6.3	10	3.8%	2.50 [-2.38, 7.38]
Song 2021	53.59	7.64	18	52.25	3.61	16	4.4%	1.34 [-2.61, 5.29]
Tang 2022	41.4	4.1	33	38.5	4.1	34	5.8%	2.90 [0.94, 4.86]
Tian 2017	37.28	5.31	29	26.15	4.86	28	5.3%	11.13 [8.49, 13.77]
Wang yizhi2023	50.14	6.54	30	40.14	3.79	30	5.3%	10.00 [7.30, 12.70]
Xie 2019	53.25	5.74	20	47.8	9.77	20	3.7%	5.45 [0.48, 10.42]
Xv 2014	43.53	1.34	40	36.42	1.28	40	6.4%	7.11 [6.54, 7.68]
Yang 2013	43.9	5.4	50	38.6	5.4	50	5.7%	5.30 [3.18, 7.42]
Zhang 2020	44.4	7.9	30	38.7	9.9	30	4.0%	5.70 [1.17, 10.23]
Zhou 2015	45.09	7.69	11	38.82	5.23	11	3.4%	6.27 [0.77, 11.77]
Zhou 2021	51.25	6.13	35	46.24	5.47	35	5.3%	5.01 [2.29, 7.73]
Total (95% CI)			**610**			**574**	**100.0%**	**5.64 [4.17, 7.11]**

Heterogeneity: Tau² = 8.74; Chi² = 152.39, df = 20 (P < 0.00001); I² = 87%
Test for overall effect: Z = 7.53 (P < 0.00001)

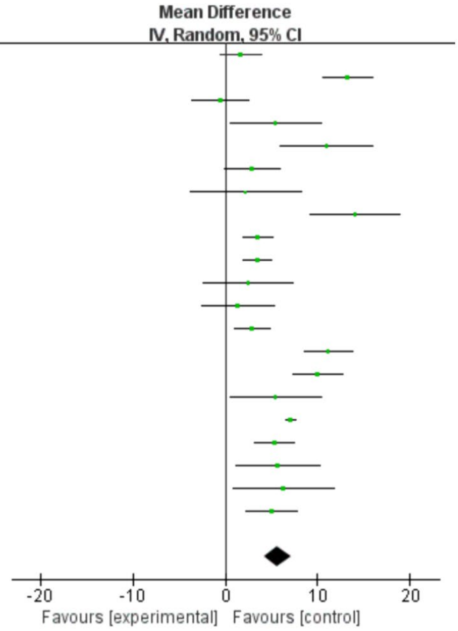

FIGURE 3
Effects of mind–body exercise on balance ability of stroke patients.

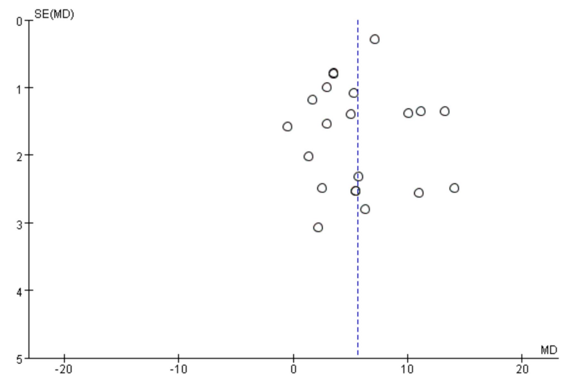

FIGURE 4
Funnel diagram of the influence of mind–body exercise on balance ability of stroke patients.

4 Discussion

Meta-analysis has become a key tool for promoting rapid scientific progress. Through the integration and comprehensive analysis of scientific results from multiple studies, the effectiveness of scientific research can be greatly improved (55).

In this meta-analysis, BBS, FMA, and TUGT were employed to evaluate the physical function changes in stroke patients, encompassing balance function, motor function, and walking ability. HAMD was utilized to assess the mental health aspect, specifically focusing on alleviating depression. The changes of life quality were evaluated using MBI and BI. These metrics collectively facilitated an in-depth exploration of the impact of mind–body exercise interventions on the physical function, mental health, and quality of life of stroke patients.

4.1 Influence of mind–body exercise on the physical function of stroke patients

Post-stroke, individuals commonly face hemiplegia, upper and lower limb dysfunction, and compromised balance and motor control, leading to reduced walking ability and unstable gait, potentially triggering fear of falling or depressive symptoms. The meta-analysis revealed significant enhancements in balance and motor function with mind–body exercise, although improvements in walking function were less pronounced. Combining mind–body exercise with conventional rehabilitation therapy effectively boosted BBS scores and balance abilities in stroke patients, aligning with prior research (11, 56). Subgroup analysis highlighted Qigong (Baduanjin) as a promising rehabilitation therapy for enhancing BBS scores and balance function. Baduanjin, a traditional Chinese fitness regimen, is universally applicable and not only enhances musculoskeletal and neuromuscular functions but also fosters mental relaxation and breathing control, promoting patient satisfaction and exercise adherence (11). Modern medical studies (57) demonstrate that Baduanjin, rooted in "breath regulation," enhances cortical function and the regulation mechanism of the cortical-ponto-cerebellar neural circuit, refining bodily movements and balance. Moreover, a duration of over 4 weeks of mind–body exercise was found to enhance patients' balance, consistent with the findings of Li et al. (58) and Tan et al. (59). Additionally, 15–40 min of exercise sessions 6–10 times a week significantly improved balance function.

The FMA score, a primary scale assessing limb motor ability post-stroke, demonstrated higher scores in the experimental group than the control group, indicating improved upper and lower limb motor function and overall motor performance with mind–body exercise, consistent with previous studies (60, 61). However, there was a high degree of heterogeneity in the included literature on limb motor ability, so it was necessary to exclude specific studies to reduce

TABLE 4 Subgroup analysis of effects of mind–body exercise on balance ability in stroke patients.

Influencing factor	Number of studies	MD [95%CI]	Heterogeneity	
			I^2 (%)	*p*-value
Mode				
Tai Chi	10	5.42 [3.40, 7.43]	85	<0.00001
Qigong (Baduanjin)	9	6.34 [3.53, 9.14]	91	<0.00001
Yoga	2	2.23 [−1.41, 6.17]	0	0.22
Cycle (w)				
≤4	10	4.59 [2.92, 6.26]	71	<0.00001
>4	11	6.56 [4.27, 8.85]	89	<0.00001
Time (min)				
15–40	12	7.44 [5.56, 9.32]	88	<0.00001
>40	9	2.99 [1.58, 4.41]	43	<0.0001
Frequency				
<6	9	3.76 [1.58, 5.94]	82	0.0007
6–10	6	8.06 [4.93, 11.20]	75	<0.00001
>10	6	6.37 [3.84, 8.90]	89	<0.00001

heterogeneity. After excluding the study by Cui et al. (32), heterogeneity remained high, which may be attributed to differences in study populations, interventions, and numbers.

The TUGT test, a rapid assessment of functional walking ability, showed that stroke patients who underwent mind–body exercise rehabilitation showed improved walking ability, but did not show statistically significant differences compared with conventional rehabilitation. Due to the limited number of literatures on this outcome indicator, it is not possible to definitively determine whether mind–body exercise has an advantage in improving walking ability in stroke patients. It is hoped that more randomized controlled trials (RCTs) will be conducted in this area in the future. Mind–body exercises contain elements of physical and mental coordination, requiring concentration and breathing control. There is growing evidence that mind–body exercise has a positive impact on the effectiveness and safety of a variety of health conditions (60, 62, 63).

4.2 Influence of mind–body exercise on the mental health of stroke patients

Emotional disorders are one of the important indicators affecting the recovery of function in stroke patients (64). After stroke, they often face problems such as movement disorders and mobility difficulties, followed by a variety of life problems and expensive rehabilitation costs, which not only increase the burden of individuals and families, but also have a certain impact on their psychology, and then appear depression, anxiety and other conditions. HAMD depression scale and HAMD anxiety Scale are commonly used to evaluate the emotional state of patients in clinical practice. In this paper, depression index is selected to evaluate the rehabilitation effect of mind–body exercise on the mental health of stroke patients. The results of meta-analysis showed that, compared with conventional rehabilitation therapy, mind–body exercise had significant advantages in improving patients' depression. However, due to its small sample size, it is still necessary to include more RCTS in the future to fully demonstrate the reliability of this result. At the same time, the relevant literature on anxiety indicators can be included to judge the improvement effect of physical and mental exercise on the anxiety of stroke patients.

4.3 Influence of mind–body exercise on the quality of life of stroke patients

The World Health Organization defines quality of life as an individual's perception of their status in life by their standards, expectations and concerns in the larger context of the society in which they live. It can be said that quality of life is a subjective evaluation embedded in cultural, social and environmental contexts (65). In order to expand the sample size of the meta-analysis and enhance the quality and clinical reliability of the systematic study, this paper combined MBI and BI indicators to jointly evaluate the quality of life of stroke patients. The results showed that, compared with conventional rehabilitation therapy, mind–body exercise also had significant advantages in improving the quality of life of stroke patients, and the difference was statistically significant. Further subgroup analysis showed that Qigong (Baduanjin) was most likely to be the best rehabilitation therapy in improving the quality of life of stroke patients. At the same time, the quantitative analysis of this index found that mind–body exercise for more than 4 weeks, 6–10 times a week, 15–40 min each time significantly improved the quality of life of stroke patients.

4.4 Possible mechanism of action of mind–body exercise influencing stroke

For the improvement of the physical function of stroke patients, the reason may be that patients can promote the blood flow of the whole body through long-term stretching exercise and supplemented by breathing, which helps to establish the branch circulation of the

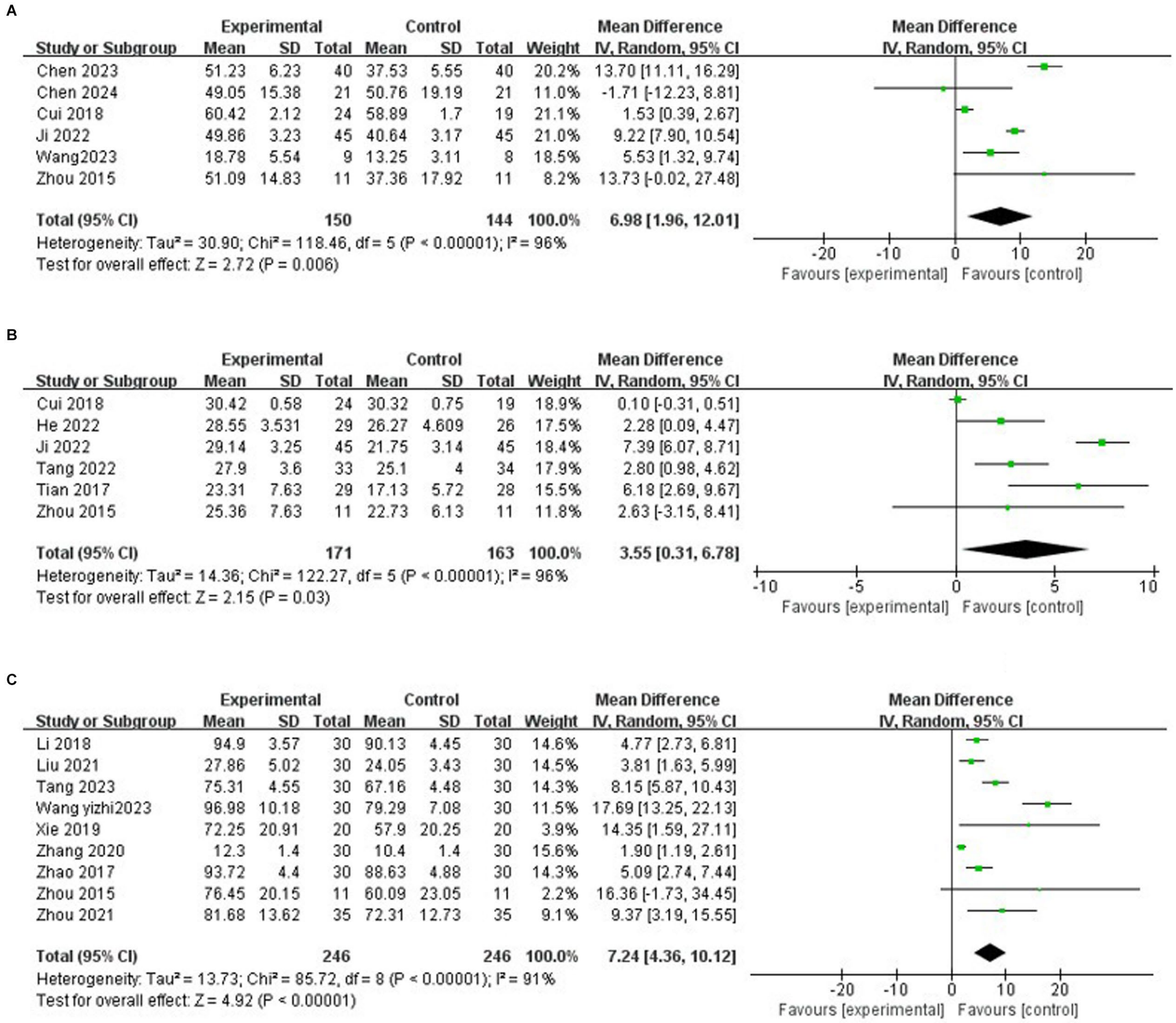

FIGURE 5
(A) Effects of mind–body exercise on upper limb motor ability in stroke patients. **(B)** Effects of mind–body exercise on lower limb motor ability of stroke patients. **(C)** Effects of mind–body exercise on the motor ability of stroke patients.

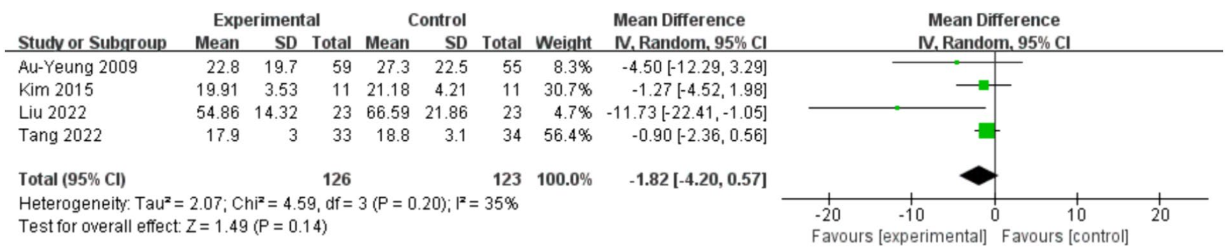

FIGURE 6
Effects of mind–body exercise on walking ability of stroke patients.

brain and replace the damaged brain tissue, thus helping to re-cover the nerve pathway and improve the physical function of patients. In addition, the practice of Taijiquan requires attention and awareness, which requires the active participation of the brain to improve the tension of the central nervous system and strengthen the regulating role of the brain (66).

Improving the mental health of stroke patients. After Tai Chi intervention, several biomarkers associated with depression improved. Superoxide dismutase (SOD) is the most commonly mentioned antioxidant enzyme in depressive disorders, and Tai Chi has an antioxidant effect, which reduces the activity of SOD and thus reduces the level of depression (67). In addition, elevated inflammatory

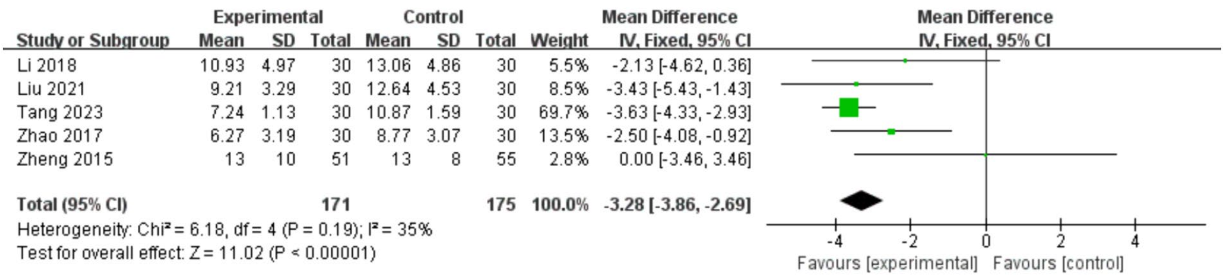

FIGURE 7
Effects of mind–body exercise on depression in stroke patients.

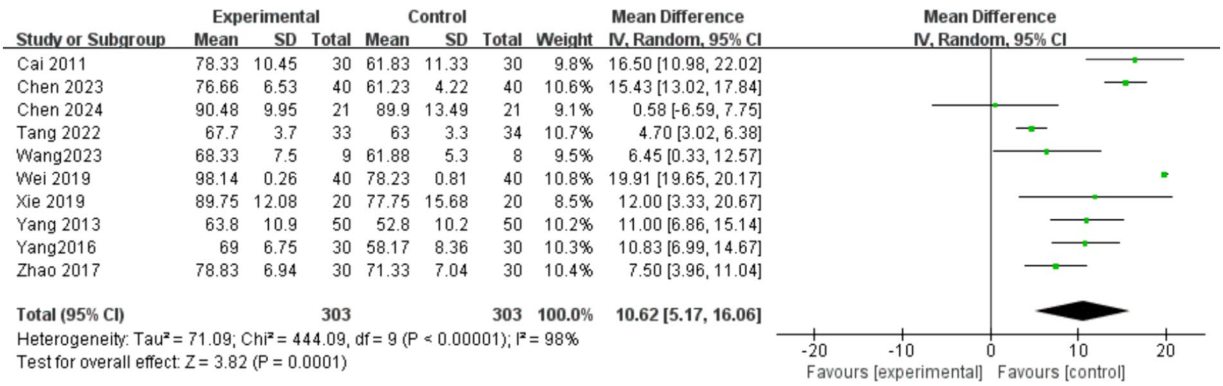

FIGURE 8
Effects of mind–body exercise on quality of life of stroke patients.

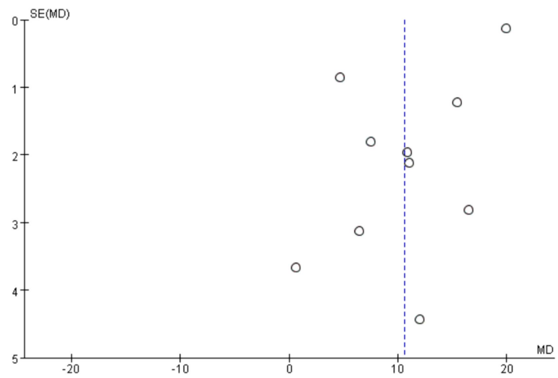

FIGURE 9
Funnel diagram of the influence of mind–body exercise on the quality of life of stroke patients.

biomarkers are also common in people with depression. Interleukin is a commonly used protein and a well-known biomarker of inflammation, stress, and depression. Studies have shown that interleukin can be down-regulated after Tai Chi intervention (66, 68). In addition, an interesting explanation is that traditional mind–body exercises, such as Qigong, can be understood as an attempt to enhance proprioception, which can improve and regulate a person's overall state and reduce anxiety by combining specific states of consciousness with posture, movement, and breathing control (67). The above is possible mechanisms for how mind–body exercises improve the psychological health of stroke patients.

4.5 Limitations and prospects

Its limitations are mainly manifested in the following aspects. First of all, the included literature only includes Chinese and English literature, which may cause some language deviation; Secondly, the geographical location of each study may affect the clinical significance and applicability. In addition, most of the included literatures did not use the blind method, which resulted in a decrease in the reliability of the studies to a certain extent. Finally, this study shows that it is feasible to perform tai chi exercises 6–10 times/week and 15–40 min each time during stroke recovery. However, large-scale applications are needed for special types of stroke patients.

In view of the above limitations, this study needs more high-quality clinical trials to standardize the optimal intervention time, form, frequency, intensity, standardized study design and intervention plan of mind–body exercise. Secondly, researchers should unify outcome evaluation indicators, and combine qualitative evaluation with quantitative evaluation to enrich outcome content. In addition, the shortcomings of methodology should be improved, the research process should be rigorous and standardized, and reliable evidence should be provided for the promotion and application of mind–body exercise intervention.

TABLE 5 Subgroup analysis of effects of mind–body exercise on quality of life in stroke patients.

Influencing factor	Number of studies	MD [95%CI]	Heterogeneity	
			I^2 (%)	*p*-value
Mode				
Tai Chi	5	7.92 [4.79, 10.87]	72	<0.00001
Qigong (Baduanjin)	5	13.88 [9.10, 18.67]	91	<0.00001
Cycle (w)				
≤4	4	7.67 [2.83, 12.51]	58	0.002
>4	6	12.46 [5.56, 19.37]	99	0.0004
Time (min)				
15–40	7	11.67 [5.22, 18.12]	98	0.0004
>40	3	7.98 [1.11, 14.84]	70	0.02
Frequency				
<6	7	10.37 [2.97, 17.77]	99	0.006
6–10	3	11.57 [6.63, 16.51]	78	<0.00001

5 Conclusion

Existing evidence shows that mind–body exercise has significant advantages in the clinical rehabilitation of stroke patients, mainly in enhancing patients' balance function, improving exercise ability, regulating depression, improving quality of life, etc. However, due to the lack of sufficient evidence, it is still unable to prove the role of mind–body exercise in improving the walking ability of stroke patients. Subgroup analysis results showed that Qigong (Baduanjin) training for more than 4 weeks, 6–10 times per week, 15–40 min each time can significantly improve balance function and quality of life in stroke patients. In this review, the two funnel plots are relatively symmetrical, which indicates that the possibility of publication deviation is small, and it has certain reliability and objectivity. Therefore, the exercise prescription obtained can be verified and applied to clinical practice to add a new exercise option for the rehabilitation of stroke patients. Based on the above discussion, mind–body exercise can be used as a supplement therapy to conventional rehabilitation therapy, which is not only low intensity, high safety, but also because it is not limited to the site, can be accepted by most people and accelerate the rehabilitation process of stroke.

Author contributions

JD: Writing – original draft. JC: Software, Writing – original draft. DW: Writing – original draft, Methodology.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1432510/full#supplementary-material

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Automated classification of stress and relaxation responses in major depressive disorder, panic disorder, and healthy participants via heart rate variability

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Background: Stress is a significant risk factor for psychiatric disorders such as major depressive disorder (MDD) and panic disorder (PD). This highlights the need for advanced stress-monitoring technologies to improve treatment. Stress affects the autonomic nervous system, which can be evaluated via heart rate variability (HRV). While machine learning has enabled automated stress detection via HRV in healthy individuals, its application in psychiatric patients remains underexplored. This study evaluated the feasibility of using machine-learning algorithms to detect stress automatically in MDD and PD patients, as well as healthy controls (HCs), based on HRV features.

Methods: The study included 147 participants (MDD: 41, PD: 47, HC: 59) who visited the laboratory up to five times over 12 weeks. HRV data were collected during stress and relaxation tasks, with 20 HRV features extracted. Random forest and multilayer perceptron classifiers were applied to distinguish between the stress and relaxation tasks. Feature importance was analyzed using SHapley Additive exPlanations, and differences in HRV between the tasks (ΔHRV) were compared across groups. The impact of personalized longitudinal scaling on classification accuracy was also assessed.

Results: Random forest classification accuracies were 0.67 for MDD, 0.69 for PD, and 0.73 for HCs, indicating higher accuracy in the HC group. Longitudinal scaling improved accuracies to 0.94 for MDD, 0.90 for PD, and 0.96 for HCs, suggesting its potential in monitoring patients' conditions using HRV. The HC group demonstrated greater ΔHRV fluctuation in a larger number of and more significant features than the patient groups, potentially contributing to higher accuracy. Multilayer perceptron models provided consistent results with random forest, confirming the robustness of the findings.

Conclusion: This study demonstrated that differentiating between stress and relaxation was more challenging in the PD and MDD groups than in the HC group, underscoring the potential of HRV metrics as stress biomarkers. Psychiatric patients exhibited altered autonomic responses, which may influence their stress reactivity. This indicates the need for a tailored approach to stress monitoring in these patient groups. Additionally, we emphasized the significance of longitudinal scaling in enhancing classification accuracy, which can be utilized to develop personalized monitoring technologies for psychiatric patients.

KEYWORDS

heart rate variability, major depressive disorder, panic disorder, stress, relaxation, machine learning, autonomic nervous system, physiological signals

1 Introduction

Psychiatric disorders are increasingly common worldwide and present significant global health challenges (1–3). The most prevalent psychiatric disorders include major depressive disorder (MDD) and anxiety disorders, which affect over 250 million and 300 million people worldwide, respectively (4, 5). MDD is characterized by a persistently depressed mood or loss of interest in activities, along with symptoms such as weight changes, sleep disturbances, fatigue, and feelings of worthlessness, making it a leading cause of global disability (6, 7). Panic disorder (PD) is a common anxiety disorder that involves recurrent, unexpected panic attacks with intense fear and symptoms, such as heart palpitations and sweating, and persistent worry about future attacks or behavioral changes to avoid them, all of which disrupt functions of daily life (7, 8). Left untreated, these debilitating mental illnesses severely impair cognitive function, reduce quality of life, and, in some cases, lead to suicide, which substantially contributes to their global burden (1–3).

Previous research has indicated that stress is associated with an increased risk of developing and exacerbating MDD and PD (9, 10). Specifically, both chronic and acute stress have significant associations with the onset of clinical episodes of depression and PD (10–14). Prolonged exposure to stressors has been linked to a more refractory course of MDD and PD (15). Additionally, acute stressful events can trigger the recurrence of depression (16). Therefore, developing technologies to evaluate the severity and persistence of stress exposure through individual patient monitoring is necessary to improve the treatment of these disorders.

Stress affects the autonomic nervous system (ANS), responsible for regulating physiological responses to external stimuli (17–19). The ANS typically presents increased sympathetic activity and withdrawn parasympathetic activity in response to stress (17–19). Increasing research has explored methods to assess stress by quantifying these autonomic responses (20). Heart rate variability (HRV), which reflects the variations in the time intervals between heartbeats, is an extensively studied measure. It is indicative of cardiac autonomic regulation mediated by both the sympathetic and parasympathetic nervous systems (17–19). HRV is recognized as a quantitative biomarker for evaluating ANS function and its responses to physiological and environmental stimuli (21). Additionally, mobile technological advancement has led to the use of wearable devices as non-invasive approaches to monitor stress based on HRV (22). Previous studies have established that the autonomic response to stress, manifested as reduced HRV, leads to detectable changes in physiological signals, which is captured by wearable devices (22).

Accordingly, recent studies have utilized machine-learning techniques to automatically detect stress based on HRV (21, 23). Various machine-learning methods, from classical to deep learning algorithms, have implemented automated stress detection based on HRV and demonstrated successful performance in classifying stress (21, 23). However, these studies have focused on detecting stress in healthy individuals rather than patients with psychiatric disorders. Particularly, stress analysis based on HRV in patients with psychiatric conditions has focused on how patients responded to stress differently compared with healthy controls (HCs) and relied on statistical methods.

Psychiatric disorders have been associated with ANS dysfunction, which can lead to autonomic imbalance toward sympathetic activation, as reflected in HRV (24–26). MDD patients in particular often show altered autonomic regulation that affects cardiovascular control, with decreased cardiac vagal modulation (27). Consequently, patients with MDD and PD typically exhibit lower HRV compared with HCs, which indicates reduced autonomic flexibility (24–26). This altered autonomic response in patients causes differences in stress reactions between patients and healthy individuals. Patients with MDD exhibited lower reactivity to stress than HCs, evidenced by lower fluctuations in their HRV (28). Research in patients with PD revealed mixed stress responses and reported higher (29), reduced (30), and similar reactivity (31) compared with HCs. Although previous studies compared stress responses via HRV between patients and healthy individuals, research on the application of machine learning to identify stressful states in psychiatric patients based on HRV data is lacking.

Our study aimed to explore the feasibility of automated stress detection based on HRV features via machine-learning algorithms in patients with MDD and PD, as well as HCs. HRV features were obtained from three distinct participant groups: MDD, PD, and HC, while they performed various experimental tasks, which included those designed to induce mental stress and relaxation. We focused on distinguishing between the states of stress and relaxation via HRV features and compared the classification results across different participant groups. We hypothesize that machine-learning algorithms can effectively classify stress and relaxation states based on HRV features, with the accuracy potentially differing among three groups, namely, MDD, PD, and HC, due to varying ANS responses. Notably, mental disorders, such as MDD and PD, demonstrated substantial individual variability among patients, a characteristic that reflected the heterogeneous nature of these conditions (32, 33). Therefore, we investigated the impact of individually scaling patient data on the classification outcomes as a pilot study. We believe that this approach could facilitate the development of further precise and automated methods for monitoring stress in patients with psychiatric problems and ultimately lead to improved management and treatment strategies.

2 Methods

2.1 Participants

Participants included 147 individuals: 41 with MDD, 47 with PD, and 59 HCs. All patients were recruited at the Samsung Medical Center in Seoul, Korea, between December 2015 and January 2017 (34). MDD and PD diagnoses were conducted by a senior psychiatrist in accordance with Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V) criteria (7). Exclusion criteria included pregnancy, history of substance or alcohol abuse, head injury, high suicide risk, personality disorders, severe physical ailments, and long-acting medication use (e.g., fluoxetine and depot neuroleptics). All patients received standard psychiatric pharmacotherapy for MDD or PD throughout the duration of the 12-week experiment, which included standard antidepressant treatments, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), norepinephrine dopamine reuptake inhibitors, and tricyclic antidepressants (TCAs) (34). HCs who lacked a psychiatric history or family background of mood disorders were recruited through general study advertisements. The study protocol was approved by the Ethics Committee of Samsung Medical Center in Seoul, Korea (No. 2015-07-151), and complied with the applicable guidelines. All participants provided written informed consent after they received a thorough explanation of the research procedures. Additionally, each participant received $50 as compensation.

2.2 Study design

The study spanned 12 weeks for each participant (Figure 1A), with five scheduled visits to our clinical laboratory: baseline and subsequent visits at 2, 4, 8, and 12 weeks. Each participant provided demographic information (e.g., age and sex) and underwent clinical evaluations. Clinical evaluations incorporated the Hamilton rating scale for depression (HAMD), Hamilton rating scale for anxiety (HAMA), and panic disorder severity scale (PDSS), which were administered during the initial and 12-week visits (35–37). Participants' body mass index (BMI) was also assessed, considering its recognized influence on ANS responses (38). This study is part of a larger investigation examining changes in clinical symptoms and inflammatory biomarkers over 12 weeks to capture treatment effects (39).

2.3 Experimental protocol

The experimental procedure was developed to examine autonomic responses to stress and relaxation tasks. The protocol comprised five phases, each lasting five minutes, totaling to a duration of 25 minutes. Furthermore, physiological signals, such as electrocardiograms (ECG), were continuously measured while the participants performed specific tasks in each phase (Figure 1B). The first phase, serving as the baseline phase, involved a rest period during which the participants were instructed to sit comfortably and minimize movement. In the second phase, the participants undertook a stress task involving a mental arithmetic test (MAT), during which they were required to subtract serial 7s starting from 500 and verbally report their answers to the researchers. The participants were prompted to recalculate in case an error occurred. If the participants reached the final answer, 10 minus 7 equals 3, before the 5-minute phase ended, they restarted the task from 500 and continued subtracting. The third phase, also a rest phase, involved participants discontinuing arithmetic calculations and resting, which allowed autonomic recovery from the stress task. In the fourth phase, the participants performed a relaxation task by observing 10 consecutive images of natural scenery on a computer screen, each displayed for 30 seconds. The final phase, another rest phase, involved resting without any image presentation to allow recovery from the relaxation task. Two trained investigator specialists conducted the experiments. Only one participant was examined at a time by a specialist in our clinical laboratory. In our study, the sequence of stress and relaxation tasks was not randomized. As randomizing the order could reduce potential biases in the results, we plan to implement this approach in future research.

The MAT task used in this study was specifically designed to induce cognitive and psychological stress by progressively increasing participants' mental load through continuous subtraction tasks (40–43). Research has demonstrated that MAT effectively induces physiological changes, including alterations in heart rate, skin conductance response, and neural activity (40–43).

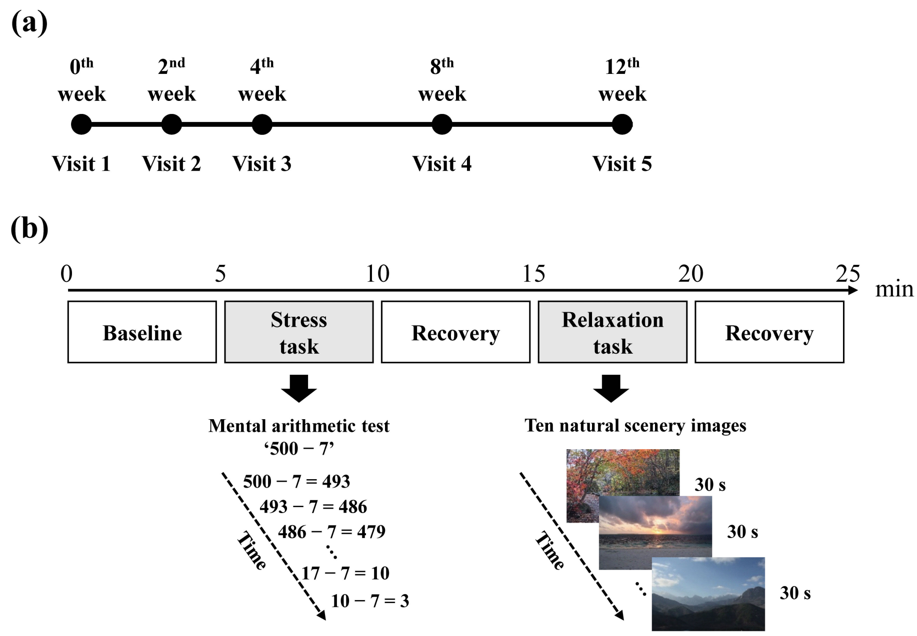

FIGURE 1
Experimental protocol. **(A)** The study lasted for 12 weeks, with each participant scheduled for a total of five visits. **(B)** During each visit, ECG signals were recorded in five consecutive phases, with each phase lasting for 5 minutes.

In our prior studies, we similarly observed a significant decrease in HRV when using the same stimulus, as compared to baseline measurements (44). Additionally, research has shown that exposure to nature scenes, which served as the relaxation task in this study, positively supports autonomic recovery from stress, as assessed by HRV and skin conductance measurements (45, 46).

2.4 Physiological measurement

We recorded physiological signals during working hours, considering the potential influence of the participant's physiological state, which included factors such as time of day, mood, and rest (47–49). The experiment was conducted in a controlled environment, specifically a sound-attenuated room maintained at a temperature of 23°C and humidity levels between 45%–55%. Participants were instructed to sit comfortably in an armchair with a headrest prior to the experiment and avoid unnecessary movement or speech while the devices to record their physiological signals were being set up and calibrated. ECG signals were collected via the ProComp Infiniti system (SA7500, Thought Technology, Canada) at a sampling rate of 256 Hz, chosen to ensure an accurate analysis of the QRS complex and R-peak (50). ECGs were captured with an ECG-Flex/Pro sensor (T9306M, Thought Technology), with three electrodes placed on both forearms: the negative lead on the right forearm and positive and ground leads on the left forearm. The collected ECG signals were filtered using a 60 Hz notch filter provided in the BioGraph Infiniti software (Thought Technology).

R-peak to R-peak interval (RRI) data from the ECG signals were analyzed via Kubios HRV Premium software (Kubios, www.kubios.com), which utilized an in-house-developed QRS detection algorithm based on the Pan-Tompkins method (51, 52). The RRI data underwent visual inspection, and any artifacts were rectified via a piecewise cubic spline interpolation method. The entire analysis was performed by the same operator to ensure consistency. Subsequently, the HRV features were calculated separately from the RRI data of the individual phases.

2.5 HRV feature extraction

A standard HRV analysis was conducted according to international guidelines (50, 53). We derived 20 HRV features from the RRI data of each phase and covered time, frequency, and nonlinear domain analyses (Supplementary Table 1). Time and frequency domains are traditional approaches widely used in numerous studies, demonstrating well-established connections with the ANS (50, 53). The nonlinear domain has gained attention more recently and is increasingly being recognized for its potential as a biomarker. Nonlinear features are now being utilized not only to assess autonomic responses to external stimuli, such as stress, but also in the context of mental health conditions (54, 55). In this study, we included the most representative features of these three domains.

Time-domain HRV features were directly calculated from the RRI time series. We extracted six features via this analysis: the mean of the RRIs, standard deviation of the RRIs (SDNN), root mean square of successive RRI differences (RMSSD), percentage of successive RRIs differing by more than 50 ms (pNN50), integral of the histogram of the RRI divided by its height (TRI), and baseline width of the RRI histogram (TINN). Seven features were calculated via the frequency domain analysis. The RRI data were converted to equidistantly sampled data via cubic spline interpolation (4 Hz). Power spectral density was estimated via Welch's periodogram-based fast Fourier transform. Absolute powers were computed in very low-frequency (VLF, 0–0.04 Hz), low-frequency (LF, 0.04–0.15 Hz), and high-frequency (HF, 0.15–0.4 Hz) bands. Additionally, the relative powers of the LF and HF bands in normalized units and the LF/HF power ratio were calculated. Absolute powers were expressed in natural logarithms to reduce skewness in the distribution.

We extracted five nonlinear measures to assess the nonlinear dynamics in heart rate signals. Approximate entropy (ApEn) measured the irregularity in short and noisy time-series data and did not assume underlying system dynamics (56). The embedding dimension and tolerance value for ApEn were set to 2 and 0.2, respectively. Sample entropy (SampEn) was developed to reduce ApEn bias from self-comparison and was more reliable for shorter time series, with parameters set identical to those for ApEn (57). Detrended fluctuation analysis (DFA) was used to assess fractal scaling properties of short-term RRI signals by integrating and detrending the time-series data and subsequently measured the root-mean-square fluctuation at different time scales (58). The fluctuation was defined by $\alpha 1$ and $\alpha 2$, which represented short-range and long-range correlations, respectively. In this study, $\alpha 1$ and $\alpha 2$ were evaluated for data lengths of 4–16 and 17–64, respectively. The correlation dimension (CorDim) estimated the number of independent variables required to model the signal, and higher values indicated greater complexity (59, 60). We derived two features from the Poincaré plot analysis, which graphically represented the correlation between successive RRIs. SD1 and SD2 represented the standard deviations perpendicular to and along the line of identity, respectively.

2.6 Statistical analyses

Statistical analyses were conducted using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Demographic and clinical characteristics from the MDD, PD, and HC groups were compared via the one-way analysis of variance (ANOVA), except for sex, which was compared via a chi-square test. HRV features among the MDD, PD, and HC groups measured during the stress and relaxation tasks, were compared via one-way ANOVA on mean values from all five visits. We conducted within-subject comparisons of HRV features between the stress and relaxation tasks during a single visit via paired samples t-tests. Differences in HRV features between stress and relaxation tasks, defined as ΔHRV, were calculated within the same participants during a single visit. We compared ΔHRV among the MDD, PD, and HC groups via one-way ANOVA. For all one-way ANOVAs reported in this study, we employed either Fisher's ANOVA with Bonferroni *post-hoc* analysis or Welch's ANOVA with Games-Howell *post-hoc* analysis based on the homogeneity of variance. A P value < 0.05 was considered statistically significant. We chose a one-way ANOVA to focus specifically on the differences in HRV across the three groups, rather than on variations introduced by factors such as visit. This approach allowed us to emphasize the primary objective of understanding HRV differences among diagnostic groups. Future studies may incorporate additional factors in a more comprehensive model.

2.7 Classification of the stress and relaxation tasks

To classify the stress and relaxation tasks based on HRV features, we implemented two machine-learning algorithms: random forest and multilayer perceptron (MLP). Although 735 samples were expected if 147 participants (41 MDD patients, 47 PD patients, and 59 HCs) visited five times each, some participants missed visits. Consequently, 650 samples were obtained each for stress and relaxation (181 MDD, 191 PD, and 278 HC). Hence, 1300 samples were used for classification. All classifications were performed with Python version 3.11.4 (Python Software Foundation).

We utilized 20 HRV features as input data. Training data were normalized by subtracting the mean and dividing it by the standard deviation. Subsequently, the same statistical values were used to normalize the test dataset. However, this normalization was not applied when we conducted personalized longitudinal scaling. The stress and relaxation tasks were defined as the positive and negative class for classification, respectively.

We used a stratified 10-fold cross-validation (CV) repeated 20 times to evaluate performance measures of classification (Supplementary Figure 1). The task was used as a stratification option. A subject-wise split was used to ensure that all data from a given participant was contained entirely within either the training or the test set, not both, to avoid data leakage. Nine folds were used for training, and the remaining fold was used for evaluation. We created 10 models and evaluated for each fold. We averaged the results from 10 folds to estimate the model's performance. This entire process was repeated 20 times. Therefore, performance metrics were presented as the mean and standard deviation calculated from 20 repeats. Performance indices included accuracy, F1, recall, precision, and area under the curve (AUC).

Sample sizes for the MDD, PD, and HC groups were 362, 382, and 556, respectively. Despite the variations in sample sizes, we initially conducted the classification without matching the sample sizes. However, we later repeated the classification via the same method after matching the sample sizes. We employed random undersampling to match the sample sizes and aligned them with the smallest sample size, which belonged to the MDD group.

Moreover, we built models trained and tested exclusively on data from one group. The entire dataset was divided into three separate datasets for the MDD, PD, and HC groups. Subsequently, three separate models were trained and tested, each using the data from one specific group exclusively, which ensured that data from different groups did not interact during the training.

2.8 Random forest and MLP classifiers

We selected the random forest algorithm owing to its capacity to effectively manage non-linear relationships and high-dimensional feature spaces and its ability to provide feature importance evaluations (61, 62). We utilized this algorithm to compute SHapley Additive exPlanations (SHAP) values and subsequently conducted an analysis of the model's classification results based on these values. We performed hyperparameter optimization using grid search within the training set with a 5-fold CV, ensuring optimal model performance while preventing data leakage into the test set. The number of trees, a key hyperparameter in the random forest algorithm, was optimized using the following values: 50, 100, and 200.

We repeated the classification via MLP with the same approach as that for random forest. This was to ensure that our results were not algorithm-dependent and demonstrate consistency across different algorithms. MLP was chosen as it was based on neural networks, which offered a completely different classification method compared with the ensemble-based random forest. This approach helped us verify the robustness and reliability of our findings across diverse machine-learning techniques. The following hyperparameters were optimized using the same approach as applied to the random forest: hidden layer sizes of (4, 8, 16) and (4, 8, 16, 32), as well as initial learning rates of 0.0001, 0.001, and 0.01. A total of six combinations were explored using the grid search method. Accordingly, we evaluated MLP architectures with three- and four-hidden-layer configurations (Supplementary Figure 2). All hidden layers were dense layers and used ReLU as the activation function. The output layer used sigmoid as the activation function to perform binary classification. Dropout was not used. Adam optimizer was the solver. We applied an L2 penalty with a coefficient of 0.0001 for regularization. Furthermore, we had set the MLP model with a maximum of 1000 iterations and enabled early stopping. The training was stopped if the validation score did not improve by at least 10^{-4} for 10 consecutive iterations.

In this study, we did not conduct feature selection separately. The random forest algorithm inherently performs a form of feature selection, since it constructs multiple decision trees, each trained on a random subset of features (63). In contrast, it should be considered that the use of an MLP could benefit from feature selection to improve model performance (64). However, our study utilized over 1000 samples to train a model with 20 features, leading to a sample-to-feature ratio that we considered sufficient. Consequently, we concluded that feature selection was not strictly necessary for this dataset.

2.9 Model interpretation via SHAP

SHAP values were calculated via random forest on test datasets to interpret classification outcomes (65, 66). SHAP, based on Shapley values, utilized cooperative game theory developed by Lloyd Shapley (67). The SHAP value quantified the impact of each input feature on predicting the output for each individual (68). Our analysis involved a 10-fold CV repeated 20 times, and the reported SHAP values represented the averages across the 20 iterations of the 10-fold CV.

2.10 Personalized longitudinal scaling

Our participants attended up to five visits over a 12-week span and completed five tasks per visit. This approach allowed for data collection at multiple time points for each individual. To utilize this advantage, data for each participant were normalized over the time axis (Figure 2). We utilized all the data from these visits and tasks for personalized longitudinal scaling, considering extensive data while subjecting participants to various experimental conditions. Means and standard deviations were calculated via the data measured from a single participant. Subsequently, the data from this participant were normalized by subtracting the mean and dividing by the standard deviation. We repeated this process individually for each participant. We performed classification analyses via the scaled HRV data to evaluate whether personalized longitudinal scaling enhanced the classification of stress versus relaxation responses and applied the same methodologies.

Furthermore, we applied t-stochastic neighbor embedding (t-SNE) to the HRV data both before and after personalized

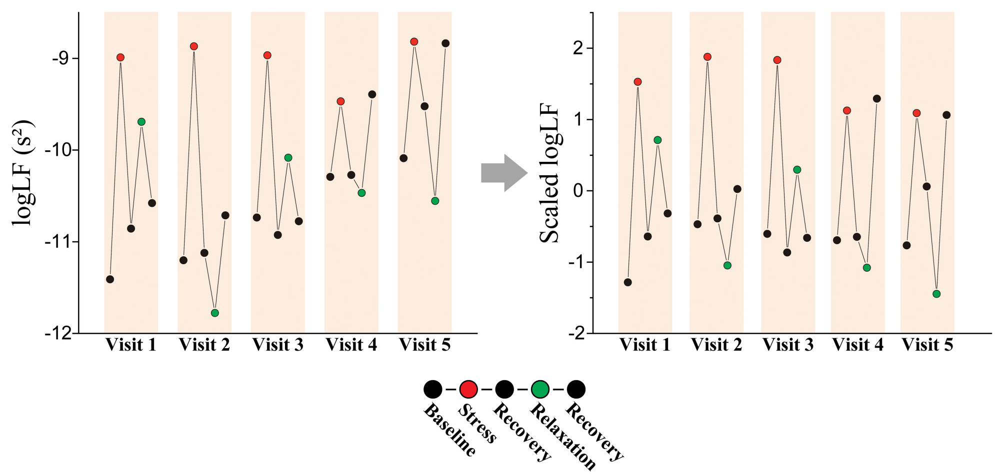

FIGURE 2
Personalized longitudinal scaling. An example of scaling on logLF measured from a patient with MDD (female, 61-year-old).

longitudinal scaling to evaluate its impact The t-SNE was a machine-learning technique designed to visualize high-dimensional data by projecting it into a low-dimensional space (69). It aimed to maintain the relative similarity between data points from the original high-dimensional space in the resulting low-dimensional representation. Projection was determined by minimizing the Kullback-Leibler-divergence between the similarity of data distributions in the high- and low-dimensional space (70). We conducted t-SNE using 5000 iterations with a perplexity of 50.

3 Results

3.1 Demographic and clinical characteristics

Our participants included 41 (30 females) and 47 (30 females) patients with MDD and PD, respectively, and 59 HCs (36 females). Table 1 summarizes the participants' demographic and clinical characteristics. No significant differences were observed in age, sex, or BMI among the groups, which indicated balanced participants and reduced the potential confounding effects of these variables on HRV outcomes. The MDD and PD groups showed significantly higher HAMD and HAMA scores than the control group, which reflected the expected clinical severity of depressive and anxiety symptoms (Supplementary Table 2). PDSS score was highest in the PD group, followed by the MDD group, and lowest in the HC group, which aligned with the diagnostic criteria and expected symptomatology of these groups.

3.2 Comparison of HRV features among the patient groups

We statistically compared the HRV features measured during the stress and relaxation tasks among the MDD, PD, and HC groups (Supplementary Tables 3, 4). Significant differences were observed among the three groups in 13 HRV features among the 20 considered. Of these, 10 features—SDNN, RMSSD, pNN50, TRI, TINN, SD1, SD2, ApEn, SampEn, and CorDim—exhibited a significant main effect of the group in both tasks and the MDD and PD groups generally had lower values compared with HCs. RRI during the relaxation task and LF/HF during the stress task had a significant main effect of the group; however, no significant result was observed in the *post-hoc* analysis. Additionally, α2 during the relaxation task had higher values in the PD group compared with the HC group. These results were consistent with the altered ANS observed in depressive and anxiety disorders, as demonstrated in previous studies (24–26).

3.3 HRV feature changes between the stress and relaxation tasks

We examined the differences in HRV features between the stress and relaxation tasks within each participant to investigate the autonomic response to these mental tasks. Supplementary Table 5 outlines the changes in HRV features (ΔHRV) between the stress and relaxation tasks. Our findings revealed that in the MDD group, 10 HRV features exhibited significant differences between the two tasks, whereas in the PD and HC groups, 14 features exhibited significant differences. Seven features—RRI, logLF, LFnu, HFnu, ApEn, α1, and α2—exhibited significant differences between the two tasks in all the three groups. These results suggested that the two mental tasks induced distinct autonomic responses, which were effectively captured by HRV metrics.

Existing literature established that HRV features generally decreased with stress, while features associated with LF, such as logLF, LFnu, and LF/HF, increased with stress owing to the dominance of sympathetic activity on LF (17–19). Consistent with these previous results, the HRV features that displayed significant differences between the two mental tasks in this study exhibited lower values in the stress condition (negative ΔHRV

TABLE 1 Demographic and clinical characteristics of the MDD, PD, and HC groups.

	MDD (N = 41)	PD (*N* = 47)	HC (*N* = 59)	*F or* χ^2 (*P* value)	*Post-hoc*
Demographic data					
Age (years)	42.02 ± 16.65	41.64 ± 14.39	38.49 ± 14.22	0.88 (.42)[a]	ns
Sex (M/F)	11/30	17/30	23/36	1.64 (.44)	ns
BMI (kg/m^2)	22.93 ± 3.41	23.29 ± 3.26	22.76 ± 3.17	0.35 (.71)[a]	ns
Clinical data					
HAMD	17.49 ± 7.07	13.87 ± 7.71	1.88 ± 1.75	143.26 (<.001)[b]	MDD, PD > HC[b]
HAMA	16.56 ± 8.46	15.11 ± 8.44	2.12 ± 2.22	103.53 (<.001)[b]	MDD, PD > HC[b]
PDSS	3.61 ± 5.74	12.53 ± 6.05	0.02 ± 0.13	107.16 (<.001)[b]	PD > MDD > HC[b]

Data are presented as means and standard deviations for continuous variables and as counts for categorical variables. See Supplementary Table 2 for *post-hoc P* values.
ns, No significant main effect; MDD, major depressive disorder; PD, panic disorder; HC, healthy control; BMI, body mass index; HAMD, Hamilton rating scale for depression; HAMA, Hamilton rating scale for anxiety; PDSS, panic disorder severity scale.
[a]Fisher's one-way ANOVA.
[b]Welch's one-way ANOVA and Games-Howell *post-hoc* analysis.

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values), whereas features related to LF were higher in the stress condition (positive ΔHRV values). However, some features demonstrated an opposite pattern, such as TRI and TINN in the MDD and PD groups, ApEn in all the three groups, SampEn in the MDD and HC groups, α1 in all the three groups, and CorDim in the PD group, which presented higher values in the stress condition (positive ΔHRV values).

3.4 Classification of stress and relaxation tasks using HRV features and differences in classification performance among the groups

A random forest algorithm was employed to classify stress and relaxation responses using HRV features. We used the 20 HRV features as input data. A 10-fold CV repeated 20 times was used to evaluate the performance of the classification, implementing a subject-wise split to avoid data leakage. Table 2 shows the performance metrics for classifying the responses. The performance measures of the overall group were evaluated by counting all the groups together in the test dataset without distinguishing among the three groups. The accuracy of the overall group was 0.7, demonstrating that stress and relaxation responses could be distinguished using HRV features. In addition, we calculated the same performance metrics separately for the three groups in the test set. The HC group had the highest scores in all the five metrics, followed by the PD and MDD groups, except the recall. The accuracy was 0.73, 0.69, and 0.67 for the HC, PD, and MDD groups, respectively. For the recall, the HC group still had the highest value, followed by the MDD and PD groups. These results suggested that the distinction between stress and relaxation responses was relatively accurate in the HC group compared with the patient groups. Particularly, there was approximately a 0.05 difference in accuracy between the MDD and HC groups, which indicated that for patients who are depressed, distinguishing between stress and relaxation based on HRV was relatively challenging compared with the healthy population.

Sample sizes for the MDD and PD groups were 362 and 382, respectively, which were smaller compared with the HC group's sample size of 556. We applied undersampling to the dataset and performed the classification again to investigate whether the relatively lower accuracy in the patient groups was owing to the difference in sample sizes during the training process. Using random undersampling, the sample sizes for the PD and HC groups were reduced to match the smallest sample size of 362. Starting with 362 samples for each group, the data was split into training and test datasets for classification, and performance was calculated.

We determined that even with undersampling applied to ensure an equal number of samples for training, the order of performance metrics remained unchanged among the groups, except for the precision (Table 2). For the precision, the PD group had the highest value, followed by HC and MDD groups. Accuracy for the HC and PD groups increased slightly with undersampling, whereas the MDD group exhibited a slight decrease. Overall accuracy based on the entire groups before and after applying undersampling remained nearly unchanged. This result suggested that the relatively higher accuracy in the HC group was not due to differences in sample sizes.

To further analyze the performance differences among the three groups, we built models exclusively trained and tested on the data

TABLE 2 Performance measures for classifying the stress and relaxation tasks.

Model	Group	Accuracy	F1	Recall	Precision	AUC
Combined data model						
Overall		0.6986 ± 0.0055	0.7002 ± 0.0060	0.7098 ± 0.0105	0.6972 ± 0.0062	0.7708 ± 0.0035
MDD		0.6703 ± 0.0107	0.6770 ± 0.0132	0.6914 ± 0.0237	0.6635 ± 0.0107	0.7452 ± 0.0068
PD		0.6872 ± 0.0144	0.6773 ± 0.0144	0.6565 ± 0.0158	0.6995 ± 0.0167	0.7537 ± 0.0085
HC		0.7255 ± 0.0099	0.7338 ± 0.0090	0.7565 ± 0.0129	0.7126 ± 0.0117	0.7943 ± 0.0056
Combined data model with undersampling						
Overall		0.6974 ± 0.0094	0.6931 ± 0.0110	0.6983 ± 0.0140	0.6966 ± 0.0107	0.7662 ± 0.0078
MDD		0.6645 ± 0.0125	0.6686 ± 0.0145	0.6771 ± 0.0212	0.6605 ± 0.0114	0.7366 ± 0.0068
PD		0.6914 ± 0.0131	0.6779 ± 0.0126	0.6459 ± 0.0148	0.7136 ± 0.0180	0.7531 ± 0.0096
HC		0.7352 ± 0.0118	0.7359 ± 0.0128	0.7720 ± 0.0194	0.7032 ± 0.0117	0.7994 ± 0.0074
Separate data models						
MDD		0.6440 ± 0.0161	0.6324 ± 0.0242	0.6402 ± 0.0321	0.6555 ± 0.0234	0.7288 ± 0.0158
PD		0.6824 ± 0.0100	0.6819 ± 0.0139	0.6952 ± 0.0224	0.6977 ± 0.0167	0.7547 ± 0.0101
HC		0.7103 ± 0.0097	0.7092 ± 0.0103	0.7229 ± 0.0142	0.7177 ± 0.0116	0.7910 ± 0.0078

For the combined data model, the metrics were calculated separately for each patient group in the test dataset, in addition to the overall evaluation based on the entire test data. Separate data models were trained and tested, each using the data from one specific patient group exclusively. Results are presented as mean and standard deviation calculated from 20 repeats.
AUC, area under the curve; MDD, major depressive disorder; PD, panic disorder; HC, healthy control.

from one group. The entire dataset was divided into three separate datasets for the MDD, PD, and HC groups. Subsequently, three separate models were trained and tested, each exclusively used the data from one specific group, which ensured that data from different groups did not interact during the training (Table 2). The HC group had the highest scores in all the five metrics, followed by the PD and MDD groups. The MDD and HC groups' performance metrics decreased compared with those evaluated from the combined data model, whereas the PD group's performance metrics remained similar to the combined data model. This could be owing to the decrease in the number of samples, and referencing data from other groups could have been helpful in training the model. These outcomes suggested that the reduced performance in the patient groups was intrinsic to the characteristics of the data.

3.5 Feature importance based on SHAP

We calculated the SHAP values via test datasets to identify the features critically responsible for the classification between stress and relaxation responses (Figure 3). SHAP values were calculated for four models: a combined data model that used data from all the three groups and three separate models based on the data from one specific group exclusively (MDD, PD, and HC). The importance of all 20 features was listed in descending order from the top for each model. For the combined data and PD-based models, the three top-ranked features were α2, ApEn, and RRI. In the MDD-based model, the top three features were ApEn, RRI, and SampEn, while in the HC group, the most significant features were RRI, ApEn, and α2. RRI and ApEn were consistently included in the top three features for all the models, which indicated their critical role in classification, although there were slight variations in their order of importance across the four models. Besides these two features, α2 and SampEn were included in the top three. Notably, α2 demonstrated dominant importance in the PD group compared with the other HRV features.

3.6 Group comparisons of ΔHRV

The ΔHRV represented the difference between relaxation and stress tasks, which was calculated to evaluate the participants' autonomic reactivity. We hypothesized that the group with higher accuracy would exhibit greater reactivity, that is, absolute ΔHRV, compared with the other groups. This was as larger differences in feature values between the two tasks would make the classification process easier. We observed differences in the classification performance among the groups of MDD, PD, and HC. Therefore, we statistically compared ΔHRV values among the groups to examine whether psychiatric disorders affected the reactivity of the ANS to mental tasks. Figure 4 illustrates the differences in ΔHRV among the groups, where the box plots illustrate the extent of HRV changes between the two tasks with red dotted lines denote the mean values.

A significant main effect of the group was observed in 11 features (Table 3). Specifically, HCs had significantly greater absolute changes than the MDD and PD groups in RRI, logHF, logTot, and SD2 and greater changes than the MDD group in logVLF. Conversely, HC had smaller absolute changes than the MDD and PD groups in TINN and logLF, while MDD had greater changes than HCs in TRI. The PD group exhibited significantly greater changes than the MDD and HC groups in α2 and greater changes than HCs in CorDim.

The HC group demonstrated greater absolute changes than the MDD group in five features, while the MDD group exhibited larger absolute changes than the HC group in three features. Comparison of the HC and PD groups revealed greater absolute changes than the other in four features. A significant difference between the MDD and PD groups was observed only in α2, and the PD group had a greater absolute change than the MDD group.

3.7 Personalized longitudinal scaling of the HRV features

Participants were measured multiple times over an extended period, which provided an opportunity to collect data at various time points for each individual. We normalized the data for each individual over the time axis to leverage this benefit (Figure 2). We performed classification based on the scaled HRV data via the same methods to determine whether this personalized longitudinal scaling improved the classification between stress and relaxation responses.

Initially, we aimed to understand the impact of scaling on the data using t-SNE for visualization to determine if the separation between stress and relaxation became more distinct after scaling (Supplementary Figure 3). The t-SNE visualization of the HRV data before and after longitudinal scaling illustrated the improved separation of stress and relaxation classes post-scaling, which suggested an improvement in classification performance.

3.8 Scaled HRV feature changes between the stress and relaxation tasks

We examined the differences in the longitudinally scaled HRV features the between stress and relaxation tasks within each participant (Supplementary Table 6). We determined that 14, 12, and 16 HRV features exhibited significant differences between the two tasks in the MDD, PD, and HC groups, respectively. Furthermore, seven features—RRI, LFnu, HFnu, LF/HF, ApEn, α1, and α2—exhibited significant differences between the two tasks in all the three groups. The MDD and HC groups exhibited a higher number of significantly different HRV features after scaling, whereas the PD group exhibited a decreased number of significantly different HRV features post-scaling.

Furthermore, similar to the unscaled HRV features, the scaled HRV features that demonstrated significant differences between the

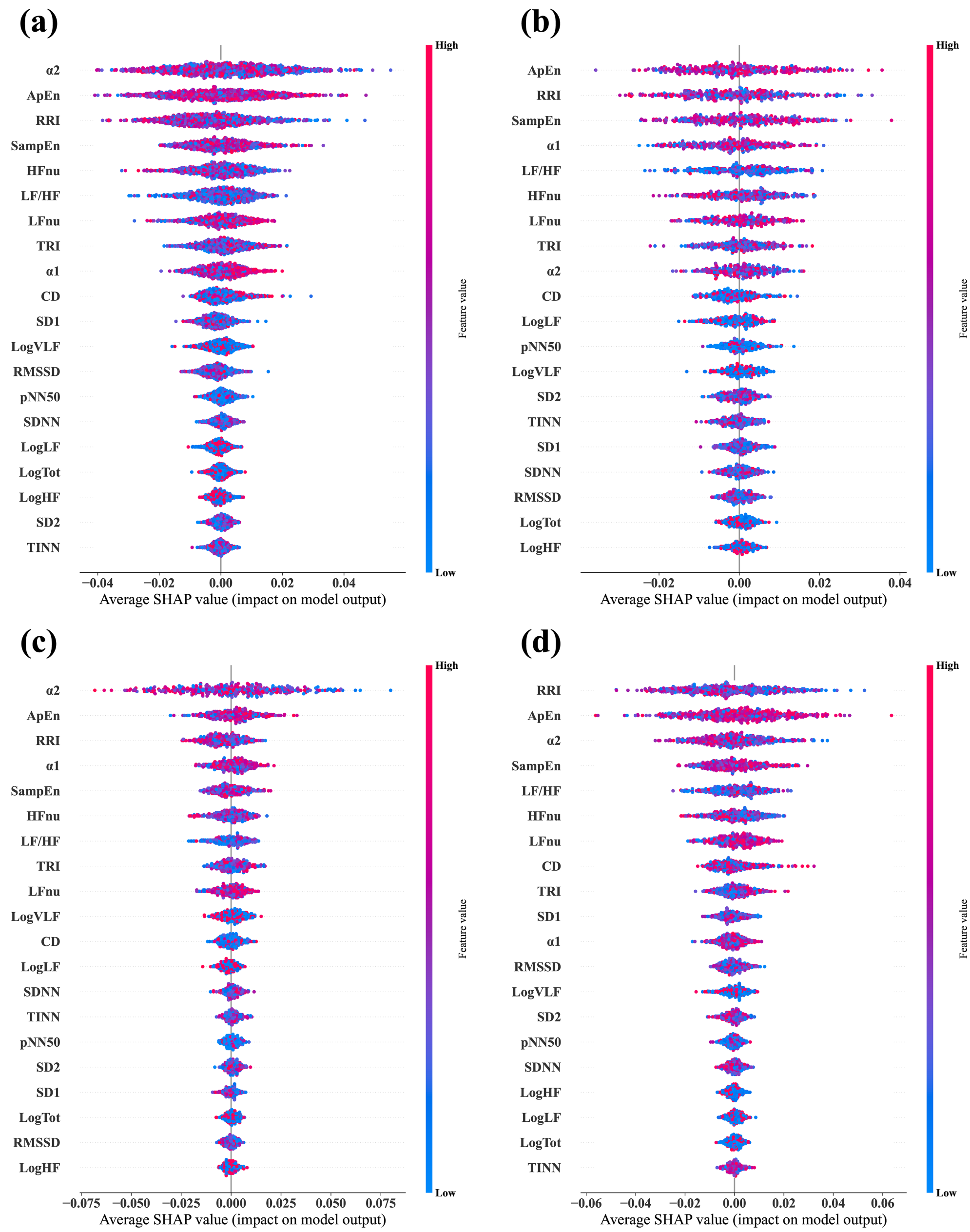

FIGURE 3
Average SHAP values evaluated from the four different classifier models. **(A)** Combined data model, which was trained and tested via data from all three groups—MDD, PD, and HC. **(B)** MDD-based model, which was trained and tested via data from the MDD group exclusively. **(C)** PD-based model, which was trained and tested via data from the PD group exclusively. **(D)** HC-based model, which was trained and tested via data from the HC group exclusively. In each plot, the features are arranged in descending order of importance.

two mental tasks exhibited lower values in the stress condition (negative ΔHRV_{scaled} values), whereas features related to LF were higher in the stress condition (positive ΔHRV_{scaled} values). However, the following features presented higher values in the stress condition (positive ΔHRV_{scaled} values): SDNN in the MDD group, TRI and TINN in the MDD and PD groups, SD2 in the MDD group, ApEn in all the three groups, SampEn in the MDD and HC groups, α1 in all the three groups, and CorDim in the MDD and PD groups.

3.9 Classification of the stress and relaxation tasks using scaled HRV features

We performed classification via scaled HRV data and followed the same methodology as with the unscaled data (Table 4). The overall accuracy increased significantly from 0.70 with unscaled data to 0.94 after scaling. When we examined the individual metrics for MDD, PD, and HC groups, the HC group demonstrated the highest values across all the metrics, followed by the MDD and PD groups, except for the precision. Accuracy was 0.94, 0.90, and 0.96 for the MDD, PD, and HC groups, respectively. These findings demonstrated differences in classification performance across the groups, and the HC group achieved the highest accuracy compared with the other two disease groups. Notably, with unscaled data, the accuracy of the PD group was slightly higher than that of the MDD group. However, after scaling, the MDD group exhibited higher accuracy than the PD group.

Furthermore, we compared the three separate models, each utilizing the data from one specific group exclusively, which was similar to our approach with unscaled data (Table 4). All the three models demonstrated a significant improvement in classification performance after scaling. Best classification results were observed for the HC group, followed by the MDD and PD groups, respectively. These results suggested the substantial impact of personalized longitudinal scaling on our classification models' performance across different groups.

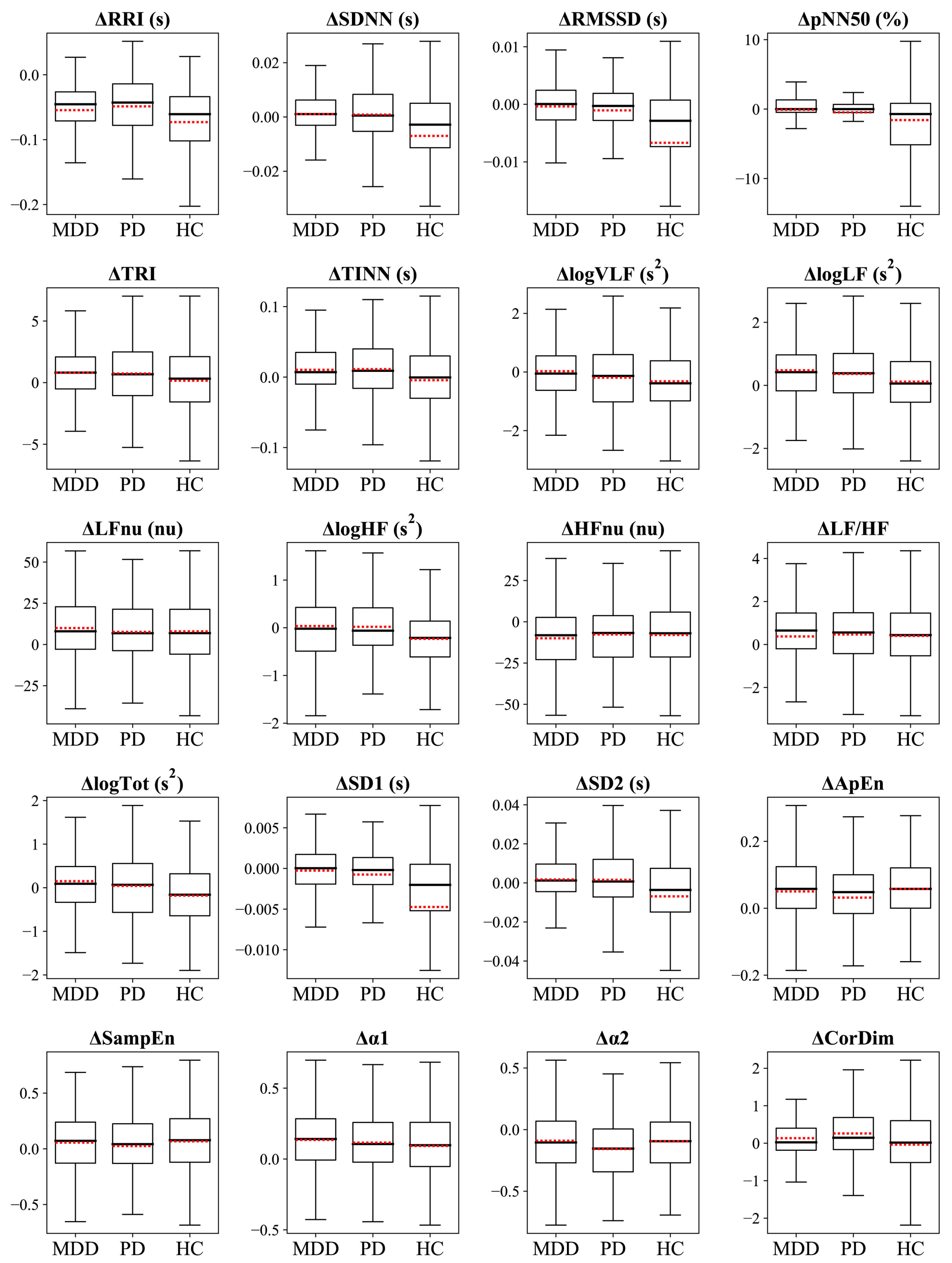

FIGURE 4
Box plots display the ΔHRV. Red dotted lines indicate mean values.

TABLE 3 Comparison of ΔHRV among the MDD, PD, and HC groups.

Feature (STR − RLX)	*F* (*P* value)	η^2	*Post-hoc P* value (Cohen's *d*)			Absolute change
			MDD vs. PD	MDD vs. HC	PD vs. HC	
ΔRRI[a] (s)	14.047 (<.001)	0.044	.452 (*d* = 0.125)	*<.001* (*d* = 0.365)	*<.001* (*d* = 0.466)	HC > MDD, PD
ΔSDNN (ms)	3.017 (.050)	0.009	1.00 (*d* = 0.022)	.117 (*d* = 0.184)	.124 (*d* = 0.178)	
ΔRMSSD (ms)	1.762 (.173)	0.005	ns			
ΔpNN50[a] (%)	2.696 (.069)	0.009	ns			
ΔTRI[a]	3.301 (.038)	0.011	.970 (*d* = 0.024)	*.042* (*d* = 0.222)	.105 (*d* = 0.188)	MDD > HC
ΔTINN[a] (ms)	4.185 (.016)	0.014	.982 (*d* = 0.019)	*.027* (*d* = 0.234)	*.024* (*d* = 0.239)	MDD, PD > HC
ΔlogVLF (s^2)	4.326 (.014)	0.013	.254 (*d* = 0.169)	*.010* (*d* = 0.263)	.839 (*d* = 0.111)	HC > MDD
ΔlogLF (s^2)	7.010 (<.001)	0.021	.886 (*d* = 0.098)	*.001* (*d* = 0.314)	*.041* (*d* = 0.266)	MDD, PD > HC
ΔLFnu (nu)	0.825 (.439)	0.003	ns			
ΔlogHF (s2)	7.607 (<.001)	0.023	1.00 (*d* = 0.017)	*.003* (*d* = 0.276)	*.005* (*d* = 0.396)	HC > MDD, PD
ΔHFnu (nu)	0.838 (.433)	0.003	ns			
ΔLF/HF	0.080 (.924)	0.000	ns			
ΔlogTot (s^2)	7.383 (<.001)	0.022	.827 (*d* = 0.103)	*<.001* (*d* = 0.318)	*.036* (*d* = 0.276)	HC > MDD, PD
ΔSD1 (ms)	1.762 (.173)	0.005	ns			
ΔSD2 (ms)[a]	4.499 (.012)	0.017	.994 (*d* = 0.011)	*.010* (*d* = 0.255)	*.013* (*d* = 0.247)	HC > MDD, PD
ΔApEn	2.331 (.098)	0.007	ns			
ΔSampEn	1.164 (.313)	0.004	ns			
Δα1	1.907 (.149)	0.006	ns			
Δα2	4.239 (.015)	0.013	*.035* (*d* = 0.258)	1.00 (*d* = 0.020)	*.031* (*d* = 0.251)	PD > MDD, HC
ΔCorDim[a]	4.147 (.016)	0.013	.494 (*d* = 0.118)	.240 (*d* = 0.153)	*.012* (*d* = 0.266)	PD > HC

Post-hoc P values in italics <.05.
ns, no significant main effect; MDD, major depressive disorder; PD, panic disorder; HC, healthy control.
[a]Welch's one-way ANOVA and Games-Howell *post-hoc* analysis were used. Except for these cases, Fisher's one-way ANOVA and Bonferroni *post-hoc* analysis were employed.

TABLE 4 Performance measures for classifying stress and relaxation tasks based on the longitudinally scaled HRV data.

Model	Group	Accuracy	F1	Recall	Precision	AUC
Combined data model						
Overall		0.9391 ± 0.0021	0.9389 ± 0.0022	0.9399 ± 0.0034	0.9389 ± 0.0030	0.9798 ± 0.0015
MDD		0.9420 ± 0.0036	0.9413 ± 0.0036	0.9301 ± 0.0041	0.9528 ± 0.0056	0.9799 ± 0.0011
PD		0.9048 ± 0.0041	0.9044 ± 0.0043	0.9005 ± 0.0072	0.9084 ± 0.0042	0.9610 ± 0.0027
HC		0.9603 ± 0.0025	0.9608 ± 0.0025	0.9732 ± 0.0041	0.9486 ± 0.0037	0.9916 ± 0.0013
Separate data models						
MDD		0.9350 ± 0.0051	0.9336 ± 0.0053	0.9291 ± 0.0079	0.9413 ± 0.0067	0.9801 ± 0.0031
PD		0.9057 ± 0.0086	0.9065 ± 0.0094	0.9238 ± 0.0104	0.8935 ± 0.0103	0.9542 ± 0.0052
HC		0.9545 ± 0.0038	0.9543 ± 0.0039	0.9572 ± 0.0044	0.9529 ± 0.0045	0.9881 ± 0.0015

For the combined data model, the metrics were calculated separately for each patient group in the test dataset, in addition to the overall evaluation based on the entire test data. Separate data models were trained and tested, each using the data from one specific patient group exclusively. Results are presented as mean and standard deviation calculated from 20 repeats.
AUC, area under the curve; MDD, major depressive disorder; PD, panic disorder; HC, healthy control.

3.10 Feature importance after longitudinal scaling

We applied the same methodology used for the unscaled data to calculate SHAP values for the classification based on scaled data (Figure 5). The key finding was that RRI emerged as the most important feature across all the models. When the top three features were considered, only the order changed in the combined data and PD models. In the MDD group, SampEn was replaced by $\alpha1$, while in the HC group, the composition and order of the top three features remained unchanged. RRI and ApEn consistently ranked as essential features across all the groups, which was consistent with the results from the unscaled data.

3.11 Group comparisons of the scaled ΔHRV

Figure 6 illustrates the differences in scaled ΔHRV among the groups. We compared scaled ΔHRV values among the MDD, PD,

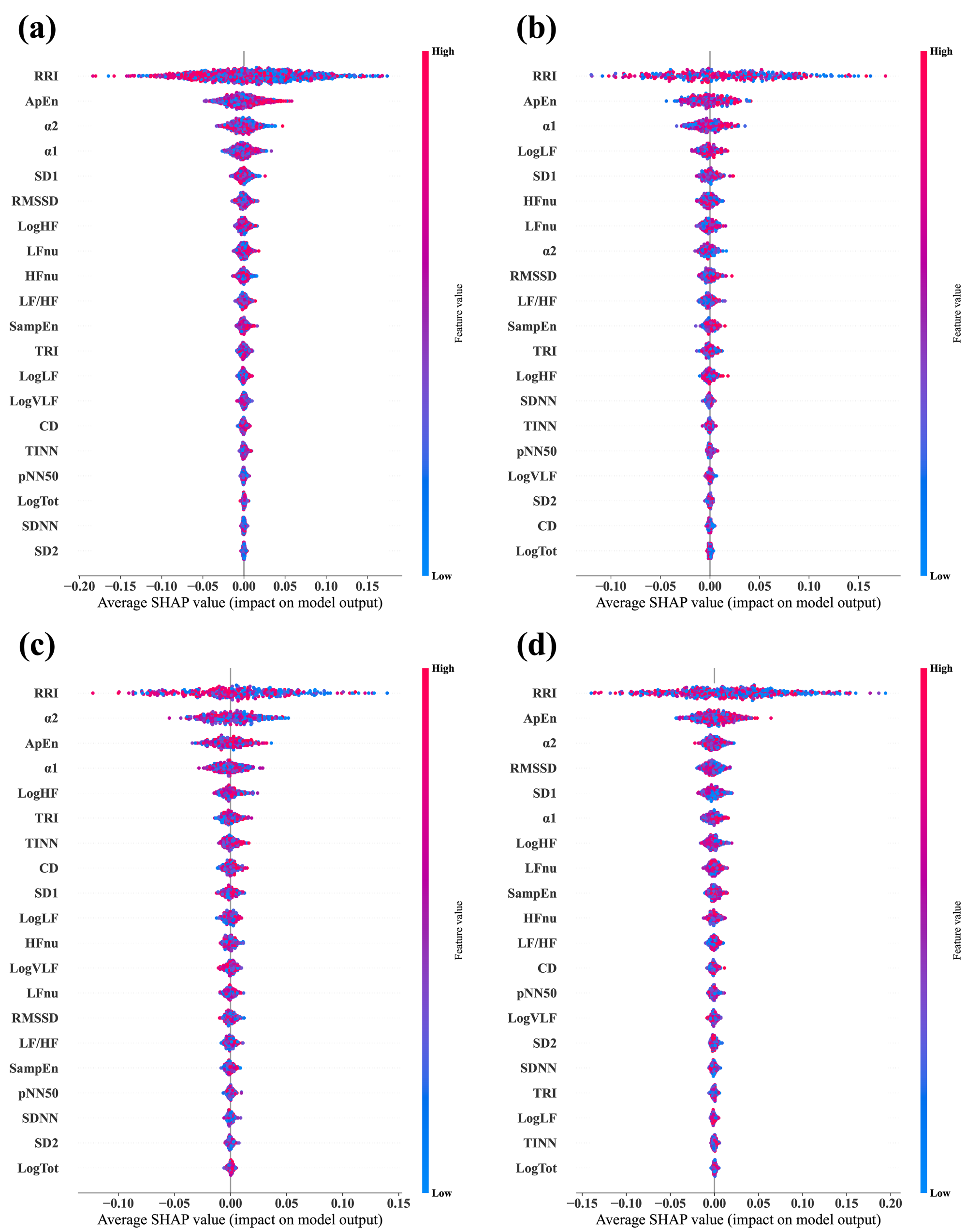

FIGURE 5
Average SHAP values evaluated from the four different classifier models via the longitudinally scaled HRV data. **(A)** Combined data model, which was trained and tested via data from all three groups, —MDD, PD, and HC. **(B)** MDD-based model, which was trained and tested via data from the MDD group exclusively. **(C)** PD-based model, which was trained and tested via data from the PD group exclusively. **(D)** HC-based model, which was trained and tested via data from the HC group exclusively. In each plot, the features are arranged in descending order of importance.

and HC groups (Table 5) and found a significant main effect of the group in 11 HRV features. HC participants exhibited greater absolute changes between the stress and relaxation tasks than the MDD and PD groups in seven features: SDNN, RMSSD, pNN50, logHF, logTot, SD1, and SD2. Conversely, the HC group had smaller changes in TINN and logLF than the MDD and PD groups. In RRI, the MDD and HC groups had greater changes than the PD group. The MDD group also demonstrated a greater change in TRI than the HC group.

The HC group had greater absolute changes than the MDD group in seven features, whereas the MDD group exhibited larger absolute changes than the HC group in three features. The HC group had greater absolute changes than the PD group in eight features, whereas the PD group exhibited larger absolute changes

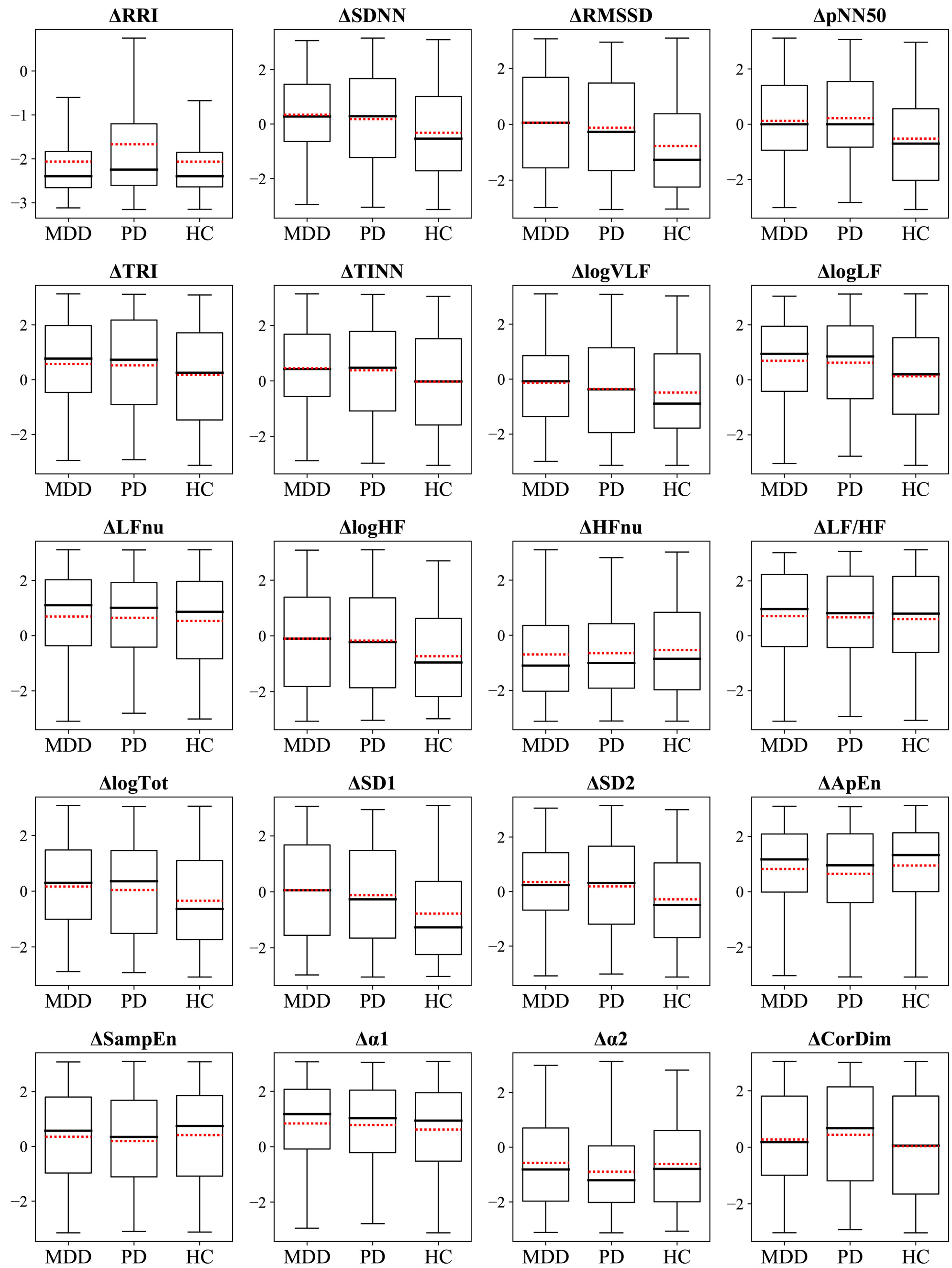

FIGURE 6
Box plots display the ΔHRV_{scaled}. Red dotted lines indicate mean values.

TABLE 5 Comparison of ΔHRV_{scaled} among the MDD, PD, and HC groups.

Feature (a.u.) (STR − RLX)	*F* (*P* value)	η^2	*Post-hoc P* value (Cohen's *d*)			Absolute change
			MDD vs. PD	MDD vs. HC	PD vs. HC	
ΔRRI[a]	6.503 (0.002)	0.027	*0.004* (*d* = 0.331)	1.000 (*d* = 0.001)	*0.002* (*d* = 0.335)	HC, MDD > PD
ΔSDNN[a]	10.500 (< 0.001)	0.031	0.594 (*d* = 0.101)	*< 0.001* (*d* = 0.412)	*0.006* (*d* = 0.293)	HC > MDD, PD
ΔRMSSD	14.496 (< 0.001)	0.043	0.986 (*d* = 0.099)	*< 0.001* (*d* = 0.467)	*< 0.001* (*d* = 0.377)	HC > MDD, PD
ΔpNN50	14.463 (< 0.001)	0.043	1.000 (*d* = 0.060)	*< 0.001* (*d* = 0.391)	*< 0.001* (*d* = 0.453)	HC > MDD, PD
ΔTRI[a]	3.834 (0.022)	0.012	0.953 (*d* = 0.030)	*0.032* (*d* = 0.238)	0.089 (*d* = 0.198)	MDD > HC
ΔTINN	5.698 (0.004)	0.017	1.000 (*d* = 0.045)	*0.008* (*d* = 0.291)	*0.029* (*d* = 0.240)	MDD, PD > HC
ΔlogVLF	2.541 (0.080)	0.008	ns			
ΔlogLF	8.594 (< 0.001)	0.026	1.000 (*d* = 0.045)	*< 0.001* (*d* = 0.350)	*0.004* (*d* = 0.303)	MDD, PD > HC
ΔLFnu	0.585 (0.557)	0.002	ns			
ΔlogHF[a]	9.541 (< 0.001)	0.028	0.924 (*d* = 0.039)	*< 0.001* (*d* = 0.362)	*0.002* (*d* = 0.325)	HC > MDD, PD
ΔHFnu	0.585 (0.557)	0.002	ns			
ΔLF/HF	0.258 (0.773)	0.001	ns			
ΔlogTot	6.038 (0.003)	0.018	1.000 (*d* = 0.076)	*0.004* (*d* = 0.314)	*0.041* (*d* = 0.228)	HC > MDD, PD
ΔSD1	14.505 (< 0.001)	0.043	0.985 (*d* = 0.100)	*< 0.001* (*d* = 0.467)	*< 0.001* (*d* = 0.377)	HC > MDD, PD
ΔSD2[a]	9.693 (< 0.001)	0.028	0.613 (*d* = 0.098)	*< 0.001* (*d* = 0.397)	*0.009* (*d* = 0.280)	HC > MDD, PD
ΔApEn	2.043 (0.130)	0.006	ns			
ΔSampEn	0.932 (0.394)	0.003	ns			
Δα1	1.214 (0.298)	0.004	ns			
Δα2[a]	2.670 (0.070)	0.008	ns			
ΔCorDim[a]	2.800 (0.062)	0.009	ns			

Post-hoc P values in italics <.05.
ns, no significant main effect; MDD, major depressive disorder; PD, panic disorder; HC, healthy control.
[a]Welch's one-way ANOVA and Games-Howell *post-hoc* analysis were used. Except for these cases, Fisher's one-way ANOVA and Bonferroni *post-hoc* analysis were employed.

than the HC group in two features. A significant difference between the MDD and PD groups was observed only in RRI, and the MDD group exhibited a greater absolute change than the PD group.

3.12 Classification using an MLP algorithm

To verify whether our findings were influenced by the choice of the machine-learning algorithm, we utilized the MLP algorithm to conduct the same classification tasks previously conducted via the random forest algorithm. Furthermore, we applied the same classification to the longitudinally scaled HRV data using MLP classifiers.

Results obtained from the MLP models were consistent with those generated by the random forest algorithm (Supplementary Table 7). Before we applied the personalized longitudinal scaling, the order of accuracy was HC, PD, and MDD in the MLP model. After its application, the accuracy increased to over 0.9, and the order of accuracy was HC, MDD, and PD in the MLP model. This consistency with the random forest algorithm results indicated that our findings were not affected by the choice of the machine-learning algorithm; rather, they stemmed from the inherent characteristics of the data itself.

4 Discussion

We differentiated stress and relaxation based on HRV features in groups with MDD, PD, and HCs via a random forest algorithm. Classification accuracies for the MDD, PD, and HC groups were 0.67, 0.69, and 0.73, respectively, which indicated that the classification of stress and relaxation was more accurate for healthy individuals compared with patients with MDD and PD (Figure 7). A personalized longitudinal scaling of HRV data improved the accuracies for all the groups, and the MDD, PD, and HC groups reached accuracies of 0.94, 0.90, and 0.96, respectively (Figure 7). This suggested the potential of personalized scaling in monitoring the condition of patients with

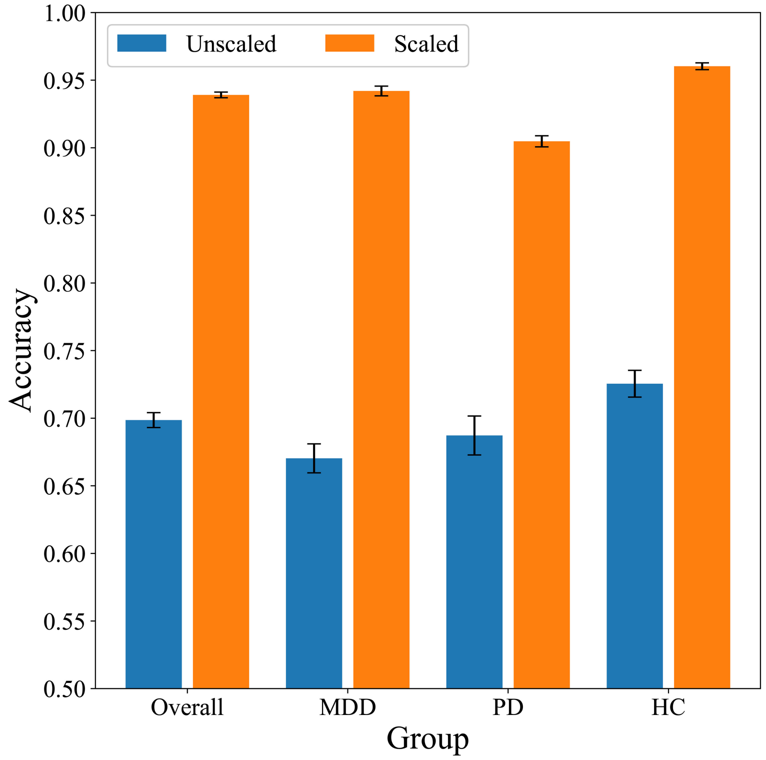

FIGURE 7
Summary of classification accuracies based on combined data models (Tables 2, 4).

psychiatric disorders. Results obtained from the MLP models were consistent with those generated by the random forest classifier, which suggested that our findings were not dependent on the specific algorithm used.

Patients' HRV values were significantly lower than those of the healthy individuals (Supplementary Table 3). We noticed significant differences among the groups in 13 HRV features. The MDD and PD groups displayed lower values compared with the HC group. These findings aligned with previous research, which indicated that individuals with depression and PD had reduced HRV. This suggested lower autonomic flexibility and higher sympathetic dominance (24–26).

Several features demonstrated significant differences between the stress and relaxation tasks, which indicated that HRV effectively distinguished between these states (Supplementary Table 5). Particularly, seven features—RRI, logLF, LFnu, HFnu, ApEn, α1, and α2—exhibited significant differences between the two tasks in all three groups. Among these, RRI, ApEn, and α2 were also identified as highly important features based on SHAP evaluation (Figure 3), which suggested their potential importance in classification. Moreover, the PD and HC groups had more features that depicted significant differences between the tasks compared with the MDD group. This indicated potential challenges for the MDD group in distinguishing between stress and relaxation based on HRV features.

Previous research determined that most HRV features decreased under stress owing to increased sympathetic and decreased parasympathetic activity (17–19, 71, 72). In contrast, LF-related features, closely linked to sympathetic activity, tended to increase under stress (17–19, 71, 72). Our results also indicated that most features with statistically significant differences between the two tasks displayed lower values during stress, whereas LF-related features increased during stress. However, exceptions were observed for geometric features, such as TRI and TINN, and nonlinear features, such as ApEn, SampEn, α1, and CorDim, which presented lower HRV values during the relaxation task. Methodological variations existed across studies, which included differences in stimulation methods, order of stimuli, and relaxation techniques (19). For instance, α1 decreased under physical stress but increase under psychological stress (73, 74). Therefore, HRV responses to a specific stress stimulus may not consistently exhibit lower values across all features. These findings emphasized the complexity of HRV responses and the importance of considering multiple factors when interpreting HRV data in the context of stress and relaxation (19). Future studies should conduct additional tests to investigate lower HRV during the relaxation task compared with the stress task.

Our most significant finding was that under the same experimental conditions, distinguishing stress and relaxation in the PD and MDD groups compared with the HC group was relatively more challenging. With unscaled HRV, the accuracy for the HC group was 0.73, whereas it was relatively lower for the PD and MDD groups at 0.69 and 0.67, respectively (Table 2). We analyzed the reasons for this difference via various methods. First, we matched the sample size through random undersampling since the HC group had the highest number of samples; however, the order of the performance metrics remained similar among the groups (Table 2). Second, we built classifier models exclusively for each group to ensure that data from different groups did not interact during the training process. However, the accuracy for the HC group remained higher than that of the other two patient groups (Table 2). These findings suggested that the diminished performance was inherent to the traits of the PD and MDD groups.

In addition, we evaluated the important features used in classifier models with SHAP (Figure 3). Although the overall ranking of the 20 features varied across the four models. ApEn and RRI were consistently among the top three features in all four models. Additionally, SampEn and α2 were included as important features. This indicated that despite group differences, the key indicators used for stress-relaxation classification based on the random forest presented no substantial differences across the models. Similar results were observed in within-subject comparison statistics (Supplementary Table 5), where RRI, ApEn, and α2 exhibited distinct differences between the stress and relaxation states across all the groups. Combining the results from SHAP and statistical analysis, we can infer that RRI, ApEn, and α2 are expected to play a crucial role in classification.

To further investigate the difference in classification accuracy among the groups, we compared their ΔHRV values (Table 3). ΔHRV was calculated to assess participants' autonomic reactivity. Our previous works demonstrated that patients with psychiatric disorders had pathologically altered autonomic responses compared with healthy individuals, which resulted in different reactions to mental tasks (44, 75–77). A larger absolute ΔHRV indicated a more distinct ANS response to the two tasks, which suggested better classification performance for groups with greater reactivity. We hypothesized that the higher-accuracy group would show greater reactivity, that is, larger absolute ΔHRV, than the other groups.

Analysis based on unscaled ΔHRV demonstrated that 11 features had significant differences among groups (Table 3). Among these, four features—RRI, logHF, logTot, and SD2—had larger absolute ΔHRV values in the HC group compared with the two patient groups. RRI, identified as a highly important indicator by SHAP, likely significantly contributed to the higher classification accuracy in the HC group (Figure 3). Furthermore, in the HC-based classifier model that used only HC data, RRI was the most important feature, underscoring its importance (Figure 3). Conversely, for α2, another important feature indicated by SHAP, the PD group exhibited greater absolute changes than the MDD and HC groups. TINN and logLF presented greater absolute changes in the two patient groups compared with the HC group.

In comparing the HC group to the MDD group, more features with greater absolute changes, including the important feature RRI, were observed in the HC group. Although the MDD group had some features with greater absolute changes than the HC group, these features were less important than RRI. These results suggested that the HC group likely achieved better classification results because they exhibited higher reactivity in both a greater number of features and more important features compared with the MDD group. We compared HC and PD groups and observed that each group had greater absolute changes in four features compared with the other. Interestingly, the PD group displayed greater absolute changes in an important feature, α2. This suggested that a comparison based on the number of highly reactive features and inclusion of important features may not be sufficient to clearly explain why the HC group outperformed the PD group regarding classification. The superiority of HRV features in the HC group over those in the PD group for classification was demonstrated through various methods in our study. We plan to further explore this reason comprehensively. Thus, the HC group exhibited significantly greater ΔHRV in a larger number of or more important features than the patient groups, indicating more pronounced autonomic reactivity. This enhanced reactivity likely contributes to the higher classification accuracy observed in the HC group.

Our participants made up to five visits over a period of 12 weeks and completed five tasks during each visit. Data collected from these visits and tasks were used for personalized scaling. Our goal was to gather as much data as possible while exposing the participants to various experimental conditions. Our study demonstrated that personalized longitudinal scaling significantly improved classification performance across all the participant groups. We utilized t-SNE visualization and observed improved separation of feature values into stress and relaxation states (Supplementary Figure 3). Individual HRV responses varied across multiple visits, which reflected the influence of both stimuli and daily state of each participant, as depicted in Figure 2 (78, 79). Changes in HRV may be more strongly influenced by daily states than by specific external stimuli. If this variability in HRV is not adequately normalized, classifying tasks based on HRV data can pose significant challenges. In cases where a substantial amount of individual data is accumulated in the long term, time-axis scaling (i.e., longitudinal scaling) can be applied, which can help reduce variability occurring at each time point (e.g., a visit in this study). Therefore, longitudinal scaling can lead to a clearer separation between HRV values measured during different tasks.

We conducted the analysis on the scaled HRV data via the same method that was applied to the unscaled data to understand classification performance based on the scaled data. Seven scaled features—RRI, LFnu, HFnu, LF/HF, ApEn, α1, and α2—exhibited significant differences between the stress and relaxation tasks in all the three groups (Supplementary Table 6). Among these, RRI, ApEn, α1, and α2 were also identified as highly important features based on the SHAP evaluation (Figure 5), which suggested their potential importance in classification. The HC group had four more features that exhibited significant differences between the two tasks compared with the PD group, which suggested a relative difficulty for the PD group in classification between stress and relaxation.

Personalized scaling dramatically improved classification performance in all the three groups (Table 4). The accuracy exceeded 0.9, which allowed for precise differentiation between stress and relaxation states. These outcomes demonstrated the potential of personalized data scaling to monitor individual patient conditions with high accuracy. Interestingly, the accuracy remained highest in the HC group, followed by the MDD and PD groups. Before the scaling, the order of accuracy was HC, PD, and MDD; however, after the scaling, the order of accuracy for PD and MDD reversed.

The SHAP analysis on the scaled HRV data revealed that RRI was the most important feature across all classification models (Figure 5). When compared with other features, RRI's importance was dominantly higher. Although RRI was already one of the top three important features in the unscaled HRV data, its importance increased significantly after scaling, as demonstrated by comparing the two in Figures 3, 5. This indicated that the role of RRI in the classification became significantly more crucial post-scaling. In the scaled HRV data, ApEn and α2 were also included in the top three important features, similar to the unscaled data.

The RRI is a sensitive indicator of changes in both the sympathetic and parasympathetic nervous systems, making it valuable for detecting autonomic variations under conditions of stress (80–82). Previous studies have identified RRI or its inverse, average heart rate, as key indicators for stress classification (80–82). Furthermore, RRI's high temporal resolution enhances its effectiveness in stress detection, allowing for accurate classification even with short measurement periods of 30 seconds (81, 82). Additionally, entropy-based measures such as ApEn capture heartbeat irregularity, which typically decreases under stress, thereby making it an effective feature for stress detection (54, 83, 84). ApEn has been used to classify stressful events, underscoring its relevance as a stress indicator (54). The DFA α2 reflects the complexity and fractal characteristics of long-term HRV, capturing self-similarity across time scales and changes in adaptability under stress (17, 53, 58). Prior studies have demonstrated that stress-induced shifts in the ANS toward sympathetic dominance alter HRV complexity, resulting in changes to α2 (85, 86). These findings underscore the utility of α2 for assessing cardiac autonomic regulation across various conditions. Although stimuli used to induce stress or relaxation in studies vary, complicating direct comparisons, our findings align with previous research where RRI and nonlinear HRV measures are identified as significant features for stress classification.

We compared the scaled ΔHRV values among the different groups to investigate differences in classification performance via the same method as the unscaled data (Table 5). We determined that the absolute change of RRI, the most important feature, was greater in the MDD and HC groups compared with the PD group. This suggested that the MDD and HC groups could have had an advantage in classification compared with the PD group. Additionally, we noticed that the HC group exhibited greater absolute changes in more features than the MDD group, which suggested a relative advantage in classification for the HC group. Overall, our findings suggested that a group that displayed a greater number of features with higher reactivity tended to exhibit better performance compared with other groups when the scaled HRV data was used for classification.

Recent studies on monitoring technologies for patients with psychiatric disorders focused on obtaining longitudinal data, such as ecological momentary assessment and physiological data, to observe patient conditions and use the findings to improve treatment (87, 88). Our results indicated that personalized data scaling could enhance the accuracy of assessing patient conditions in studies that monitored patients via physiological signals. Although personalized scaling requires a substantial amount of accumulated data for each individual, it is expected to significantly improve classification performance.

In the recent times, artificial intelligence techniques are increasingly being used in research to detect stress based on HRV (21). Such studies employ diverse methods, from classical rule-based techniques such as fuzzy logic to classical machine learning approaches including support vector machine, random forest, and k-nearest neighbors. Advanced methods, including deep learning and hybrid approaches combining classical algorithms with neural networks, further demonstrate the variety of stress detection techniques that are used in studies (21, 89). Many studies have investigated beyond just HRV, leveraging multimodal sensor data. Signals such as ECG, photoplethysmogram (PPG), electrodermal activity (EDA), electromyogram, or respiration are simultaneously measured and utilized (21). Whether using HRV or multimodal sensors, most studies report classification accuracies between 70% and 99% (21). For example, one study achieved 75% accuracy using HRV and a random forest algorithm (90), while another reached 90% with an artificial neural network and HRV (91). Our results, with HRV-based random forest and MLP models achieving 70% to over 90% accuracy, align with these prior findings.

However, most studies focus on non-clinical populations, and analysis of stress detection for individuals with psychiatric conditions is lacking (21). Private datasets used in previous studies primarily focus on healthy individuals; furthermore, publicly available datasets such as SWELL-KW and PhysioNet's driving database also mainly target healthy individuals (21, 90, 91). However, studies addressing stress detection in psychiatric population groups, such as those with MDD or PD, are uncommon.

Our study addresses this gap by conducting comparative experiments with clinical populations (MDD and PD) and HCs under controlled stress-relaxation protocols. The observed differences in stress-relaxation classification highlight the need to consider disparities between patients and healthy individuals when developing ANS monitoring technologies. These findings emphasize the importance of tailored solutions for both clinical and everyday settings, thereby addressing the unique autonomic characteristics of psychiatric populations.

Thus, the clinical implications of this study indicate that HRV has significant potential as a biomarker for stress, particularly in differentiating between stress and relaxation states across the three groups. Our findings suggest that effective stress monitoring should consider the varying autonomic responses of patient groups and healthy individuals to improve classification accuracy. Furthermore, the implementation of personalized data scaling significantly enhanced classification performance, indicating that individualized HRV-based monitoring could offer a more reliable and tailored stress assessments for managing psychiatric conditions.

4.1 Limitations

The number of participants measured by the experiment was small. Although the sample size exceeded 1000 owing to multiple individual visits, the number of participants per group was approximately 40–60. Particularly, the number of patients in the

PD and MDD groups was smaller than that in the HC group. Recruiting more participants would enable further research into how this might impact classification accuracy between groups.

Importantly, our patient groups were on medication during the 12-week experiment, and we did not specifically analyze their potential impact on our results. Ongoing research into the effects of therapeutic drugs on HRV suggests varying impacts. Antidepressants have been linked to alterations in HRV; however, definitive evidence remains inconclusive. One meta-analysis reported that TCAs substantially reduced HRV, while other antidepressants showed minimal effects (92). In contrast, a large study involving more than 2000 participants found no association between HRV and MDD itself. However, MDD patients on SSRIs, SNRIs, and TCAs displayed a significantly reduced HRV (93). These findings imply that the antidepressants, rather than MDD alone, may explain the reduced HRV observed in the study participants, as all were undergoing treatment. Therefore, we cannot entirely eliminate the possibility that the observed differences in classification performance and HRV reactivity among the groups could be influenced by medication. Nevertheless, considering that patients are likely to be on medication in real-world applications, our findings remain relevant for practical therapeutic environments. Furthermore, this study did not distinguish between treatment responders and non-responders within the patient groups. In future, we intend to differentiate these response groups, enabling a more detailed analysis of differences in stress reactivity and stress-relaxation classification performance between responders and non-responders.

We utilized SHAP as a representative method to calculate feature importance and employed statistical analysis methods to obtain complementary data on HRV reactivity. Alternative calculation methods for feature importance, such as permutation feature importance and local interpretable model-agnostic explanations, exist (94, 95). These methods can be explored in future studies. The statistical test identifies features that differ significantly among groups, while SHAP values highlight features that most contribute to the model's predictions and considered the full complexity of the data. Both statistical analysis and SHAP values play distinct yet complementary roles in indicating important metrics. Features that are both statistically significant and have high SHAP values might be considered as candidates for essential predictors.

We used only a basic MLP model. With recent advancements in deep learning, various neural network models have shown promising results in medical sciences, including psychiatry (96). The reason for applying MLP was to demonstrate that our results are not confined to a specific algorithm. We chose MLP to perform the same classification via an entirely different algorithm from random forest. For future studies, we aim to experiment with more advanced neural network architectures to enhance classification performance.

In this study, we focused exclusively on HRV as a measure of responses to stress and relaxation. Although there are several other physiological markers that can be employed to monitor stress responses, such as EDA, respiratory rate, blood pressure variability, and electroencephalography, HRV provides several advantages (97–100). For example, the development of wearable devices has made it more accessible for continuous monitoring of HRV. Moreover, HRV measurements are typically less susceptible to external noise and environmental factors, resulting in more reliable and stable outcomes. The EDA is one of the physiological signals measured by wearable devices, commonly used in stress research, and has demonstrated promising results. However, unlike HRV, which measures both sympathetic and parasympathetic activity, EDA can only measure sympathetic activity. Considering the limited research conducted on automated stress detection in psychiatric disorders, we prioritized HRV for its ability to provide a more comprehensive view of autonomic balance. In this study, HRV features were extracted from ECG signals. Use of commercial or research-grade wearable devices to measure PPG and derive HRV can help future research, enabling real-time stress monitoring for individuals with psychiatric conditions.

5 Conclusion

Our study utilized HRV features to distinguish stress and relaxation responses among groups with MDD and PD and HCs via a random forest algorithm. Classification accuracies were 0.67, 0.69, and 0.73 for the MDD, PD, and HC groups, respectively, which indicated higher accuracy in healthy individuals. Personalized longitudinal scaling of HRV data improved classification accuracies, and reached 0.94, 0.90, and 0.96 for the MDD, PD, and HC groups, respectively, which suggested the potential of personalized scaling in monitoring a patient's conditions based on HRV measurements. Results produced by the MLP models were in line with those by the random forest classifier, which indicated that our findings were not reliant on a particular algorithm.

Our findings revealed that it was more challenging to differentiate stress and relaxation in the PD and MDD groups than in HCs, partly owing to the intrinsic characteristics of patient data that reflected altered autonomic responses. Additionally, the HC group demonstrated greater autonomic reactivity in a larger number of and more significant features, which potentially contributed to higher classification accuracy. These results underscore the potential of HRV metrics as biomarkers for stress and emphasize the importance of accounting for differences in autonomic responses between patients and healthy individuals when developing stress monitoring technologies in both clinical and everyday settings.

Data availability statement

The datasets presented in this article are not readily available because of privacy restrictions. Requests to access the datasets should be directed to david0203@korea.ac.kr.

Ethics statement

The studies involving humans were approved by Ethics Committee of Samsung Medical Center in Seoul, Korea (No. 2015-07-151). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AK: Conceptualization, Data curation, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. MS: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. HJ: Supervision, Writing – original draft, Writing – review & editing. CC: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

Author HJ was employed by Meditrix Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1500310/full#supplementary-material

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The effect of a one-time mindfulness intervention on body and mind in healthy adolescents using multimodal measurements

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Background: Mindfulness-based interventions can improve psychological well-being and reduce symptoms of mental burden, including among adolescents. Relationships between basic mindfulness (trait mindfulness) and the immediate effects of a single mindfulness intervention have not been thoroughly researched, especially in adolescents. In this study, we aimed to elucidate these aspects by using a multimodal approach—measuring the effect of a single mindfulness intervention on both subjective and physiological parameters.

Methods: A total of 78 healthy adolescents (12–19 years of age, 50% female) were assigned to either a mindfulness or an active control group. Before and after the interventions, subjective parameters (mood, stress, and state mindfulness) were assessed using bipolar visual analogue scales. Physiological parameters (heart rate and heart rate variability) were measured before and during the interventions. Participants also completed the Self-Compassion Scale (SCS-D) with the subscale "mindfulness" as an assessment of trait mindfulness, and the State-Trait Anxiety-Depression Inventory (STADI).

Results: Our results showed no significant interactions between time and intervention, either subjectively or physiologically. For heart rate, we found a main effect of time. For all subjective parameters, we observed a main effect of trait mindfulness. Age was a relevant factor for heart rate and state mindfulness, suggesting age effects. We also observed strong correlations between trait mindfulness, trait anxiety, and depression scores.

Conclusion: A single mindfulness intervention had no immediate observable effects in our healthy adolescent sample, and possible reasons for this finding are discussed. Nevertheless, the present data show the potential for increased resilience through mindfulness in adolescence.

KEYWORDS

mindfulness, body scan, state mindfulness, mental burden, heart rate, heart rate variability, adolescents

1 Introduction

Among adolescents, high stress levels are linked to increased mental health problems and reduced well-being. Mental health problems affect up to 20% of children and adolescents worldwide (1–4). This alarmingly high rate is particularly worrying due to the prolonged impact into adulthood (4). Therefore, it is of particular interest to strengthen the resilience of youths, to prevent progression to mental health issues at an early stage.

Mindfulness-based interventions (MBIs) have become increasingly popular, especially for promoting psychological well-being and symptom reduction regarding stress or depressive symptoms (5). In a recent review, Porter and colleagues (6) examined 27 studies of children and adolescents using MBIs, and found that most studies showed effects of symptom reduction, e. g. depression symptoms, anxiety and stress. However, these effects were observed over a relatively long-term period, ranging from four weeks to five months (6). While general improvements of mindfulness were observed, the review also highlighted notable methodological inconsistency in the operationalization of mindfulness across studies (6).

When examining mindfulness, it is important to distinguish between mindfulness as a state versus a trait (7). Trait mindfulness refers to an individual's general tendency to act mindfully in daily life and across various situations (8). Such dispositional mindfulness can be improved by regularly practicing mindfulness exercises over an extended period (7, 9). On the other hand, state mindfulness refers to the level of mindfulness at a given moment, characterized by being attentive and accepting of all present sensations (7). This state can be immediately heightened through mindfulness-related exercises (10). Thus, the improvements attained through MBIs primarily relate to trait mindfulness. An increase of state mindfulness can be measured immediately after a mindfulness intervention—for example, breathing exercises, body scans, attention to movement, and mindful walking, which are basic exercises in mindfulness (11). In a recent study, Sparacio and colleagues (12) reported that the most widely used mindfulness exercise was the body scan, which most effectively reduced stress. Investigations of state mindfulness can help to illuminate the specific psychological and physiological mechanisms involved in mindfulness. Moreover, the application of quick and easy one-time mindfulness exercises is particularly suitable for children and adolescents.

To date, research on the immediate effects of one-time mindfulness exercises has been limited, and mainly confined to the adult domain. One study revealed that a single use of a web-based mindfulness exercise yielded a significantly increased post-intervention mindfulness state in the mindfulness condition, and not in the passive control group (13). Moreover, one-time mindfulness exercises are reportedly effective for reducing induced distress (14), perceived stress, preservative thinking, symptoms of depression, and anxiety, all with small-to-medium effect sizes (15). A meta-analysis by Schumer et al. (16) revealed that a mindfulness practice influenced affect in a manner that did not depend on the intervention's duration, but these results are based on adult samples. Overall, the available studies indicate that even brief mindfulness exercises can be sufficient to foster a non-judgmental and non-reactive attitude towards occurring events and thoughts, as well as positive effects on well-being.

Fewer studies have examined the effect of a single MBI among children and adolescents, and these studies are often focused on specific topics. For example, Petter and colleagues (17) examined how mindful attention manipulation influenced pain responses in healthy adolescents with different meditation experiences. They found that state mindfulness was related to improved pain reactions, but the mindfulness intervention was only effective among adolescents engaged in regular meditation practice (17), which may reflect the interplay of state and trait mindfulness. Another study investigated the effect of a ten-minute mindfulness practice (stretching and mindful breathing), versus a control condition (quiet play with non-stimulation toys), which revealed no change in self-reported calmness (18). These findings suggest that children and adolescents may experience immediate effects of MBI. However, several questions remain unanswered and require further investigation: can state mindfulness be enhanced in healthy children and adolescents through a single MBI, and if so, in a comparable effect size to adults? What influence does daily meditation practice have for this effect? Are there developmental or gender-related differences? Addressing these gaps will be essential to deepen our understanding of the impact of MBIs on young individuals.

In addition to the subjective effects of MBIs on mood or symptom severity, autonomic nervous system (ANS) changes can also be examined as a physiological indicator of the effects of mindfulness exercises. Such investigations can help uncover the biological mechanisms underlying the effects of MBIs. In particular, parameters of heart rate variability (HRV) seem promising (19). High HRV is associated with a more efficient ANS (i.e., in reaction to stress), which is reportedly affected by MBIs (20). HRV has been used as a short-term indicator of MBI effectiveness—for example, to assess acute cardiovascular effects during each mindfulness session in a study involving ten days of mindfulness practice, which resulted in higher HRV compared to a passive control group (21). When examining an even shorter time period (i.e., a single session), HRV was slightly improved after mindfulness-based cognitive training in an adolescent sample with attention-deficit/hyperactivity disorder compared to a control condition (22). As another parameter of the ANS, heart rate (HR) has also been investigated in MBI studies, with decreased HR indicating a relaxing effect of MBIs (23). Thus, ANS parameters—primarily HRV and HR—have a strong ability to reflect the effect of MBIs on physiological processes, and can be easily and non-invasively assessed. Studies in which the multimodal approach has proven effective for investigating the effects of mindfulness induction on both subjective and objective outcomes in adolescents include those conducted after a psychosocial stress induction, for example after a psychosocial stress induction (24, 25).

Overall, there remain uncertainties in samples of healthy adolescents regarding the strength of the association between state and trait mindfulness, the effectiveness of a single mindfulness intervention, and the transferability of prior findings and interventions to adolescents. There exists a need for a comprehensive evaluation of the multimodal (subjective and objective) effects of single mindfulness interventions. Therefore, in the present study, we aimed to investigate whether a single MBI has positive effects on healthy adolescents, with specific focus on subjective measures of well-being and state mindfulness, as well as on objective measures of HRV and HR. We additionally aimed to explore the role of trait mindfulness in these effects. We expect that the mindfulness intervention will result in increased subjective well-being, higher HRV, and reduced HR, more so than in the control condition. Additionally, we anticipate that trait mindfulness may play an important role in these mechanisms.

2 Methods

2.1 Design

The study was conducted as a 2 × 2 design. The between-subjects factor was group: mindfulness-based intervention (MBI) vs. active control group. The within-subjects factor was time: pre-intervention vs. post-intervention. We conducted an a-priori power analysis to determine the required sample size. For a desired power of 95%, and an expected mean effect size of $f = 0.31$ (13), a sample size of $N = 36$ participants ($n = 18$ per condition) was estimated to be sufficient. Since Mahmood et al. (13), was the first study to investigate the immediate effect of a single mindfulness intervention, the effect sizes were based on an adult sample (mean age: 33.56 years). The first half of participants ($n = 39$) were randomly assigned to one of the groups, and later participants were matched according to age and sex, until achieving the final sample size in each group. Participants and their parents or legal guardians were blinded to group assignment.

2.2 Sample

The study included $N = 78$ participants. The average age was 15.33 years ($SD = 2.41$), and 50% were female. Table 1 presents a detailed overview of demographic variables. Inclusion criteria were age between 12–19 years, and sufficient understanding of the German language. Exclusion criteria were past or current psychiatric, psychotherapeutic, or neurological treatments; pregnancy; breastfeeding; intellectual impairment; or attendance at a special school. Recruitment was carried out using e-mail distribution lists, social media accounts, and flyers. This study was approved by the Ethics Committee of the University of Regensburg (No.: 20–2095–101). All participants and their legal guardians gave written informed consent. Participants received a gift voucher worth €25 for their participation.

2.3 Materials

2.3.1 Body scan

For the MBI condition, the body scan was selected as the mindfulness exercise because it is categorized as a basic mindfulness exercise (9), and has been associated with the best stress reduction (12), and is thus highly suitable for preventative approaches. In our study, the participants were instructed to consciously be aware of individual areas of their body, to accept all sensations and feelings and not to judge them. If their attention wandered, participants were asked to lead it back to the task, with a non-judgmental attitude (26). To increase the standardization of the procedure, each participant performed the body scan under audio guidance. The duration of the body scan audio was approximately 10 min.

2.3.2 Active control group

To compare the mindfulness intervention with an active control group, we utilized an audiobook excerpt from “Mary Poppins comes back”, of the same duration as the body scan audio guidance. Participants were instructed to listen attentively, as they would in the mindfulness intervention, but without explicitly focusing on mindfulness and awareness of their own physical sensations. While the sensory input was similar between the two conditions, the input explicitly differed in the construct of mindfulness being examined.

2.4 Measures

2.4.1 Questionnaires

2.4.1.1 Subjective assessment

Visual analogue scales were utilized to measure the immediate subjective effect before and after the interventions. The three areas examined were mood, stress, and mindfulness (state). Formulations of the scales were adapted from the German “Der Mehrdimensionale Befindlichkeitsfragebogen” [multidimensional mood questionnaire] (MDBF) (27). Participants were asked “How do you feel right now?”, and answered using the following eight 11-point bipolar scales: *mood*, “bad to good” and “tired to awake”; *stress*, “stressed to calm” and “tensed to relaxed”; *mindfulness state*, “critical and judgmental towards myself to accepting myself”, “critical and judgmental towards my environment to accepting my environment”, “unfocused to concentrated”, and “distracted to being in the present moment”. Thus, according to the two-dimensional definition of mindfulness (10), all basic facets of mindfulness were assessed using a small number of items. All items were combined into a mean score according to their respective scale, with scores ≥6 indicating positive well-being, and those <6 indicating a lack of well-being.

2.4.1.2 Trait mindfulness

To assess the participants’ general mindfulness (trait), we used the mindfulness subscale from the Self-Compassion Scale (28), in its German version (SCS-D) (29). This questionnaire comprises 26 items scored on a 5-point Likert scale, ranging from 1 (very rarely) to 5 (very often). A total score can be calculated from the six subscales: mindfulness, common humanity, self-judgment, isolation, over-identification, and self-kindness, with higher scores indicating higher self-compassion. The subscale mindfulness score has shown

TABLE 1 Demographic and psychometric characteristics and group comparisons.

	Total sample	Group		Group comparisons
		Mindfulness	Control	
Number of participants	N = 78	n = 40	n = 38	
Age in years				
M (SD)	15.33 (2.41)	15.40 (2.43)	15.26 (2.41)	$t(75.8) = 0.25$, $p = .804$[a] TOST: $ps > .124$[b]
Range	12–19	12–19	12–19	
Sex				
Female (%)	39 (50.0)	19 (47.5)	20 (52.6)	$t(75.8) = 0.45$, $p = .656$[a] TOST: $ps < .001$[b]
Male (%)	39 (50.0)	21 (52.5)	18 (47.4)	
School type				
Mittelschule (%)	4 (5.1)	3 (7.5)	1 (2.6)	$Z = -0.49$, $p = .621$[c]
Realschule (%)	14 (17.9)	7 (17.5)	7 (18.4)	
Gymnasium (%)	39 (50.0)	18 (45.0)	21 (55.3)	
FOS/BOS (%)	5 (6.4)	4 (10.0)	1 (2.6)	
University (%)	11 (14.1)	6 (15.0)	5 (13.2)	
Other (%)	3 (3.8)	–	3 (7.9)	
Missing information (%)	2 (2.6)	2 (5.0)	–	
Mindfulness experience				
No (%)	34 (43.6)	19 (47.5)	15 (39.5)	$Z = -0.55$, $p = .585$[c]
A little (%)	16 (20.5)	7 (17.5)	9 (23.7)	
Some (%)	19 (24.4)	7 (17.5)	12 (31.6)	
Much (%)	5 (6.4)	4 (10.0)	1 (2.6)	
Very much (%)	2 (2.6)	1 (2.5)	1 (2.6)	
Missing information (%)	2 (2.6)	2 (5.0)	–	
Anxiety and Depression				
M (SD)	38.31 (10.83)	40.10 (11.09)	36.42 (10.35)	$t(75.98) = 1.52$, $p = .134$[a]
Range	23–66	24–66	23–61	
Trait Mindfulness				
M (SD)	13.5 (3.02)	12.95 (3.27)	14.11 (2.65)	$t(74.2) = -1.72$, $p = .090$[a]
Range	6–20	6–20	8–18	

Sex: all participants were asked about sex and gender, which were congruent in all cases. School types: secondary schools following elementary school in Germany; Mittelschule: 9 years of elementary school; Realschule: intermediate level of secondary school, regular duration of 6 years; FOS (Fachoberschule)/BOS (Berufsoberschule): tertiary school to achieve advanced technical college certificate, subject-related entrance qualification or general qualification for university entrance after visiting Realschule, duration: 2–3 years additionally beyond the duration of Realschule; Gymnasium: highest level of secondary school, regular duration of 8–9 years, qualification: general qualification for university entrance. Mindfulness experience was assessed using one item, examples of mindfulness exercises were yoga or meditation. Anxiety and Depression was assessed with via STADI trait. Trait Mindfulness was assessed via SCS-D, subscale mindfulness.
[a]*t*-test for independent samples, [b]Welch's *t*-test using the TOST equivalence test method, [c]Mann-Whitney-*U*-test.

nearly acceptable internal consistency (Cronbach's α = .66) and confirmed validity (29).

2.4.1.3 Anxiety and depression

The State-Trait Anxiety-Depression Inventory (STADI) (30) was used to assess anxiety and depression scores, as an indicator of the absence of well-being/mental burden. This questionnaire comprises two subscales (anxiety and depression) as state and trait. In total, the STADI contains 40 items, which are answered using a 4-point Likert scale. Trait item responses range from 1 (almost never) to 4 (almost always), and state item responses from 1 (not at all) to 4 (very). The trait scale was used to evaluate the participants' mental burden. The anxiety and depression scales exhibit reliability within an appropriate range (α = 0.87–0.90). Validity testing has confirmed the convergent and discriminant correlations, as well as the factorial validity of the questionnaire (30).

2.4.2 Heart rate and heart rate variability

HR and HRV were measured using the wireless sensor EcgMove 4 (movisens GmbH, Karlsruhe, Germany), which was attached to the participants' chest using patches. Raw data were preprocessed using the software "DataAnalyzer" (version 1.13.5; movisens, Munich, Germany). As a parameter of HRV, we selected the root mean square of successive differences (RMSSD) as a time-specific marker, which is particularly suitable for short-term changes (31). We also included the frequency-based parameters low frequency (LF) and high frequency (HF), and the LF/HF ratio, which are especially notable as indicators of relaxation (32–34). HR and HRV were assessed before the intervention (baseline measurement) and throughout the complete intervention. For the analyses, we selected time-points from the end of baseline (second minute) and at the final third of the intervention (tenth minute) for comparison. This intervention interval was chosen because mindfulness exercises typically end with a return of one's attention to the surroundings, and small body movements.

2.5 Procedure

Participants and their accompanying parent or legal guardian were provided detailed information about the study, and gave their informed consent. Subsequent testing occurred without the presence of the accompanying person. At the beginning of the examination, the participants themselves attached the wireless sensor. Next, the participants used a laptop to digitally provide demographic information and complete questionnaires: SCS-D, STADI, and subjective well-being (pre-intervention). Afterwards, participants were instructed to lay comfortably on their backs on a provided mattress, and were given the option of closing their eyes, while listening to the audio file via headphones. They were asked to attentively follow the audio file, and the implemented instructions, when required. After the baseline and intervention, all participants again answered the subjective well-being questions (post-intervention). Finally, participants were informed about the scope of the study, were invited to give feedback or ask further questions about the study, and removed the attached sensor. Upon completion, participants were given a voucher worth 25€.

2.6 Statistical analysis

Group differences in demographic variables were examined using *t*-tests, Welch's *t*-test, Mann-Whitney *U*-tests, and Two One-Sided Tests (TOST) for equivalence analysis. Bivariate correlations were evaluated using Kendall's τ. Possible changes due to the intervention were investigated by within-subject comparisons of a two-factor analysis of variance (ANOVA) with repeated measures (pre/post) of subjective scores (mood, stress, and state mindfulness), as well as changes in HR and HRV. To examine the effect of the mindfulness exercise compared to the control intervention, condition was included in the analysis as a between-subject factor, to investigate an interaction effect between time and condition. The analyses also included the following covariates: sex, age, mindfulness trait (subscale "mindfulness" from SCS-D), and experience with mindfulness exercises. Mental burden (STADI trait) was not included as a covariate, due to its high inter-correlation with the mindfulness trait. Exploratory analyses revealed comparable results when including mental burden instead of mindfulness trait. Due to violation of the normal distribution assumption, all HRV parameters and STADI scores were log-transformed regarding their positive skewness, while subjective answers were log-transformed regarding their negative skewness, to achieve the best approximation of a normal distribution. The partial eta-square (η_p^2) was calculated as a measure of effect size, with 0.01 considered a small effect, 0.06 a medium effect, and 0.14 a large effect. Statistical analyses were performed using SPSS Statistics 29 software. Equivalence tests were conducted using the TOSTER 0.4.0 module in jamovi version 2.3.28 for Windows. The significance level was set as $\alpha = 0.05$.

Data regarding the physiological variables were available for only a part of the surveyed sample, due to technical difficulties in the measurements, likely related to the supine position of the participants. Heart rate was available for $n = 62$, and heart rate variability for $n = 56$. Due to a technical issue with the survey platform, one participant could not complete the SCS-D and STADI questionnaires, and three participants had to complete "paper and pencil" versions, which were missing questions regarding school type and mindfulness experience. No other technical difficulties occurred.

3 Results

Table 1 presents the demographic information for the study sample, according to group, revealing no significant group differences in age, sex, school type, or prior mindfulness experience. Regarding psychometric characteristics, the groups did not differ significantly in trait mindfulness (subscale mindfulness SCS-D, $t(74.21) = -1.72$, $p = .090$) or in anxiety or depression scores (STADI state: $t(66.53) = 1.62$, $p = .111$; trait: $t(75.98) = 1.52$, $p = .134$). These similarities indicated that the groups can be compared without restriction. Trait mindfulness and trait anxiety and depression scores showed a medium inter-correlation (subscale mindfulness SCS-D× STADI Trait: $\tau = -0.34$, $p < .001$); therefore, they were not considered together in the following models. Rather, the analysis focused on trait mindfulness, in line with the research question. However, for exploratory purposes, each model was also tested with trait anxiety and depression, and these results did not differ from those obtained using trait mindfulness.

The courses of the parameters during the intervention (MBI or active control) are presented in Figure 1 (subjective data) and Figure 2 (physiological data). Table 2 shows the results of the ANOVAs on the various variables. Overall, none of the investigated parameters exhibited the expected effect of the mindfulness intervention (time × condition). Nevertheless, the analysis revealed interesting results. All subjective measures (mood, stress, and state mindfulness) showed a main effect for trait mindfulness, with positive correlations in the subsequent analysis of the direction for all post measurements ($\tau = [0.18; 0.30]$, all $p < .026$), suggesting

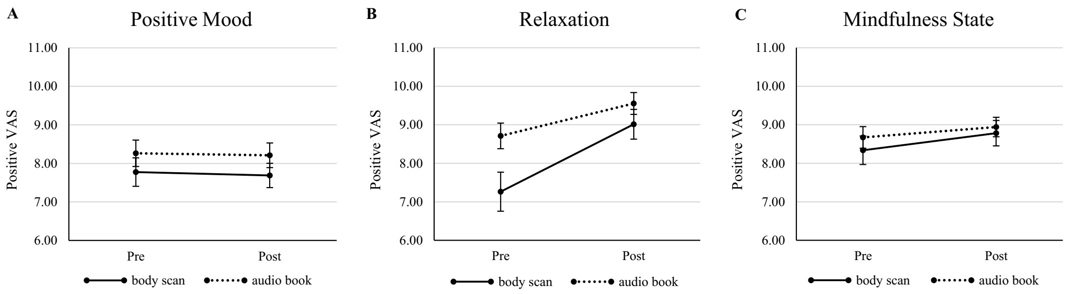

FIGURE 1
Courses of subjective parameters pre-intervention to post-intervention regarding **(A)** Positive Mood; **(B)** Relaxation; and **(C)** Mindfulness State. VAS, visual analogue scale [1;11], bipolar scale, meaning values <6 represent the negative pole, and ≥6 represent the positive pole. Since all values ranged in positive pole, only positive VAS are depicted. Error bars show standard error.

that individuals with higher trait mindfulness also experienced feeling better, more calmness and greater state mindfulness, especially after the intervention across both conditions. Additionally, for state stress and state mindfulness, age was a significant covariate. In state mindfulness, lower age was linked to higher state mindfulness values, except among 18-year-olds. In state stress, no clear trend was detectable. For the physiological parameters, mixed results were found. HF showed a main effect for trait mindfulness (suggesting higher HF values with higher trait mindfulness values) and a main effect of condition, revealing a general effect observable in the descriptive data: participants in the MBI condition showed higher HF values than participants of the active control group, before as well as after the intervention. LF and LF/HF both exhibited a significant effect of sex (females < males), while LF/HF also exhibited a main effect of trait mindfulness, similar to HF, but suggesting an inverse relationship (higher trait mindfulness associated with lower LF/HF). On the other hand, RMSSD showed a main effect for time, with pre-intervention values being higher than post-intervention values. Additionally, the RMSSD showed an effect of condition, with MBI group showing higher RMSSD values than the active control group. Lastly, for HR, we observed an effect of time (pre-intervention > post-intervention) and an interaction effect of time × age. The courses between pre-intervention and post-intervention diverged from the age of 16. Starting at this age, we observed a descriptive effect of the interventions, namely a lower heart rate after the intervention than before. In contrast, participants of 13–15 years old exhibited barely any differences between pre-intervention and post-intervention.

4 Discussion

In the present study, we used multimodal measurements (i.e., subjective and physiological indicators) to investigate the effects of a single-session mindfulness intervention, and compared it to an active control group. A total of 78 adolescent participants were divided into two groups, and we assessed their subjective mood, stress, and state mindfulness before and after the intervention. We also recorded and analyzed the physiological parameters of heart rate and heart rate variability. Our analysis considered demographic characteristics, including sex and age, as well as potentially influencing factors, such as mindfulness trait, experience with mindfulness exercises, and general levels of anxiety and depression.

Our results did not show the expected effect that only the group participating in the mindfulness intervention would exhibit improvements of subjective well-being, state mindfulness, HR, and HRV. The only notable change was a HR reduction after the intervention compared to baseline; however, this effect was observed across both groups, not exclusively in the mindfulness group. Thus, listening to an audiobook was as effective for reducing HR as following a guided body scan, which is consistent with the findings of prior studies (35–37). One possible explanation may be the similar attentional processes required for both the body scan and the active control task (38). Our results also revealed an effect of age for HR: older participants benefited from the interventions, whereas younger participants showed little change in HR throughout the interventions. This could reflect an actual developmental effect based on age, or could indicate problems with the intervention for younger participants, e.g., a lack of age-appropriate instruction (6). However, the latter explanation is unlikely because we paid much attention to age-appropriate instruction during the design of the study. In further studies, it would be interesting to investigate whether another age limit can be found, above which a single intervention with attention control has an effect on HR. Furthermore, in both conditions, one must consider the effect of the supine position, which alone can lead to a decrease in HR. It could be helpful to also compare different positions during the exercises in future studies.

While previous research has shown positive outcomes on HRV due to brief mindfulness interventions (21), our present HRV results showed a very mixed, inconsistent and, in some cases, counterintuitive picture. We did not observe any changes over time in the frequency-based parameters of HRV. We found effects of trait mindfulness for HRV HF and the ratio of high and low frequency, but with inconsistent trends, suggesting trait mindfulness as a potentially relevant factor which needs extended attention in the future. Moreover, in contrast to prior findings (21), the time-based parameter RMSSD showed higher values before interventions than after, indicating an increase of stress rather than

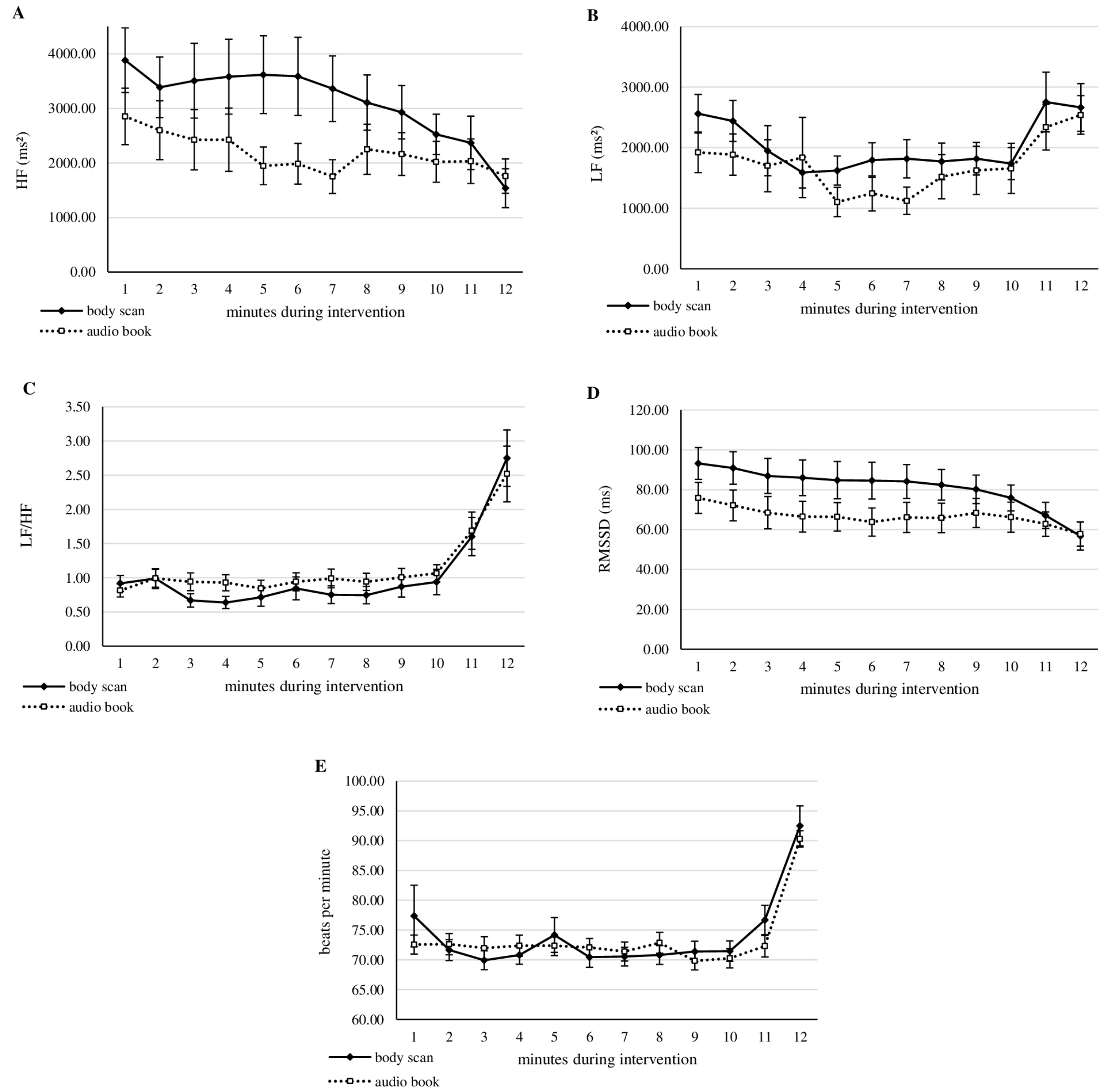

FIGURE 2
Courses of physiological parameters during intervention. For all courses, the first 2 minutes cover the baseline measurement, minutes 3–12 cover the intervention, while body movements were possible during the 2 last minutes of intervention. **(A–D)** The parameter of heart rate variability. HF, high frequency; LF, low frequency; LF/HF, ratio of low to high frequency; RMSSD, root mean square of successive differences. **(E)** Heart rate. Error bars show standard error.

a decrease, since lower RMSSD values indicate stress (39). Further studies are needed to investigate whether the testing situation was perceived as stressful by participants, or if other mechanisms underlie these results. We observed group differences in the HR and HRV levels—with higher HR, indicating more stress, and higher HRV, indicating less stress, even before the interventions. This finding cannot be fully explained, but it may have contributed to the failure to detect the expected effects, as seen in previous studies. Overall, while the presently reported results regarding the physiological effects of a single mindfulness intervention are interesting, they should be carefully interpreted.

Similar to the physiological parameters, the subjective measures did not indicate any immediate effect of the (mindfulness) intervention. One possible explanation could be that the participants' subjective responses were already in a positive range before the interventions, potentially leading to a ceiling effect that limited the possibility for further improvement. Another possible explanation might be that youths do not subjectively benefit from a single mindfulness intervention, as suggested by prior research (13, 40). Notably, the assessed domains of subjective well-being (mood and stress/relaxation) and state mindfulness showed positive correlations with trait mindfulness—with higher trait mindfulness being associated with more positive mood, lower stress/higher relaxation, and higher state mindfulness, each with a large effect. While our results did not demonstrate the effect of a single mindfulness intervention, they did indicate the interplay between

TABLE 2 ANOVAs regarding psychological and physiological parameters.

	SS	*df*	*MS*	*F*	*p*	η_p^2
ANOVA subjective mood						
Time	0.14	1	0.14	1.38	.244	0.02
Time*Age	0.02	1	0.02	0.16	.693	<0.01
Time*M_Experience	0.03	1	0.03	0.32	.574	<0.01
Time*T_Mindfulness	0.06	1	0.06	0.61	.437	0.01
Time*Condition	<0.01	1	0.00	0.02	.878	<0.01
Time*Sex	0.04	1	0.04	0.40	.532	0.01
Time*Condition*Sex	0.06	1	0.06	0.57	.454	0.01
Error	7.10	69	0.10			
Age	2.28	1	2.28	3.75	.057	0.05
M_Experience	0.05	1	0.05	0.08	.772	<0.01
T_Mindfulness	**4.09**	**1**	**4.09**	**6.71**	**.012**	**0.09**
Condition	0.16	1	0.16	0.25	.615	<0.01
Sex	0.77	1	0.77	1.26	.265	0.02
Condition*Sex	0.20	1	0.20	0.33	.569	<0.01
ANOVA subjective stress						
Time	0.04	1	0.04	0.22	.637	<0.01
Time*Age	<0.01	1	<0.01	0.01	.910	<0.01
Time*M_Experience	0.04	1	0.04	0.23	.632	<0.01
Time*T_Mindfulness	0.06	1	0.06	0.35	.556	0.01
Time*Condition	0.42	1	0.42	2.50	.119	0.03
Time*Sex	0.46	1	0.46	2.72	.104	0.04
Time*Condition*Sex	0.03	1	0.03	0.17	.677	<0.01
Error	11.663	69	0.17			
Age	**4.37**	**1**	**4.37**	**5.58**	**.021**	**0.07**
M_Experience	0.78	1	0.78	0.99	.322	0.01
T_Mindfulness	**16.22**	**1**	**16.22**	**20.73**	**<.001**	**0.23**
Condition	0.01	1	0.01	0.01	.904	<0.01
Sex	0.77	1	0.77	0.98	.326	0.01
Condition*Sex	0.40	1	0.40	0.52	.475	0.01
ANOVA subjective mindfulness						
Time	0.01	1	0.01	0.16	.691	<0.01
Time*Age	0.06	1	0.06	0.83	.364	0.01
Time*M_Experience	0.08	1	0.08	1.07	.304	0.02
Time*T_Mindfulness	0.06	1	0.06	0.79	.376	0.01
Time*Condition	0.07	1	0.07	0.99	.323	0.01
Time*Sex	0.12	1	0.12	1.64	.204	0.02
Time*Condition*Sex	<0.01	1	<0.01	0.07	.795	<0.01

(Continued)

TABLE 2 Continued

	SS	*df*	*MS*	*F*	*p*	η_p^2
ANOVA subjective mindfulness						
Error	5.02	69	0.07			
Age	**5.76**	**1**	**5.76**	**10.02**	**.002**	**0.13**
M_Experience	0.01	1	0.01	0.02	.893	<0.01
T_Mindfulness	**6.54**	**1**	**6.54**	**11.37**	**.001**	**0.14**
Condition	0.33	1	0.33	0.57	.452	0.01
Sex	0.64	1	0.64	1.11	.296	0.02
Condition*Sex	0.16	1	0.16	0.27	.602	<0.01
ANOVA HRV HF						
Time	0.38	1	0.38	2.41	.128	0.05
Time*Age	0.16	1	0.16	1.05	.310	0.02
Time*M_Experience	0.14	1	0.14	0.89	.350	0.02
Time*T_Mindfulness	0.03	1	0.03	0.20	.660	<0.01
Time*Condition	<0.01	1	<0.01	0.02	.898	<0.01
Time*Sex	0.34	1	0.34	2.21	.144	0.05
Time*Condition*Sex	0.11	1	0.11	0.67	.416	0.01
Error	7.17	46	0.16			
Age	5.32	1	5.32	3.14	.083	0.06
M_Experience	1.10	1	1.10	0.65	.426	0.01
T_Mindfulness	**7.74**	**1**	**7.74**	**4.56**	**.038**	**0.09**
Condition	**11.35**	**1**	**11.35**	**6.70**	**.013**	**0.13**
Sex	0.89	1	0.89	0.53	.472	0.01
Condition*Sex	0.08	1	0.08	0.05	.830	<0.01
ANOVA HRV LF						
Time	0.05	1	0.05	0.13	.720	<0.01
Time*Age	<0.01	1	<0.01	0.01	.913	<0.01
Time*M_Experience	0.64	1	0.64	1.60	.212	0.03
Time*T_Mindfulness	0.22	1	0.22	0.56	.459	0.01
Time*Condition	0.72	1	0.72	1.81	.185	0.04
Time*Sex	0.21	1	0.21	0.53	.469	0.01
Time*Condition*Sex	0.10	1	0.10	0.26	.611	0.01
Error	18.29	46	0.40			
Age	0.72	1	0.72	0.50	.485	0.01
M_Experience	0.17	1	0.17	0.12	.731	<0.01
T_Mindfulness	1.37	1	1.37	0.95	.335	0.02
Condition	4.55	1	4.55	3.15	.082	0.06
Sex	**6.44**	**1**	**6.44**	**4.46**	**.040**	**0.09**
Condition*Sex	0.78	1	0.78	0.54	.465	0.01

(Continued)

TABLE 2 Continued

	SS	*df*	*MS*	*F*	*p*	η_p^2
ANOVA HRV R HF/LF						
Time	0.71	1	0.71	2.33	.134	0.05
Time*Age	0.15	1	0.15	0.48	.494	0.01
Time*M_Experience	0.19	1	0.19	0.62	.435	0.01
Time*T_Mindfulness	0.35	1	0.35	1.14	.292	0.02
Time*Condition	0.53	1	0.53	1.73	.195	0.04
Time*Sex	0.01	1	0.01	0.03	.874	<0.01
Time*Condition*Sex	0.37	1	0.37	1.20	.279	0.03
Error	14.07	46	0.31			
Age	2.31	1	2.31	3.38	.073	0.07
M_Experience	0.37	1	0.37	0.54	.466	0.01
T_Mindfulness	**2.81**	**1**	**2.81**	**4.11**	**.049**	**0.08**
Condition	1.66	1	1.66	2.43	.126	0.05
Sex	**11.67**	**1**	**11.67**	**17.07**	**<.001**	**0.27**
Condition*Sex	0.32	1	0.32	0.47	.498	0.01
ANOVA HRV RMSSD						
Time	**0.12**	**1**	**0.12**	**5.00**	**.030**	**0.09**
Time*Age	0.02	1	0.02	0.94	.338	0.02
Time*M_Experience	0.08	1	0.08	3.25	.078	0.06
Time*T_Mindfulness	0.05	1	0.05	1.97	.167	0.04
Time*Condition	<0.01	1	<0.01	0.20	.659	<0.01
Time*Sex	0.04	1	0.04	1.71	.198	0.03
Time*Condition*Sex	0.04	1	0.04	1.70	.199	0.03
Error	1.16	48	0.02			
Age	1.13	1	1.13	2.26	.139	0.04
M_Experience	1.13	1	1.13	2.27	.139	0.05
T_Mindfulness	1.22	1	1.22	2.45	.124	0.05
Condition	**2.81**	**1**	**2.81**	**5.63**	**.022**	**0.10**
Sex	0.22	1	0.22	0.44	.512	0.01
Condition*Sex	0.11	1	0.11	0.22	.644	<0.01
ANOVA HR						
Time	**43.86**	**1**	**43.86**	**6.51**	**.014**	**0.11**
Time*Age	**65.98**	**1**	**65.98**	**9.80**	**.003**	**0.15**
Time*M_Experience	13.03	1	13.03	1.93	.170	0.03
Time*T_Mindfulness	0.01	1	0.01	<0.01	.975	<0.01
Time*Condition	2.06	1	2.06	0.31	.582	0.01
Time*Sex	0.49	1	0.49	0.07	.789	<0.01
Time*Condition*Sex	10.86	1	10.86	1.61	.210	0.03
Error	363.71	54	6.74			

(Continued)

TABLE 2 Continued

	SS	*df*	*MS*	*F*	*p*	η_p^2
ANOVA HR						
Age	11.10	1	11.10	0.06	.801	<0.01
M_Experience	104.01	1	104.01	0.60	.442	0.01
T_Mindfulness	619.44	1	619.44	3.58	.064	0.06
Condition	27.93	1	27.93	0.16	.689	<0.01
Sex	2.93	1	2.93	0.02	.897	<0.01
Condition*Sex	78.86	1	78.86	0.46	.502	0.01

SS, Type III Sum of Squares; df, degrees of freedom; MS, mean square; η_p^2, Partial eta Square; M_Experience, Experience with mindfulness exercises [no; very much]; T_Mindfulness, Trait Mindfulness, assessed with a questionnaire (Self-Compassion Scale, subscale mindfulness); Condition, Mindfulness exercise or active control group. Significant effects are highlighted in bold font.

psychological well-being and a generally mindful attitude in an adolescent sample. Consistently, we found a strong negative association between trait mindfulness and trait anxiety and depression scores—with a higher generally mindful attitude being correlated with lower levels of anxiety and depression in our sample. This finding is in line with previous results (7, 41, 42), and highlights that even in this young age group, trait mindfulness could constitute a factor supporting resilience against common mental health challenges (43). Moreover, the data support the relevance of trait mindfulness, as it was correlated with both anxiety and stress in our study, making its connection to the improvements seen in MBI programs among adolescents particularly evident (44, 45). It is also interesting that our results only showed an effect of age for state stress and state mindfulness as subjective parameters. This could be a development-specific effect (6), in which younger individuals may exhibit higher levels of state mindfulness and, therefore, greater resilience. Further studies are needed to investigate whether this is the explanation, or if these findings result from an age-related bias in ratings. In any case, age is an aspect that should definitely be considered in studies involving adolescents, as specific characteristics have been found, both physiologically and subjectively. Additionally, age has been found to be a moderator for trait mindfulness in a prior study, i.e. regarding dispositional mindfulness and ostracism—the social exclusion or rejection by others. In this context, higher age was more beneficial regarding trait mindfulness (46). This demonstrates the potential of trait mindfulness throughout development and suggests that focusing on it earlier could enhance resilience. The present findings should be interpreted with caution since there are currently very few studies of a single mindfulness exercise in a healthy adolescent population. Notably, single mindfulness interventions seem to particularly affect attention mechanisms, whereas longer training periods are required to affect the usual subjective and physiological outcomes (47), and even then only with small effects (48). Further research in this age group, possibly with different mindfulness exercises and an additional passive control group, could provide interesting insights.

The limitations of this study must be considered when interpreting the results. Notably, we examined only one type of mindfulness exercise: the body scan. Therefore, we cannot make generalizations regarding the lack of effect of a single mindfulness intervention among healthy adolescents, and further investigation is required. However, the lack of effect, despite the body scan being considered the most promising mindfulness exercise (12), is not encouraging for other interventions. Another limitation of this study is the potential for undetected mental health issues among participants. We relied on self-reported data regarding previous psychological treatments and the absence of high emotional distress or mental illnesses. However, we believe that such cases are likely rare and would not significantly impact our findings given our sample size. Additionally, this study did not include a passive control group. Another notable limiting aspect is the assessment of subjective parameters. The categories were surveyed using two or four items, meaning that the reliability of the survey was not optimal. However, this approach was chosen to pragmatically survey the specific constructs of interest. Moreover, an established measurement instrument, the MBFB (27), was used to ensure validity. Future studies should critically examine this aspect.

The present study also has several strengths that must be highlighted. The study included a large well-characterized sample of healthy adolescents, and various important control variables, i.e., the assessment of mental burden and trait mindfulness. The selected age range covers the early and middle puberty age groups, which Porter and colleagues (6) have defined as interesting in this context, due to the developmental trajectories and socioemotional skills of children and adolescents. Additionally, the demographic and psychometric characteristics did not differ between the groups, enabling unrestricted interpretations of the results. Although we conducted an a-priori power analysis, a pre-intervention condition effect was identified upon reaching the required sample size. Therefore, the sample size was doubled to account for missing HR and HRV values and to enable the detection of even smaller effects in adolescents, with effects observed up to an eta of 0.04 with a power of 80%. This adjustment was made to be able to provide the most conclusive results possible. Another strength of this study is our multimodal assessment of the effects of a mindfulness intervention. In addition to subjective questions, which can be prone to bias, we also assessed objective physiological parameters, i.e., HR and various HRV parameters. This combination of subjective and objective measures provides a more comprehensive overview.

5 Conclusion

In summary, our present results indicated that a single mindfulness exercise did not improve subjective well-being, state mindfulness, or physiological parameters in healthy adolescents aged 12–19, compared to an active control group. Although previous studies have observed immediate effects of such interventions in adults, this does not yet appear to occur in adolescents. Further research is needed to investigate the underlying mechanisms. A generally mindful attitude is associated with lower mental burden in healthy adolescents, and thus represents a resilience factor for greater well-being.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Ethics statement

The studies involving humans were approved by Ethics Committee of the University of Regensburg. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants and their legal guardians.

Author contributions

AE: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. CF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. DS: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. RJ: Data curation, Methodology, Supervision, Validation, Writing – review & editing. SK: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing, Validation. RB: Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing. IJ: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Investigating the psychophysiological effects of NaiKan Therapy: salivary oxytocin and cortisol release

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NaiKan Therapy, a method of self-reflection and introspection, has garnered considerable interest for its psychological benefits. However, its physiological impacts, particularly on hormonal regulation, remain underexplored. In this study, we aimed to investigate the effects of NaiKan Therapy on salivary oxytocin and cortisol release, shedding light on the psychophysiological mechanisms underlying this introspective practice. Sixty participants underwent Naikan Therapy sessions over five consecutive days, during which salivary samples were collected at multiple time points. Salivary oxytocin and cortisol levels were measured using enzyme-linked immunosorbent assay (ELISA) kits. Our results revealed significant increases in salivary oxytocin levels following NaiKan Therapy, suggesting a potential role of this practice in enhancing social bonding and emotional regulation. Conversely, salivary cortisol levels exhibited a decrease post-therapy, indicating a reduction in stress reactivity. These findings provide novel insights into the neuroendocrine mechanisms underlying NaiKan Therapy and highlight its potential as a holistic approach to improving mental wellbeing. Further research exploring the long-term effects of NaiKan Therapy and its implications for clinical practice is warranted.

KEYWORDS

NaiKan Therapy, salivary oxytocin, salivary cortisol, psychophysiology, stress resilience

Introduction

NaiKan Therapy, a traditional Japanese method rooted in mindfulness and Naikan practices, has gained attention for its potential therapeutic benefits in promoting mental wellbeing and stress reduction (Ozawa-de Silva, 2015). Central to NaiKan Therapy is the practice of inward reflection, where individuals engage in deep introspection to explore their inner thoughts, emotions, and experiences. While anecdotal evidence suggests its efficacy in enhancing emotional resilience and fostering self-awareness, the underlying psychophysiological mechanisms of NaiKan Therapy remain largely unexplored (Ozawa-de Silva, 2015; Samuel, 2016). While NaiKan Therapy is inherently subjective and often difficult to measure objectively, recent advances in psychobiological research have shed light on its potential physiological correlates, including alterations in hormonal signaling.

Two key hormones that have garnered significant attention in the context of social cognition, emotional processing, and stress regulation are oxytocin and cortisol. Oxytocin, known for its role in social bonding, trust, and affiliative behaviors, is implicated in a wide range of social interactions and emotional experiences (Ross and Young, 2009; Olff et al., 2013). Cortisol, the primary glucocorticoid in rodents, serves as a crucial mediator of the stress response and plays a pivotal role in regulating various physiological and behavioral responses to stressors (Nicolaides et al., 2014; Gray et al., 2017).

While previous studies have demonstrated the influence of external social cues and stressors on oxytocin and cortisol release (Olff et al., 2013; Smith and Wang, 2012), relatively little is known about the effects of NaiKan Therapy on these hormonal systems. Given the intimate connection between NaiKan Therapy and self-awareness, as well as the potential emotional and cognitive implications of self-reflection (Machizawa and Enns, 2015), investigating the hormonal responses associated with NaiKan Therapy represents a novel and intriguing avenue of inquiry.

Salivary measurements offer a non-invasive and convenient method for assessing hormonal changes in response to psychological stimuli (Groschl, 2008; Clow and Smyth, 2020; Giacomello et al., 2020). Recent advances in salivary bioscience have enhanced the sensitivity and specificity of oxytocin and cortisol assays, allowing for more accurate detection of subtle hormonal fluctuations associated with psychological states (İnanıcı et al., 2024; Schneider et al., 2023; Moscovice et al., 2022; Bowling et al., 2022). Studies have demonstrated that examinations, a common academic stressor, lead to heightened salivary cortisol secretion, emphasizing the hormone's role in stress responses (İnanıcı et al., 2024; Špiljak et al., 2022). In addition, this methodology can be utilized to assess the potential application value of stress management interventions (Špiljak et al., 2024; Mizuhata, 2021). These recent literatures suggest that mindfulness-based interventions and introspective therapies may modulate stress-related hormonal pathways, highlighting the need to explore the specific role of oxytocin and cortisol in NaiKan Therapy. By examining how NaiKan Therapy activities, such as self-reflection, self-awareness, and metacognition, influence salivary hormone levels, we can gain valuable insights into the psychophysiological mechanisms underlying NaiKan Therapy processes.

In this research paper, we aim to investigate the psychophysiological effects of NaiKan Therapy by examining its influence on salivary oxytocin and cortisol levels. We hypothesize that engaging in NaiKan Therapy will lead to alterations in salivary hormone levels, indicative of changes in emotional state and stress response. Through a series of controlled experiments involving participants undergoing NaiKan Therapy sessions, we will assess salivary oxytocin and cortisol levels before and after the intervention. Additionally, we will explore potential moderators, such as individual differences in trait mindfulness and baseline stress levels, to better understand the variability in hormonal responses to NaiKan Therapy.

Materials and methods

Participants

Participants, aged between 18 and 45 years old, were recruited for the study, totaling 60 individuals, both males and females (Table 1). Participants who dropped out before completing the intervention or had incomplete saliva samples were excluded from the final analysis. The sample size was determined based on practical considerations. Given the exploratory nature of this study and resource constraints, a sample size of 60 was deemed sufficient to detect meaningful hormonal changes while ensuring feasibility. Prior to the experiments, participants were provided with detailed verbal and written information regarding the study procedures and gave their informed consent. All experimental procedures were approved by the Shanghai Nanhui Mental Health Center Ethics Committee (No. 2023-C-002-E02).

TABLE 1 General information about the participants.

	Female	Male	*p*-value
Number of participants	37	23	
Age (years)	25.2 ± 1.8	20.3 ± 0.9	0.0479[1]
Previous COVID-19 infection	31/37	17/23	0.5081[2]
Hypertension	–	–	–
Diabetes	–	2/23	0.1429[2]
Coronary heart disease	–	–	–
Chronic obstructive pulmonary disease	–	–	–
Tumor	–	–	–
Stroke	–	–	–

[1]Unpaired t test.
[2]Fisher's exact test.

NaiKan Therapy

In intensive NaiKan Therapy (INT), the participant sits in the corner of a room, walled off by a folding screen to cut off visual stimulation from the outside so that it is easier for them to observe their own thinking. Sitting in a quiet place and staying in a relaxed position, the participant begins to seriously look into his/her thoughts, continuing his/her introspection daily from 06.00 h to 08.00 h (five consecutive days). The participants examine how they have lived according to three themes: (i) What have I received from a particular person? (ii) What have I returned to that person? and (iii) What troubles and difficulties have I caused that person? To begin with, the participants are asked to examine the relationship with their mothers or their main caretakers through every period of their life, starting from childhood and gradually moving to the present. Then, they are asked to examine themselves regarding other people who are close to them, such as their fathers, spouses, friends, colleagues, and so forth (Sengoku et al., 2010).

Assessment of anxiety

Assessment of anxiety levels was conducted using the PHQ-9 (Patient Health Questionnaire-9) and DASS (Depression Anxiety Stress Scales) (Peters et al., 2021; Sun et al., 2020) before and after the NaiKan Therapy. These scales are widely utilized to measure individuals' levels of depression and anxiety by inquiring about their psychological and emotional states over the past week. The PHQ-9 covers a range of depressive symptoms such as mood, insomnia, and fatigue, while the DASS provides a comprehensive evaluation of depression, anxiety, and stress. Through these assessment tools, changes in participants' anxiety levels before and after the introspection sessions were quantified, allowing for an evaluation of the effects of NaiKan Therapy on anxiety symptoms. The cutoff score was set 50.

Saliva sample collection

Saliva samples were collected from participants following standardized protocols (Bellagambi et al., 2020; Szabo and Slavish, 2021). Participants were instructed to abstain from eating, drinking (except water), brushing teeth, using mouthwash, chewing gum, or undergoing dental procedures for at least 60 min prior to sample collection. Saliva samples were collected at different time points: upon waking (between 6:00 and 8:00 AM), 20 min before and after the Nai Kan Therapy session, and 30 min before dinner (between 5:00 and 7:00 PM) (Figure 1, Day 1, Day 2 and Day 6). Upon collection, saliva samples were centrifuged to obtain clear saliva supernatant. The supernatant was then transferred to new tubes for subsequent analysis.

Enzyme-linked immunosorbent assay (ELISA)

Saliva samples were analyzed for oxytocin and cortisol levels using commercially available ELISA kits (D751010 for oxytocin, D711340 for cortisol, Songon, China) (López-Arjona et al., 2024). Quantification of oxytocin concentrations was commercially performed by radioimmunoassay with a sensitivity of 0.1–0.5 pg/sample as described previously (Schladt et al., 2017). Intra- and inter-assay coefficients for oxytocin were <10 and <12%, respectively. Quantification of cortisol concentrations was performed using a commercially available chemiluminescence immunoassay with high sensitivity. Intra- and inter-assay coefficients for cortisol were below 8% (Schladt et al., 2017). ELISA plates were coated with specific capture antibodies for oxytocin or cortisol and incubated to allow antibody binding. Standard solutions with known concentrations of oxytocin or cortisol were prepared, and serial dilutions of these standards were added to the ELISA plates to generate standard curves.

Saliva samples and standards were added to appropriate wells of the ELISA plate and incubated to allow oxytocin or cortisol in the samples to bind to the capture antibodies. After washing to remove unbound substances, detection antibodies specific to oxytocin or cortisol were added, followed by a secondary antibody conjugated to an enzyme. Substrate solution was then added to initiate an enzymatic reaction, resulting in a color change.

The absorbance of each well was measured at a specific wavelength using a microplate reader, and absorbance values were recorded for subsequent analysis. Standard curves were generated using the absorbance values of the standards, and the concentrations of oxytocin and cortisol in the saliva samples were interpolated from these curves. Statistical analysis was performed to analyze the data, including calculation of means, standard deviations, and statistical significance where applicable. Quality control measures were implemented throughout the assay to ensure accuracy and reliability of the results.

Statistics

All data were analyzed by GraphPad 8.0 with $p \leq 0.05$ considered statistically significant. All data are shown as means ± S.E.M. Changes in salivary oxytocin and cortisol were analyzed using one-way ANOVA for repeated measures. Since salivary oxytocin and cortisol concentrations were not normally distributed and basal concentrations showed considerable individual variability, these values were normalized to percentage of their corresponding baseline as follows: (value *x*)/(value of Basal)*100% (Schladt et al., 2017). Multiple comparisons were adjusted using Bonferroni correction or false discovery rate correction. To ensure the stability and reliability of the statistical analysis, only participants with complete data were included. Participants who withdrew before completing the intervention or had incomplete saliva samples were excluded from the final statistical analysis. Given the exclusion of incomplete data, no data imputation methods were necessary. Subgroup analyses investigated differences based on participant characteristics. Results were reported descriptively with effect sizes, *p*-values, and presented in figures legends.

Results

Improvement in anxiety and depression symptoms with NaiKan Therapy

Prior to engaging in introspection sessions, the cohort of 60 individuals underwent assessment using the Zung Self-Rating

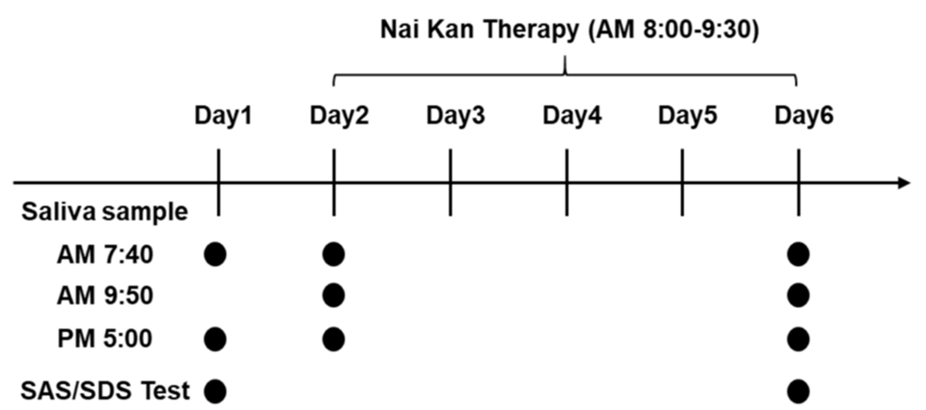

FIGURE 1
Experimental timeline.

Anxiety Scale (SAS) and Zung Self-Rating Depression Scale (SDS). Based on these evaluations, 26 participants were categorized as having no symptoms of anxiety or depression, while 34 individuals exhibited symptoms indicative of anxiety and depression. Following a structured regimen of NaiKan Therapy spanning 5 days, significant improvements were observed in SAS and SDS scores across both groups (Figure 2).

To evaluate the effects of training on anxiety and depression, we conducted paired t-tests comparing pre- and post-training scores in both normal and affected participants. For anxiety, normal subjects exhibited a significant reduction in scores following training (before: 39.04 ± 0.88, after: 35.79 ± 1.01, $n = 35$, paired t-test, $p = 0.0007$). Similarly, anxious subjects showed a significant decrease in anxiety scores post-training (before: 56.92 ± 1.71, after: 47.12 ± 2.91, $n = 13$, paired t-test, $p = 0.0036$) (Figures 2A,B). For depression, normal subjects also demonstrated a significant reduction in scores after training (before: 39.01 ± 1.47, after: 35.21 ± 1.38, $n = 24$, paired t-test, $p < 0.0001$). Additionally, individuals with depression exhibited a significant decrease in depression scores following training (before: 60.11 ± 1.42, after: 54.67 ± 1.90, $n = 34$, paired t-test, $p = 0.0037$) (Figures 2C,D). These results suggest that NaiKan Therapy holds potential as an effective intervention for alleviating symptoms of anxiety and depression, warranting further investigation into its therapeutic mechanisms and long-term efficacy.

Effect of NaiKan Therapy on salivary oxytocin and cortisol

Our investigation into the impact of introspection therapy on salivary oxytocin and cortisol levels revealed noteworthy trends. Initially, individuals with anxiety and depression exhibited elevated

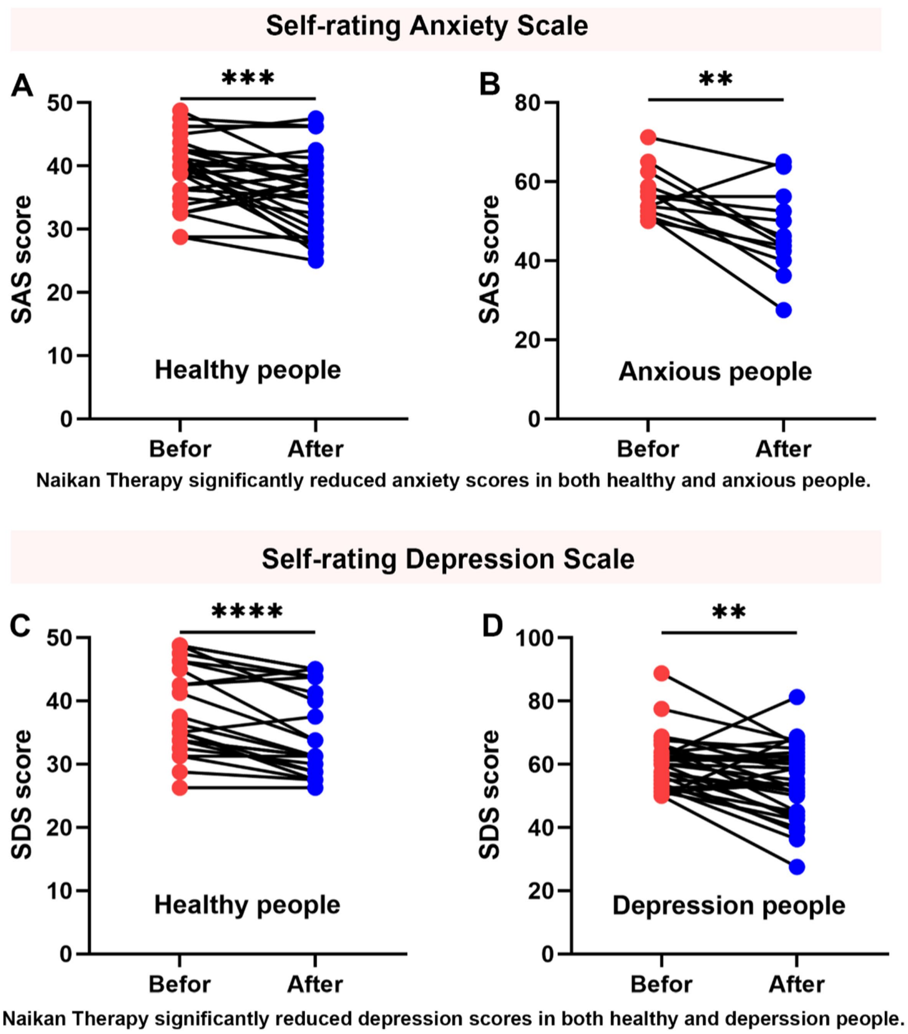

FIGURE 2
Improvement in anxiety and depression symptoms with NaiKan Therapy. **(A)** Anxiety scores of normal subjects before and after training (before: 39.04 ± 0.88, after: 35.79 ± 1.01, $n = 35$, paired t test, $p = 0.0007$). **(B)** Anxiety scores of anxious subjects before and after training (before: 56.92 ± 1.71, after: 47.12 ± 2.91, $n = 13$, paired t test, $p = 0.0036$). **(C)** Depression scores of normal subjects before and after training (before: 39.01 ± 1.47, after: 35.21 ± 1.38, $n = 24$, paired t test, $p < 0.0001$). **(D)** Depression scores of depression subjects before and after training (before: 60.11 ± 1.42, after: 54.67 ± 1.90, $n = 34$, paired t test, $p = 0.0037$). The values presented are raw measurements. Means ± SEMs.

baseline oxytocin and cortisol levels compared to their healthy counterparts. However, following introspection sessions, oxytocin and cortisol levels decreased uniformly within 20 min, irrespective of the participants' initial status. Importantly, prolonged exposure to introspection over 5 days resulted in a change in baseline oxytocin and cortisol levels among individuals with anxiety and depression (Figure 3).

For oxytocin levels in normal subjects, a significant increase was observed after training ($F_{(4, 125)} = 11.59$, $p < 0.0001$). Baseline oxytocin concentration (Day 1) was 100.00 ± 21.24 pg/mL, with no significant change at −20 min on Day 2 (87.78 ± 32.23 pg/mL). However, a marked increase was detected at +20 min on Day 2 (467.59 ± 117.40 pg/mL). On Day 6, oxytocin concentration at −20 min was 128.42 ± 55.30 pg/mL, rising significantly to 834.59 ± 166.12 pg/mL at +20 min (Figure 3A). A similar trend was observed in anxious and depressed participants, with a significant overall effect of training on oxytocin levels ($F_{(4, 165)} = 8.47$, $p < 0.0001$). Baseline levels (Day 1) were 100.00 ± 61.24 pg/mL, with a slight increase at −20 min on Day 2 (113.72 ± 62.60 pg/mL). Notably, oxytocin levels significantly rose at +20 min on Day 2 (402.91 ± 125.50 pg/mL) and continued increasing at +20 min on Day 6 (797.21 ± 143.41 pg/mL) compared to their respective baseline values (Figure 3B). For cortisol levels, a significant reduction following training was observed in both normal ($F_{(4, 125)} = 2.735$, $p = 0.0319$) and anxious/depressed subjects ($F_{(4, 165)} = 2.634$, $p = 0.0381$). In normal participants, baseline cortisol levels (Day 1) were 100.00 ± 11.51 pg/mL, with no notable change at −20 min on Day 2 (101.09 ± 7.01 pg/mL). However, a significant reduction was observed at +20 min on Day 2 (81.98 ± 17.05 pg/mL), which persisted on Day 6 (+20 min: 57.50 ± 7.11 pg/mL) (Figure 3C). Similarly, in anxious and depressed participants, baseline cortisol levels were 100.00 ± 10.57 pg/mL, with a slight increase at −20 min on Day 2 (100.79 ± 8.81 pg/mL). However, a significant decline was observed at +20 min on Day 2 (81.38 ± 8.65 pg/mL), which was further reduced at +20 min on Day 6 (67.55 ± 17.02 pg/mL) (Figure 3D).

These findings suggest that introspection may exert an effect on oxytocin and cortisol secretion, potentially contributing to the amelioration of anxiety and depression symptoms over time.

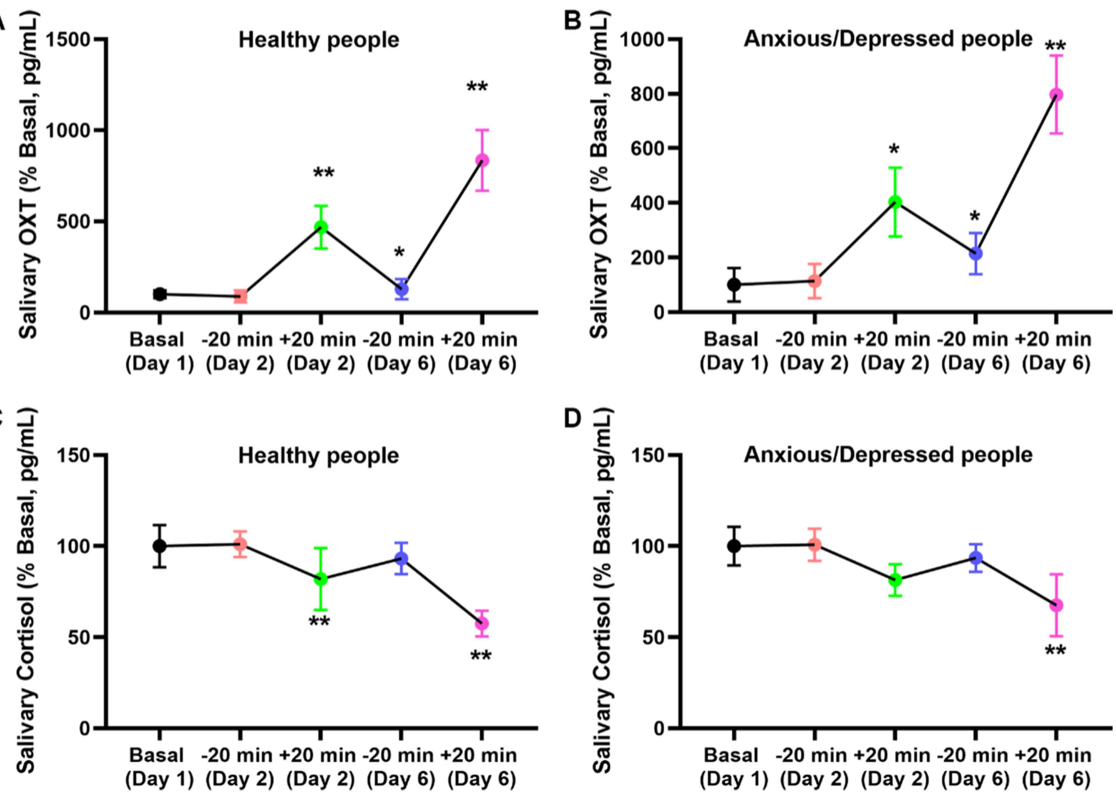

FIGURE 3
Effect of NaiKan Therapy on salivary oxytocin and cortisol. **(A)** Oxytocin concentration of normal subjects before and after training (Basaline [Day 1]: 100.00 ± 21.24, −20 min [Day 2]: 87.78 ± 32.23, +20 min [Day 2]: 467.59 ± 117.40, −20 min [Day 6]: 128.42 ± 55.30, +20 min [Day 6]: 834.59 ± 166.12, *n* = 26, One-way ANOVA, $F_{(4, 125)} = 11.59$, $p < 0.0001$). **(B)** Oxytocin concentration of anxious/depression subjects before and after training (Basaline [Day 1]: 100.00 ± 61.24, −20 min [Day 2]: 113.72 ± 62.60, +20 min [Day 2]: 402.91 ± 125.50, −20 min [Day 6]: 214.53 ± 75.40, +20 min [Day 5]: 797.21 ± 143.41, *n* = 34, One-way ANOVA, $F_{(4, 165)} = 8.47$, $p < 0.0001$). **(C)** Cortlsol concentration of normal subjects before and after training (Basaline [Day 1]: 100.00 ± 11.51, −20 min [Day 2]: 101.09 ± 7.01, +20 min [Day 2]: 81.98 ± 17.05, −20 min [Day 6]: 93.24 ± 8.60, +20 min [Day 6]: 57.50 ± 7.11, *n* = 26, One-way ANOVA, $F_{(4, 125)} = 2.735$, $p = 0.0319$). **(D)** Cortlsol concentration of anxious/depression people before and after training (Basaline [Day 1]: 100.00 ± 10.57, −20 min [Day 2]: 100.79 ± 8.81, +20 min [Day 2]: 81.38 ± 8.65, −20 min [Day 6]: 93.54 ± 7.56, +20 min [Day 6]: 67.55 ± 17.02, *n* = 34, One-way ANOVA, $F_{(4, 165)} = 2.634$, $p = 0.0381$). The values presented are baseline-adjusted. Means ± SEMs.

Correlation analysis of oxytocin and cortisol concentration changes with anxiety and depression ratings

To elucidate the relationship between hormonal changes and improvements in anxiety and depression symptoms, we conducted correlation analyses. Our results demonstrated a negative correlation between changes in oxytocin concentrations and anxiety and depression ratings, indicating that greater increases in oxytocin levels were associated with lower symptom severity. Conversely, changes in cortisol concentrations exhibited a positive correlation with anxiety and depression ratings, with greater reductions in cortisol levels corresponding to lower symptom severity. These findings underscore the intricate interplay between hormonal dynamics and psychological wellbeing following introspection therapy.

Discussion

The results of our study align with prior research indicating the therapeutic potential of NaiKan Therapy in alleviating symptoms of anxiety and depression. Our findings corroborate those of previous studies that have reported significant improvements in mental health outcomes following Naikan interventions (Sengoku et al., 2010; Zhang et al., 2015). By demonstrating consistent reductions in both anxiety and depression scores, our study adds to the growing body of evidence supporting the efficacy of Naikan approaches in mental health management.

In addition to psychological assessments, the inclusion of saliva testing in our study provided several advantages for investigating the effects of Naikan therapy on mental health outcomes. Saliva sampling offers a non-invasive and convenient method for assessing neuroendocrine responses to psychological interventions (Giacomello et al., 2020). This non-invasive nature enhances participant compliance and reduces the burden associated with sample collection, facilitating longitudinal studies with multiple sampling time points. Moreover, saliva contains various biomarkers that reflect neuroendocrine activity, including oxytocin and cortisol, which play key roles in stress regulation and emotional processing (Young Kuchenbecker et al., 2021; Ali and Nater, 2020; Wirobski et al., 2024). By measuring these biomarkers, our study gained insights into the physiological mechanisms underlying the therapeutic effects of NaiKan Therapy. Some study indicates that conducting daily NaiKan Therapy is effective for maintaining the psychological and psychosomatic state at 3 months following the intensive NaiKan Therapy (Sengoku et al., 2010). Changes in salivary oxytocin and cortisol levels following Naikan interventions may indicate alterations in stress reactivity, emotion regulation, and social bonding processes (Olff et al., 2013; Young Kuchenbecker et al., 2021; Engert et al., 2016). Additionally, prior research suggests that oxytocin and cortisol in saliva are influenced by a variety of activities, such as exercise or music (Schladt et al., 2017; de Jong et al., 2015), raising the possibility that NaiKan Therapy may exert its effects through similar mechanisms. Therefore saliva testing allowed for a comprehensive assessment of the neurobiological pathways implicated in mental health disorders and their response to therapeutic interventions.

The differential response to NaiKan Therapy observed between individuals with and without symptoms of anxiety and depression is consistent with findings from studies investigating personalized treatment approaches (Yeshi, 2018; Captari et al., 2022). Tailoring interventions based on individual symptomatology and therapeutic response has emerged as a promising strategy for optimizing treatment outcomes and enhancing patient engagement (Rush and Thase, 2018; Ng and Weisz, 2016). Our results underscore the importance of considering individual differences in treatment planning and delivery to maximize the effectiveness of NaiKan Therapy.

The mechanisms underlying the therapeutic effects of NaiKan Therapy warrant further exploration, as highlighted by recent neuroscientific investigations. Neuroimaging studies have implicated neural circuits involved in self-awareness, emotion regulation, and cognitive control in mediating the effects of Naikan interventions (Herwig et al., 2010; Opialla et al., 2015). Additionally, biomarker analyses have revealed changes in neuroendocrine signaling pathways, including alterations in oxytocin and cortisol levels, following Naikan practices (Opialla et al., 2015; Iovino et al., 2021; Li et al., 2019). Oxytocin is primarily synthesized in the hypothalamus and plays a key role in social bonding, emotion regulation, and stress attenuation through its interactions with the amygdala and prefrontal cortex (Olff et al., 2013; Triana-Del Rio et al., 2022). Engaging in introspective practices such as NaiKan Therapy may stimulate oxytocin release by enhancing social cognition and fostering a sense of self-compassion and emotional regulation. Similarly, cortisol, a critical stress hormone regulated by the hypothalamic–pituitary–adrenal (HPA) axis, responds to psychological stressors by modulating energy metabolism, immune function, and emotional processing (Mbiydzenyuy and Qulu, 2024; Smith and Vale, 2006). Our findings suggest that NaiKan Therapy may mitigate HPA axis hyperactivity, thereby reducing cortisol levels and promoting stress resilience. However, it remains unclear whether these hormonal shifts are driven by Naikan-specific mechanisms or whether they arise from broader relaxation responses, placebo effects, or increased social bonding. Future research integrating neurobiological assessments with psychological measures could provide a comprehensive understanding of the underlying mechanisms of NaiKan Therapy.

A more comprehensive understanding of NaiKan Therapy's effectiveness could be achieved by comparing it with other established psychological interventions, such as mindfulness-based stress reduction (MBSR) or cognitive behavioral therapy (CBT) (Fujisaki, 2020). Comparative studies could elucidate whether NaiKan Therapy offers unique benefits beyond general mindfulness practices. Furthermore, future investigations should explore how the observed hormonal changes might be leveraged in clinical settings to treat stress-related disorders. If NaiKan Therapy reliably modulates oxytocin and cortisol pathways, it could serve as an adjunct intervention for conditions such as generalized anxiety disorder, major depressive disorder, or post-traumatic stress disorder.

In conclusion, our study contributes to the growing body of evidence supporting the efficacy of NaiKan Therapy in improving mental health outcomes, particularly for individuals experiencing symptoms of anxiety and depression. By elucidating the mechanisms underlying its therapeutic effects and exploring its long-term sustainability, future research has the potential to enhance the accessibility and effectiveness of Naikan interventions in diverse clinical settings. Addressing the limitations of short-term follow-up, self-reported biases, and cultural generalizability will be crucial for advancing NaiKan Therapy as an evidence-based mental health intervention.

Limitations

Despite the promising findings, several limitations should be acknowledged. First, our study evaluated only short-term hormonal changes following NaiKan Therapy, without incorporating long-term follow-ups. As a result, it remains uncertain whether the observed effects on oxytocin and cortisol are sustained or revert to baseline over time. Future research should include follow-up assessments (e.g., one week or one month post-therapy) to determine the durability of these effects. Longitudinal studies with extended follow-up periods are needed to assess the durability of treatment effects and identify factors contributing to sustained improvements in mental health outcomes (Breier et al., 1991; Winzer et al., 2018). Second, our reliance on self-reported anxiety and depression scores introduces a potential subjective bias. Although validated psychological scales were used, self-report measures remain susceptible to individual differences in perception and reporting. Future studies should incorporate clinician-administered assessments or physiological measures of stress reactivity to enhance the robustness of findings. Third, we did not control for external factors that may have influenced hormonal changes, such as participants' engagement in other stress-reducing activities (e.g., meditation, exercise, or social interactions). These confounding variables could have contributed to the observed effects and should be addressed in future research through stricter control measures or study designs that directly compare NaiKan Therapy with other mindfulness-based interventions. Fourth, the sample size, while adequate for initial insights, may limit the generalizability of our results, particularly as the study primarily focused on individuals already exhibiting symptoms of anxiety and depression. Additionally, given that NaiKan Therapy has its origins in Japan, cultural influences may affect its generalizability to populations outside of East Asia (Shantha, 2019; Kirmayer, 2015). The introspective nature of NaiKan Therapy may resonate differently with individuals from Western cultures, where self-reflection is often conceptualized through different frameworks (Kirmayer, 2015). Future cross-cultural studies are needed to determine whether NaiKan Therapy's effects extend across diverse populations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Shanghai Nanhui Mental Health Center Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MQ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. MW: Data curation, Writing – review & editing. SS: Data curation, Writing – review & editing. HX: Data curation, Writing – review & editing. RH: Data curation, Writing – review & editing. QY: Data curation, Formal analysis, Writing – review & editing. ZZ: Data curation, Writing – review & editing. HW: Data curation, Writing – review & editing. MC: Formal analysis, Writing – review & editing. QM: Data curation, Writing – review & editing. HZ: Conceptualization, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2025.1476654/full#supplementary-material

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Integrating mind-body processes and motivational interviewing in health coaching: enhancing support for health behavior change

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The global rise of chronic disease presents a need for effective prevention and treatment grounded in mind–body science and autonomy-promoting lifestyle interventions. Health and wellness coaching (HWC) has emerged as a new field as the evidence for it has grown. However, there continue to be significant discrepancies in how the HWC role is defined, trained, and practiced. HWC is an evidence-based approach integrating well-established behavior change theories and techniques to help individuals explore and sustain self-determined health targets. The National Board for Health and Wellness Coaching in the United States guides credentialling for the field and establishes minimum training standards and competencies for practicing health coaches. Foundational knowledge of the mind–body connection is newly included in these coach competencies. In this paper, we present the overall process of HWC used in the Vanderbilt Health Coaching Program, emphasizing how mind–body processes can be integrated with motivational interviewing. We specifically present three mind–body processes that we have entwined with motivational interviewing and iterated with over 700 trainees: use of mindfulness, the whole person Wheel of Health, and guided visualization. We also present two structural tools that overlay the mind–body processes and motivational interviewing: the Vanderbilt Health Coaching Funnel and it's brief derivative for clinical encounters, the IVA (Importance Visioning Activation) Funnel. Each mind–body process and the two structural tools are described in detail as each promotes the underlying development of sustainable behavior change. Our aim is that these mind–body processes and structural tools will help clarify the evidence-based strategies upon which true coaching is developed and that other clinicians, researchers, and coaches will utilize them to empower their patients in pursuing their best health.

KEYWORDS

health coaching, health and wellness coaching, motivational interviewing, mindfulness, guided visualization, Wheel of Health, Vanderbilt Health Coaching Funnel, IVA funnel

Introduction

The study of mind–body medicine focuses on how the iterative relationships between the mind–body connection and behavior produce health and disease. Not only do biopsychosocial factors affect lifestyle, but lifestyle iteratively affects these factors creating patterns that lead toward or away from health and disease (Schulz et al., 2023). Lifestyle intervention is imperative to prevent and treat chronic disease including cardiovascular disease, diabetes, obesity, many cancers, and even anxiety and depression, in large part through impacting chronic inflammation (Bodai et al., 2018). As evidence for autonomy-promoting approaches to build healthy and sustainable behavior patterns has increased over the past decades, so have new job roles such as health and wellness coaching (HWC) (Wolever et al., 2016; Jordan et al., 2015). The growth of these roles and the global need to create and evaluate effective approaches for sustainable lifestyle behavior change establishes a unique opportunity to leverage mind–body processes (Schulz et al., 2023).

Definitional problems

As with any rapidly-growing field, there continue to be significant discrepancies in how the HWC role is defined, trained and practiced. Since the term "health and wellness coach" is not protected by any title acts or regulations, even peer-reviewed papers evaluating "health coaching" often use these terms to describe interventions that do not use the foundational and empirically-based elements of HWC. Unfortunately, the problem is further confounded when apparently well-conducted systematic reviews of health coaching use as their inclusion criteria authors' statements that the intervention was "coaching" (Sieczkowska et al., 2021; Rethorn and Pettitt, 2019) rather than clear indicators of well-established definitions for coaching (Sforzo et al., 2021). Most people—including trialists—do not understand the difference between coaching and other active interventions that are better referred to as clinical, educational or advising interventions (Wolever and Eisenberg, 2011). In fact, some interventions referred to as "health coaching" provide clinical assessment and recommendations, and are heavily educational in nature [e.g., (Karhula et al., 2015; Patja et al., 2012)]. HWC does not involve the process of diagnosis nor treatment. Further, HWC, by definition, provides only minimal education and does so in a specific autonomy-promoting manner (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022; National Board for Health and Wellness Coaching, 2022; Olsen, 2014). Instead, HWC uses well-established theories and evidence-based behavioral techniques to help individuals explore their self-determined health targets, elicit intrinsic motivation, and promote individual autonomy to identify and experiment with problem-solving techniques in an exploration for how to shift their lives in a way that only they can assess and sustain (Wolever et al., 2010; Wolever et al., 2011; Wolever et al., 2016; Matthews et al., 2024).

Guiding the field

Despite equivocal findings (Sieczkowska et al., 2021; Rethorn and Pettitt, 2019) and challenges in the growing field of HWC, the HWC approach solidly rests on empirical work that has demonstrated effectiveness in helping individuals improve health behaviors (Matthews et al., 2024; Sforzo et al., 2020; Sforzo et al., 2018; An and Song, 2020; Boehmer et al., 2016; Kivelä et al., 2014; Ahmann et al., 2024; Radwan et al., 2019; Budzowski et al., 2019). To guide the field and ensure at least a minimal bar of HWC skill for practicing health coaches, the National Board for Health and Wellness Coaching (NBHWC) has emerged in the United States. Faculty from one of the NBHWC approved training programs, the Vanderbilt Health Coaching Program (VHCP), have been involved in collaborative efforts with other leading HWC programs/experts to bring clarity to what HWC is (and is not) (Wolever et al., 2016; Wolever and Eisenberg, 2011; Wolever et al., 2011; Sohl et al., 2021; Caldwell et al., 2013; Caldwell et al., 2020) and to strengthen the field through the development of evidence-informed tools and processes while also using them to train professionals in a reproducible intervention (Sohl et al., 2021; Caldwell et al., 2020; Wolever et al., 2017). As with any new and emerging field, rigorous research is needed to establish feasibility and effectiveness across different groups and settings; VHCP faculty is committed to contributing to the growing evidence demonstrating the potential of HWC (Wolever et al., 2010; Edelman et al., 2006; Wolever and Dreusicke, 2016; Wolever et al., 2022). In this paper, we present the overall process of HWC used in the VHCP, highlighting three mind–body processes and two structural tools developed and iterated with over 700 trainees in the VHCP and the Meharry Vanderbilt Health Coaching Program. It is our hope that these structural tools will help other researchers, clinicians and coaches recognize that the foundation of true coaching is MI, which can be leveraged with mind–body processes to further empower individuals in pursuing better health for themselves.

Health and wellness coaching: models and background

Prior to presenting our overall HWC process and its integration with mind–body processes, we present the generally accepted methods of HWC with supporting background on their evidence base. We then highlight the integration of the mind–body processes that we use to enhance the behavioral change process. Specifically, we present how mindfulness training enhances coaching, a whole person model for self-assessment called the Wheel of Health, the use of guided visualization to assist with self-discovery, the Vanderbilt Health Coaching (VHC) Funnel as a motivational interviewing (MI) based tool for use in routine follow-up coaching sessions and its derivative, the Importance Visioning Activation (IVA) Funnel, for use in brief clinical encounters.

Health coaching models in general

While there are different health coaching models (Wolever et al., 2017; Smith et al., 2013; Purcell et al., 2021; Malecki et al., 2020), the evidence base is founded on the empirically derived definition of HWC on which the work of the NBHWC rests (Wolever et al., 2013). There is also consensus that HWC generally involves the following: an early "self-discovery" phase wherein the client explores their vision of improved health and well-being and sets a goal for the duration of the coaching (e.g., 6 months); a middle phase wherein the client explores a topic of their choosing and sets small action steps to take between sessions that move them toward their goal; and a final session where-in they review their progress and focus on maintaining improvement (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022; National Board for Health and Wellness Coaching, 2022). HWC rests on a handful of theories: Self-Perception Theory (Bem, 1967), Social Cognitive Learning Theory (Bandura, 1977; de la Fuente et al., 2023), Goal-Setting Theory (Locke and Latham, 2002), Self-Determination Theory (Ryan and Deci, 2000; Spence and Oades, 2011), and the Transtheoretical Model (Prochaska and Velicer, 1997; Prochaska and Prochaska, 2019). In addition, while many coaches may not realize it, HWC borrows heavily from the counseling style of MI (Miller and Rollnick, 2023). In fact, while additional evidence-based behavioral techniques are also used in coaching (Wolever et al., 2013; Simmons and Wolever, 2013), most models (unfortunately not all) utilize MI as a core component of health coaching (Budzowski et al., 2019; Linden et al., 2010; Butterworth et al., 2006).

Motivational interviewing as a foundational process

MI is "a particular way of talking with people about change and growth to strengthen their own motivation and commitment" (Miller and Rollnick, 2023). Effective application of MI requires an embodiment of the "spirit" of MI, dubbed the CAPE of coaching (CAPE: compassion, acceptance, partnership and empowerment) (Lanier et al., 2024). Effective application of MI also utilizes foundational communication skills, [i.e., open questions, affirmations, reflections, and summaries (OARS)], key MI processes (i.e., cultivating change talk and softening sustain talk), and an understanding of the four fundamental tasks of MI (Miller and Rollnick, 2023). Per the NBHWC competencies, health coaches must demonstrate competency, at a minimum, in the "spirit of MI" through creation of a patient-centered, empathic, non-judgmental, and empowering relationship in which the coach guides rather than dictates the change process (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022). They must also demonstrate competency in a number of communication skills that are also used in MI: deep listening and OARS (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022). Using these foundational communication skills and autonomy-supportive processes, coaches must be able to competently elicit change talk from clients and soften sustain talk (National Board for Health and Wellness Coaching, 2022). Across health coaching models and training programs, there is wide variability in the degree to which coaches are trained in MI, including how to cultivate change talk, soften sustain talk, and move clients through the four tasks of MI (Lundgren, 2024).

Innovative foundation of the VHCP

The overarching VHCP model is unique in at least two ways. First, it walks individuals through the four tasks of MI over the course of the coaching relationship with all four tasks simultaneously being addressed in each ongoing session. While NBHWC provides approved training programs with a list of competencies in which entry level coaches must demonstrate proficiency, NBHWC does not specify a clear structure in which to utilize the skills or advise specifically on when coaches should utilize them in practice. Thus, many approved training programs teach MI as an underlying theory and introduce MI skills in isolation without a supportive structure. Coaches utilizing the VHCP session structure integrate the evidence-based communication skills and processes of MI in a systematic fashion. Upon completion of the program, health coaches can modify the structure to fit their varied settings; during training, the structure serves as an educational tool while they learn how various skills and processes work together.

The second way in which the VHCP model is innovative is that it entwines mind–body processes with MI in a manner that deepens client learning and ensures a whole person approach. Very little evidence or even description is available in the peer-reviewed literature regarding the overlay of mind–body processes and MI in coaching. There are multiple descriptions of health coaching from a whole person model, particularly in holistic nursing (Wolever et al., 2017; Purcell et al., 2021; Dossey et al., 2014; Bark, 2011; Delaney and Bark, 2019; Jordan, 2022). There are also a handful of studies that evaluate a coaching model that also uses mind–body techniques (Wolever et al., 2010; Edelman et al., 2006; Purcell et al., 2021; Gordon et al., 2023; Hudlicka, 2013; Malecki et al., 2020), but most do not even mention MI. In fact, literature searches in multiple databases [i.e., PubMed, PsycINFO, OVID (Medline and others)] using "mind–body" and "motivational interviewing" as key words reveal only minimal work that includes both mind–body processes and MI in intervention models. Furthermore, we could find no empirical work specifically evaluating the potential contribution of mind–body approaches to MI. In PubMed, we found four studies that assessed interventions that combined holistic breathing techniques with MI, and a case study using MI to address spirituality; none of these five involved coaching. Similarly, searching PsycINFO using the same key words revealed only 3 peer-reviewed pieces, all of which were irrelevant. Finally, a literature search using the database OVID (including Medline) and the key words "mind–body," "motivational interviewing" and "coach" produced 33 links; of these, 14 were conference abstracts, 12 were non-empirical descriptions, 3 were reviews and only 4 were actual studies (or protocols) that included both mind–body approaches and MI; again, none empirically tested the contribution of mind–body processes. While HWC in the field is often delivered with the addition of mind–body processes, the use of mind–body processes to specifically augment MI has not received much empirical focus. Nonetheless, the recognition of the role of mind–body processes in behavior change is growing rapidly. This is evidenced by the NBHWC mandate that foundational knowledge of the mind–body connection is now needed by health and wellness coaches to meet the 2026 required competencies (National Board for Health and Wellness Coaching, 2024; see Table 1). The VHCP model is thus unique in that it integrates mind–body processes and whole person care with the evidence-based tasks of MI to promote sustainable behavior change.

Mind–body processes entwined with MI

The foundational change process taught in the VHCP is based on MI, with the integration of mind–body processes to enhance the client's change process. First, mindfulness training is seminal for both the coach and to a lessor degree, the client. Second, a whole person integrative Wheel of Health is used to expand the client's exploration in the self-discovery phase. Third, guided visualization is used to cultivate and amplify intrinsic motivation in the self-discovery phase as well as in ongoing sessions. In this visioning, the invitation to

TABLE 1 National Board for Health and Wellness Coaching required knowledge competency for mind-body connection (National Board for Health and Wellness Coaching, 2024).

5.2. Components of proactive health and wellbeing
5.2.8. Mind-body connection
5.2.8.1. Changes in the mind impact the body, and vice-versa
5.2.8.2. Impact of thoughts, beliefs and mindset on behavior as well as physical and mental health
5.2.8.3. Impact of mindset shifts on moving toward health and wellbeing, even in the presence of disease or disability
5.2.8.4. Impact of mind-body techniques and practices to support behavior change, personal growth, and overall health and wellbeing

integrate sensory information is used to strengthen and deepen the learning to enhance confidence, self-efficacy and creative problem solving. In addition, multiple adult learning principles are woven throughout both the training program and the actual coaching process. For example, adults are self-directed learners whose wealth of experience facilitates learning (Cox, 2015). Learning should be relevant to their lives and is best delivered through hands-on involvement and practice (Cox, 2015). Two structural tools are also presented in this paper to ensure that core MI and mind–body processes are baked into the coaching practice: the VHC Funnel and the IVA funnel. The latter is a simplified version of the VHC funnel that can be used in 3–5 min during a clinical encounter.

Mindfulness training

Mindfulness is practiced by intentionally bringing close attention to the present moment with a gentle noticing, curiosity and non-judgment (Kabat-Zinn and Hanh, 2009; Siegel et al., 2009). Burgeoning evidence shows that practicing mindfulness has cognitive, emotional, and intrapersonal benefits, such as improving focus, increasing attention to percepts (thoughts, emotions, sensations) without elaboration, enhancing decision-making processes, and supporting cognitive flexibility (Didonna and Zinn, 2009). Mindfulness practice also promotes compassion, self-regulation, self-awareness (Gawande et al., 2019), presence (McCollum and Gehart, 2010), and interconnectedness, all of which are supportive of the coaching role (Rimban et al., 2024).

These same outcomes have made mindfulness an evidence-based strategy to support sustained behavior change as it promotes self-awareness, emotional regulation, self-regulation (Gawande et al., 2019), values clarification (Carmody et al., 2009), and thus, access to intrinsic motivation (Sohl et al., 2016). Self-awareness can be seen as a first step in developing the self-regulation required for sustainable behavior change (Brown et al., 2007), establishing the need for change and increasing insight into an individual's own motivations and behaviors (Dossey et al., 2014). This insight, coupled with mindfulness, creates a space in which the individual is more likely to intentionally choose a behavior in alignment with their values system rather than out of habit (Roche et al., 2019; Schuman-Olivier et al., 2020). Furthermore, this lowers the cognitive effort around behavior change to nearly effortless (Roche et al., 2019; Schuman-Olivier et al., 2020; Redwine et al., 2022). In essence, mindfulness practice increases one's awareness of how their relationships with their own thoughts, emotions and sensations bundle together to drive behavior (Wolever and Best, 2009).

The NBHWC includes mindful awareness as a foundational competency for coaches to promote therapeutic presence through active listening, "holding space," empathy, and non-judgment (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022; National Board for Health and Wellness Coaching, 2022). While the depth of mindfulness training varies widely across NBHWC approved programs, qualitative and quantitative studies support its efficacy as a seminal part of the coaching process for both coach and client (Wolever and Best, 2009; Goble et al., 2017; Wolever et al., 2011; Spence et al., 2008). Hence, VHCP's training centers on mindfulness as a necessary tool. Mindfulness is introduced as a means for coaches to personally deepen their ability to self-regulate, practice self-management, promote active listening, support therapeutic presence and develop positive rapport. Importantly, those with a mindful disposition are better able to deliver patient-centered care (Beach et al., 2013). VHCP trainees are first taught to use mindfulness to settle themselves, then later taught how to invite clients to be led in brief mindfulness practices at the beginning of sessions as a way to become fully present for the session. While always presented as a choice, practicing mindfulness with clients allows clients to experience being attuned with sensations and contextual cues, a practice they can use to support their own behavior change. Trainees are taught to use the MI tool "Ask-Offer-Ask" (Miller and Rollnick, 2023) to present the opportunity to be led in a mindful moment. The VHCP coaching process further promotes moment-to-moment awareness as coaches frequently inquire about client learnings, somatic experiences, and emotions throughout the coaching session.

VHCP model with mind–body processes used throughout the structure

In the VHCP, we utilize a semi-structured model designed to promote sustainable behavior change through the integration of mind–body processes, MI, positive psychology, and other evidence-based behavior change techniques. Aligning with NBHWC structure recommendations, the VHCP model provides a structure to help coaches learn to guide clients through the following: (1) early sessions in which they self-discover intrinsic motivation and set behavioral targets using goal-setting theories; (2) ongoing sessions where clients build momentum while experimenting with what works in their lives; and (3) a closing session which includes relapse prevention planning and celebrating the client's progress and learning. The duration of coaching is highly variable and often determined by health plans or payors rather than science; it is often a 3–6 month timeframe.

The discovery phase

Also referred to by NBHWC as "early sessions" and by MI as the engaging task, the discovery phase occurs in the first one to two sessions. Early sessions are critical for establishing positive coach-client rapport and establishing the client-centered nature of health coaching (McCollum and Gehart, 2010; McKay et al., 2006; Krogh et al., 2019). Over the early sessions, a coach reviews the nature of the coaching relationship, explores the client's motivation for seeking coaching, supports the client in a self-assessment, and explores the client's optimal health vision, values and personal strengths. Unlike other healthcare relationships and the traditional MI model, VHCP early sessions typically last for 60 to 90 min, most of which is spent in self-discovery and the engaging task of MI.

Whole person Wheel of Health

The VHCP model uses a whole person self-assessment (Wheel of Health) to support clients in identifying their current versus optimal state in nine different areas of health and well-being (see Figure 1). Clients rate their current satisfaction on a scale of 1 to 10, with 1 being "not at all satisfied" and 10 being "completely satisfied," in each of the domains of health and well-being. In addition to indicating their current state in each domain, they indicate where they want to be in the same domain, and note their readiness for change in this arena. Coaching questions regarding the client's desired state (where they want to be in a certain realm) begin to plant seeds of inspiration as clients imagine what would be best for them (Wolever and Dreusicke, 2016). Importantly, the use of this whole person self-assessment allows individuals to discover for themselves their own interrelationships between thoughts, emotions, body sensations and behavior. In essence, the self-assessment invites the client to think from a mind–body perspective about their daily routines and lifestyle habits. There are many different Wheels of Health, developed by different programs for different contexts; the one currently used in our program has been described elsewhere (Wolever et al., 2017).

Guided visualization

Following the exploration of the Wheel of Health, coaches using the VHCP model invite clients to a guided visualization exercise to imagine the experience of their default and optimal health visions. Again, the coach uses Ask-Offer-Ask to explain the process prior to leading the visualization. After the experience, the coach uses open questions and reflections to explore the client's vision, values, and strengths, amplifying the gap between the client's current and desired states. In doing so, the coach briefly moves to the evoking task of MI, cultivating preparatory change talk (DARN), building intrinsic motivation, and further nurturing the planted seeds of hope and possibility. In essence, guided visualization is used to magnify the gap between the client's current behavior and their values as imagined in their desired state; this is a core process well-described in MI (Lanier et al., 2024). Creative guided visualization is a mind–body process with growing utilization in psychology, clinical care, integrative medicine, and behavior change therapies (Conroy and Hagger, 2018; Giacobbi et al., 2017). Guided visualization (also called guided imagery) has demonstrated effectiveness to promote healthy behavior change in eating (Conroy and Hagger, 2018), exercise (Cramer et al., 2014), substance use (Conroy and Hagger, 2018), and management of pain, anxiety, and stress (Giacobbi et al., 2017). The neural networks activated during guided imagery have the same effect on the body and mind as physically being present for an event or experience (Kosslyn et al., 2001). It is through these pathways that guided imagery impacts prevention and management of chronic disease. Thus, visualization can be used to increase an individual's motivation, anticipated pleasure, anticipated reward, intention to change and likelihood of sustaining a behavior (Conroy and Hagger, 2018; Cramer et al., 2014).

End of the discovery phase: focusing, evoking, planning

To conclude the discovery phase, the client chooses an area of focus in which to work for the duration of coaching. The coach evokes the importance of this area using an importance ruler (also an MI tool) and elicits how the area connects to the client's vision, personal values, and meaning (Goble et al., 2017; Wolever et al., 2011; Vorderstrasse et al., 2013). Early self-exploration is followed by goal-setting in which the coach guides the client to set an "umbrella goal" that covers the duration of the coaching relationship. Also known as a long-term goal, the self-selected umbrella goal defines a target behavior pattern the client wishes to achieve by the end of the coaching relationship. Per the VHCP model, NBHWC competencies, and MI strategies, the umbrella goal is as Specific, Measureable, Action-Oriented, Realistic and Timebound (SMART) (National Board of Medical Examiners and National Board for Health Wellness Coaching, 2022) as reasonable for the client's knowledge and visioning at the beginning of coaching. Importantly, while many clients name outcome goals first, coaches support clients in translating their desires into behavioral goals or targets over which they have direct control (Bailey, 2019). A weight loss maintenance goal, for example, is turned into a specific physical activity goal. A "sleep better" goal is translated into sleep hygiene, and/or limited time in bed goals. A "feel less stressed" goal is translated into specific routines or behaviors the client commits to in order to lower their stress. Clients are also encouraged to have "approach" goals rather than "avoidance" goals (Oettingen and Gollwitzer, 2010; Bertholet et al., 2010). Instead of "limit beer intake at night," the client might frame this as "after one beer, drink flavored water at night." Or rather than "avoid screens one hour before bed," the client might work toward, "reading, journaling, or practicing self-care one hour before bed." According to neuroscience principles, focus on feared outcomes or avoidance tends to engage the amygdala (LeDoux, 2009; Frick et al., 2022). On the other hand, using approach goals that focus on building health, engenders creativity and iterative problem-solving, engaging the pre-frontal cortex and instilling a sense of imagination and hope (Cramer et al., 2014; de Souza et al., 2014).

In addition, the long-term goal(s) are tied to the client's optimal health vision and values, increasing intrinsic motivation and likelihood of success (Locke and Latham, 2002; Kimsey-House et al., 2018). Goal-setting in HWC is distinct from that in MI in that goals are client-determined rather than shared, promoting client ownership, empowerment, and autonomy. Health coaches may bring in medical guidance from the client's provider team, but do not push other-determined goals. They simply ask what the client thinks about their provider's recommendations, and how, if at all, they want to integrate them. This goal-setting difference in coaching and MI can be significant, since in coaching, the promotion of client autonomy trumps medical advice in the immediate future. Anecdotal clinical reports suggest that clients tend to develop confidence from their success in making whatever changes they find highly relevant and for which they are ready (Ryan and Deci, 2000; Berkman, 2018). This confidence breeds success as one area of health and well-being tends to positively impact other areas. Because the VHCP model embraces whole person health, there are myriad places that the client may choose to focus. Hence, clients are encouraged to start with areas in which they feel most ready to work and even show excitement. After the specific long-term goal is set, coaches then support clients in setting successive SMART action steps (or short-term goals), moving to the planning task of MI and cultivating commitment and confidence from the client.

FIGURE 1
Wheel of Health (Courtesy of Osher Center for Integrative Health at Vanderbilt).

Middle phase: ongoing or follow-up sessions

In the middle phase of coaching (NBHWC routine, ongoing sessions), the VHCP model walks clients through the four tasks of MI in each session. Sessions are typically 30–45 min in duration and clients usually have 6 to 9 routine ongoing sessions, on average, depending on the clients' needs, interest and long-term goals. VHCP coaches are trained to utilize the session structure as a guide to facilitate the coaching session. Coaches are equipped with mindfulness, communication skills, and MI strategies to effectively honor client needs, desires, and autonomy above adherence to a rigid structure. The structure of routine, ongoing sessions is outlined below and correlated with the four tasks of MI as shown:

Engaging

- o Assess client current state with an open question. Doing so helps the coach become attuned to the client and often opens the opportunity to practice mindfulness as a way to self-regulate and deepen awareness.
- o Invitation to a mindful moment, and leading of a brief practice if client desires.
- o Review of session agenda with input from client as desired.
- o Check-in on previous action steps with client permission
  - ■ The coach uses open questions and reflections to elicit client successes and learnings with each action step, taking the opportunity to affirm client successes, insights, and efforts. Like much of HWC, this process draws on Self-Perception Theory in which clients hear their own narrative and begin to infer their qualities and skills from what they see themselves do and hear themselves say (Bem, 1967).
  - ■ Learning is specifically elicited for each action step to support the client in developing an awareness of and self-efficacy in creating their unique behavior change journey, as explained by Bandura's Social Learning Theory (Bandura, 1982).
  - ■ If the client brings up barriers, challenges, or lack of action on an action step, the coach acknowledges the barrier to the extent necessary to establish and maintain rapport and understanding, but follows this with a reframe or inquiry regarding what the client learned that may be pulled forward in the behavior change journey. The check-in should occur at each session to build traction over time, allowing the client to link the action and learning from each experimental step as they move toward their umbrella goal. Consistently reinforcing and iterating action steps is important since behavioral repetition is one of the core components of establishing a new behavior pattern (Wood and Neal, 2016).
  - ■ Learning is specifically elicited for each action step to support the client in developing an awareness of and self-efficacy in creating their unique behavior change journey, as explained by Bandura's Social Learning Theory (Bandura, 1982).
  - ■ As the check-in process is repeated frequently, clients also vicariously learn to look for success on which to build, and how to reframe failure as learning opportunities (Bandura, 1997).

Focusing

Coach elicits client-selected topic to discuss during the session. The topic may be related to an obstacle that arose in pursuing the client's latest commitments to action steps. The topic may also be about what needs to happen next to continue building the desired behavior pattern. However, the topic may also be about something seemingly unrelated that has arisen and must be managed in order to keep attention and energy focused on the lifestyle goal, rather than habitual patterns of coping (Fournier et al., 2017; Schwabe and Wolf, 2009).

Evoking

- o Coach uses the VHC funnel, described in detail below, to evoke the client's desire, ability, reasons, need, commitment, and activation for change.

Planning

- o Coach guides client to develop a SMART, behavioral action step that connects to client's umbrella goal and/or optimal health vision. To set the client up for success, the coach uses open questions and reflections to investigate any needed environmental and interpersonal supports and a plan to engage each support. The coach invites the client to forecast potential barriers and supports them in establishing a contingency plan should those barriers arise (Bailey, 2019). Accountability and tracking plans are established, given the importance of self-monitoring in successful behavior change (Michie et al., 2009). Furthermore, tracking promotes client ownership of the new behavior and helps the client learn what does and does not work for them. Finally, the coach elicits the client's confidence using a 1 to 10 scaling question and further explores how the client might increase their confidence if needed (i.e., < 7 on the 10-point scale).

Session closing

At the end of each follow-up session, the coach elicits client takeaways or key insights from the session. This process serves in the same manner as the check-in, emphasizing what the client is learning about their own behavior change process. The hope is that the client will not only clarify and attain their goals, but understand enough about the process that they can recontextualize the process for other changes.

Final session

The final session of the entire health coaching engagement follows a similar structure to that of the routine follow-up session, but in place of developing a next action step, the focus and the closing of the session are used to review what the client has achieved and what the client has learned about how they best change their own behavior relevant to their goal. In addition, the coach reviews the client's maintenance plans asking the client to describe yellow flags that would indicate that the client may need more HWC or a stronger intervention to stay on track.

VHCP structural tools

Session focus: the VHC funnel

As shown in Figure 2, a structural tool unique to the VHCP program is the VHC funnel, a framework utilized in the session focus to explore the client-selected topic and ensure that key MI tasks are covered with respect to the chosen topic while also allowing for the incorporation of mind–body processes. The VHC funnel intentionally integrates evidence-based strategies from MI to evoke preparatory change talk before moving to eliciting commitment change talk while simultaneously integrating visualization techniques and the use of multisensory information. By utilizing the VHC funnel, coaches explore the importance of change, connect desired change to a client's vision and values (Caldwell et al., 2020; Wolever et al., 2017; Wolever et al., 2011), elicit client strengths that may serve them in the changes they desire, and invite client-determined steps. The coach uses powerful open questions, affirmations, reflections, and summaries throughout the funnel to cultivate change talk, soften sustain talk, and increase intrinsic motivation before planning for change with an action step.

Opening of the funnel

Coaching is a whole-person approach in which you start where the client is now and support them imagining into where they want to be, creating a space in which the client can move toward something rather than away from an undesirable behavior. The coach begins the session focus (at the top of the funnel) by eliciting what the client would like coaching around. The topic is always client-determined, rather than coach-selected, to maintain client autonomy.

Importance

Rather than moving directly into problem-solving, the funnel opens with an open question to elicit importance around the desired change. Questions may be straightforward, such as "What is important to you about this?" or "What matters to you about this area right now?" The intent is to elicit preparatory change talk and begin the exploration behind the "why" for change (Morris et al., 2022). Regardless of how specific the client-selected topic is, the coach explores how the area relates to their values rather than moving to problem-solving or goal-setting, as is often the case in typical healthcare settings. The coach listens for and reflects change talk, further exploring client desires and reasons for change with directional questions to evoke more change talk. Discussion of how the topic at hand connects to the client's personal meaning, sense of purpose and values has important implications for health (Alimujiang et al., 2019; Mulahalilović et al., 2021; Friedman and Teas, 2023).

Visioning and values

Furthering this intrinsic motivation are two key components of implementing change: hope and confidence (Miller and Rollnick, 2023). While a client may cognitively understand reasons for change, change is unlikely without a belief in one's own ability to change (Bandura, 1977) and a vision of what is possible (Conroy and Hagger, 2018; Cramer et al., 2014). By utilizing the VHC funnel, the coach invites the client to envision an optimal state in the selected area, using questions such as:

- How will your life be different when you have this just as you wish?
- What benefits will there be for you? For others you love?
- What will be possible for you when you make this change?
- If you could wave your magic wand, how would this area look in your life right now?
- When you envision yourself living as your best self in this area, what does that feel like in your body?
- What other areas in your life will be impacted when you make this change?

By describing their optimal state in detail, including the sensory component of it, the client is creating a felt sense of where their intrinsic motivation could take them (Patrick and Williams, 2012; Jack et al., 2013). Coaches ask clients to describe multisensory components of their vision, pulling for multisensory integration to enhance associative learning, anchoring in the potential impact of the desired behavior change (McGann, 2015; Lauzon et al., 2022). The coach may weave back and forth between linking the desired change to a client's values and optimal vision, listening for and reflecting change talk from the client, amplifying client insights, and further exploring the desired change.

Throughout the session focus, the coach is listening for and reflecting stated and inferred values. Skillful coaches make explicit connections between the desired change and how it connects to client values, deepening desires, reasons, and need for change. The coach may explicitly ask the client how their values are connected to the desired change with an open question ("How does making this change support what matters most to you?") or further explore stated or inferred values with meaningful reflections and powerful questions.

Building self-efficacy

A great deal of correlational research has shown individuals with higher degrees of self-efficacy are more likely to successfully implement and sustain behavior change (Bandura, 1982; Sheeran et al., 2016; Nezami et al., 2016; Kulik et al., 2019). More importantly, a meta-analysis of randomized controlled trials clarifies that it is the increase in self-efficacy that leads to improvements in both behavior intentions and behavior change. This meta-analysis included 50 studies (12,450 participants) on change in behavioral intention, and 90 studies (29,520 participants) on change in behavior itself, all of which included

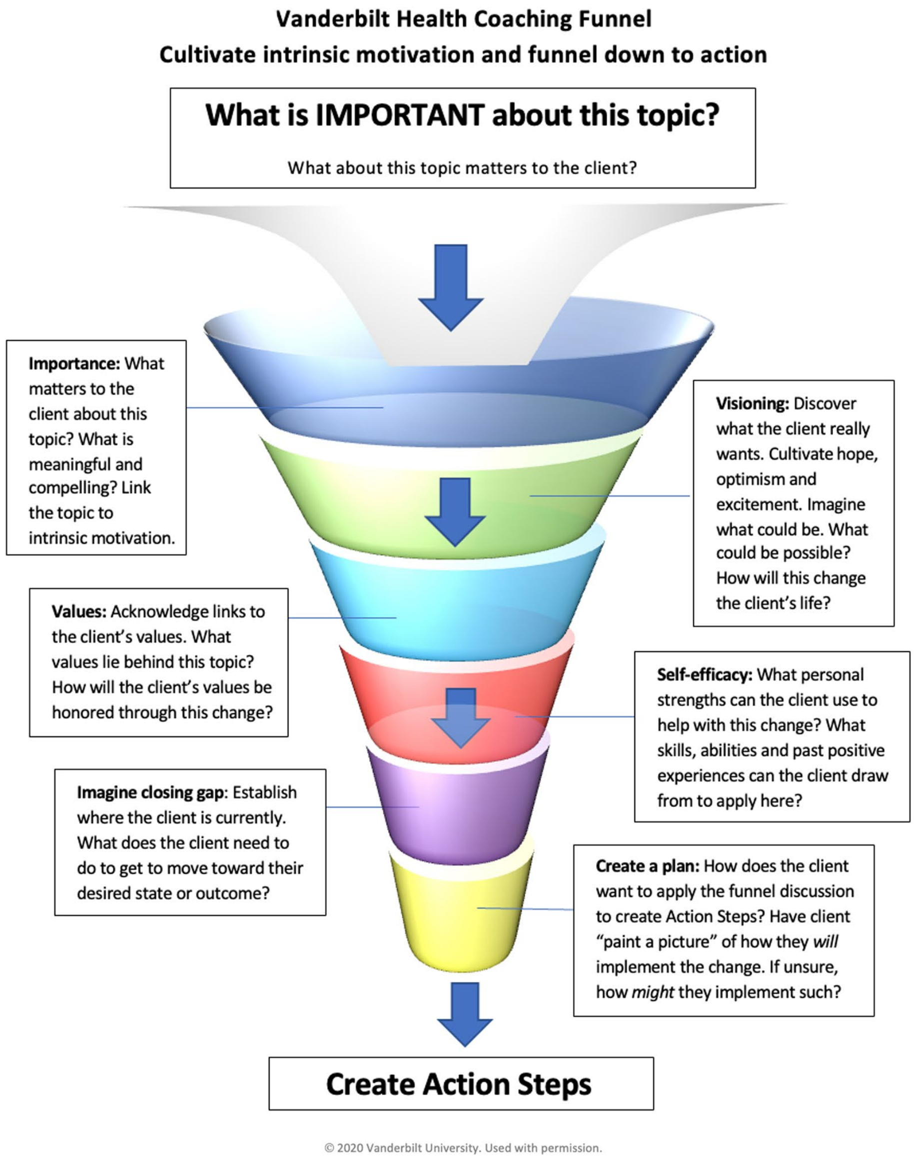

FIGURE 2
Vanderbilt Health Coaching Funnel (Courtesy of Vanderbilt Health Coaching Program).

trials where participants were randomized to conditions where self-efficacy was empirically manipulated and tested for potential increases in intentions or behavior. Experimentally induced improvements in self-efficacy led to medium effect-sizes (Cohen's $d = 0.51$) in intention to change and small to medium effect sizes for actual behavior change ($d = 0.47$) (Sheeran et al., 2016).

The VHC funnel moves deeper into cultivating preparatory change talk by inviting clients to verbalize their ability for change. Questions designed to promote self-efficacy and link client strengths to the desired change are built into the VHC funnel. Examples include:

- Which of your personal strengths can you use to help you with this change?
- How will your strengths help you move forward in this area?
- What have you done in the past to support success in a similar manner? How can you use that experience to help you move forward now?

Effective use of these strategies involves not only eliciting strengths and past successes from clients but making explicit links between a client's strengths and successes and their ability to change moving forward. Throughout the funnel, the coach is listening for, reflecting, and amplifying client insight to promote empowerment and self-efficacy for change. Ideally, coaches will spend 12–18 min moving a client through the VHC funnel in a full-length coaching session. In using this tool with over 700 trainees, we have found that this amount of time consistently allows for cultivation of intrinsic motivation while also guiding clients toward clarity and readines to plan their next step(s) *(Commitment, Activation, Taking Steps)*.

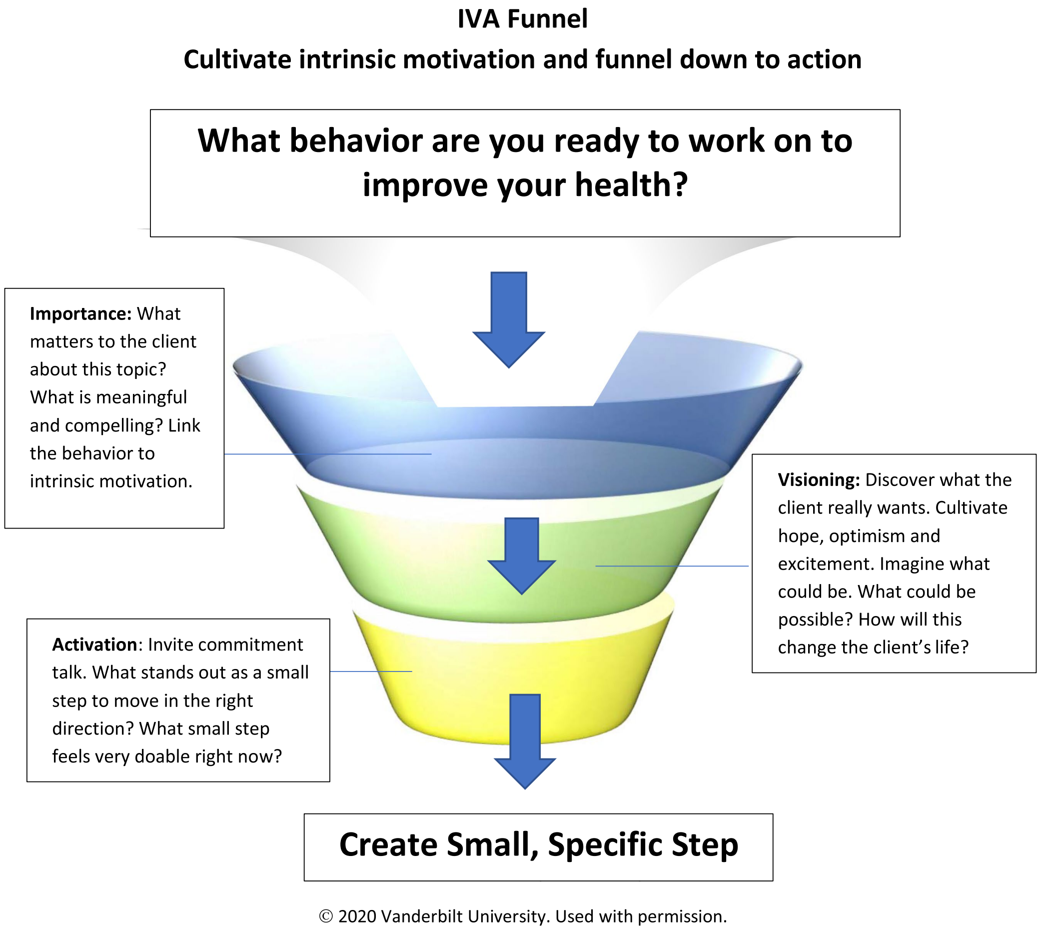

FIGURE 3
IVA Funnel (Courtesy of the Vanderbilt Health Coaching Program).

Planning

As the VHC funnel narrows, the coach evokes mobilizing change talk by eliciting signs of their optimal vision and what next step is needed to move forward. Unlike shared goal-setting in traditional MI, the VHCP model promotes client-determined goals and action steps. The coach elicits a client-determined action step that feels realistic for the client to attempt in the next 1 to 2 weeks. The coach guides the client to set an action step that is SMART (Bailey, 2019), connected to their optimal health vision, and leads toward the long-term goal. To further move into planning, the coach invites exploration of what will help the client achieve the desired task, including potential environmental and interpersonal supports, potential barriers, contingency plans, accountability and tracking measures before assessing the client's confidence using a 1 to 10 confidence scale. This planning process is completed for each action step to promote a sense of preparation, self-efficacy, and commitment to take the next step. These action steps aim to further concretize the commitment, activation and taking steps components of mobilizing change talk as described in MI.

Trainees have found that the VHC Funnel provides a structure for them to lean on as they develop their interpersonal and MI skills. There are many potential questions to be used in each section, but the intention and general process remain the same.

IVA funnel for clinical encounters

We recognize the need for these same evidence-based strategies to be integrated into brief clinical encounters to elicit patient motivation and activation for change. The current MI model of brief action planning (BAP) supports clinicians in developing well-supported SMART behavioral shared goals (Cole et al., 2023). However, the BAP does not address importance, values, visioning, or fully patient-centered goals. To this end, we have developed the IVA (Importance, Visioning, Activation) funnel as a structural tool for clinicians to explore personal importance of the change to the patient, elicit their vision, and support their activation in a brief clinical encounter while maintaining a patient-centered approach (see Figure 3). To begin, the clinician elicits from the patient a health behavior they are ready to change. Importance is then assessed using open questions and reflections, linking the desired change to intrinsic motivation, the patient's desires, needs, or reasons for change.

Visioning questions follow to invite the patient to consider how the desired change will benefit their life. The intent in visioning is to cultivate hope and optimism around the desired change. Finally, action-oriented questions activate the patient toward change, inviting commitment before supporting the patient to set one small, specific action step. Clinicians can use the IVA funnel in less than 5 min while still cultivating intrinsic motivation, hope, optimism, and commitment for change. Unlike BAP and other action planning models, the IVA funnel is largely patient-directed and emphasizes strategies to deepen motivation and commitment for change over specific action planning.

Limitations and future directions

The integration of mind–body processes in coaching is happening across the HWC field. Nonetheless, it has not been well-described in the peer-reviewed literature, particularly in terms of its integration with MI. Further, the integration of mind–body processes and MI has not been studied empirically in coaching. The contribution of these processes to specifically augment MI, as well as health coaching in general, needs significant further investigation. While our trainees report that the tools are useful with diverse patient populations in varied clinical settings, neither has been systematically studied. It is our hope that the rationale and justification explained in this paper will support moving these important studies forward.

It is important to note that our integration of mind–body processes with MI and other behavioral change techniques aimed to support coaches who practice in healthcare settings in which patients have sought out or specifically been referred for health coaching (versus a clinical encounter). Except for the IVA funnel, these processes need further iteration to be used in clinical settings where time is quite limited. Even in the coaching setting, the Wheel of Health exploration can take multiple sessions when used with patients with complex health needs who are very incapacitated. The beauty of the Wheel of Health, however, is that it usually works with even those with low intrinsic motivation for behavior change. With the broad exploration of one's life that is inherent in use of the Wheel of Health, almost everyone finds some area they wish to change.

Conclusion

Knowledge of the mind–body connection is becoming more important in HWC. Mind–body processes are easily integrated with MI and other evidence-based tools to support behavior change in both HWC training and in providing coaching. Mindfulness supports the learning process for the coach and the behavior change process for the client. Client self-discovery using a whole person Wheel of Health provides the opportunity for the client to consider a broader context as they choose among multiple life domains and experiment with behavior change processes that will be sustainable in the context of their full lives. Guided visualization deepens the cultivation of intrinsic motivation and allows clients to link their optimal visions to multisensory learning. This intrinsic motivation is further supported by self-efficacy strategies to help clients implement and sustain behavior change. Finally, the VHC funnel provides a clear framework that ensures core MI processes are used in coaching, and integrated with the mind–body processes discussed. A simplified version (the IVA funnel) can be used in a clinical context when time is tight.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

RQW: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. RW: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

RQW is the Director of the Vanderbilt Health Coaching Program, the tools from which are described in the article. RW is employed by Weinand Coaching Services, LLC that has a faculty contract with the Vanderbilt Health Coaching Program. However, no funding was provided for work on the manuscript.

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The gut and heart's role in reward processing

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Reward processing, which ensures survival, has evolved to also shape emotions, learning, and overall well-being. While traditional models of reward have focused predominantly on central neural circuits, emerging evidence underscores the role of peripheral bodily signals. This represents a new opportunity by which we may understand neurological and neuropsychiatric health. In this review, we explore the gut-brain and heart-brain interfaces in reward processing, delineating their contributions across distinct phases of reward and offering insights into their bioenergetic significance. By framing this interplay within an adaptive and clinical context, we propose new avenues for understanding and treating neuropsychiatric disorders through a mind–body medicine lens.

KEYWORDS

reward, gut-brain, heart-brain, adaptive behavior, bioenergetics, interoceptive therapeutics

1 Introduction

Reward processing systems have developed to regulate internal states, promote well-being, and motivate adaptive behaviors essential for survival and reproduction (O'Connell and Hofmann, 2011). These systems, which are shaped by evolutionary pressures, organize adaptive decision-making into a series of phases that include anticipation, motivation, consumption, and a post-consummatory learning phase often referred to as satiation (Figure 1A). For example, as temperatures drop in late autumn, a mouse's diminishing energy stores trigger hunger (anticipation) and prompt a search for food in familiar foraging sites or caches (motivation). Eating the food reward (consumption) elicits hedonic pleasure, facilitating memory consolidation (satiation) of the locations, conditions, and food availability that reinforce future behavior and enhance survival. Throughout this process, the gut communicates with the brain to coordinate internal states with behavior, first by releasing hunger signals that prompt food seeking, then by gradually shifting to satiety signals as nutrients are detected. In parallel, the heart rate decelerates in anticipation of reward, rises during energy-demanding seeking, and stabilizes following consumption (Graham and Clifton, 1966; Eubanks et al., 2002). This seamless coordination between internal systems and the brain across reward processing phases is essential for adaptive behavior and survival. However, clinical populations often exhibit dysfunctions in these stages of reward processing, manifesting as misjudgments in the value, desirability, or predictability of pleasurable outcomes (Linnet, 2014; Volkow and Morales, 2015; Serretti, 2023). And while traditional frameworks of reward processing in healthy and disordered states have predominantly focused on the central nervous mechanisms, there is much to learn about the role of bodily signals in regulating these processes.

Interoception is a mechanism evolved to support homeostasis and adaptive behavior by synergizing bodily signals (Chen et al., 2021). Given the extensive research on the roles of the gut and heart in mediating interoception, we will focus this review on these organs. The gut and heart are both essential for linking survival needs with adaptive behaviors as they each provide critical, real-time feedback to the brain about the body's internal states (Chen et al., 2021). These organs

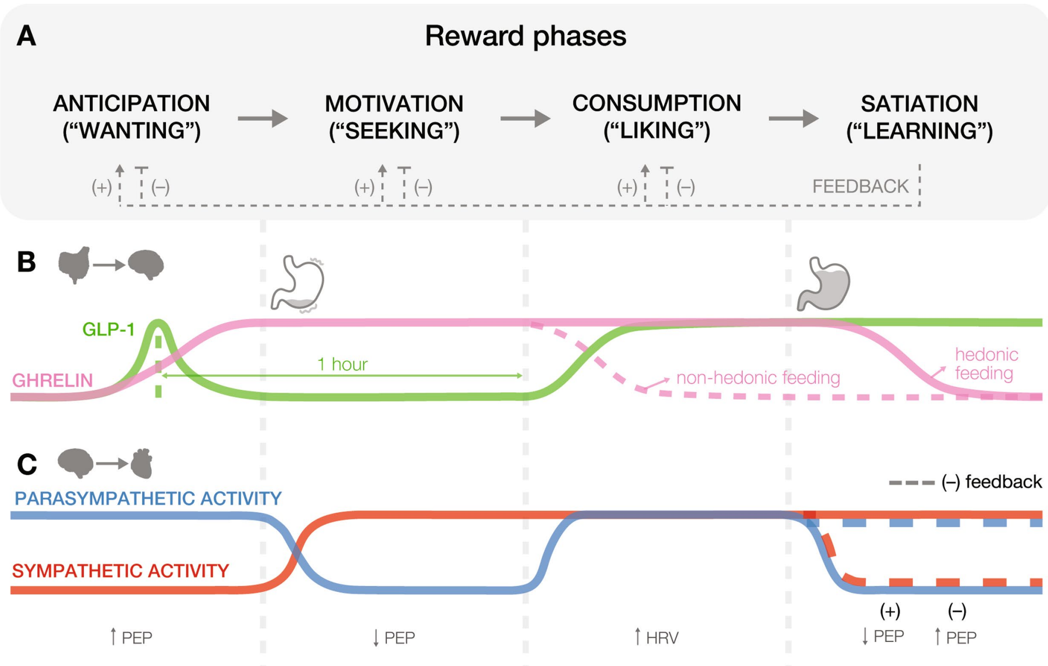

FIGURE 1
Gut and heart physiology across reward processing phases. **(A)** Reward processing unfolds in four phases: anticipation ("wanting"), motivation ("seeking"), consumption ("liking"), and satiation ("learning"). Positive (+) and negative (–) feedback loops emerge during the satiation phase, influencing how earlier phases are re-engaged in future cycles. Positive feedback, resulting from pleasurable stimuli, reinforces learning and increases future anticipatory, motivational, and consummatory responses toward similar rewards. In contrast, negative feedback, arising from aversive or unsatisfying stimuli, dampens the reward cycle by decreasing anticipatory, motivational, and consummatory responses to those stimuli. These feedback mechanisms function as internal updates to optimize future reward-seeking behavior based on past experiences. **(B)** Gut peptides influence hedonic eating and food preferences at various stages of feeding and reward. Hormones like ghrelin and glucagon-like peptide-1 (GLP-1) exhibit dynamic changes that drive food-related behaviors, balancing hunger and satiety cues. **(C)** Cardiac physiology responds to reward states through parasympathetic and sympathetic activity, as reflected in biomarkers like heart rate variability (HRV) and pre-ejection period (PEP).

can also directly contribute to homeostasis and reward processing, shaping an organism's capacity to anticipate, engage with, and learn from rewarding stimuli. Governing energetic demands, visceral sensations, and autonomic control, the gut and heart work in concert with the brain to fine-tune reward processes and organize adaptive, energy-efficient decisions that optimize survival and well-being (Kimura, 2019; Liu and Bohórquez, 2022). Emerging research highlights the interplay between these peripheral systems and central reward circuits, offering new avenues to understand and treat neuropsychiatric disorders (Zheng et al., 2009; Critchley and Harrison, 2013; Seth, 2013; Karaivazoglou et al., 2024). This mini-review explores the role of gut-brain and heart-brain communication in reward processing, considering perspectives that underscore the adaptive significance of these interactions.

2 Gut-brain and heart-brain signals in reward processing

2.1 Gut-derived signals in reward processing

The gut senses diverse internal stimuli, such as nutrients, distension, and microbial metabolites, and influences reward processing through both hormonal and neural pathways. These influences fall into three domains: hormonal signaling, synaptic signaling, and microbiota (not covered here, see: González-Arancibia et al., 2019; García-Cabrerizo et al., 2021; de Wouters d'Oplinter et al., 2022). Gut epithelial enteroendocrine cells (EECs) detect these signals and communicate with the brain through multiple mechanisms (Gribble and Reimann, 2016), including slow systemic release of hormones, or rapid synaptic communication with vagal and spinal neurons through a subset of EECs known as neuropod cells (Bohórquez et al., 2015; Bellono et al., 2017; Kaelberer et al., 2018; Figures 2A–C). Together, these pathways enable the gut to modulate reward circuits across varying timescales.

Ghrelin and glucagon-like peptide-1 (GLP-1) are two key gut-derived peptides that influence reward. Ghrelin primes the stomach for food intake by stimulating gastric acid secretion and motility via vagal pathways (Masuda et al., 2000), aiding digestion and generating interoceptive signals perceived as hunger (Carlson, 1993). In rats and humans, elevated ghrelin levels track hedonic (Merkestein et al., 2012; Monteleone et al., 2012; Rigamonti et al., 2015) and caloric (Hogenkamp et al., 2013) values of an anticipated meal, enhancing food motivation (Figures 1A,B: ANTICIPATION). Interestingly, blocking GLP-1 receptors (GLP-1Rs) before feeding, when GLP-1 levels rise in anticipation, reduces food intake, suggesting an appetite-stimulating role for GLP-1 (Vahl et al., 2010). Notably, this effect was reported under highly restricted feeding schedules, raising questions about its relevance in naturalistic contexts (Williams, 2010).

During motivational phases (Figures 1A,B: MOTIVATION), ghrelin enhances reward-seeking behaviors, such as nose pokes for high-fat food

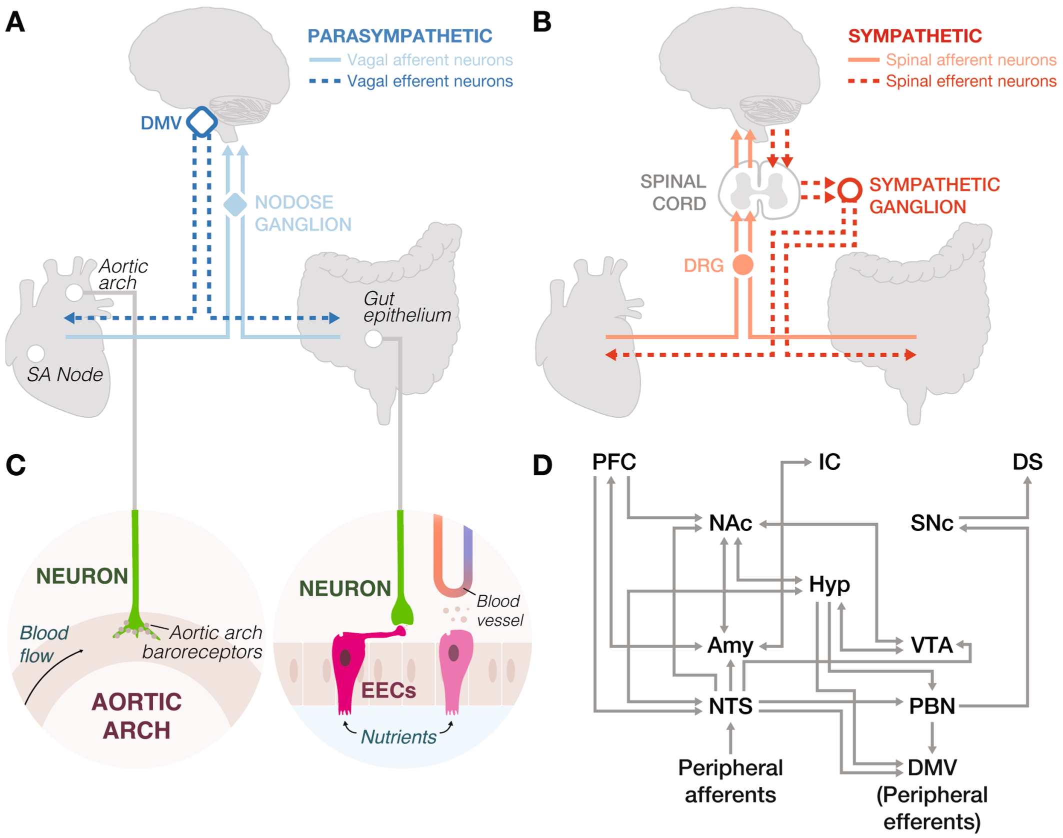

FIGURE 2
Peripheral innervation and neural circuits underlying interoception. **(A)** Parasympathetic nervous system: Vagal afferent neurons in the nodose ganglia transmit sensory signals from the sinoatrial (SA) node and gut epithelium to the brainstem. These signals are processed and relayed back to the body via vagal efferent neurons in the dorsal motor nucleus of the vagus (DMV). **(B)** Sympathetic nervous system: Spinal afferent neurons in the dorsal root ganglia (DRG) relay sensory information from the periphery to the spinal cord, which is then transmitted to the brain. Spinal efferent neurons project from the spinal cord to sympathetic ganglia, innervating peripheral organs. **(C)** Left: Peripheral neurons in the aortic arch express baroreceptors to detect changes in arterial pressure. Right: Enteroendocrine cells (EECs) sense nutrients, mechanical stretch, and microbial metabolites, and secrete hormones into the bloodstream. However, they can also form synapses with peripheral neurons to send fast signals to the brain. **(D)** Central integration of gut and heart signals involves the central autonomic network and dopaminergic systems, connecting to higher-order brain regions. This circuitry underscores the complex interplay between interoceptive inputs and reward processing. Amy: amygdala, DMV: dorsal motor nucleus of the vagus, DS: dorsal striatum, Hyp: hypothalamus, IC: insular cortex, NAc: nucleus accumbens, NTS: nucleus tractus solitarius, PBN: parabrachial nucleus, PFC: prefrontal cortex, SNc: substantia nigra pars compacta, VTA: ventral tegmental area.

pellets, independent of caloric need (Sun et al., 2004; Perello et al., 2010). In rodents, blocking ghrelin receptors abolishes these behaviors (Egecioglu et al., 2010), suggesting a role in sustaining motivational drive. Conversely, GLP-1R activation reduces the motivation to consume palatable foods (Dickson et al., 2012; Howell et al., 2019), underscoring its action as a satiety sensor (Wang et al., 2015). These mechanisms help organisms prioritize high-energy rewards when resources are abundant.

During consumption (Figures 1A,B: CONSUMPTION), ghrelin levels drop in response to caloric intake (Tschöp et al., 2000; Callahan et al., 2004), while satiety peptides such as GLP-1, cholecystokinin (CCK), and peptide YY rise to signal fullness (Murphy and Bloom, 2006). However, elevated ghrelin levels (Monteleone et al., 2012) and diminished CCK responses (Monteleone et al., 2013) during hedonic feeding can override homeostatic regulation, reinforcing consumption even in the absence of need.

Satiation, or the process of learning from hedonic pleasures of reward consumption, parallels associative and reinforcement learning strategies (Figures 1A,B: SATIATION). Although traditionally defined as reduced hunger, in reward literature, satiation more broadly refers to the integration of post-consummatory signals that inform future behavior, including food, social (Kohls et al., 2012), or musical rewards (Witek and Vuust, 2016). This expanded interpretation aligns with findings that gut-derived hormones and peripheral circuits shape learning following reward. For example, GLP-1R agonists restore impaired associative learning in humans (Hanssen et al., 2023) and reduce excitatory drive onto ventral tegmental area (VTA) dopamine neurons projecting to the nucleus accumbens (NAc; Wang et al., 2015). Similarly, optogenetic stimulation of gut-innervating vagal neurons promotes operant self-stimulation, real-time place preference, and flavor conditioning (Han et al., 2018), highlighting gut-brain contributions to reward learning.

While these mechanisms characterize systemic gut-brain communication, peripheral circuitry provides a complementary and fast synaptic pathway (Figures 2A–C). For instance, CCK-expressing EECs mediate flavor preferences through vagal afferents, while serotonin-expressing EECs drive taste aversion via spinal afferents (Bai et al., 2022; Buchanan et al., 2022), rapidly protecting organisms from ingesting harmful substances. Activation of rodent vagal neurons by nutrient-rich foods triggers mesolimbic dopamine release, reinforcing adaptive feeding (Han et al., 2018; Kim et al., 2023; McDougle et al., 2024). This gut-brain communication is also observed in zebrafish (Ye et al., 2020; Isabella et al., 2021) and flies (Kim et al., 2021; Min et al., 2021; Gao et al., 2024), highlighting conserved mechanisms to distinguish beneficial from toxic foods.

In the brain (Figure 2D), anticipation and motivation are primarily driven by the arcuate nucleus of the hypothalamus (ARC), a target of gut hormones, which receives input from the nucleus tractus solitarius (NTS) and modulates mesolimbic and mesocortical reward circuits (Rossi and Stuber, 2018). For instance, ghrelin acts on ARC neuropeptide Y neurons to release orexigenic peptides and promote feeding (Nakazato et al., 2001; Cowley et al., 2003). During consumption, hedonic value is encoded by endogenous opioids acting at "hotspots" within the NAc, orbitofrontal cortex, insular cortex, and interconnected regions of the hypothalamus, VTA, and amygdala (DiFeliceantonio et al., 2012; Morales and Berridge, 2020). GLP-1R agonists suppress intake of palatable food via receptors in the NTS and VTA, reducing synaptic strength onto NAc-projecting VTA dopamine neurons (Alhadeff and Grill, 2014; Wang et al., 2015), whereas blocking GLP-1 signaling promotes consumption of calorie-dense foods (Alhadeff et al., 2012, 2017). Satiation integrates sensory, emotional, and cognitive inputs across distributed circuits to give rise to learning via reward prediction errors (RPEs; Lokshina et al., 2021). While primarily encoded by mesolimbic dopamine, nascent evidence suggests RPEs exist across various regions. For example, amygdalar activity heightens when novel foods are paired with delayed gastrointestinal malaise, but fade in the absence of unexpected consequences, illustrating the role of postingestive feedback in learned aversions (Zimmerman et al., 2025).

Interestingly, ghrelin and GLP-1 influence non-food rewards as well. Ghrelin predicts gambling persistence in humans (Sztainert et al., 2018) and enhances alcohol's rewarding effects in mice (Jerlhag et al., 2009). Conversely, GLP-1R activation in rodent VTA decreases the motivation to consume cocaine (Schmidt et al., 2016), alcohol (Shirazi et al., 2013), and nicotine (Tuesta et al., 2017), suggesting a conserved role for modulating non-food rewards and holding clinical therapeutic potential (Jerlhag, 2023).

Together these findings demonstrate how gut-derived signals shape central reward circuits by integrating immediate neural responses with sustained hormonal effects to balance hedonic pursuits with survival needs.

2.2 Cardiac signals in reward processing

Cardiac interoceptive signals support survival by influencing both homeostatic and hedonic choices (Figure 1C). While gut signals primarily influence natural rewards like food, cardiac fluctuations inform choices involving uncertainty, effort, or risk. These adaptive behaviors include foraging, exploration, or competition, as well as modern analogs like gambling, which engage similar neurophysiological mechanisms (Kimura, 2019; Kimura et al., 2023).

During reward anticipation (Figures 1A,C: ANTICIPATION), humans show parasympathetic-induced heart rate deceleration that orients attention towards ecologically relevant stimuli (Graham and Clifton, 1966), enhances cognitive-motor efficiency to support rapid action (Alam et al., 2023), and emerges before placing gambling bets (Sayão et al., 2021). Mediated by the central autonomic network, this deceleration primes the body for focused effort, much like an animal preparing to evade a predator or initiate a chase (Löw et al., 2008; Panitz et al., 2013), underscoring its role in reward anticipation.

As anticipation shifts to motivated behaviors (Figures 1A,C: MOTIVATION), dopaminergic activity triggers the sympathetic nervous system, shortening the pre-ejection period (PEP) in humans (Ahles et al., 2017). PEP is the interval between left-ventricular depolarization to blood ejection into the aorta and occurs following sympathetic stimulation of the heart via beta$_1$-adrenoreceptor activation (Lanfranchi and Somers, 2010). Compared to healthy adults, individuals at risk for neuropsychiatric disorders exhibit exaggerated heart rate changes during alcohol use, gambling, or anhedonia, indicating sympathetic activation and a shortened PEP (Richter and Gendolla, 2009; Brenner and Beauchaine, 2011; Ahles et al., 2017; Silvia et al., 2020). These cardiac signals optimize energy expenditure through shared autonomic and central regulatory circuits (Critchley and Harrison, 2013), balancing between exploring new opportunities and exploiting known resources.

Cardiac signals also shape consumption and learning (Figures 1A,C: CONSUMPTION and SATIATION). For example, negative feedback, such as losing money, triggers a parasympathetic response, while positive feedback activates sympathetic pathways, reinforcing the reward experience (Dekkers et al., 2015; Kastner et al., 2017; Figures 2A,B). Causal evidence from optogenetic studies further supports this link, showing that increasing heart rate in mice induces anxiety-like behaviors in anxiety-provoking contexts (Hsueh et al., 2023). These cardiovascular signals that heighten stress and anxiety modulate decisions by shaping responses to future internal and external cues. Future studies should aim to advance from correlational findings to developing causal relationships between cardiac function and reward processing phases.

The heart-brain axis reflects evolutionary refinements aimed at maintaining cardiovascular stability and facilitating rapid adaptive responses. Parasympathetic vagal neurons (Figure 2A) and sympathetic spinal neurons (Figure 2B) mediate heart-brain communication, allowing the heart to relay sensory information about blood flow and chemical composition to the brain (Prescott and Liberles, 2022; Rajendran et al., 2024). Baroreceptors in the aortic arch, linked to vagal afferents, detect blood pressure changes (Figure 2C) and signal the brain to modulate vagal efferent neurons controlling heart rate, such as those innervating the sinoatrial node, the heart's pacemaker (Capilupi et al., 2020). Spinal afferents trigger reflexes that elicit sympathetic activity and dopaminergic responses, supporting fight-or-flight behaviors, crucial for survival in dynamic environments (Malliani and Montano, 2002). Like the gut, peripheral afferents from the heart relay to brainstem regions, such as the NTS and parabrachial nucleus (Scott et al., 2025; Figure 2D). These cardiac signals are tightly regulated by the brain's reward processing centers such as the VTA, amygdala, and ventral striatum (Camara et al., 2009; Lewis et al., 2021; Weinstein, 2023). This neural innervation of the heart is conserved across diverse organisms, including hermit crabs (Yazawa and Kuwasawa, 1994), flies (Dulcis and Levine, 2003), and zebrafish (Stoyek et al., 2015), underscoring its foundational role in cardiovascular regulation and adaptive behaviors.

3 Bioenergetic explanations for the body's role in reward processing

3.1 Integration of homeostatic and hedonic mechanisms

The brain's primary role is to maintain physiological balance by driving behaviors that restore homeostasis. This section examines how physiological signals drive reward processing and motivation, emphasizing the body's role in adaptive behaviors for survival. Evolution has shaped the brain to prioritize rewarding stimuli that align with bodily needs. Discomfort from hunger, thirst, or social isolation motivates behaviors that restore balance. This process, known as positive alliesthesia, describes how stimuli become more rewarding when they meet homeostatic demands (Cabanac, 1971).

These adaptive mechanisms promote survival by supporting goal-directed responses to internal disruptions. Beyond food and water, social interactions maintain homeostasis, fulfilling emotional and psychological needs, contributing to "social homeostasis" across species (Matthews and Tye, 2019). In this way, these rewards similarly engage homeostatic and hedonic reward pathways to support survival and well-being (Rossi and Stuber, 2018; Matthews and Tye, 2019; Grove et al., 2022; Wee et al., 2024).

3.2 Motivational intensity theory

The classical motivational intensity theory posits that an organism's energy expenditure is proportional to the difficulty of obtaining a reward, up until the required effort surpasses the perceived value (Richter and Gendolla, 2009; Richter et al., 2016). This framework highlights how gut-derived and cardiac signals modulate energy allocation during reward pursuit.

Gut signals influence motivational intensity by integrating physiological readiness with behavioral drive. Ghrelin enhances the perceived value of energy-rich foods and promotes effortful food-seeking (Perello et al., 2010), while GLP-1 dampens motivation for palatable (Dickson et al., 2012) and non-food rewards (Egecioglu et al., 2013a, 2013b). Beyond reward signaling, ghrelin-mediated anticipatory digestive processes represent a metabolic investment, aligning energetic costs of digestive readiness with expected intake (Masuda et al., 2000; Secor, 2009). Insufficient preparation may impair digestion or promote microbial overgrowth, underscoring ghrelin's role as a metabolic "bet," balancing effort with internal needs.

Cardiac responses similarly reflect the body's energy expenditure during different phases of reward processing. Parasympathetic activity conserves energy during anticipation, preparing the body for action (Lovallo and Sollers, 2007). It acts as a real-time biomarker for prioritizing responses to environmental stimuli (Richter et al., 2016), including food (Zebunke et al., 2011), social (Zupan et al., 2016), and sexual cues (Creswell et al., 2013) across species, including pigs, dogs, and humans. During reward-seeking, sympathetic activity increases with task difficulty, but decreases when effort outweighs the reward's value (Richter, 2010), selectively mobilizing energy.

Evolutionarily, these integrated mechanisms ensure strategic allocation of energy toward high-value rewards, optimizing resource acquisition and adaptability.

3.3 Predictive interoception coding

Predictive interoception coding provides a framework for how the brain anticipates and integrates internal bodily signals to maintain homeostasis and guide reward-related behaviors. The brain's ability to generate internal expectations has evolved from simple reflexes to complex predictive models (Pezzulo et al., 2021). For example, false heart rate feedback can create interoceptive illusions, making participants perceive greater effort during exercise when they believe their heart rate is elevated (Iodice et al., 2019), illustrating the brain's reliance on predicted internal states to calibrate effort. Beyond homeostasis, predictive interoception also shapes emotional and reward-based decisions (Seth, 2013). In a gambling task, participants with greater anticipatory awareness of emotional states made faster, more advantageous financial decisions (Marshall et al., 2019).

Understanding the interaction between reward circuits and the peripheral nervous system reflects how predictive mechanisms have adapted to regulate physiology, motivation, and reward seeking. This integration highlights the brain's role in optimizing responses to internal and external challenges, enhancing survival.

4 Therapeutic implications of interoception

Neural processing of peripheral organ signals regulates stress, enhances resilience, and holds promise for neuropsychiatric treatment (Benton et al., 2021; Natterson-Horowitz et al., 2023). In humans, gut-derived signals influence emotional states and reward processing. For example, intragastric fat infusion attenuates experimentally induced sadness and dampens activity in emotion-related brain regions (Van Oudenhove et al., 2011), while striatal dopamine release during pleasurable meals predicts subjective pleasure ratings (Small et al., 2003). These psychophysical links between the gut and emotional experience underscore the promise of interoceptive therapeutics.

Originally developed for diabetes and weight management, GLP-1R agonists are now being explored for reducing cravings in addiction and mitigating symptoms of psychotic and neurocognitive disorders (Klausen et al., 2022; Leggio et al., 2023; Xie et al., 2025). Similarly, heart rate variability, a physiological marker of emotional regulation and reward sensitivity, has emerged as a therapeutic target, showing efficacy in reducing substance (Eddie et al., 2014), alcohol (Penzlin et al., 2015), and food cravings (Meule et al., 2012).

Looking ahead, interoceptive therapeutics, including trainings to enhance bodily awareness and advanced vagus nerve stimulation (VNS), hold promise for improving emotional resilience and mental health (Khalsa et al., 2017; Kim et al., 2024; Schuman-Olivier et al., 2024). Although current VNS techniques show efficacy in treating conditions like depression and anxiety, improving specificity remains a challenge. Technologies like optogenetics and targeted gene delivery aim to define cell-type-specific neuromodulation, minimizing off-target effects and enhancing efficacy (Bansal et al., 2023). Collectively, brain–body interventions hold immense potential for the treatment of various conditions, including depression, autism, and anxiety disorders (Paulus and Stein, 2010; DuBois et al., 2016; Rogers et al., 2016).

5 Conclusion

This mini-review provides an adaptive framework for understanding brain–body communication in reward processing. While focused on select interoceptive signals, other sensory inputs (e.g., gut microbiota) and organs (e.g., pancreas) also shape reward behaviors (Davis et al., 2010; Kim et al., 2023). A truly holistic view requires acknowledging multi-organ interactions, such as gut-heart-brain communication. For example, duodenal glucose infusions can lower blood pressure in healthy adults (O'Donovan et al., 2002), while gastric distension raises arterial pressure via sympathetic activation to offset digestive-related blood redistribution (Rossi et al., 1998). Such visceral signals likely modulate reward circuits by influencing physiological states. Simultaneous investigation of these systems allows for the discovery of both direct and emergent properties that govern brain–body communication, underscoring the need to integrate such complexities into a holistic view of reward processing and its role in survival and well-being.

Author contributions

MA: Data curation, Supervision Conceptualization, Visualization, Validation, Writing – original draft, Writing – review & editing. KA: Validation, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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