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

Edited by
Steffen Schulz, Georg Seifert and Dirk Cysarz

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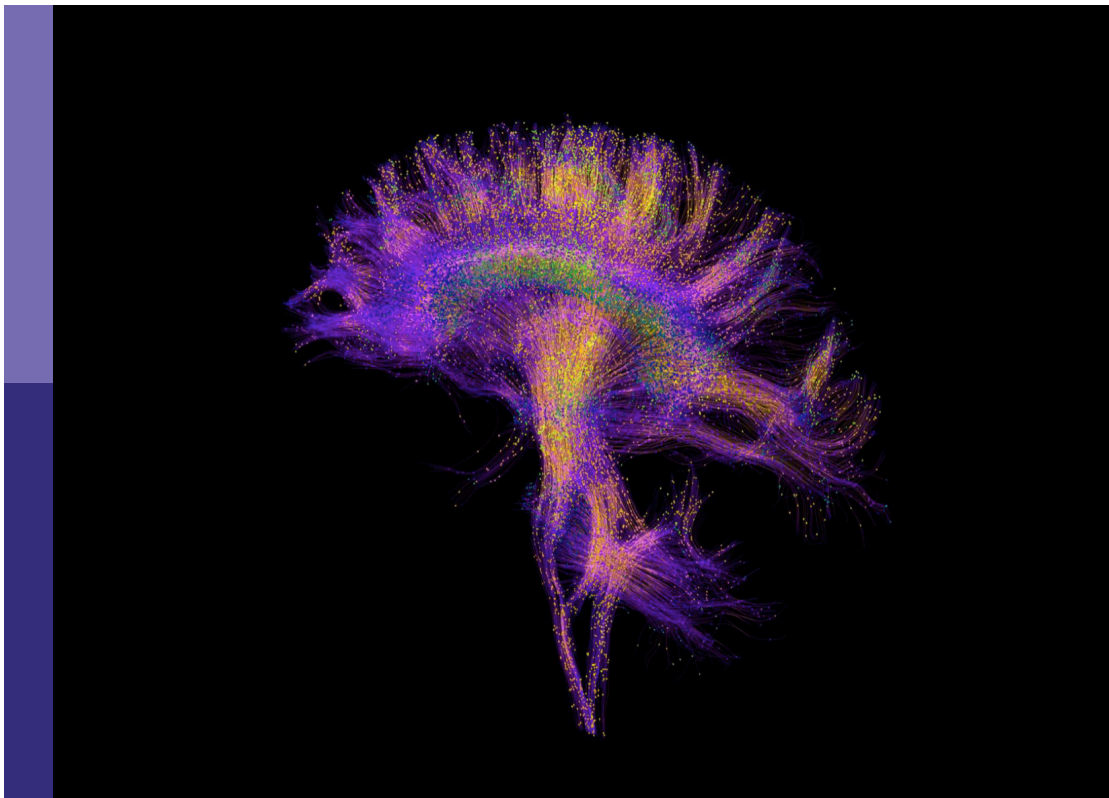

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Mind-body medicine and its impacts on psychological networks, quality of life, and health

Topic editors

Steffen Schulz — Charité University Medicine Berlin, Germany
Georg Seifert — Charité University Medicine Berlin, Germany
Dirk Cysarz — Witten/Herdecke University, Germany

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EDITED AND REVIEWED BY
Elizabeth B. Torres,
Rutgers, The State University of New Jersey, United States

*CORRESPONDENCE
Steffen Schulz
✉ steffen.schulz@charite.de

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

Steffen Schulz[1]*, Dirk Cysarz[2] and Georg Seifert[1,3]

[1]Department of Pediatrics, Division of Oncology and Hematology, Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany, [2]Integrated Curriculum for Anthroposophic Medicine, Faculty of Health, Witten/Herdecke University, Witten, Germany, [3]Department of Pediatrics, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

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

Living conditions in industrialized countries have led to a significant increase in life expectancy in recent decades. Likewise, the proportion of chronic diseases is growing. This includes cardiovascular diseases, chronic pain, inflammatory bowel diseases, and cancer. Unfavorable lifestyle factors, such as accumulative stress, lack of exercise, and poor nutrition, compounded by the persistent imbalance between exertion and recovery, lead to the manifestation and chronification of disease. A fundamental awareness of the connection between our mind, emotions, lifestyle, and health has grown. Understanding of body and mind interaction is increasing and is supported and confirmed by evidence, demonstrating a high level of clinical relevance. It is out of this field of research that mind–body medicine (MBM) has developed. MBM targets the interplay of body, mind, emotions, and behavior, extending to the regulation of vegetative physiological signaling pathways. The goal of MBM is to use scientifically-based knowledge on the interactions between body, mind, and emotions to promote salutogenetically-based resources. In this context, the body, mind, and emotions are regarded as working in unity while illnesses can be understood as producing a disbalance in complex biopsychological systems. A central theme of MBM is the need for lifestyle changes. Psychological aspects of MBM affect lifestyle factors and thus indirectly affect many different areas of the mind-body connection. MBM techniques include mindfulness-based stress reduction, meditation, active movement, relaxation, mindfulness, stress management and relaxation, habits of perception, and evaluation among others. These work through complex biopsychological and social systems on different areas of lifestyle, providing a set of tools to increase the sense of self-efficacy and promoting health. The therapeutic approaches of MBM encompass a variety of different methods that often facilitate cost-effective preventive or therapeutic options. Relevant evidence-based data are available, and this is an area with high scientific and clinical growth potential for lifestyle change and prevention of some of the most important health issues. Complementary treatments, developed from the emotional, mental, social, spiritual and behavioral factors, are combined with a variety of conventional medicine practices to influence health. The analysis of these signaling pathways have structural, dynamic, and regulatory mechanisms, and the information transfer

in healthy and diseased states, provides insights into the physiological structures and functions of the whole integrated system with its different types of interactions.

This Research Topic focuses on the evidence-based investigations based 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. This Research Topic has collected a diverse range of research content from multidisciplinary contributions in the field of MBM, ranging from comprehensive data analysis to clinical practice applications. This Research Topic included six original research articles, two clinical trials, one article of hypothesis and theory, and five reviews.

Jeitler et al. investigates the use of self-care and lifestyle interventions as well as mental/emotional state experienced during the COVID-19 pandemic via an online survey for 1,138 participants. Individual health promotion strategies, such as spending time in nature, increasing physical activity, using naturopathic remedies, consuming a plant-based diet, or practicing mind-body interventions feature predominantly with participants who are female, middle-aged, and well-educated. Most participants were found to demonstrate an overall balanced mental/emotional state (Jeitler et al.). Xie F. et al. evaluated the effect of a Qigong exercise, prolong life with nine turn method (PLWNT), with 90 participants experiencing chronic fatigue syndrome (CFS) as a complex illness of unknown etiology and mechanisms focusing on fatigue, sleep quality, depression, and anxiety symptoms. The PLWNT Qigong showed the potential to be an effective rehabilitation method for CFS symptoms, including fatigue, sleep disturbance, anxiety, and depression. Testing whether increases in heart rate variability (HRV) could be detected after a 6-week smartphone-based HRV-biofeedback training, Schumann et al. investigate whether reductions in rumination levels in depressed patients were accompanied by the change in HRV. They found a significant correlation between resting HRV and rumination levels and suggested that HRV biofeedback intervention can be applied to improve cardiovagal function and to reduce depressive symptoms, including self-rated rumination tendencies. Liang et al. explore the relationship between physical fitness, calcium intake, calorie intake, and adolescent mental health to promote a healthy lifestyle and preventing mental problems. They showed that adequate calcium intake and the improvement of cardiopulmonary fitness in adolescents aged 12–13 are essential for the good development of their mental health. An aspect of how asthma affects adults' quality of life through social, emotional, physical, and occupational impacts was highlighted by Kharaba et al. Furthermore, with a focus on the influence of family support on the healing of gastric ulcers caused by endoscopic submucosal dissection, Gao et al. found that the occurrence and degree of negative emotions such as psychological anxiety and depression, in addition to the occurrence of gastric pain, may be reduced.

In a pilot trial, a 60-h MBM and comprehensive lifestyle modification training program, Bauer et al. demonstrates findings over a 10-week-period for patients with Crohn's disease (CD) in rural regions under pandemic conditions, including practices for stress reduction, stress management, relaxation, mindfulness meditation, breathing, yoga, and Qigong, elements of cognitive behavioral therapy, psychoeducational approaches. Xie Y. J. et al. studied the efficacy and feasibility of 12 weeks of Tai Chi training as a prophylactic treatment to prevent migraine in Chinese women and showed a significant reduction in the frequency of migraine attacks.

In the hypothesis and theory paper by McParlin et al., an entwined model that combines touch for alignment and active inference is presented to explain how the brain develops "priors" necessary for the health care provider to engage with the patient effectively. Touch is surmised to play a crucial role in achieving successful clinical outcomes and adapting previous priors to create intertwined beliefs.

The systematic review by Mühlenpfordt et al. intends to summarize the typical indications and outcomes and to systematically assess the effectiveness and safety of external, touch-based applications of anthroposophic medicine (e.g., rhythmical massages, embrocations, and compresses) given as complementary treatment for various conditions. In both a systematic review and meta-analysis, the current state of research assesses the effectiveness of mindfulness-based interventions on the academic performance of students as measured by their grade point average (Ostermann et al.) while illuminating the remaining lack of clarity of the exact mechanisms of action. Another systematic review and meta-analysis by Wang et al. analyzes the risk of dementia or Parkinson's disease (PD) with individuals with Sjogren's syndrome (SS), finding in their analysis that people with SS are likely at higher risk of PD and dementia than the general population (Wang et al.). In a critical mini review (Leça and Tavares), scientific evidence for the use of mindfulness-based interventions (MBI) for fibromyalgia were evaluated and conclude that despite the sparsity of well-structured longitudinal studies, there are some promising results showing that the MBI are effective in reducing the negative aspects of fibromyalgia. In a narrative review (Esch and Stefano) the basic principles of MBM, including the introduction of a rational framework for the implementation of MBM-based interventions are presented through the BERN framework (behavior, exercise, relaxation, and nutrition). The BERN model aims to strengthen health and resilience, and reduce stress. The mechanisms of action of these processes involve the central nervous system reward systems and correlate with the placebo and self-healing pathways.

The objective of this Research Topic aspires to understand how different physiological control systems, from the mind to the body, interact and to improve quality of life and health. We aimed to provide a foundation of evidence for new theoretical and practical approaches to solving problems and challenges in MBM. Contributing to a comprehensive overall picture of MBM, this unique set of multidisciplinary approaches and visions will expand the knowledge of integrative medicine and have a positive impact on future therapeutic developments.

Author contributions

SS, GS, and DC: conceptualization, funding acquisition, roles/writing—editorial, and writing—review and editing.

All authors contributed to the article and approved the submitted version.

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 Qigong of Prolong Life With Nine Turn Method Relieve Fatigue, Sleep, Anxiety and Depression in Patients With Chronic Fatigue Syndrome: A Randomized Controlled Clinical Study

Fangfang Xie[1,2†], *Yanli You*[3†], *Chong Guan*[2], *Jiatuo Xu*[2*] and *Fei Yao*[1,2*]

[1] Department of Acupuncture and Massage Rehabilitation Center, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2] Department of School of Basic Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [3] Department of Traditional Chinese Medicine, ChangHai Hospital, Naval Medical University, Shanghai, China

Background: Chronic fatigue syndrome (CFS) is a complex disease of unknown etiology and mechanism. The purpose of this study was to investigate the effect of Prolong Life with Nine Turn Method (PLWNT) Qigong exercise on CFS focusing on fatigue, sleep quality, depression, and anxiety.

Methods: A total of 90 participants diagnosed with CFS were randomly assigned into two parallel groups: PLWNT and cognitive behavioral therapy (CBT). The participants in the PLWNT or CBT group participated in qigong exercise or cognitive behavior education program, respectively, once a week in-person and were supervised online during the remaining 6 days at home, over 12 consecutive weeks. The primary outcome was fatigue (Multi-dimensional Fatigue Inventory 20 [MFI-20]), and secondary outcomes were sleep quality (Pittsburgh Sleep Quality Index [PSQI]), anxiety, depression (Hospital Anxiety and Depression Scale [HADS]), and changes in the Neuropeptide Y (NPY) of peripheral blood.

Results: The within-group comparisons of the PLWNT and CBT groups revealed significant improvement in both groups in MFI-20, PSQI, and HADS scores ($P < 0.05$). No significant difference were found between the PLWNT and CBT groups, even though the effective rate of the PLWNT group was 62.22%, which is slightly than 50.00% of the CBT group. The fatigue scores in the PLWNT group were positively correlated with sleep degree ($r = 0.315$) and anxiety degree ($r = 0.333$), only anxiety degree ($r = 0.332$) was found to be positively correlated with fatigue in the CBT group. The analysis of peripheral blood showed that NPY decreased after PLWNT intervention but increased significantly in the CBT.

Conclusion: The PLWNT qigong exercise has potential to be an effective rehabilitation method for CFS symptoms including fatigue, sleep disturbance, anxiety, and depression.

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Edited by:
Steffen Schulz,
Charité Universitätsmedizin Berlin, Germany

Reviewed by:
Liyuan Tao,
Peking University Third Hospital, China
Lutz Liese,
Hochschulambulanz der Charité-Universitätsmedizin Berlin des Immanuel Krankenhauses Berlin am Standort Wannsee, Germany
Wen Liu,
University of Kansas Medical Center, United States

***Correspondence:**
Jiatuo Xu
xjt@fudan.edu.cn
Fei Yao
doctoryaofei@126.com

†These authors have contributed equally to this work and share first authorship

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Future studies should expand study sample size for in-depth investigation to determine the optimal frequency and intensity of PLWNT qigong intervention in CFS patients. The study was registered in the ClinicalTrials.gov database on April 12, 2018, with registration number NCT03496961.

Keywords: qigong, prolong life with nine turn method, chronic fatigue syndrome, fatigue, sleep quality, depression and anxiety

INTRODUCTION

Chronic fatigue syndrome, also called myalgic encephalomyelitis, is a complex multisystem disease commonly characterized by severe fatigue, cognitive dysfunction, sleep problems, autonomic dysfunction, and post-exertional malaise severely impairing activities of daily living (1). According to global statistics, approximately 1% of the worldwide population (17–24 million people) suffer from CFS, along with significant incidence rates of comorbidities including psychiatric disorder and cognitive symptoms (2). Patients with CFS are forced to reduce 50% of their daily activities (3), and 87% to 95% of them have related daytime dysfunction (4, 5). A large sample of 1,409 CFS patients showed that 95% of people with higher education and full-time work had sleep disorders, while 68 to 80% suffered from anxiety and depression symptoms (6), further exacerbating the decline in quality of life (7, 8). In addition, fatigue can occur independently of other symptoms of CFS, but it is usually related to sleep and mood disorders (9, 10). A study reported that fatigue has a negative impact on all areas of quality of life, including physical and emotional health, activity ability, and activities of daytime living (11). The increasing incidence of CFS means that it not only threatens the personal wellbeing of more people but also brings a heavy burden to families and society.

Since the etiology and pathology of CFS are unknown, symptomatic treatments are used clinically, including drugs, graded exercise therapy (GET), and cognitive–behavioral therapy (CBT), to attempt to relieve CFS symptoms and improve quality of life. The CFS treatment guidelines emphasize a change in the overall treatment attitude of CFS—for instance, drug therapy as the main rule for the management of patients with CFS should be revised and non-pharmaceutical therapies should been recommended in CFS patients (12). Both the GET and CBT interventions were built on a behavior/disadaptation model of CFS. The GET was designed to help CFS patients overcome this purported fear of exercise and intense symptom-focusing through graded exposure to exercise, and thereby reversing any deconditioning that had occurred (13). The CBT had similar aims, but addressed the fear of activity, maladaptive disease beliefs and symptom focusing by combining CBT and practical activities (14). Several researchers have proposed that graded exercise therapy and CBT might be effective treatments for CFS to improve fatigue and poor mental health, including depression, anxiety, and schizophrenia (13, 15). However, evidence of persistent and sustained significant outcomes in CFS patients is not sufficient (16). The clinical manual published by the International Association for Chronic Fatigue Syndrome recommends traditional Chinese medicine (TCM) treatments as a complementary alternative therapy, including acupuncture and massage (17).

Qigong (pronounced "chee-gun") is one of the TCM methods that has been used for thousands of years to optimize and restore the energy of the body, mind, and spirit (18). It is a regular, moderate-intensity aerobic exercise (19). Specifically, the term "qigong" involves two theories: "qi," the righteous qi of the body, which represents the essence flowing in the human body, it is manifested in the constant movement of body energy and the constant alternation of inhalation and exhalation, supporting all life processes and connecting all vital organs of the body (20). "Gong," the training or cultivation of qi. Qigong, such as Tai Chi, is a mind-body techniques, specific postures and movements based on breathing exercises to achieve a state of deep focus and relaxation, all of which aim to cultivate righteousness and achieve functional enhancement, thereby improving related symptoms (21). Acupuncture, Tuina and Qigong can all regulate Qi, and it has been clinically proven to be effective in the treatment of CFS (6, 22, 23).

Prolong Life with Nine Turn Method (PLWNT) is a type of qigong practice that uses external energy to strengthen the limbs and internal energy to reconcile the viscera. This practice sims to smooth the circulating qi and blood that was introduced by a centenarian named Kai Fang in the Qing Dynasty. It has been written into the college textbook of Tuina and Qigong, which includes eight kinds of massage manipulations of the abdomen and a kind of upper body shaking (24). The abdominal massage techniques included in PLWNT act on the movement of the pelvic and abdominal muscles, coordinated with diaphragmatic breathing. It may trigger the contraction of the intestinal and rectal muscles (25), which can train the function of the intestines (26), but also have an impact on the nervous system, including reducing the excitability of the sympathetic nerve and enhancing the excitability of the parasympathetic nerve to reduce anxiety when rubbing the internal organs (27, 28). Specifically, abdominal massage manipulation included in PLWNT therapy may relieve muscle tension and nerve rhythm to relieve sleep disorders, fatigue, and depression symptoms of fibromyalgia syndrome (FMS) similar to CFS patients (29), and fatigue is a coexisting symptom of FMS and CFS, with up to 80% of CFS

Abbreviations: CFS, Chronic fatigue syndrome; PLWNT, Prolong life with nine turn method; IACFS, International association of chronic fatigue syndrome; CBT, Cognitive behavioral therapy; TCM, Traditional chinese medicine; MFI-20, Multidimensional Fatigue Inventory-20; PSQI, Pittsburgh sleep quality index; HADS, Hospital anxiety and depression scale; HPA, Hypothalamic-pituitary-adrenal.

patients reported a history of clinician-diagnosed FMS (30, 31). Previous studies have proved the efficacy of PLWNT in the treatment of patients with gastrointestinal diseases (32, 33), but it is not clear whether PLWNT has an effect on fatigue, sleep and mood. Our published protocol for this project has predicted that PLWNT qigong exercise can improve fatigue, sleep disorders, and depression in CFS patients (34), therefore, this study compares the effects of PLWNT and CBT therapies to verify the effective methods to improve fatigue, sleep, anxiety and depression in CFS patients.

The current study was to evaluate the effects of PLWNT. We hypothesized that PLWNT would help mitigate related fatigue, sleep, and depression symptoms of CFS (primary outcomes) and better than CBT. We present the following article/case in accordance with the Consolidated Standards of Reporting Trials reporting checklist.

MATERIALS AND METHODS

Study Design

The present study was a randomized controlled trial involving the following two parallel groups: PLWNT and CBT. All participants were recruited from December 2018 to September 2019 at the Shanghai University of Traditional Chinese Medicine and Yueyang Hospital of Integrated Traditional Chinese and Western Medicine in Shanghai, China. A statistician who did not participate in the recruitment randomly placed eligible CFS patients into the two groups using sealed envelope randomization using a computer software program (Strategic Applications Software, version 9.1.3; SAS Institute Inc., Cary, NC, USA) to create a random number table, then compiled a set of sealed envelopes on the basis of the random sequence and put the patient's information, treatment method, time, and location in an opaque envelope according to the random numbers. Finally, they handed the envelopes over to the research team. The study was conducted in accordance with the Declaration of Helsinki and the International Code of Ethics for Biomedical Research Involving Human Subjects, was approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (ethics approval no. 2018-043), and was registered in the ClinicalTrials.gov database run by the United States National Library of Medicine on April 12, 2018, under registration number NCT03496961.

Sample Size Calculation

According to our recently published protocol (34), the efficacy of the PLWNT group was assumed to be better than that of the CBT group. With reference to studies on the efficacy of CFS on the FSS scale (35, 36), it was calculated that the final difference between the two groups in terms of FSS average scores is 0.915 and the standard deviation is 1.147. The Bonferroni conservative comparison method was used, and the sample size of this trial was calculated using the following formula (37):

$$n = \frac{2 \times (Z_{\alpha/4} + Z_{\beta})^2 \times \sigma^2}{\delta^2} \quad (1)$$

$$= \frac{2 \times (2.2414 + 1.282)^2 \times 1.1479^2}{0.915^2} = 39.08 \approx 40 \quad (2)$$

Considering the allowable 10% dropout rate, the sample size of each group in this experiment was set at 45. Therefore, this randomized controlled trial needed to recruit 90 participants in total.

Subjects

A total of 90 participants were recruited via WeChat (Tencent co., Ltd., China) or posters positioned at the Shanghai University of Traditional Chinese Medicine and Yueyang Hospital of Integrated Traditional Chinese and Western Medicine in Shanghai, China. Hospitalized patients were also included with a preliminary diagnosis of CFS, according to the latest guidelines for the treatment of CFS revised in 2021 (38).

The study inclusion criteria were as follows: (1) age between 20 and 60 years; male or female; (2) severe chronic fatigue lasting at least 6 months, unexplained after clinical evaluation, not caused by work performed during the trial, and unable to be alleviated after rest; and (3) at least four of eight specific symptoms (memory or concentration decline, failure to regain energy after sleep, sore throat, headache, lymph node tenderness, muscle pain, multiple joint pain, and myalgia after exertion for more than 24 h). Separately, the study exclusion criteria were as follows: severe cardiovascular and cerebrovascular diseases, endocrine system diseases, motor system diseases, autoimmune diseases, infectious diseases, and use of medications that may affect the judgment of the results.

Patients who met the inclusion and exclusion criteria underwent baseline measurements (T_0) and were randomly assigned to the PLWNT group or CBT group. The clinical scale evaluation was conducted at the end of the intervention (T_1). All of the patients involved in this study signed an informed consent form. More detailed fundamental information of CFS patients is provided in our previously published protocol (34).

Intervention

PLWNT Group

The PLWNT intervention program and operating standards refer to the Chinese general higher TCM compiled college textbook of Tuina and Qigong. Experienced qigong teachers at Shanghai University of TCM, who have been teaching qigong for at least 5 years, were placed in charge of the supervision of the exercise and corrected participants' exercise postures during the entire intervention period for 1 h every Sunday. The first 10 min of each session were for stretching and relaxation exercises as well as movement introductions and demonstrations. In addition, precautions were mentioned and participants' questions were answered. The subsequent 20 min were allotted for individual guidance and correction of actions. Finally, all of the participants practiced PLWNT for 30 min together. For the remaining 6 days of the week, all participants had to practice by themselves for 30 minat 6 o'clock every day at home, under the remote supervision of one of the directors. Their practice videos were required to be posted in a WeChat that it is similar to WhatsApp of all participants. If some of the participants found it inconvenient, videos could be sent privately to the study investigators. All participants were also asked to write down their feelings in the practice recording notebook after every exercise. Before we did the exercises, we gave the patient a 3-day training in the amount

of abdominal stimulation, During the period, we let patients wear manual stimulation data gloves, the average amount of abdominal stimulation for the first eight rubbings was 0.5 ± 0.1 kg, and monitor the strength of the manual in real time in the LABVIEW2017 software, so that patients can feel the amount of stimulation. The entire practice process lasted for 12 weeks. The content of PLWNT qigong intervention was the same as in our previous research (34). The nine specific forms of manipulations are shown in **Figure 1**. The following are the three steps of qigong.

Step 1. Preparatory Position

During this step, the participant should relax their whole body, concentrate their thoughts, breathe evenly, place their tongue against the upper jaw, hold their Dantian with their mind, and progress through the exercise step by step.

Step 2. PLWNT's First Eight Types of Abdominal Massage

1. Press the Danzhong acupoint (under the xiphoid process) with the middle three fingers in both hands and make a circle 21 times from the left, within3 min.
2. With three fingers of both hands, rub down from the Danzhong acupoint and move to the pubic symphysis below the umbilicus. Repeat 21 times within 3 min.
3. With three fingers in both hands, rub up from the pubic symphysis from two sides back to the Danzhong acupoint until the hands are overlapped. Repeat this 21 times within 3 minutes.
4. With three fingers of both hands, push down from the Danzhong acupoint and push it straight to the pubic symphysis. Repeat 21 times within 3 min.
5. Rub the abdomen with the right hand from the left 21 times within 3 min.
6. Rub the abdomen with the left hand from the right 21 times within 3 min.
7. Place the left hand on the left side of the lower waist and kidney, with the thumb forward, and, using the four fingers supporting the back, gently pinch it; meanwhile, with three fingers of the right hand, push straight from the bottom of the left breast to the groin, and repeat this 21 times in 3 min.
8. Place the right hand on the right side of the lower waist and kidney, with the thumb forward, and, using the four fingers supporting the back, gently pinch it; additionally, with three fingers on the left hand, push straight from

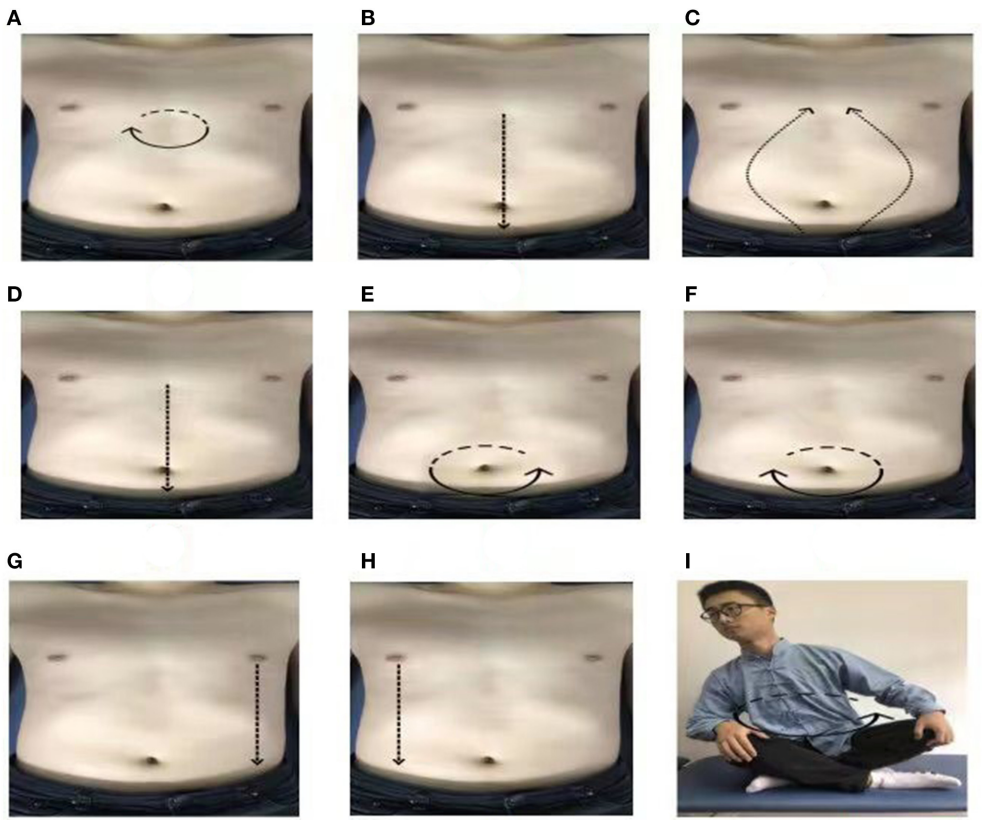

FIGURE 1 | The postures of PLWNT (34). **(A)** Press and knead acupoint in Danzhong. **(B)** Rubbing from Danzhong Acupoint to Pubic Symphysis. **(C)** Rubbing from Pubic Symphysis to Danzhong Acupoint. **(D)** Pushing from Danzhong Acupoint to Pubic Symphysis. **(E)** The right hand massages the abdomen by the left circle. **(F)** The left hand massages the abdomen by the right circle. **(G)** Pushing with the right hand from the left breast to the groin. **(H)** Pushing with the left hand from the right breast to the groin. **(I)** Turn left and right. Every movements will be carried out 21 times. PLWNT, prolong life with nine turn method.

under the right breast to the groin, and repeat this 21 times in 3 min.

Step 3. Seated Rocking Method

Sit cross-legged, the participant should hold their hands up slightly and press them on the knees. The toes of both feet should be slightly bent. The participant should revolve the upper body clockwise 21 times and then counterclockwise 21 times.

CBT Group

Qualified CBT therapists [e.g., those with a diploma in CBT or other professionally accredited qualifications involving CBT as a major part of training (e.g., a clinical or counseling psychologist degree)] were invited to conduct CBT by giving lectures or psychological consultations on the prevention and treatment of CFS for 1 h each week. On the remaining 6 days of the week, all participants were required to listen to lectures on WeChat for 30 min every day. If some of the participants found it inconvenient, they were allowed to learn at their own pace using provided PowerPoints. Each participant was asked to write down their feelings in the practice recording notebook after each online session to ensure that the other conditions were the same as those of the PLWNT group. The entire practice process lasted for 12 weeks. Detailed information is available in the previously published protocol (34).

Outcomes

Outcome evaluations included the basic characteristics of personal information, the detection of peripheral blood of CFS, the quality of sleep, mental and physical fatigue, and anxiety and depression symptoms. The patient's basic information was evaluated at baseline using relevant self-assessment scale and peripheral blood concentration to assess the primary and secondary outcomes after 12 weeks of intervention, including the Multi-dimensional Fatigue Inventory 20 (MFI-20), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HADS).

Primary Outcomes

MFI-20

The MFI-20 is widely used for CFS measurement of mental and physical fatigue (39), including a total of 20 items, including five dimensions of general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Each item can be scored on a scale of zero to five points, and the total possible score is 100 points. The higher the score is, the more severe the fatigue is. The MFI-20 was found to have good internal consistency (Cronbach's alpha = 0.89) and reliability (Pearson correlation of the total score = 0.73) (40).

Secondary Outcomes

Overall Efficacy Evaluation

The overall efficacy evaluation was formulated with reference to the efficacy standard established by the "Discussion on the Curative Effect Standards for Diagnosis and Treatment of Chronic Fatigue Syndrome" (41, 42) and combined with the MFI-20 score. Full recovery was defined as the complete disappearance of the main clinical symptoms and concurrent symptoms and a reduction in MFI-20 score of more than 95%. A markedly effective result was defined as the disappearance of more than two-thirds of the main clinical symptoms and concurrent symptoms and a reduction in MFI-20 score of more than 70%. An effective result was defined as the disappearance of more than one-third of the main clinical symptoms and concurrent symptoms and a reduction in MFI-20 score of more than 30%. An ineffective result was defined as the disappearance of less than one-third of the main clinical symptoms and concurrent symptoms and a reduction in MFI-20 score of $<$30%. The total effective rate was the sum of the recovery rate, the markedly effective rate, and the effective rate.

PSQI

PSQI is a self-assessment questionnaire used to evaluate sleep quality. The scale consists of 24 items, with 19 self-reported items and five additional items rated by the director but not scored. The 19 items belong to one of the following seven subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (43). The score range for each dimension is from zero to three points, and the total possible score is 21 points. The higher the score is, the worse the sleep quality is. The Cronbach's α coefficient of the PSQI was 0.68, and it increased to 0.78 after two components (medication use and daytime dysfunction) were removed. The PSQI has sufficient internal consistency (Cronbach alpha = 0.79), and test-retest reliability and validity (44, 45).

HADS

The HADS is used to evaluate the degree of anxiety and depression of patients. The scale consists of 14 items, including seven items that assess anxiety and seven items that assess depression. Scores for each item range from zero (nothing at all) to three points (the extreme form of each symptom) (46). The higher the total score is, the more severe the degrees of anxiety and depression are. The Cronbach's alpha reliability statistic of 0.70 for HADS is considered as the minimum acceptable criterion of instrument internal reliability (47, 48).

Peripheral Blood Biomarkers

NPY is an objective blood indicator of peripheral biomarkers for detecting sleep, anxiety, and depression in CFS (49). After the patients were grouped, non-fasting blood samples were collected. All blood samples in this study were sent to the clinical immunology laboratory of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, where the plasma was separated from the cells within 2 hafter collection, aliquoted into cryovials, and stored at -80°C until laboratory testing. The sample was only thawed once.

Correlations

Possible determinants of the total scores of fatigue, sleep quality, and anxiety and depression at the end of treatment (T_1) were investigated. The linear relationship among them was further explored.

Adverse Events

We did our best to prevent and treat damage that may have been caused by this research. If an adverse event occurred during the clinical trial, including any discomfort, new changes in the condition, or any unexpected situation, details would be sent to the nearby Yueyang Hospital of Integrated Traditional Chinese and Western Medicine for review, where a medical expert committee determined whether the event was related to the study treatment or not. If the expert committee determined that the adverse event was related to treatment, the cost of treatment and corresponding financial compensation were provided to the participant. All expected and unexpected reactions reported by each participant were recorded on an adverse event reporting form, and all adverse events were followed up with until they were resolved. A score range of one to four points (1, definitely not related; 2, probably not related; 3, probably related, 4, definitely related) was used to indicate the degree of relationship between PLWNT treatment and adverse events.

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. For measurement data, such as age and scale score, average value ± standard deviation ($\bar{X}\pm$ S) values were used. For measurement data conforming to normal distribution and homogeneity of variance test, paired-samples *t*-tests were used for comparisons before and after the test. For non-normally distributed measurement data, the Wilcoxon paired non-parametric test were used before and after the test, and $P < 0.05$ indicated that the difference was statistically significant. The Spearman correlation analysis was used to study the possible relationship between the MFI-20 and the clinical features of the PSQI and HADS scale scores.

RESULTS

A total of 90 participants who met the criteria were recruited in this study. They were randomly divided into a PLWNT group and CBT group, with 45 people placed in each group. Among them, one case in the CBT group withdrew due to shoulder fracture, which was a lost case. In the end, 89 participants completed the entire treatment plan. The process is shown in a flowchart (**Figure 2**).

Demographic and Clinical Characteristics

The baseline characteristics of the PLWNT group and CBT group are shown in **Table 1**, which reveals that no difference existed in aspects such as the ratio of men to women, age, height, and education level between the two groups. Fatigue, sleep, and depression scale scores between the PLWNT and CBT groups were comparable, with *P*-values were all 0.05. These results

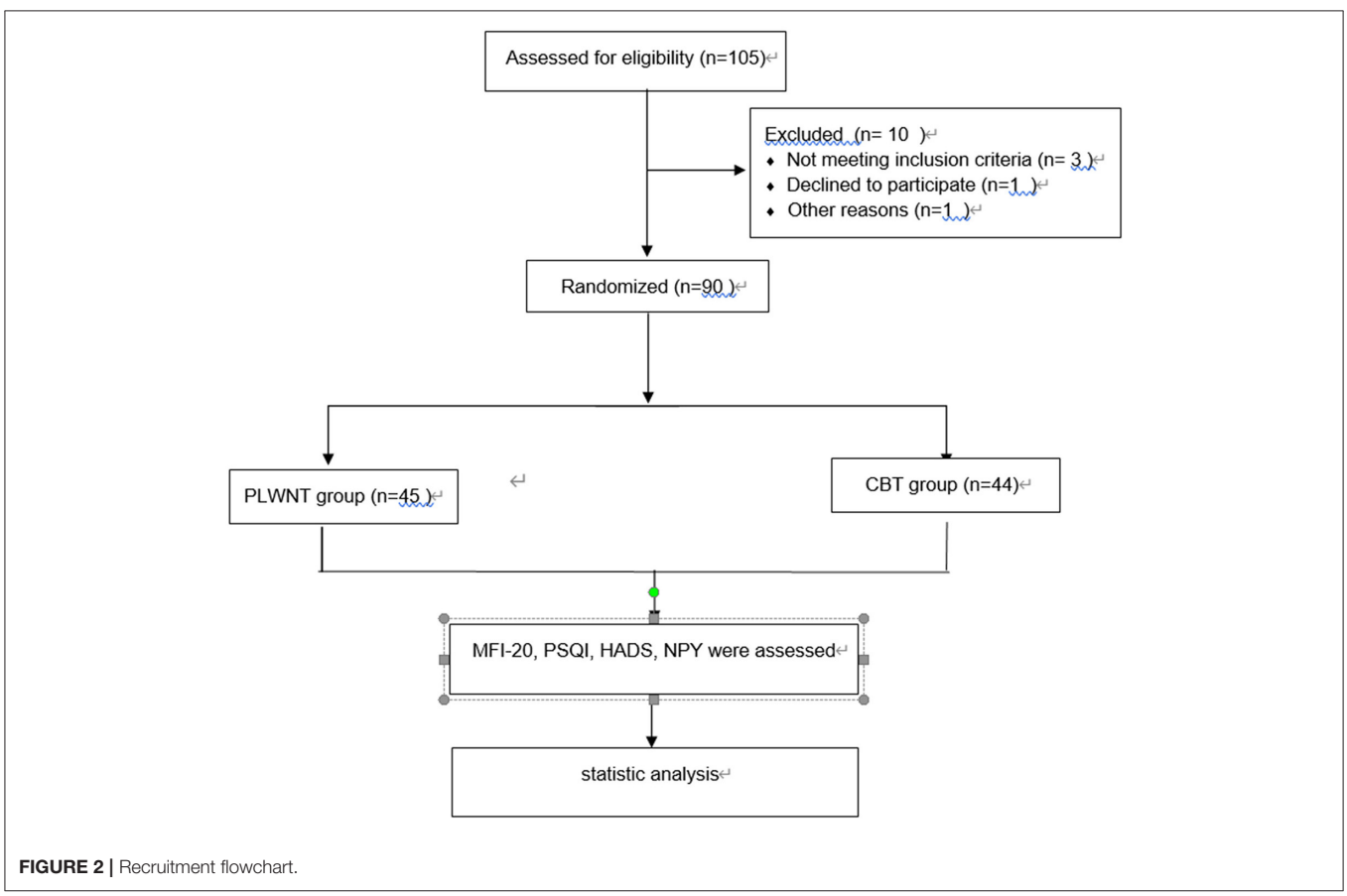

FIGURE 2 | Recruitment flowchart.

TABLE 1 | Demographic and clinical characteristics of the patients.

	PLWNT ($n = 45$)	Control ($n = 44$)	*P*-vaule
Age (year)	37.943 ± 11.344	37.343 ± 9.864	>0.05
Weight (kg)	59.804 ± 10.893	61.943 ± 12.061	>0.05
Height (cm)	163.514 ± 6.679	165.000 ± 7.376	>0.05
Gender(M\F)	17\28	19\25	>0.05
Education(year)	11.823 ± 3.25	11.232 ± 2.86	>0.05
Married	21	20	>0.05
Single	23	22	>0.05
Divorce	1	2	>0.05
Clinical score	10.556 ± 2.896	10.932 ± 2.872	>0.05
MFI-20	9.067 ± 3.962	10.614 ± 3.674	>0.05
General fatigue	8.622 ± 3.6,200	9.818 ± 3.611	>0.05
Physical fatigue	8.200 ± 4.257	8.091 ± 3.672	>0.05
Reduced activity	10.022 ± 4.104	9.886 ± 3.357	>0.05
Reduced-	1.444 ± 0.724	1.545 ± 0.697	>0.05
Motivation	1.333 ± 1.066	1.705 ± 0.904	>0.05
Mental fatigue	0.911 ± 0.821	1.023 ± 0.792	>0.05
PSQI	0.644 ± 1.171	0.455 ± 0.730	>0.05
Subjective sleep	1.467 ± 0.625	1.614 ± 0.618	>0.05
Sleep latency	0.200 ± 0.757	0.091 ± 0.473	>0.05
Sleep duration	1.022 ± 0.657	1.273 ± 0.624	>0.05
Habitual sleep	6.756 ± 3.523	7.705 ± 2.953	>0.05
Sleep disturbances	7.000 ± 3.855	7.682 ± 3.969	>0.05
Use of medicine	6.844 ± 4.033	6.705 ± 3.927	>0.05
Daytime function			
Total score			
HADS			
Anxiety			
Depression			

indicated that the baseline values were relatively uniform. The participants were between 20 and 50 years of age. Most were female students in high schools or universities. Nearly half were married. They joined in the trial mainly due to referral by the hospital. In terms of MFI-20, PSQI, and HADS scores, patients who scored higher suffer more severe symptoms of fatigue, sleep disorders, and depression.

Outcome Measurements

Table 2 suggests the total effective rate of the PLWNT and CBT groups. The results showed that the total effective rate of the PLWNT group was 62.22%, in which zero cases were cured, seven cases had markedly effective results, 21 cases had effective results, and 17 cases had ineffective results. The total effective rate of the CBT group was 50%, in which zero cases were cured, zero cases had markedly effective results, 22 cases had effective results, and 22 cases had ineffective results. There was a significant difference between the two groups ($P < 0.05$), indicating that the treatment effectiveness of the PLWNT group in the management of CFS was greater than that of the CBT group.

Table 3 shows the changes in the primary and secondary scores of the MFI-20, PSQI, and HADS scales from T_0 to T_1 in the two groups. The results indicate that the primary outcome of MFI-20 significantly decreased after 12 weeks of intervention in the PLWNT and CBT groups, which show a statistically significant difference ($P < 0.001$). Thus, in both groups, conditions improved in terms of general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. As for the secondary outcomes, the overall scores of the PSQI and HADS scales had also improved when comparing T_1 to T_0 in the PLWNT and CBT groups. The comparison of HADS scores within the groups showed statistical significance after PLWNT and CBT intervention. According to the PSQI results, significant improvements in overall sleep quality, subject sleep quality, sleep latency, sleep duration, sleep disturbance, and daytime dysfunction after intervention were noted ($P < 0.05$). However, in terms of habitual sleep efficiency and sleep medicine usage, there was no statistically significant difference between the groups ($P > 0.05$). The total scores and the average value of each score considering the changes of MFI-20, PSQI, and HAS scales in the PLWNT group were greater than those in the CBT group, although there was no statistical significance between the groups.

The distribution of plasma NPY values between the two groups is shown in **Table 4**. The analysis showed that NPY decreased after PLWNT intervention (126.17 ± 16.88 vs. 123.55 ± 17.14) but increased significantly after CBT treatment (142.99 ± 17.86 vs. 201.01 ± 22.83). Compared to the CBT group (201.01 ± 22.83), the plasma NPY of CFS patients in the PLWNT group (123.55 ± 17.14) was decreased, and there was a statistical difference between the groups ($P = 0.008$).

Correlations

Fatigue was the primary result of the study, and the treatment groups underwent additional correlation analysis to compare

TABLE 2 | Efficacy evaluation of PLWNT group and CBT group after 12 weeks of intervention (Cases/effective rate).

Group	Cases	Cases/cured (%)	Cases/markedly effective (%)	Cases/effective (%)	Cases/no effective (%)	Total effective (%)
PLWNT	45	0/0	7/15.56	21/46.67	17/37.78	62.22
CBT	44	0/0	0/0	22/50	22/50	50

TABLE 3 | Shows the changes primary and secondary outcomes in fatigue, sleep, anxiety and depression scores measured by MFI-20, PSQI, and HADS scales from T0 to T1.

	CBT ($n = 44$)			PLWNT ($n = 45$)			*PLWNT vs. CBT*
	T_0 ($\bar{X} \pm S$)	T_1 ($\bar{X} \pm S$)	*Within group p*	T_0 ($\bar{X} \pm S$)	T_1 ($\bar{X} \pm S$)	*Within group P*	*Between group P*
Primary outcome: MFI-20							
General fatigue	10.932 ± 2.872	7.341 ± 3.403	0.000*	10.556 ± 2.896	6.511 ± 2.897	0.000*	0.516
Physical fatigue	10.614 ± 3.674	6.727 ± 3.172	0.000*	9.067 ± 3.962	4.511 ± 2.785	0.000*	0.435
Reduced activity	9.818 ± 3.611	6.545 ± 3.238	0.000*	8.622 ± 3.6, 200	4.0.911 ± 2.502	0.000*	0.593
Reduced motivation	8.091 ± 3.672	5.114 ± 2.508	0.000*	8.200 ± 4.257	4.644 ± 2.854	0.000*	0.482
Mentalfatigue	9.886 ± 3.357	6.318 ± 2.752	0.000*	10.022 ± 4.104	5.578 ± 2.759	0.000*	0.282
Secondary outcome: PSQI							
Total score	7.705 ± 2.953	5.295 ± 2.378	0.000*	6.756 ± 3.523	4.200 ± 2.085	0.000*	0.828
Subject sleep quality	1.545 ± 0.697	1.159 ± 0.079	0.002*	1.444 ± 0.724	0.956 ± 0.424	0.000*	0.532
Sleep latency	1.705 ± 0.904	1.386 ± 0.813	0.021*	1.333 ± 1.066	0.933 ± 0.720	0.011*	0.685
Sleep duration	1.023 ± 0.792	0.409 ± 0.622	0.000*	0.911 ± 0.821	0.200 ± 0.405	0.000*	0.609
Habitual sleep efficiency	0.455 ± 0.730	0.364 ± 0.718	0.439	0.644 ± 1.171	0.378 ± 0.912	0.209	0.142
Sleep disturbance	1.614 ± 0.618	1.205 ± 0.461	0.000*	1.467 ± 0.625	1.022 ± 0.452	0.000*	0.783
Sleep medicine using	0.091 ± 0.473	0.091 ± 0.291	1.000	0.200 ± 0.757	0.089 ± 0.468	0.168	0.326
Daytime dysfunction	1.273 ± 0.624	0.682 ± 0.601	0.000*	1.022 ± 0.657	0.356 ± 0.609	0.000*	0.593
Secondary outcome: HADS							
Anxiety	7.682 ± 3.969	5.727 ± 3.083	0.000*	7.000 ± 3.855	4.111 ± 2.113	0.000*	0.198
Depression	6.705 ± 3.927	4.705 ± 3.069	0.001*	6.844 ± 4.033	3.444 ± 2.563	0.000*	0.105

*$P < 0.05$.

TABLE 4 | The distribution of plasma NPY values of the three groups.

	PLWNT group ($n = 45$)	CBT group ($n = 44$)	*P*
T0	126.17 ± 16.88	142.99 ± 17.86	0.498
T1	123.55 ± 17.14	201.01 ± 22.83	0.008*
d-value	−2.62 ± 23.77	58.03 ± 28.98	0.110

*$P < 0.05$.

between the primary and secondary outcomes. Pearson's correlation coefficient was used to explore the relationship between fatigue and sleep quality as well as fatigue and anxiety. In the PLWNT group, fatigue level was positively correlated with sleep quality ($r = 0.315$) and anxiety level ($r = 0.333$) ($P < 0.05$). However, fatigue level was only related to anxiety level ($r = 0.332$) ($P < 0.05$) and showed no correlation with sleep quality in the CBT group ($P > 0.05$). The specific results are shown in **Figure 3**.

Adverse Events

Table 5 displays data from a total of six participants who reported six adverse events in our study. Among them, two cases were determined to be definitely or probably related to the exercises, with mild symptoms caused by improper massage manipulations on the abdomen. Except for one patient who chose to quit the study due to shoulder fracture, all other participants continued with treatment after their adverse events had been properly dealt with. There was no significant difference in AE statistics between the two groups ($p = 0.096$).

DISCUSSION

This study was performed to evaluate the efficacy of PLWNT on fatigue, sleep disorders, and depression symptoms in CFS patients and to discern the linear correlation between fatigue and sleep quality as well as fatigue and depression levels. As

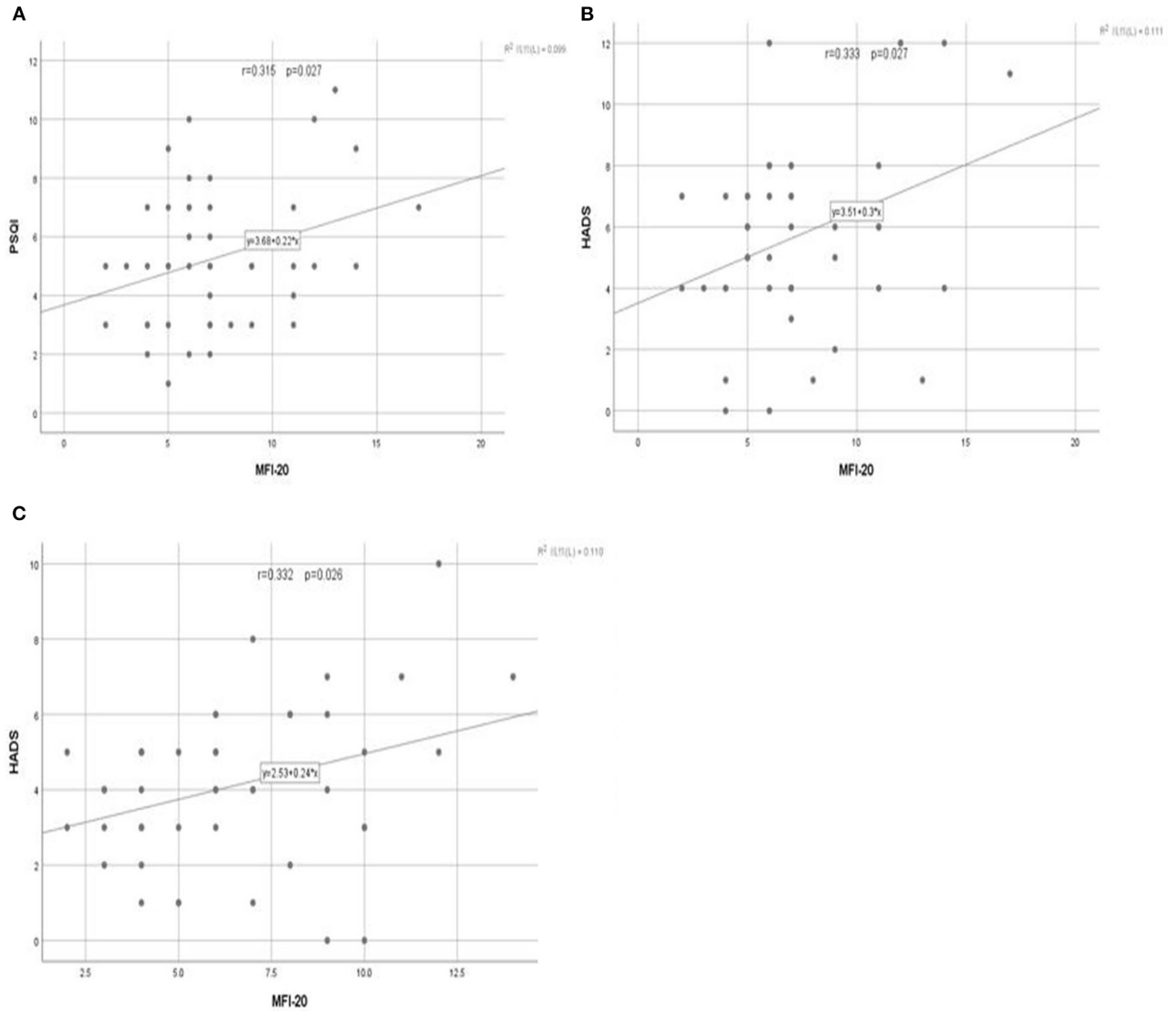

FIGURE 3 | The linear relationship between the total score of fatigue and the total score of sleep and anxiety at the end of treatment. The relationship between the **(A)** total score of fatigue and the total score of sleep after PLWNT exercise. **(B)** total score of fatigue and the total score of anxiety after PLWNT exercise. **(C)** total score of fatigue and the total score of anxiety after CBT intervention.

the results show, the levels of fatigue, anxiety, and depression as well as sleep quality of CFS patients were significantly improved after PLWNT or CBT intervention, and the overall efficacy of the two groups was effective after intervention with no significant difference between the groups. The self-reported sleep time increased to the minimum of 7 h after PLWNT intervention, which is the amount recommended in many guidelines. However, no improvement was reported from T_0 to T_1 in terms of the habitual sleep efficiency or sleep medicine usage. These findings must be interpreted with caution, because the levels of fatigue, anxiety, depression and sleep quality did not have significant differences between the PLWNT group and the CBT group due to the relatively small between-group effect size.

CFS is characterized by long-term, unexplainable fatigue (50), and it can be treated by PLWNT qigong. Previous studies have indicated the efficacy of moxibustion, auricular acupoint pressure, Chinese medicine, and other therapies for the alleviation of fatigue symptoms in CFS patients (23, 51, 52). Patients who suffer from fatigue cannot carry out or maintain a physiological activity. If not treated properly and promptly, the symptoms can deteriorate into chronic fatigue of a certain degree (53, 54). Studies have confirmed that the body's ability to scavenge oxygen free radicals decreases when it is in a fatigue state, and, if the free radicals in the body cannot be eliminated in due time, the fatigue will worsen (55, 56). PLWNT qigong is an effective treatment for CFS. It incorporates eight

TABLE 5 | Adverse event.

Symptom	Group	Patients numbers	Start date	End date	Relationship	Treatment	Action related to intervention	Outcome
Leg pain	PLWNT	1	2019/02/24	2019/03/03	Probably	None	No change	Cured
Shoulder	CBT	1	2019/03/09	2019/03/10	Definitely not	Medication	Withdraw	Unknown
Dizziness fracture	PLWNT	1	2019/05/12	2019/05/12	Probably not	Measure blood pressure and eat breakfast	No change	Cured
Left thumb pain	PLWNT	1	2019/07/21	2019/08/04	Definitely not	None	No change	Cured
Diarrhea	PLWNT	1	2019/08/11	2019/08/12	Probably not	Catch cold	No change	Cured
Chest pain	PLWNT	1	2019/08/15	2019/08/29	Definitely	Relieve acupoint stimulation	No change	Cured

kinds of massage manipulations on the abdomen and a kind of upper body shaking method. The active mechanisms that relieve fatigue symptoms may be to render the whole-body skeletal muscles, especially those of the upper limbs, in a state of relaxing limb activity; enhancing the body's antioxidant enzyme activity; removing oxygen free radicals; and stabilizing the body's environment (57). It has been reported in a previous study (58) that traditional qigong exercises can increase the activity of the diaphragm and abdominal muscles, strengthen peripheral skeletal muscle function, and improve fatigue symptoms. These may be speculated that the main reason for the improvements in reduced activity and reduced motivation shown in the MFI-20 scores of CFS patients after PLWNT intervention in this study. In addition, patients with CFS fatigue often have problems with immune dysfunction, which may be one of the causes of persistent fatigue (59, 60). A previous study has reported that abdominal massage manipulations can enhance the body's immunity by clearing lactic acid from the blood after fatigue, improving the patient's autonomic nerve function, and bringing the sports center into a benign state of excitement (61). This may be the main mechanism by which PLWNT relieves mental fatigue and physical fatigue.

Sleep quality, subjective sleep quality, sleep latency, sleep duration, sleep disturbance, and daytime dysfunction of CFS patients were significantly improved after PLWNT intervention. These findings are consistent with the results of a previous study results following the conduct on Baduanjin qigong, which improved the sleep latency and sleep duration in CFS patients but did not improve subjective sleep quality or sleep disturbance (62). In this study, the effect of PLWNT qigong on the multi-dimensional improvement of sleep quality may also be related to the abdominal massage manipulations. Studies have indicated that abdominal massage manipulations can regulate nerve conduction connections through the brain–gut axis, stimulate nerve-conduction pathways and nerve-emotional pathways through internal organs, and strengthen the connection between the abdomen and cranial nerves to regulate fatigue and sleep in CFS patients (63, 64). It is worth noting that no improvement was found in terms of the habitual sleep efficiency or the use of sleep drugs by the participants in this study. These findings are consistent with several previous studies on CFS, which reported that CFS patients are more likely to be awakened and have a longer sleep latency than healthy people (65, 66). Therefore, it is speculated that the lack of improvement in habitual sleep efficiency may be caused by sleep interruptions or a prolonged sleep latency, leading to more time spent in bed. However, the fact that the present study excluded all subjects taking medications may be why the difference in the use of sleep drugs was not significant.

In our study, the anxiety and depression levels of CFS patients decreased significantly after PLWNT intervention. Baduanjin qigong exercise has been reported to have antidepressive effects in women with CFS-like diseases (67). The limbic system of the human brain is responsible for emotional regulation. Therefore, anxiety and depression may be correlated with dysfunction of the brain network connection the limbic system and cortex (68). In some studies, antidepressants are used to increase serotonin levels and reduce cortisol secretion in the brain to deal with the anxiety and depression of CFS patients, but these drugs have side effects, such as headache, sleep disturbance, changes in cardiovascular function, and bone loss (69). It has been reported that rubbing the abdomen can increase serotonin and endorphins to activate the spinal cord and subcortical nucleus activity to reduce the levels of anxiety and depression (70). PLWNT may be used to relieve anxiety and depression symptoms through abdominal pressing and rubbing.

Improvements in fatigue, sleep, and anxiety symptoms were directly related to the amount of qigong exercises, which was consistent with previous studies of other types of qigong (71, 72). In this study, Pearson's correlation coefficient indicated that the fatigue level was positively correlated with the anxiety level and sleep quality. A new study conducted by Russell et al., in which the sleep quality of 27 adult CFS patients (73) was evaluated using a sleep–wake diary and activity recorder, had similar results, indicating that sleep disorders induce a more serious level of fatigue. Similarly, in the case of perception of external stress and fatigue, the hypothalamic–pituitary–adrenal axis is activated and overactive, and a large amount of glucocorticoids will be released into the body to perceive anxiety (74). This shows that fatigue is closely related to sleep and anxiety symptoms, so maybe we need to increase the time of PLWNT exercise

or make it as a daily exercise to relieve fatigue so as to gain more benefits.

Enzyme-linked immunosorbent assay blood indicators were used to objectively show the relationship between NPY and CFS symptoms of fatigue, sleep, anxiety, and depression after PLWNT intervention, and the findings were consistent with those of some previous studies (75, 76), which showed that different forms of exercise can reduce the level of expression of NPY and inhibit the development of the disease. Another study of NPY comparing CFS patients with HC patients showed that NPY was significantly increased in CFS patients, which means that the reduction of NPY level leads to the relieve of anxiety and depression (49). This finding is consistent with our results that the relief of anxiety and depressive symptoms after PLWNT intervention may be associated with significantly lower levels of NPY in our study. However, there are many factors affecting NPY, and the content of NPY in different diseases is different, one study showed no overall difference in NPY concentrations before and after the intervention (77). So the blood level of NPY is whether dependent to other diseases/parameters is still unclear. In addition, the cause of the increased NPY results after CBT treatment cannot be determined at present, and it may be related to the intervention method.

In the future, we will conduct more in-depth studies to further explore the possible mechanisms by which NPY levels affect CFS-related symptoms after PLWNT and CBT interventions.

This study did not report adverse events due to exercise, and only one case withdrew due to her own reasons. This shows that PLWNT exercises guided by professionals can be safely adopted by CFS patients. In general, our research indicates that PLWNT represents an alternative and more acceptable form of exercise for CFS patients. This has great significance in health care for CFS patients, who may not be able to perform traditional exercises due to physical limitations or comorbidities. PLWNT is a mild, low-intensity form of exercise, usually accepted by CFS patients, and it is an advantageous method for them to comply with the World Health Organization's physical activity recommendations.

However, there are some limitations in this study. First of all, the study's experimental design itself had potential limitations. Ideally, participants should remain uninformed about the intervention; however, it is difficult to do this in non-drug trials. Second, patients over 60 years old are excluded in this study. Therefore, the results should not be generalized to the elderly over 60 years old. Future research will be performed with interventions controlling all non-specific factors so as to better understand the specific efficacy of PLWNT. Despite these limitations, to our knowledge, this study is the first large-scale randomized controlled trial to prove the beneficial effects of PLWNT on CFS. Another obvious advantage is that this study reports all the adverse events in detail. We described the adverse symptoms, the time of appearance and disappearance, the relationship between the adverse events and the trial, and the related treatments and results. During the clinical trial, no one quit due to an adverse event. The safety of qigong treatment has been reported on before (78–80) and has now been demonstrated in our study.

CONCLUSION

In summary, PLWNT has a positive effect in the treatment of fatigue, sleep disorders, and anxiety and depression symptoms of CFS patients, and fatigue level is positively correlated with sleep quality as well as anxiety and depression levels. PLWNT can be considered as a treatment option for CFS patients, but more rigorous research is needed to provide clear evidence. Future studies will be carried out using a larger sample size for further in-depth research to determine the effective frequency and intensity of PLWNT qigong intervention in the treatment of CFS. This study has significant translational significance because our findings will support the inclusion of PLWNT in the global physical activity guidelines for CFS patients.

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 human participants were reviewed and approved by Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (Ethics Approval No. 2018-043). The patients/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

FX, YY, FY, and JX contributed to data analysis and interpretation. FX, YY, CG, JX, and FY drafted the revised manuscript and conceived and received the project. All authors contributed to the article and approved the submitted version.

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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.2022.828414/full#supplementary-material

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Therapeutic Alliance as Active Inference: The Role of Therapeutic Touch and Biobehavioural Synchrony in Musculoskeletal Care

*Zoe McParlin[1], Francesco Cerritelli[1], Giacomo Rossettini[2], Karl J. Friston[3] and Jorge E. Esteves[1,4,5]**

[1] Clinical-Based Human Research Department, Foundation COME Collaboration, Pescara, Italy, [2] School of Physiotherapy, University of Verona, Verona, Italy, [3] Institute of Neurology, Wellcome Centre for Human Neuroimaging, London, United Kingdom, [4] Malta ICOM Educational, Gzira, Malta, [5] University College of Osteopathy, London, United Kingdom

Touch is recognised as crucial for survival, fostering cooperative communication, accelerating recovery, reducing hospital stays, and promoting overall wellness and the therapeutic alliance. In this hypothesis and theory paper, we present an entwined model that combines touch for alignment and active inference to explain how the brain develops "priors" necessary for the health care provider to engage with the patient effectively. We appeal to active inference to explain the empirically integrative neurophysiological and behavioural mechanisms that underwrite synchronous relationships through touch. Specifically, we offer a formal framework for understanding – and explaining – the role of therapeutic touch and hands-on care in developing a therapeutic alliance and synchrony between health care providers and their patients in musculoskeletal care. We first review the crucial importance of therapeutic touch and its clinical role in facilitating the formation of a solid therapeutic alliance and in regulating allostasis. We then consider how touch is used clinically – to promote cooperative communication, demonstrate empathy, overcome uncertainty, and infer the mental states of others – through the lens of active inference. We conclude that touch plays a crucial role in achieving successful clinical outcomes and adapting previous priors to create intertwined beliefs. The ensuing framework may help healthcare providers in the field of musculoskeletal care to use hands-on care to strengthen the therapeutic alliance, minimise prediction errors (a.k.a., free energy), and thereby promote recovery from physical and psychological impairments.

Keywords: therapeutic alliance, active inference, touch, manual therapy, physiotherapy, osteopathy, musculoskeletal care, pain

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****Correspondence:***
Jorge E. Esteves
osteojorge@gmail.com

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INTRODUCTION

For over 50 years, the medical community has recognised the beneficial therapeutic effects of touch on health and wellbeing (McGlone et al., 2017). Consequently, hands-on care is recommended for a range of musculoskeletal (MSK) conditions, including low back pain (LBP), neck pain, headaches, carpal tunnel syndrome and hip and knee osteoarthritis (Deyle et al., 2000;

Akalin et al., 2002; MacDonald et al., 2006; Rubinstein et al., 2011; Gross et al., 2015; Cerritelli et al., 2017). A significant body of evidence demonstrates that hands-on techniques in MSK care have a particularly important role on pain modulation (Deyle et al., 2000; Bialosky et al., 2009; Vigotsky and Bruhns, 2015; Cerritelli et al., 2017; Geri et al., 2019; Sánchez-Romero et al., 2021). Therefore, the hand plays a crucial role in delivering MSK care through the sense of touch. Touch in the clinical context forms part of a range of examination and therapeutic interventions such as manual therapy (Rondoni et al., 2017). It is also central to enhancing communication, patient compliance, cueing and assisting patients to reduce pain, and improving clinical outcomes (Roger et al., 2002). On this point, Lederman (2017) argues that manual therapy techniques should be viewed as a vehicle to deliver touch effects, which can have a positive influence on the sense of "self," wellbeing, and body image, as well as a profound calming and soothing influence on the individual.

This article will focus on therapeutic touch as a synonym for human touch-based interventions used in MSK care. Hands-on care relies on three crucial dimensions of touch, i.e., analgesic, somatoperceptual and affective (Geri et al., 2019). Arguably, these dimensions fall broadly into two categories – discriminatory and affective touch (McGlone et al., 2014, 2017). Most people understand the sense of touch as a discriminative sense, enabling us to detect, for example, a fly landing on our face, or the texture of the surface being manipulated – discriminatory or "fast touch" relies on large myelinated (Aβ) afferents which project primarily to the somatosensory cortex (McGlone et al., 2014). Discriminatory touch has been traditionally associated with the observed modulatory effects of manual therapy and therapeutic touch on the central and autonomic nervous system (i.e., Mancini et al., 2014; Geri et al., 2019).

On the other hand, affective touch is the "slow" touch system that is dependent on a system of unmyelinated low threshold mechanosensitive c-fibres called c-tactile (CT) afferents, which project mainly to emotion-related paralimbic cortical systems (insular cortex), the posterior superior temporal sulcus (pSTS) and the medial prefrontal cortex (mPFC)/dorsoanterior cingulate cortex (dACC) (McGlone et al., 2014). CT afferents cannot provide helpful discriminative information due to the slow conduction velocity of C-fibres (McGlone et al., 2014, 2017). The CT afferent system plays a crucial role in providing or supporting emotional, hormonal, and behavioural responses to skin-to-skin contact with conspecifics (McGlone et al., 2014). Therefore, affective touch is associated with tactile stimuli with a hedonic and often emotional component, encompassing aspects of reward and significance in social communications (Morrison et al., 2010; Morrison, 2016a).

The insular cortex integrates the sensory and emotional systems creating an interoceptive modality. Interception is defined as the perception of internal physiological states within an individual's body and the sensations of an external stimulus such as touch or pain (Craig, 2002; Panagiotopoulou et al., 2017). CT and Aβ afferents are required for the complete feeling of pleasant touch on the hairy skin (McGlone et al., 2014). Moreover, the insular cortex's activation during therapeutic touch affects the modulation of interoceptive precision (attention) and contributes to the pleasant feelings associated with therapeutic touch. Crucially, the modulation of interoceptive precision (attention) by the insular cortex also alters body awareness, autonomy, and sense of self, updating interoceptive beliefs associated with the use of therapeutic touch while also being innervated by the transcutaneous auricular vagus nerve (Craig, 2008; Crucianelli et al., 2013, 2018; Ainley et al., 2016; Park et al., 2017; Bradran et al., 2018; Paciorek and Skora, 2020).

The vagus nerve can also provide inhibitory inputs to the heart, which are crucial for self-regulation, as proposed through the neurovisceral integration model (NVIM) (Park and Thayer, 2014). The NVIM suggests that an individual's ability to adapt to its environment depends on the physiological flexibility within the different hierarchical levels and attractor basins of the central autonomic network (CAN), in which the vagus nerve and vagal control are crucial to the feedback mechanism (Thayer and Friedman, 2002; Condy et al., 2020).

The clinical benefits of therapeutic touch in MSK care are likely to depend on both discriminatory, "fast" touch and affective, "slow" touch (McGlone et al., 2017). Therapeutic touch has shown to be effective for pain relief, reducing heart rate and systolic blood pressure in patients with persistent non-malignant pain and even in those with other comorbidities such as breast cancer (Billhult et al., 2009; Olufade et al., 2015; Pinheiro da Silva et al., 2019). Moreover, therapeutic touch in the form of massage initiates relaxation, sense of safety, reduces fear-avoidance and physiological markers of stress, i.e., cortisol and heart rate through deactivating the threat of noxious stimulus and possibly initiating autonomic regulation, particularly in chronic LBP, arthritis, fractures, and pain conditions (Hernandez-Reif et al., 2004; Billhult et al., 2009; Maratos et al., 2017; Miciak et al., 2019).

Touch with the intention to care for another, such as in a clinical environment, provides better relief from physical and emotional distress than self-care by decreasing the activation of pain-related regions, particularly the dorsal Anterior Cingulate Cortex (ACC) and the Anterior Insular Cortex (AIC) (Shamay-Tsoory and Eisenberger, 2021). The insula is a crucial region in pain processing, and developing evidence indicates that the insula encodes the magnitude of an unexpected outcome – unsigned prediction errors (Horing and Büchel, 2022). Prediction errors occur in events where there is a mismatch between an expected and actual event or sensory signal (Rossettini et al., 2022). Prediction errors are crucial in updating a generative model and, therefore, in driving learning (Parr et al., 2022). Recent evidence indicates that a misrepresentation of learning relevant prediction errors in the insula is likely an underlying factor in persistent pain (Horing and Büchel, 2022).

Moreover, the insular cortex is also part of the Salience and Default Networks that assist with regulating the nervous, immune, and neuroendocrine systems, which play a crucial role in regulating allostasis (Atzil et al., 2018). Allostasis is the adaptive anticipatory process of, which delivers the right kind of context for achieving homoeostatic balance; namely, to achieve the primary goal of maintaining a stable bodily state through a series of physiological (i.e., autonomic) or behavioural (i.e., sensorimotor) closed feedback loops (i.e., reflexes). Crucially, the

primary function of the nervous system is to manage allostasis, i.e., predicting the physiological needs for survival (Barrett, 2020; Esteves et al., 2022). Importantly, in the context of MSK care, allostatic load, and overload – the cumulative burden of chronic stress and life events – has been linked to poorer health outcomes, including pain, depression, anxiety and MSK disorders (see Guidi et al., 2021, for a recent review). The role of the insular cortex in allostatic regulation is also crucial in building trust and attachment through a collaborative relationship to secure joint attention, with synchronisation allowing empathy and acknowledging it as being rewarding, and thus decreasing pain (Barrett and Fleming, 2011; Tomasello et al., 2012; Shamay-Tsoory and Eisenberger, 2021; McParlin et al., 2022). Moreover, the insular cortex is also central to oxytocinergic modulation, encouraging and modulating the development of bonding, trust, and processing of therapeutic touch, which can also contribute to building a robust TA (Morrison, 2016a; Fotopoulou et al., 2022; McParlin et al., 2022). Therefore, it is crucial that clinicians understand the role of allostatic load and its regulation on patient care. Arguably, therapeutic touch can play a key role in allostatic regulation and achieving embodied predictions regarding social attachments, achieving balance amongst all bodily systems needed for survival and physiological co-regulation with others, through caregiving touch in specific social interactions (see Fotopoulou et al., 2022, for a review).

The therapeutic alliance (TA) is referred to as the collaborative relationship or working alliance between the patient and Health Care provider (HCP) and is necessary for establishing a positive rapport and trust, ensuring patient satisfaction, and achieving positive clinical outcomes following treatment, particularly in patients with persistent MSK pain (Taylor et al., 2015; Kinney et al., 2018; Miciak et al., 2018; McCabe et al., 2021b). This article will refer to an HCP as an orthopaedic manual physical therapy practitioner specialising in managing neuro-musculoskeletal conditions using manual techniques and therapeutic exercises, including physiotherapists, osteopaths, chiropractors, and massage therapists (International Federation of Orthopaedic Manual Physical Therapists [IFOMPT], 2004).

The TA is centred around the tripartite elements of a working alliance described by Bordin (1979), including the agreement on goals, agreement on a task, and the development of attachment bonds, which are the foundation for a successful TA (Rossettini et al., 2020). An HCP who creates a successful person-centred TA can gain the trust of anxious and sceptical patients. Moreover, in patients, particularly those with chronic low back pain, a good TA can result in positive clinical outcomes for both physical and mental capacities, overall patient satisfaction, and quality of life (Ferreira et al., 2013; Fuentes et al., 2014; Taccolini Manzoni et al., 2018; Rossettini et al., 2020). To form a collaborative agreement needed for a robust TA, one needs to adapt their personal opinions to be in tune with other individuals. We argue that this can be formulated as active inference.

Active Inference (AI) is a "first principles" approach to understanding sentient behaviour—perception, planning and action in terms of probabilistic inference—framed as a single imperative to minimise free energy (Esteves et al., 2022; Parr et al., 2022). AI enables an organism or an agent to adjust to its environment to fit its expectations and therefore construct its niche (Bruineberg et al., 2018; Constant et al., 2018; Esteves et al., 2022). In particular, agents build shared expectations through engagement with everyday social and material affordances, allowing adaptive niche construction by, for example, thinking through other minds (Laland et al., 2001; Boyd et al., 2011; Veissière et al., 2020; Esteves et al., 2022). Taken together, AI reflects the natural inclination of all living organisms to regulate themselves – within their environment – by optimising their internal world model in a series of self-fulfilling action-perception cycles. Subsequently, it will minimise "surprise" by becoming in tune with others (Bruineberg et al., 2018; Constant et al., 2018; Vasil et al., 2020). Surprise, in this context, can be read as a prediction error or, mathematically, the implausibility (i.e., negative log-likelihood) of some sensory outcome, given a world model or narrative that would predict that outcome.

The NVIM can also explain an individual's ability to adjust to their context-specific niche as it proposes the flexibility to adapt to an external environment is dependent on weighting attributed to each prior as well as the hierarchical model proposed for vagal control and corresponding attractor basins within the CAN (Smith et al., 2017). Each layer of the neurovisceral integration loop transfers prediction errors from lower to higher sensory levels, which could involve the overall state-space of the CAN, which is partly vagally mediated (Thayer et al., 2009; Park and Thayer, 2014). Through AI, the hierarchical nature-space of the CAN allows for the effective minimisation and adjustment of prediction errors through attention to determine which level and output of the CAN is appropriate for regulating both visceral and skeletal motor physiology (Thayer and Lane, 2000; Smith et al., 2017).

Active inference has been applied to therapeutic practices as a model to explain symptomatic presentations of predicted sensory information compared to current sensory stimulus, with persistent pain being a overestimate of prior beliefs compared to current and often less noxious sensory stimulus, also called a failure of inference (Henningsen et al., 2018; Pezzulo et al., 2019; Bohlen et al., 2021). Inappropriate estimation of low precision for maladaptive beliefs could be due to higher CAN levels for the specific prior, inappropriately lower precision with higher weighting at lower hierarchical levels (Hechler et al., 2016; Smith et al., 2017; McParlin et al., 2022). Moreover, difficulty in updating maladaptive embedded priors and prediction errors is also found with sustained autonomic response reflected in the creation of more set points across the hierarchical levels of the CAN, with individuals getting "stuck" in the maladaptive attractor basin.

Active inference has also been applied to TA, patient-centred care and biobehavioural synchrony in combination with touch as a sensory stimulus to intentionally share, update and generate new prediction errors in an attempt to reduce symptoms, restore allostasis, self-regulation and agency (Bohlen et al., 2021; Esteves et al., 2022; McParlin et al., 2022). Cooperative communication is the intentional interaction between individuals to align their mental states (Tomasello, 2019). Therefore, gathering evidence to endorse an individual's beliefs by synchronising their mental states with another's mental states in a shared situation strengthens the ability for cooperative communications and an

effective TA (Vasil et al., 2020). Arguably, therapeutic touch can be an efficient way to achieve attunement and collaborative interpersonal relationships and biobehavioural synchrony and alignment with others (Csibra, 2010; McParlin et al., 2022).

We propose that therapeutic touch in MSK care can help develop and enhance cooperative communications and strengthen the TA between the patient and the HCP, while restoring homoeostasis and allostatic balance to resolve the patient's clinical problem. A predictable and positive relationship between the HCP and a positive TA is considered more influential than individual attachment preferences, including any pre-existing anxieties when developing a new relationship with another individual (Taylor et al., 2015). In clinical practice, collaborative interpersonal relationships also contribute to patient control and self-efficacy by encouraging active participation and adherence to exercises (Babatunde et al., 2017; Kinney et al., 2018). Therefore, touch could help develop a successful collaborative and therapeutic relationship contributing to the good clinical benefits of a positive TA (Miciak et al., 2019). The remaining sections unpack the clinical application of touch in MSK care, through the lens of active inference.

PERSON-CENTRED APPROACH: RECOGNISING PRIORS

A person-centred approach to treatment is crucial for achieving shared attention and cooperative communication, producing positive outcomes in managing MSK conditions (Shannon and Hillsdon, 2007; Kim and Park, 2017; Hutting et al., 2022). Person-centred care is structured around the individual's specific needs and preferences, enabling confidence-building and the development of a robust TA, particularly in rheumatoid conditions and chronic LBP (Haugli et al., 2004; Lærum et al., 2006; Reynolds, 2009; Barbari et al., 2020). Person-centred occurs when, for example, an HCP adapts a standard rehabilitation protocol to make it more time-efficient or acknowledges that a single mother or individual with financial constraints may not complete the protocol in its entirety (Miciak et al., 2019). On this point, patients with LBP and other MSK conditions express appreciation and a stronger bond with their HCP when personal adjustments are made (Del Baño-Aledo et al., 2014; GMC, 2020). A person-centred approach underpinned by a robust TA provides opportunities for discussing personal beliefs and fears. Moreover, it improves adherence to treatment advice and rehabilitation in patients with LBP, shoulder, and hip osteoarthritis (Lequerica et al., 2009; Hall et al., 2010; Cheung and Soundy, 2021).

Bayesian beliefs are the – sub-personal war propositional – dispositions and narratives that guide a person's choices and behaviour, based on their prior experiences and cultural legacy. Bayesian beliefs are important adaptive priors to consider in the context of patient care: they are evolutionary, subpersonal, socially and culturally inherited (Badcock et al., 2019a,b). These priors will have been developed over time to create more adaptive and veridical predictions of outcomes in the lived, prosocial world (Ramstead et al., 2018; Badcock et al., 2019a). It has been suggested that empirical assumptions of Bayesian beliefs with personal priors and sensory input [$s = g(\eta,a) + \omega$], including touch accounting for an individual's internal states (μ) and affecting how an individual chooses to interact with their external world (Ramstead et al., 2018; Badcock et al., 2019a). The external world can be empirically quantified through equations of motion [$\eta = f(\eta,a) + \omega$], specifying the hidden dynamics of the world accounting for random fluctuations (ω) of internal and external states synergistically attempting to minimise free energy. Free energy is the probability of hidden environmental causes [$q(\eta{:}\mu)$] and sensory inputs determined by the individual's internal states ($F = Energy\text{-}entropy$). Free energy can be minimised by increasing the accuracy of sensory data, i.e., picking more reliable data based on priors ($F = complexity–Accuracy$) or synchronising with more experienced individuals, i.e., HCP allowing the variation of free energy to impose tighter bonds reducing surprise from sensory or physiological states ($F = divergence + surprise$).

We use Bayesian belief to denote a specific viewpoint or expectation encoded by neural representations in higher cortical regions that send predictions to hierarchically lower levels (Friston and Frith, 2015; Vasil et al., 2020). These descending predictions can then be compared with expectations at lower levels to form a prediction error. Subsequently, the prediction error is then passed back to high levels to revise Bayesian beliefs – and thereby instantiate a process of Bayesian belief updating that enables the patient to, literally, make sense of their world. These priors regulate and influence information processing within treatment sessions and contextualise any approach any treatment issues (Hasson et al., 2015). HCPs must understand their patients' perspectives, goals, and priors by mentalising higher-order cognitive processes. This facilitates a common ground – or shared narrative – and a beneficial clinical outcome (Frith and Frith, 2006; Miciak et al., 2019). Therefore, the development of a robust TA is dependent on the HCP's ability to identify, accept and acknowledge an individual's unique priors, context, and expectations. Consequently, HCP can gain trust and therefore develop a personalised patient-centred treatment.

Recognising priors is particularly crucial in chronic pain due to its complexity and multifactorial nature when compared with acute pain. In the context of chronic LBP, social factors are as significant as physical factors in the patients' pain experience (Hill and Fritz, 2011; Louw and Puentedura, 2013). To this end, patients with chronic non-malignant pain and other MSK disorders consider being listened to, believed and viewed more than just their symptoms or condition to be crucial to their quality of care (Bordin, 1979; Lærum et al., 2006; Clark, 2013; Wilson et al., 2017; Søndenå et al., 2020). This genuine interest in the person beyond their clinical condition can put patients at ease, allowing them to relax and be more comfortable with their HCP (Miciak et al., 2018). Arguably, in the context of MSK care, an individual's preferences and responses to therapeutic touch are also modulated by the same factors that affect a therapeutic relationship, including cultural and social priors (Sorokowska et al., 2021). Therefore, a person-centred approach with the treatment specifically tailored to the individual is essential in all aspects of a clinical encounter.

Prior beliefs regarding pain and a range of MSK disorders are not always conducive to patient recovery (Rossettini and Testa, 2018). Levels of maladaptive (i.e., false) beliefs and accompanying attitudes are high among patients with

chronic LBP (Christe et al., 2021). These include catastrophising and fear avoidance, leading to higher levels of pain, disability and poorer clinical outcomes. One pernicious aspect of these "false" beliefs is that they preclude actively seeking evidence that would revise them (e.g., "I can't move because it would hurt"). These maladaptive beliefs are often linked to unaffectionate HCPs (Wertli et al., 2014a,b; Cheung and Soundy, 2021). Therefore, personalised, attentive care targetting and updating these beliefs are significant in aiding recovery (Main et al., 2010; Linton and Shaw, 2011).

APPLICATION OF ACTIVE INFERENCE TO TOUCH AND THERAPEUTIC ALLIANCE

In active inference, our choices and behaviour determine the sensory data we use to make inferences, including touch. This includes overt action such as "palpation" of the visual world through saccadic eye movements or touch, to covert action such as the deployment of attention, or precision to newsworthy sensory information (Seth and Friston, 2016; Parr and Friston, 2017; Parr et al., 2018; Sterzer et al., 2018; Smith et al., 2019; Limanowski et al., 2020). In AI's predictive processing (i.e., predictive coding) formulations, the newsworthy information corresponds to prediction errors, namely, the difference between our predictions based on our prior beliefs and what we actually sensed. These prediction errors update beliefs when and only when they are considered dependable or precise (Kok et al., 2012; Brown et al., 2013; Veissière et al., 2019; Limanowski et al., 2020). However, it is essential to note that the reliability or precision given to prediction errors can be irrational and maladaptive, particularly in persistent pain sufferers.

Physiologically, this corresponds to increasing the synaptic gain of various neuronal populations encoding prediction errors (Vossel et al., 2014; Auksztulewicz and Friston, 2015). Psychologically, this can be thought of as sensory attenuation or selective attention, depending upon whether the precision is inferred to be high or low (Feldman and Friston, 2010; Adams et al., 2013; Moran et al., 2013; Limanowski, 2017). In short, "precision" describes the reliability or "trustworthiness" afforded prediction errors. The consequent precision weighting of prediction errors may depend upon epistemic trust and a mutual narrative (Fonagy and Allison, 2014). This also implicates the building of trust essential to a robust TA.

In addition to increasing the precision via selective attention, the attenuation of certain prediction errors (via reducing their precision) is necessary to ignore certain sensations. Sensory attenuation is crucial in this context because sensory attenuation is necessary to act upon the world. In other words, to execute a predicted or intended movement, it is essential to ignore sensory evidence that the movement has not yet been initiated. Anecdotally, sensory attenuation may explain why "rubbing one's neck" attenuates nociceptive signals that would otherwise be explained by the prior belief or experience "I have a neck pain." This maladaptive overestimate in the weighting of sensory information is commonly found in chronic pain patients whose overly precise prior beliefs predict their pain symptoms before the noxious sensory information actually occurs (Hechler et al., 2016; Van den Bergh et al., 2017; Kube et al., 2020). Furthermore, alternating augmentation and attenuation of sensory precision may be crucial in dyadic interactions, in the sense that it underwrites "turn taking" in communication (i.e., Wilson and Wilson, 2005; Ghazanfar and Takahashi, 2014; Friston and Frith, 2015). In other words, listening and speaking when establishing a shared narrative requires a reciprocal attenuation and augmentation of the shared sensory modality, commonly found in therapeutic touch and MSK care.

Therapeutic touch with a solid affective component may be a particularly potent interoceptive modality for this kind of communication, allowing the updating of priors at two levels. Firstly, it establishes a sensory modality of exchange, which provides sensory evidence that "you are like me." This is a crucial inference that enables the use of the same (shared) narrative to finesse predictions of "self" and "other." The notion of a shared narrative or generative model of interpersonal exchange may be an essential aspect of the TA, especially regarding the agreement on goals and treatment plans. Secondly, the particular effect of therapeutic touch may draw attention (i.e., precision) to the sensory levels of hierarchical inference, thereby reducing the relative precision or commitment to higher-level prior beliefs. A reduction or relaxation of the precision and reliance of prior beliefs is generally thought to be a fundamental prerequisite for belief updating in a therapeutic setting (please see Ainley et al., 2012, 2016; Duquette, 2017, 2020; Carhart-Harris and Friston, 2019) for treatments of precision and interception in psychotherapy.

Moreover, many aspects of psychotherapy have played a role in the research and practice of manual therapies, particularly in the care of patients with chronic LBP and other MSK disorders (McCabe et al., 2021a; Hutting et al., 2022). In short, synchronous exchange between individuals enables more accurate inference of the partner's subsequent actions and coordinates joint attention and implicit precision weighting. Through the hierarchically organised model it helps to facilitate belief updating under a shared narrative through equal collaboration and (mutual) epistemic trust that may underwrite the TA, creating symmetrical coupling and synchronisation (Moran et al., 2013; Fonagy and Allison, 2014; Hasson and Frith, 2016). In other words, it assists HCPs in navigating and implementing the most effective communication strategies while minimising prediction errors and uncertainty necessary to establish an optimal therapeutic alliance and maintain homoeostasis which can be done through therapeutic touch and resulting in biobehavioural synchrony with the other individual (Duquette, 2017, 2020; Carhart-Harris and Friston, 2019).

BIOBEHAVIOURAL SYNCHRONY INITIATED THROUGH TOUCH

Touch can often provide the sensory evidence to help conclude that "you are like me" through stimulating biobehavioural synchrony in which different individuals harmonise their

biological and behavioural processes during social interaction (Feldman, 2012, 2017; Koole and Tschacher, 2016; Tschacher et al., 2017). Therapeutic touch during a massage in healthy individuals affects the modulation of psychological and neuroendocrine function through the stimulation of mechanical receptors, which share the same innervation as vagal afferent fibres, which are subsequently involved in the regulation of the autonomic nervous system, thus causing decreased heart rate, blood pressure and stress (Diego and Field, 2009). The processes involve coupling physiological and behavioural processes across the four systems of matching non-verbal behaviour, coupling heart rhythms, respiratory, autonomics, brain to brain synchrony, motor movements, and coordinated oxytocin, dopamine, and cortisol (Feldman, 2017; Goldstein et al., 2017).

Biobehavioural synchrony can be evident immediately with therapeutic touch by increased heart rate variability, decreased anxiety, anger and pain in patients with chronic tension-type headaches (Toro-Velasco et al., 2009). Hands-on techniques can also influence the autonomic nervous system and cause bidirectional release of neurotransmitters such as oxytocin between the HCP and the patient (Uvnäs-Moberg, 2004; Cerritelli et al., 2020a). This supports the argument that therapeutic touch can help in the embodied transfer of an individual's parasympathetic regulation to another (Van Puyvelde et al., 2019). The exact mechanism behind biobehavioural synchrony varies depending on the type of bond; for example, patient-practitioner synchrony would be different from a romantic partnership. The threat level also plays a role with higher synchronisation of their actions and posture even if they are not aware of it in situations of stress or threat, i.e., a painful MSK injury (Goldstein et al., 2017). The release of oxytocin is dependent on the level of attachment which determines the coupling of oxytocin and dopamine before being combined in the subcortical to cortical networks involved in reward, embodiment and mentalisation (Feldman, 2017). Consequently, when consolidating interpersonal relationships and achieving biobehavioural synchrony in social situations, synchronous activation of the temporoparietal regions and heart rate is considered a key component to achieving brain to brain alpha coupling (Shamay-Tsoory et al., 2019). The synchrony is often visible within a therapeutic relationship in the clinician's temporoparietal, prefrontal, and AIC activation, indicating social cognition and mirroring with the patients' dyads (Ellingsen et al., 2020). The right prefrontal cortex becomes activated when one individual is perceived as the leader, inhibiting another individual's self-representation (Fairhurst et al., 2014a,b).

DEVELOPING AND UPDATING PRIORS THROUGH TOUCH

Socio-affective touch can adjust the relative importance and response of noxious stimulus in the AIC and cingulate cortices (Krahé et al., 2013; Von Mohr et al., 2018). Touch can create bio-feedback loops that help develop and learn to develop new or update less precise priors by altering the setpoint in crucial survival demands. Touch can create bio-feedback loops that help develop and learn to develop new or update less precise priors by altering the setpoint in crucial survival demands (Rossettini et al., 2022). This viewpoint was initially proposed by Sterling and Eyer (1988) and has been expanding to include the integration of active inference to interception, regulation of homoeostasis and allostasis, all based on recent advances in anatomical knowledge, empirical models, and computational neuroscience (Stephan et al., 2016; Fotopoulou et al., 2022). When developing a prior, brain regions such as the AIC, Anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and subgenual cortex (SGC) will generate allostatic predictions to embody a generative model of the current input (Pezzulo et al., 2015; Corcoran et al., 2020; Tschantz et al., 2022). We would argue that one can include therapeutic touch in predicting the bodies currently and future state. These brain regions will receive prediction errors about interception from the posterior and mid insula. Other allostatic top-down predictions enable them to modulate the current homoeostatic beliefs found in the subcortical regions fulfilled by reflex arcs in areas such as the hypothalamus and brainstem (Stephan et al., 2016; Fotopoulou et al., 2022).

The descending projections from the AIC, ACC, OFC, and SGC could relay the individuals top-down predictions to the posterior and mid insular cortex to compare them with bottom-up sensory afferents to form the prediction errors necessary for precise allostatic responses to the current situation. A clinical example of unpredicted sensory stimulation – incorporating therapeutic touch – is through guided exercises or passive movements. The HCP will help the patient complete a series of movements they may previously find painful or were too nervous about doing independently. Moreover, it allows the patient to observe and gain tactile sensory information, actively. They can do the movement, even if the HCP is physically doing the action for them, such as a passive joint examination. All areas mentioned above connect to the granular layer IV of the primary interoceptive insular cortex allowing the integrative modulation of homoeostatic beliefs (Sterling and Eyer, 1988; Fotopoulou et al., 2022). These assumptions are sustained and expanded upon from the recognised anatomical and hierarchical structure of laminar patterns in Macaque monkeys (Li et al., 2017). Neuroimaging studies have discovered projections between the AIC, ACC, OFC, and SGC regions during the activation of CT fibres suggesting further interconnectivity (McGlone et al., 2012; López-Solà et al., 2019; Shamay-Tsoory and Eisenberger, 2021).

Ascending prediction errors target the frontoparietal network, thereby revising descending self-efficacy automatic sensory predictions to help update future allostatic predictions. This process creates a better generative model of the "self" that is increasingly precise and aligned within the current situation, potentially de-threatening the noxious stimuli (Fotopoulou and Tsakiris, 2017; Owens et al., 2018). In essence, the HCP introduces a "surprise" to the system through the tactile sensory stimulus, which is part of the hands-on techniques. This "surprise" enables a functional belief updating that revises prior beliefs that underwrite the patients "illness." Subsequently, this enables the patient to increase the weighting of interoceptive prediction errors about the current state of the "self" ascending to

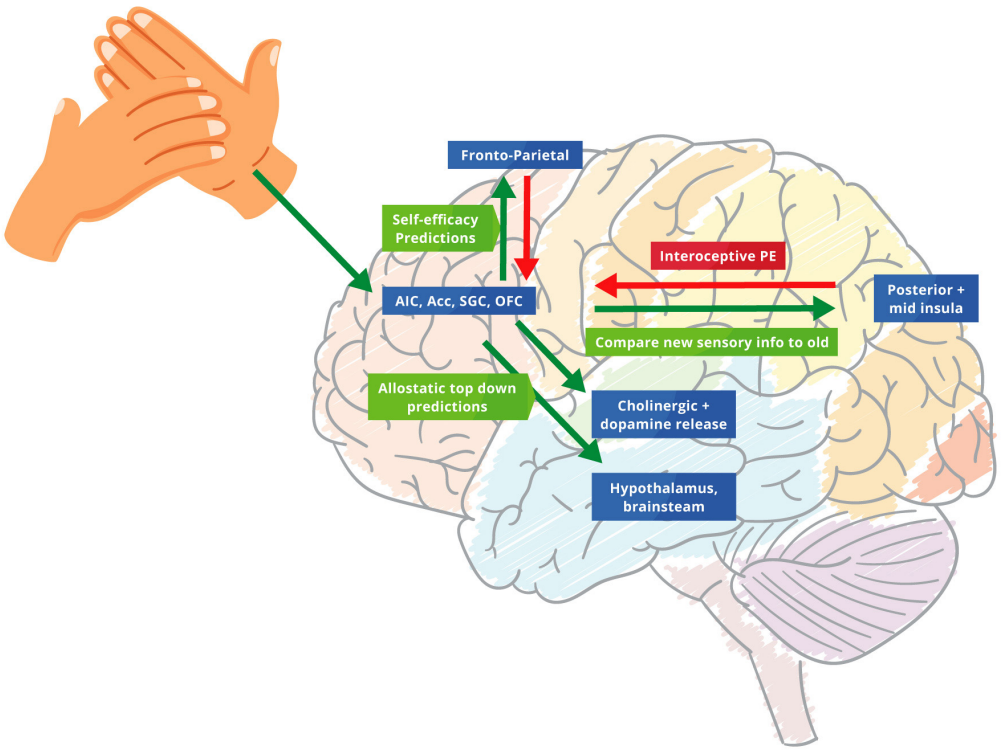

FIGURE 1 | The biofeedback loop of therapeutic touch. Green arrows: predictions errors; Red arrows: predictions. Touch biofeedback loop adapted from Sterling and Eyer (1988) and Fotopoulou et al. (2022) to help modify and adjust the importance of priors through new allostatic predictions from therapeutic touch. We suggest that the AIC, ACC, SGC, and OFC create allostatic therapeutic touch predictions that underwrite interceptive prediction errors in the posterior and mid insula. These predictions modulate homoeostatic beliefs in the hypothalamus and brainstem. Descending projections from the AIC, ACC, OFC, and SGC replay top-down predictions to the mid and posterior insula to protect the new bottom-up stimulus of therapeutic touch. The ensuing prediction errors are then sent to the frontoparietal network that revises prior beliefs and future allostatic predictions, identifying more precise and newsworthy prediction errors for this specific situation for the future.

higher hierarchical levels (Hechler et al., 2016). Moreover, this process helps predict the right level of precision to be deployed in certain situations. This process of predicting precision appears to be mediated by cholinergic, dopamine and other neuromodulators – to optimise attentional set (Atzil et al., 2018; Cox and Witten, 2019; Crucianelli et al., 2019; Nguyen et al., 2021). This contextualisation of predictive processing rests on top-down predictions occurring before the consequences of touching or being touched (Friston et al., 2015; **Figure 1**).

THE EFFECT OF TOUCH IN THE MANAGEMENT OF CHRONIC MUSCULOSKELETAL PAIN

There is substantial evidence showing that the expectation and prediction of severe pain alone in chronic MSK pain can increase the pain felt and cause symptoms before the trigger occurs (Rossettini et al., 2018). This is observed in patients with fibromyalgia and arthritis who often predict the source or trigger to their increase in symptoms, falsely interpreting a non-noxious stimulus as painful, in order to fulfil their belief of recurrent, persistent pain (Vlaeyen and Linton, 2000; Brown et al., 2013; Henningsen et al., 2018). In these instances, it can be argued that therapeutic touch can help re-establish their misinterpreted bodily sensations or develop new explanations for their symptoms (Xu et al., 2014; Barrett and Simmons, 2015). In the absence of such therapeutic interventions, pain sufferers can have a persistent and self-fulfilling "failure of inference" (Tracey, 2010; Di Lernia et al., 2016; Hechler et al., 2016). Subsequently, persistent pain patients may be cognitively immunised to updating or changing their priors, so that they discount the interactions with the HCP and anticipate that the clinical encounter will be irrelevant; thereby reaffirming their maladaptive priors, even before they present for treatment. This can lead to the HCP being regarded as an imprecise source of sensory information, and their sensory input and stimulation are dismissed (Fonagy and Allison, 2014).

The tactile and proprioceptive stimulation from handsoncare conveys interoceptive and affective information that adjusts the processing of sensory information that undergirds symptoms (McGlone et al., 2014; D'Alessandro et al., 2016; Quadt et al., 2018; Bohlen et al., 2021) (see **Figure 2**). Cerritelli et al. (2020b) endorse this view by finding that osteopathic treatment increases the interoceptive accuracy of patients with chronic LBP – with accompanying decreases in the blood oxygenation

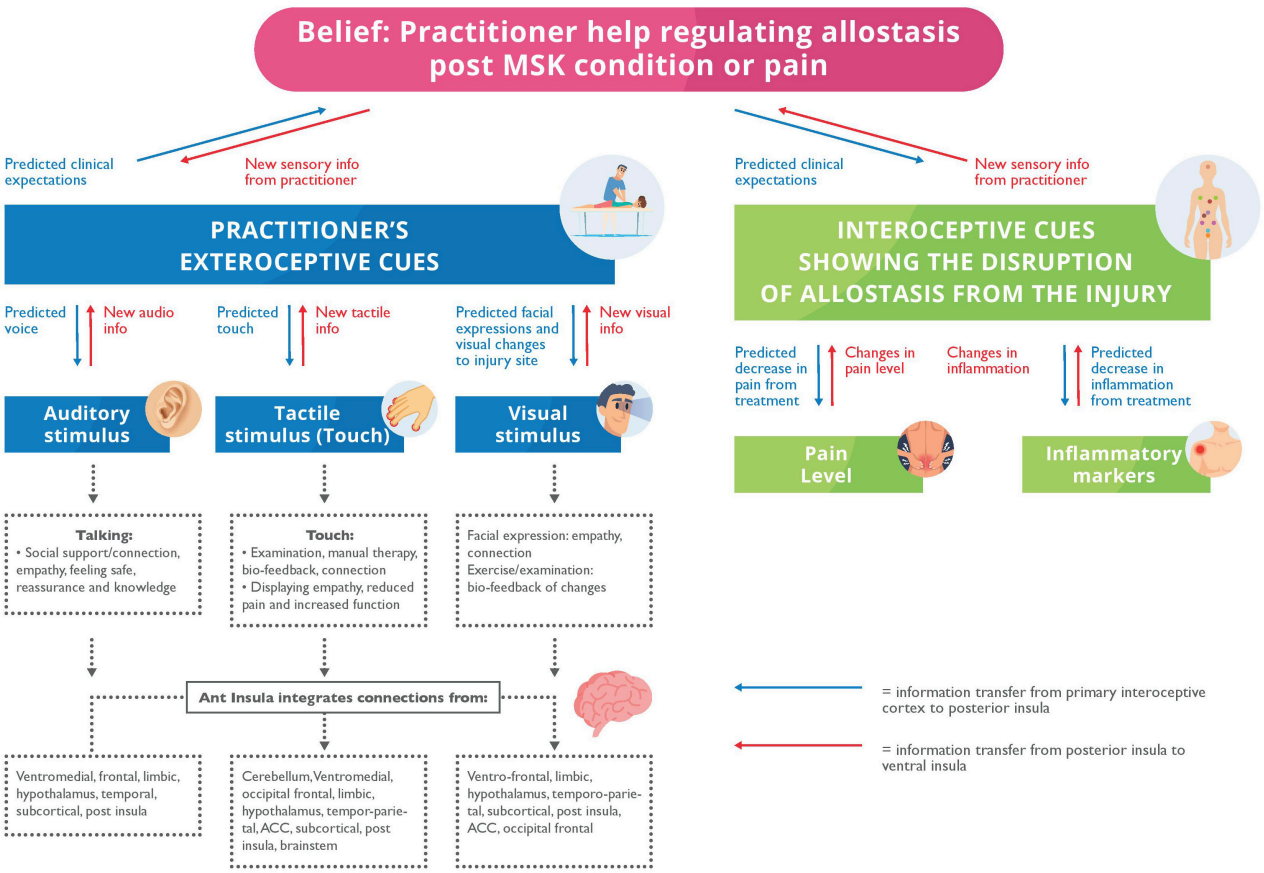

FIGURE 2 | A mode to describe the allostatic regulation by a Health Care Provider (HCP). Blue arrows: The predicted expectations and priors transferring information from the primary interoceptive cortex to posterior insula. Red arrows: New sensory information from the posterior insula to the ventral insular. Exteroceptive: We propose that the patient has predicted expectations for the clinical appointment and predictions about the HCP's stimuli. We offer putative multisensory mechanisms, i.e., auditory, touch and visual – for allostatic regulation from the HCP. They help display support, empathy, reassurance, and improved clinical function; all are originating from the anterior insula. The anterior insula integrates this multisensory input for allostatic regulation from the cerebellum, ventromedial, limbic, temporoparietal, subcortical, posterior insular, occipital frontal, temporal cortices, anterior cingulate cortex, hypothalamus, and brainstem. Interoceptive: The patient will predict or expect clinical expectations of interoception because of treatment including reduced pain and inflammation which we propose originate from new tactile and proprioception (i.e., haptic) stimulation from the HCP.

level dependant (BOLD) levels in the bilateral insula, ACC, left striatum and right middle frontal gyrus; brain regions implicated in interception. This suggests that the brain becomes sensitised to touch as a precise and newsworthy sensory modality (Scalabrini et al., 2019). Additionally, this modification in body perception, awareness of pain levels, and location through touch is specific to patients – with conditions like LBP – who cannot visualise the source of symptoms and may therefore imagine the symptomatic area being more extensive than it is (Nishigami et al., 2015; Puentedura and Flynn, 2016).

Therapeutic touch – supported appropriate and non-nocebic language – can create new interoceptive biofeedback loops to promote reassurance, communication, and joint attention over the injury: for example, by commenting, "This muscle feels tense, or the joint is stiff. Do you agree?" or showing that pressing the injury while painful is not making the injury worse (Rossettini et al., 2018). By physically exploring the area, it will provide insight and a link to the "internal situation" beneath (Harman et al., 2011). Arguably, the body is the physical manifestation of our hidden thoughts or world, and HCPs can uncover hidden beliefs through physical examination (Thornquist, 2001). In short, changing the patient's prior beliefs that she is a patient with "chronic pain" into a belief that she is "recovering from a chronic pain condition" enables the patient to ignore and reinterpret interoceptive signals, emulating the attenuation of sensory (interoceptive) precision (Hoskin et al., 2019; Gerrans, 2020; Seymour and Mancini, 2020). Nonetheless, it is more difficult to form new priors if entrenched through self-reference (Siu and Humphreys, 2015). Despite the HCP's best intentions, it is possible that over-precise priors will cause a lack of attention – and therefore effectiveness – to hands-on care and interventions of the HCP.

Crucially, not only should the HCP consider the patient's priors, but they must be aware of their own priors that may influence and modulate interpersonal behaviour (Horton et al., 2021). If the HCP is aligned with their patients,

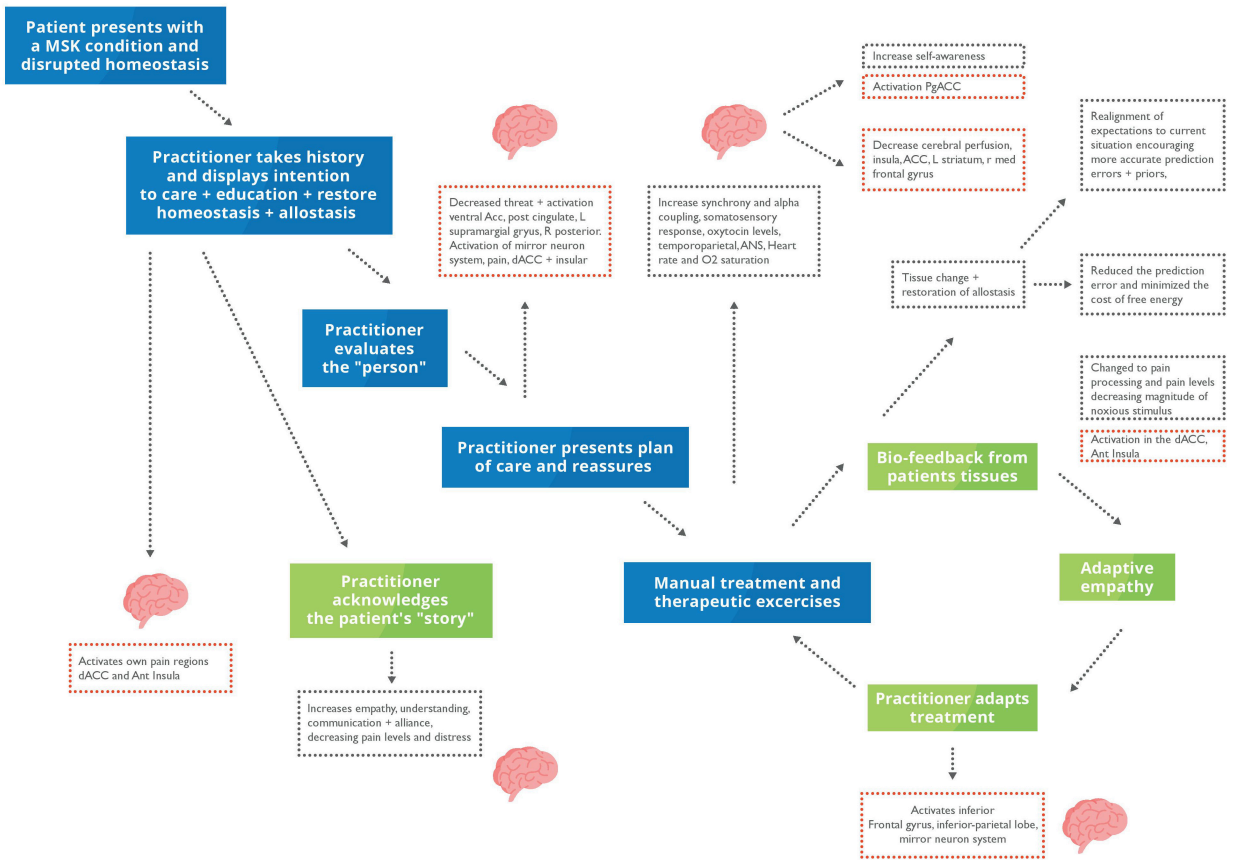

FIGURE 3 | Putative model homoeostatic regulation in musculoskeletal (MSK) care during a clinical encounter. Blue box, clinical presentation and practitioner's actions; Green box, interoceptive metacognitions; Red dotted box, changes in brain activity; Black dotted box, changes to interoception and mental states. The patient will present with disrupted homoeostasis because of their clinical condition. During a clinical encounter, the HCP will take a case history, examine their patient, and discuss their condition and care plan. The HCP will reassure, educate, understand, acknowledge, and empathise with their patient. We propose that hands-on care which is underpinned by a robust therapeutic alliance and communication can putatively restore homoeostasis through increasing biobehavioural synchrony and active inference – thus updating the patient's generative model.

some disclosure of the HCP's past can frequently deepen the connection and help the patient feel that they are just like them (Meltzoff, 2007; Miciak et al., 2019). While not all HCPs are comfortable with this, revealing some of their inner personal experiences can help increase the TA, trust, and bond between patient and HCP, thereby increasing the common ground and synchrony. In patients with MSK disorders, if the HCP is more open, approachable and expresses themselves more freely and personally, it can help patients to freely express their feelings, increasing trust, which can extend to taking more of a leap of faith with their physical symptoms and injuries (Miciak et al., 2018).

JOINT ACTION-PERCEPTION CYCLES WITHIN TREATMENT

The TA principles revolve around an agreement between patient and HCP on the treatment plan and goals of the patient, which is particularly important for managing many MSK conditions, including LBP. With a closer bond, the patient may perceive others to be more similar and isomorphic with themselves, than an inanimate replica (Scalabrini et al., 2019). This increase in synchrony may also contribute to teamwork and interpersonal collaboration in manual therapy, which is developed through collaboratively agreeing on a set goal (Miciak et al., 2019; Brun-Cottan et al., 2020) (See **Figure 3** for the application to MSK clinical encounters). AI and cooperative communication both suggest that the alignment of mental states with another helps to minimise supplies and resolve uncertainty (Constant et al., 2019; Tomasello, 2019). Similarly, the Social Baseline Theory suggests that humans are built to be social and work with familiar individuals in uncertain situations or when approaching problems (Coan and Maresh, 2014; Beckes and Sbarra, 2022).

Individuals generate and modify their own feedback loops to achieve the end goal of aligning their mental states with others (Friston and Frith, 2015). Universally, this involves action and perception loops that reliably connect the two distinct policies until they become entwined and produce a shared narrative (Friston and Frith, 2015). Social collaboration to achieve and maintain allostatic needs helps decrease the risk of death and

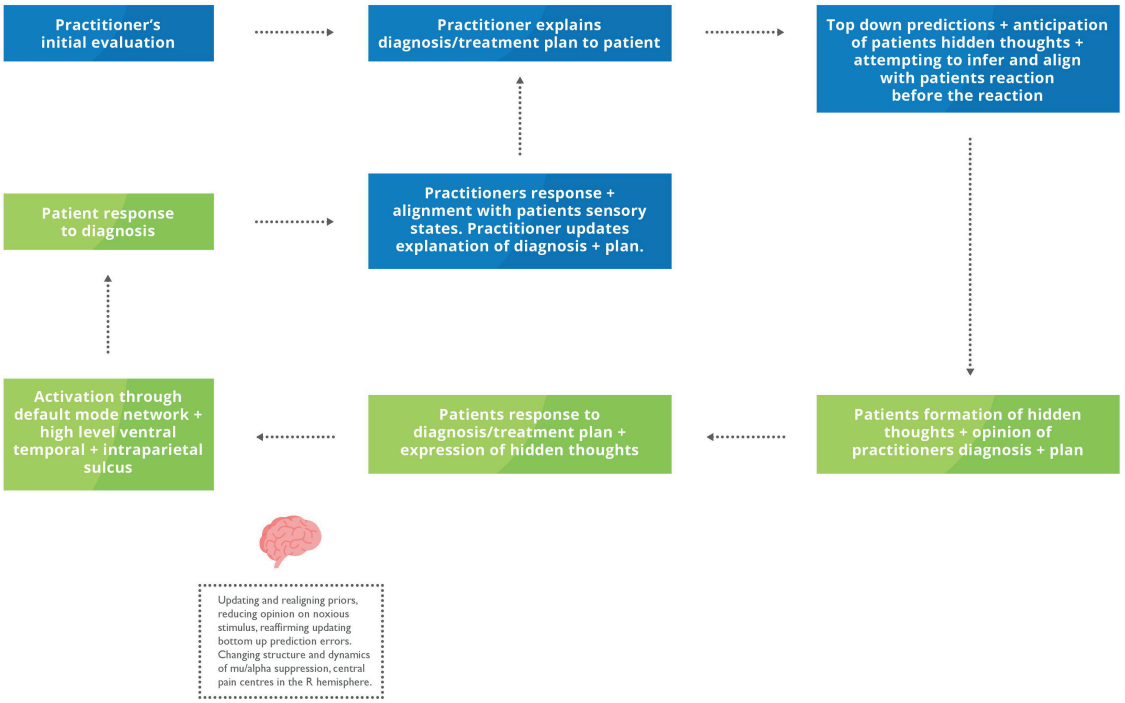

FIGURE 4 | Proposed feedback loop during an explanation of the problem and plan of care. Blue box, HCP inner mental states and actions; Green box, Patient internal mental states and actions. The HCP conducts an initial examination, often using verbal and non-verbal communication – including touch to reach a summary of their evaluation and plan of care. As the practitioner communicates the outline of their assessment, they will start to mentalise their patient's reactions and hidden throughs. The patient may begin developing hidden thoughts regarding their diagnosis before verbalising them. Based on their patient's responses, the HCP may modify their previous explanation to achieve a more robust and collaborative description considering the patient's reactions.

injury due to the shared goal, trust, and familiarity between the groups' individuals (Vasil et al., 2020). Touch is often considered a standard modality to achieve this through socio-affective regulation involving cognitive, metacognitive process and embodiment (Roberts and Bucksey, 2007; Aureli and Presaghi, 2010; Coan and Maresh, 2014; Fotopoulou et al., 2022). Examples of the socio-affective regulation include positive changes in immunity, inflammation, and neuroendocrine function by decreasing stress, allostatic load and subsequently effort to maintain homoeostasis in critically ill or multifactorial conditions such as chronic pain that have all been achieved through touch (Papathanassoglou and Mpouzika, 2012; Coan and Maresh, 2014; Morrison, 2016a; Kerr et al., 2019). The clinical appointment is one example of a coupled action-perception cycle and social collaboration; both in the agreement of the diagnosis and within the hands-on therapeutic intervention. That patient will present with pain or abnormal physiology, resulting in an allostatic overload and seeking help from the HCP to re-establish her allostatic balance (McEwen and Wingfield, 2003; Beckes and Coan, 2011; Miciak et al., 2019; Guidi et al., 2021; Vasil et al., 2020) (see **Figure 4**).

With explanation of the diagnosis – and with the use of therapeutic touch – the HCP can establish mutual synchrony by continuously inferring the patient's reaction, pain and symptoms and adjusting their explanation or touch to align with the patient's sensory states. For example, if the HCP infers the tactile pressure is excessive compared to the patient's pain or physiological response, they will adjust their predictions and decrease the pressure and its subsequent effects and vice versa if not strong enough. Additionally, it has been shown that different massage strengths, light vs. moderate, have slightly different effects, with moderate massage increasing parasympathetic and light increasing the sympathetic nervous system (Lindgren et al., 2010). The HCP will continue to constantly adjust their touch until they are satisfied with the change in tactile feedback from the technique, i.e., increased movement in the joint space of exchange and restoring the patient's homoeostasis. Restoring homoeostasis and hopefully decreasing the symptoms can be considered a reduction in the prediction error (a.k.a., free energy) to regulate allostasis (Peters et al., 2017; Atzil et al., 2018; Koban et al., 2019; Nguyen et al., 2021). This particular coupled action-perception cycle is regarded as the touch feedback loop (Shamay-Tsoory and Eisenberger, 2021).

THE ROLE OF TOUCH IN DEVELOPING A CONNECTION

At the centre of the TA is the harmonious relationship between the patient and the HCP in which the patient can trust, communicate, and have a mutual understanding of their goals and purpose, which patients with MSK disorders see as crucial to

their treatment (Pinto et al., 2012; O'Keeffe et al., 2016; Miciak et al., 2019). Moreover, creating a collaborative relationship where the HCP and patient are seen as equals enables successful treatment outcomes, allowing HCPs to establish a meaningful connection (Miciak et al., 2018).

Therapeutic touch and hands-on techniques in MSK care help build an interpersonal connection by using the body as a pivot point (Miciak et al., 2018). An HCP's role is to encourage the patient to reconnect to their body often through therapeutic touch to empathise how the body reacts and feels in response to the tactile stimulus from the HCP, essential to rehabilitation (Miciak et al., 2018; Geri et al., 2019). In patients with chronic LBP, the increased knowledge and awareness of their body will reaffirm the connection with the HCP as they feel their HCP understands their symptoms (Harman et al., 2011; Krueger, 2015, p. 263). This phenomenon encourages them to take ownership of their treatment plan (Miciak et al., 2018). Even the most rudimentary form of touch, such as, for example, a half-second of physical hand contact from a librarian, can increase positive perceptions of the library; similar acts have also helped establish the foundation for trust, compliance, cooperative and prosocial communication (Fisher et al., 1976; Morrison et al., 2010).

Touch is the most intuitive mode of expressing and detecting another's emotional and mental states and sensory and communicative intentions, providing the context and clarity to ambiguous interactions (Hertenstein et al., 2006; McParlin et al., 2022). The different modes and manipulations of touch enable individuals to accurately infer at least six different emotions, including love, fear, and anger, with 48–83% accuracy (Herteinstein et al., 2006). As individuals become more precise at inferring another's emotional and mental states, they also become better at establishing crucial elements of the TA such as common ground, trust and synchrony. Additionally, accurately inferring another's hidden thoughts can simulate reward pathways as the individual minimises prediction errors, thereby increasing the enjoyment of the task (Beckes and Coan, 2011; Pan et al., 2017; Goldstein et al., 2018).

Health Care providers are in a unique position: it is often considered central and expected to clinically examine and therefore touch a wide area of the body, including the head and neck, generally reserved for more intimate or significant relationships (Geri et al., 2019). Additionally, it helps in the accuracy of HCP to infer the other individual's emotions, detected through touch (Hertenstein et al., 2009; Geri et al., 2019).

Suvilehto et al. (2015) showed a correlation in the areas individuals will allow others to touch and the strength of the relationship. Therefore, HCPs who can touch more sensitive areas within their ethical boundaries are afforded a higher baseline level of trust and a greater opportunity to develop social bonds to build a stronger alliance and the overall analgesic effect. Therapeutic touch, when examining and validating their clinical condition, can frequently alleviate the patient's anxiety and increase emotional support, empathy, mentalisation and be rewarding for all individuals (Gentsch et al., 2015). Additionally, it helps in emotional and communication regulation, as reflected in activating the right AIC, inferior parietal lobe and prefrontal cortex (Etkin et al., 2015; Goldstein et al., 2018; Redcay and Schilbach, 2019). It is the activation of the inferior parietal lobe that has been suggested to contribute to a significant role in the ability to infer another's intentions and thoughts through observations, which may allow us to modulate and reduce the threat of noxious stimulus creating an analgesic effect (Kilner et al., 2007; Krahé et al., 2013; Von Mohr et al., 2018). Clinically, this has been shown in patients with acute postoperative pain, who reported decreased pain and anxiety after receiving massage therapy daily during their 5-day postoperative period (Mitchinson et al., 2007). Reduced anxiety associated with the dysfunction may aid in updating the autonomic and bottom-up interoceptive prediction errors that impair metacognitive motor homoeostatic and allostatic systems, which dictate dysfunction. This adds to the growing body of evidence that a more effective, stronger TA can improve clinical outcomes and patient satisfaction in treating MSK pain patients with manual therapy (Hush et al., 2011).

Touch and Oxytocin

One of the most significant measures of bonding is the neurotransmitter oxytocin. It has been labelled as the social hormone as it enables the processing of social and non-social cues (Graustrella and MacLeod, 2012). Oxytocin also helps achieve biobehavioural synchrony and allostatic regulation and is released in therapeutic touch during hands-on techniques like massage (Uvnäs-Moberg, 2004). It has been argued that the somatosensory stimulations from touch-based therapies encourage anti-stress effects via the stimulating somatosensory pathways, subsequently activating the oxytocin system in the hypothalamus (Takahashi et al., 2021). Moreover, cervical spinal manipulations often used by HCPs in MSK care to treat acute non-specific mechanical neck pain have been shown to immediately affect neuromodulation, including oxytocin, potentially by modifying the neuropeptide expression (Lohman et al., 2019).

Moreover, multimodal sensory stimulation, including tactile touch, not only aid in the increase of cortical oxytocin levels but also helps with reduced social interaction, potentially increasing trust, and empathy essential for a successful TA (Green and Hollander, 2010; Yamasue et al., 2012; Zheng et al., 2014). Repeated stimulation of the CT afferents in the skin during affective touch increases the frequency and duration of the release of oxytocin receptors with tighter cross-links to dopamine and opioids; as well as regulating and increasing synchronisation within the autonomic nervous system (Löken et al., 2009; Ackerley et al., 2014; Pawling et al., 2017). Furthermore, a decrease in cortisol is observed when patients can recognise the repetition of similar techniques, exercises, appointment structure, and therapeutic touch with a familiar HCP (Uvnas-Moberg et al., 2015). Collectively, the evidence demonstrates that the repeated release of endogenous peptides, oxytocin, and opioids has therapeutic benefits, including analgesia, autonomic system regulation, and synchrony. Therefore, it can be argued that hands-on techniques still play a crucial role in MSK care.

Crucianelli et al. (2019) proposed that predictions of affective touch, could also be modulated by neuropeptides like oxytocin to optimise interoceptive attention. Therefore, oxytocin is likely

to play a central role in interoception by modulating the precision of sensory stimuli in social contexts. The oxytocin-interoceptive nexus includes the multisensory effects of touch – somatosensory, thermoregulation and cardiorespiratory – on homoeostatic control (Quintana and Guastella, 2020; Kirsch et al., 2021). Oxytocin neuromodulation has been proposed as an aetiological factor in the failure to develop coherent models of "self" and "[m]other" (Quattrocki and Friston, 2014). Moreover, it has been suggested that the role of oxytocin is best characterised through allostasis; as it can help facilitate the dynamic adjustment and consolidation of homoeostatic setpoints, and is crucial to many of life's essential survival needs (Quintana and Guastella, 2020). Therefore, the effective activation of the oxytocin system could help achieve positive physical and psychological clinical results through its ability to help patients adapt and encourage successful recovery (Takayanagi and Onaka, 2021). Additionally, oxytocin can help with analgesia due to its connection with decreased activity in the AIC in response to noxious stimuli, regulation of noxious threats, and increased activity in the prefrontal lobe (Kreuder et al., 2019). These findings are reflected in the use of therapeutic touch in MSK care, including in pregnant women with back and leg pain who experienced a reduction of pain and cortisol levels (Field, 2010; Mueller and Grunwald, 2021).

BEYOND THE HEALTH CARE PROVIDER-PATIENT DYAD: THE ROLE OF HIERARCHY IN TRIADIC SYNCHRONY IN THE CLINICAL ENCOUNTER

To develop a robust and successful TA, HCPs need to work as a team to develop a collaborative relationship. In many circumstances, clinical interactions in MSK care are often triadic, with interactions occurring between the HCP, next of kin and the patient, i.e., an elderly relative or patient needing a translator. The active inference model of precision and weighting can be applied to clinical triadic situations through shared clinical goals, coordinated hands-on techniques, and therapeutic touch commonly used in MSK care. There is an increase in the coupling between the mirror neuron and mentalising systems in the brain during triadic social interactions, including the temporoparietal junction and prefrontal context, which are also influenced by therapeutic touch, including osteopathic manipulative treatment (Trapp et al., 2014; Tamburella et al., 2019). Crucially, the temporoparietal and medial temporal lobes are also intrinsic to the manipulation, validation, and reinforcement of adapting prior memories to specific contexts (Hasson et al., 2015).

The coordinated, complementary, triadic interactions increase the activation and coupling of mirror neurons and the inferior parietal lobe, which are engaged when two people make physical contact or participate in co-operative communication (Trapp et al., 2014; Miller et al., 2019). The three individuals will eventually synchronise their actions as they become more familiar with each other's responses, increasing their communication intent. Therefore, triadic interactions activate both the mirror neuron and mentalisation systems, rather than the single activation of the mentalisation system observed in more direct interactions (Schilbach, 2010). The overlapping mapping of neural structures such as the pregenual anterior cingulate cortex, amygdala, and AIC, and the mentalisation systems are also activated similarly via tactile communication and hands-on care.

Touch is crucial to mentalisation, and the probabilistic inference frequently encountered through multisensory interoception, which is developed through the accumulation of multisensory autonomic and motor predictions of the body's physiological states and coupling with the outside world (Fotopoulou and Tsakiris, 2017; Fotopoulou et al., 2022). The mirror neuron system suggests the utilisation of joint coding for one's actions and perceptions with the understanding and ability to infer another individual's actions, which is essential to co-operative communications (Koban et al., 2019). It is common for triadic situations to incorporate touch as a method of communication, combining the benefits of triadic interactions and touch into one scenario and increasing the overall synchrony. This can be applied to a clinical setting, when the HCP frequently determines the communication hierarchy delegating their expertise and advice to the next of kin, assisting with the patient's regulation (O'Shea et al., 2019). While more verbal communications may be targetted at the next of kin than the patient, the patient receives significantly more stimulation from sensory information and repetition of movements throughout the treatment, utilising more direct tactile communication than the accompanying individual (Harman et al., 2011). We argue that understanding the mechanisms underpinning triadic communication and synchrony is crucial to providing effective person-centred MSK care, particularly in the care of the elderly, where the use of a translator is needed, and in contexts with a solid family-centred culture.

TOUCH AS A METHOD TO EXPLORE AND GAIN EXPERTISE

According to patients, an essential quality of an HCP in MSK care is their expertise in the field (Peersman et al., 2013). Most patients believe their HCP has excellent clinical skills and is trustworthy, possibly due to their more precise prediction errors and priors on MSK disorders and associated symptoms such as pain, combined with their ability to help to resolve their symptoms (Cooper et al., 2008; Peiris et al., 2012; Del Baño-Aledo et al., 2014; Vasil et al., 2020). Despite a collaborative relationship, society's hierarchical social strata reflect that as the HCP has superior knowledge, expertise, qualifications, and access to resources, they will always be seen higher in the hierarchical order of the relationship between HCP and patient (O'Shea et al., 2019). Thus, while strategies such as the person-centred approach allow for greater integration of patients' voices in healthcare, HCPs will fundamentally make top-down decisions regarding their patients' care.

Patients are frequently perceived to have an "interrogative motivation" in which they have a more receptive and motivated mindset to learn and create opportunities to adapt their current prior beliefs to some extent due to asymmetry entrainment (Harris and Corriveau, 2011; Harris et al., 2017). Patients with MSK-related pain typically receive cognitive reassurance through increased knowledge of their condition from their HCP – arguably, it helps develop more precise priors, decreases maladaptive beliefs, and improves patient confidence and condition management (Miciak et al., 2018; Cheung and Soundy, 2021). Touch and proprioception, i.e., haptics, is used to explore and gain information about the world around us. The haptic system enables us to discriminate and recognise objects through palpation (McLinden and McCall, 2002). Palpation is commonly used in MSK care. Despite its variable validity and reliability (see Nolet et al., 2021, for a recent review), patients believe that their HCPs can manually detect their clinical problem's origin, thus explaining why they frequently expect an HCP to examine the area of dysfunction, particularly in subacute LBP.

THE ROLE OF TOUCH IN OVERCOMING UNCERTAINTY BY CREATING A SAFE CLINICAL ENVIRONMENT

Attachment theory suggests that an attachment figure can provide another individual with a strong sense of security Bowlby (1988). Through the lens of attachment theory, a therapist can take on this role and act as a "secure base" by instilling a sense of security in the clinical setting and thus strengthening the TA (Sauer et al., 2010). A safe environment and attachment can be created with the help of therapeutic touch and effective communication by acknowledging the clinical problem, receiving reassurance, the expectation of allostatic regulation and symptom modification, and encouraging the patient to engage in rehabilitation exercises, which they may not have felt confident to do (Bright et al., 2015; Taylor et al., 2015). Moreover, it is considered crucial and expected by patients with MSK disorders for a successful TA, rapport, installing patient confidence, motivation, ownership while showing empathy and reducing anxiety (Murray and Corney, 1991; Hill and Fritz, 2011; O'Keeffe et al., 2016; Cederbom et al., 2020; Cheung and Soundy, 2021). Therapeutic touch is also considered "comfort contact," as it can contribute to patients feeling more comfortable with their HCP, especially in the case of LBP (GMC, 2020). Consequently, it can help to decrease stress through reassurance and achieving a secure attachment, a more vital relationship and a sense of safety that helps to regulate and accurately predict the physiological effects of stress and general health (Harlow and Zimmermann, 1959; Coan et al., 2006; Morrison, 2016b; López-Solà et al., 2019; Mühlenpfordt et al., 2020; Norholt, 2020). Compared to verbal reassurance, caring touch reduces stress significantly, reiterating its superiority in providing social support (Ditzen et al., 2007).

Individuals who experience persistent pain are more likely to suffer from anxiety, depression and fear-avoidance, thus a long-term obstacle to recovery that should be addressed (Linton and Shaw, 2011). Thus, increasing social support and a sense of safety can decrease the likelihood of the brain detecting and modulating potential threats, such as nociceptive signals, by increasing ventral medial prefrontal lobe activation, modulating pain and increasing the individual's quality of life (Shamay-Tsoory and Eisenberger, 2021; Krahé et al., 2013). The evidence demonstrates that touch-based therapeutic interventions contribute to patients' increased quality of life for many MSK conditions, including fibromyalgia, MSK, chronic pain, and headaches (Yuan et al., 2015; Crawford et al., 2016). Therefore, touch-based therapies are being recommended in the care of elderly patients with chronic MSK conditions, as increasing quality of life is often considered the main goal in symptomatic management, crucial to this demographic (Kopf, 2021). This speaks to the effect of touch of Aβ but also Aα, and CT afferents on the modulation of nociceptive signals at a subcortical level in conjunction with a high-level cortical response that can disrupt pain signalling, resulting in spinal gating that prevents signals from reaching the brain (Melzack, 1996; Mancini et al., 2015). Moreover, touch can moderate another individual's level of pain, synchrony, and level of analgesia (Goldstein et al., 2017). The reduction in pain levels from hands-on care, particularly massage therapy, can be seen in a range of chronic pain conditions, including migraine headaches, fibromyalgia, LBP in different contexts, juvenile rheumatoid arthritis, and chronic paediatric conditions (Field et al., 2007; Suresh et al., 2008).

THE ROLE OF TOUCH AND EMPATHY WITHIN THE CLINICAL ENCOUNTER

Health Care provider and patients consider empathy as one of the fundamental elements required for establishing a TA, and significantly, it demonstrates positive effects on patient clinical outcomes and reducing distress by shared feelings and higher-order concerns with another, in the hope, they will help regulate them (Decety and Fotopoulou, 2015; O'Keeffe et al., 2016). Empathy is crucial in acknowledging the difficulties and sacrifices that the patient may face on the road to recovery by accepting and being willing to change or alter their prior and personal preferences to achieve full recovery (Bordin, 1979). Additionally, it contributes to the connection and synchrony between HCP and their patients by establishing a shared narrative, experience, emotional transfer, reinforcing the belief that everyone is the same. Moreover, it encourages the patient to relate to their current environment and discriminate their representations between self and others (Frijda and Mesquita, 1994).

When two people share similar emotions, they accurately infer the other's actions, motivations, pain and suffering, thus reinforcing their relationship and priors by reducing the psychosocial barriers. Additionally, it helps patients with LBP and other MSK disorders to perceive their HCP as caring and empathic (Harman et al., 2011; Geri et al., 2019). In combination with repetitive dynamic hands-on techniques, the patient and HCP will often synchronise during spoken recall of a situation both had experienced – or when holding hands while experiencing noxious stimuli. This synchronisation is achieved through the activation of the Default Mode Network, high-level

ventral temporal regions, intraparietal sulcus, pain-neuromatrix, anterior mid-cingulate cortex, AIC, inferior parietal lobe and IFG in both individuals, thus creating a prosocial effect (Preston, 2007; Romero et al., 2010; Goldstein et al., 2016; Chen et al., 2017; Korisky et al., 2020). Arguably, we are able to understand and share others' emotions by partially processing them within our own emotional systems (Jackson et al., 2005; Vogt, 2005; Kilner et al., 2007; Friston, 2010; Lamm and Majdandžić, 2015).

Empathy is often associated with physiological responses in both the HCP and the patient, such as increased sympathetic nervous system activation, including skin conductance in chronic pain patients (Block, 1981). Moreover, more empathic individuals show more extradural synchrony and coupling, thus leveraging empathy – and learning the preferred coping strategies (Goldstein et al., 2017; Ellingsen et al., 2020; Reddan et al., 2020; Kozakevich Arbel et al., 2021; Shamay-Tsoory and Eisenberger, 2021). Indeed, it has been suggested that the degree of empathy demonstrated during touch correlates with the level of analgesia experienced by the partner through the toucher's tactile stimulus (Goldstein et al., 2016; Korisky et al., 2020). All reaffirm the integral role that empathy plays in the TA and the patient management in MSK care.

THE ROLE OF REPETITION WITHIN A CLINICAL ENCOUNTER IN AIDING SYNCHRONY

Clinical encounters are multifaceted and often have a repetitive structure, repeated each session to incorporate new external factors, changing symptom patterns and reactions or adjustments to the treatment (Pricop, 2016). Manual therapists generally have longer and more frequent appointments and patient continuity of care than a general medical practitioner (Miciak et al., 2018). In combination with repeated physical movements and hands-on care, these factors will influence the development of the TA. Moreover, they could contribute to the individual being more accurate, sensitive, and motivated to align with the HCP's hidden mental states and recognise their unique therapeutic touch resulting in them potentially enhancing saliency, precision, synchrony, and confirming their priors more quickly (Tronick, 1989; Vasil et al., 2020). Additionally, it will increase the representation of social and cultural coherence and the likelihood of repeating the experience (Feldman, 2015; Begus et al., 2016). Finally, it bolsters the concept of repeated therapeutic touch, helping to promote self-awareness and synchrony – this could help explain why patients with high TA relationships adhere more closely to their physical rehabilitation programmes for many conditions, including neurological patients (Schönberger et al., 2006).

Repeated physical movements can putatively reinforce the patient's pre-existing biological rhythms (Lester et al., 1985). It has been suggested that physiological synchrony, including HRV, is contingent on attention, similar processing of natural stimuli, and similar brain activity during memory processing (Pérez et al., 2021). As a result, the HCP and their patients' physiological synchrony may be aided by the memory and expectations of previous hands-on care. Furthermore, it is imperative to MSK patients to have continuity of care and have "their HCP" who understands their body, activity levels and treatment preferences (Miciak et al., 2018).

The repetition of hands-on techniques during treatment increases sensitivity to pre-existing priors and allostatic regulation as a means of achieving homoeostasis. This is most notably seen bilaterally in the autonomic nervous system, precisely the cardiac and sympathetic tone. To this end, Tamburella et al. (2019) demonstrated that osteopathic manipulative therapy increased PCC perfusion significantly for 3 days, followed by an immediate decrease in resting cerebral perfusion within a cluster containing the Posterior Cingulate Cortex and Superior Parietal Lobe. The observed changes in cerebral perfusion suggest that touch may play a role in the observed improvements in sympathetic tone following sympathovagal modulation. Additionally, it has been hypothesised that behavioural synchrony and intimacy are associated with the evolution of the polyvagal system and its capacity to adapt to changes in our external environment (Porges, 2003, 2007). Several studies have demonstrated that the decreased heart rate and increased oxygen saturation following treatment could be sustained for 5–65 min after touch-based therapies (Lindgren et al., 2010; Manzotti et al., 2019). Touch has been shown to regulate physiological function and promote the development of precise embodied social behaviour and attachments, which can be influenced by the HCP's treatment and personal predispositions (Hardin et al., 2020). The repetitive touch used in treatment can increase alpha EEG asymmetry, predominantly found in the left frontal hemisphere, and associated with emotional processing and cognitive maturation. Moreover, consciously processing audio-visual stimuli is associated with the degree and development of heart rate synchrony (Pérez et al., 2021). Therefore, we would argue that hands-on care supported by effective verbal and non-verbal communication strategies create an adequate multisensory environment to promote biobehavioural synchrony.

CONCLUSION

In this article, we have proposed a model to explain the crucial role of touch and hands-on care in developing a robust TA, regulating allostasis and subsequently restoring homoeostasis in the field of MSK care. This model is based on AI and furnishes an integrative account of neurophysiological and biopsychosocial processes within a clinical encounter in MSK care. This formulation emphasises the foundational role of synchrony and cooperative communication between HCPs and their patients, hoping to engender successful clinical outcomes. While it is recognised that touch and skin contact is vital for survival – and has therapeutic benefits for patients – we consider a similar benefit for all individuals. This model reveals how touch and hands-on care can be used to revise an individual's prior beliefs to create a person-centred care approach to promote allostasis and restore homoeostasis after an injury or to manage persistent pain and other functional medical symptoms. We

have considered multiple feedback loops that offer potential mechanisms that can be leveraged during a treatment session. In short, the framework on offer enables HCPs to use touch and hands-on care techniques to strengthen the TA, minimise prediction errors (a.k.a., free energy), and thereby promote recovery from physical and psychological impairments.

Musculoskeletal care utilises therapeutic touch and communication to expose an individual to sensory stimuli and surprise, develop new associations and reactions to "overwrite" maladaptive priors and revise existing generative models (Stewart and Watt, 2008; Boettcher et al., 2016; Paulus et al., 2019; Smith et al., 2021). While this article focuses on touch-based interventions for treating and managing individuals suffering from MSK disorders, there are crossovers between mental health and MSK disorders – MSK related pain is associated with mood disorders (Bekhuis et al., 2015; Bohlen et al., 2021). Notwithstanding this association between chronic pain and mood disorders, MSK practitioners must acknowledge their limits of professional competence in mental health (Ianì, 2019; Bohlen et al., 2021). Psychotherapy also uses the body to elicit aspects related to embodied memory. Therefore, the complex, layered perceptions of memories and magnitude of uncertainty in understanding how bodily experience contributes to mental health must be respected (Ianì, 2019; Paoletti and Ben Soussan, 2019). HCPs must critically recognise the central and irreplaceable role of psychotherapy in treating and managing somatic and somatoform symptoms (Chemero, 2009; Gentsch and Kuehn, 2022).

Future research could consider the bidirectional neurobiological synchrony implied by the exchange of touch between HCP and patients in MSK care. This research line would help establish and consolidate the role of touch and hands-on care when characterising the complex and dynamic interactions during a clinical encounter. Moreover, an increased understanding of how touch and hands-on techniques could be implemented and manipulated to develop a successful TA could help dissolve the barriers encountered with patients who struggle to update their priors, particularly in multifactorial chronic MSK disorders.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ZM wrote the first draft of the manuscript. All authors contributed to the conception of the study and manuscript revision, and approved and accountable for the submitted manuscript.

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Conflict of Interest: GR leads education programmes on placebo, nocebo effects and contextual factors in healthcare to under- and postgraduate students along with private CPD courses.

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Physical Fitness and Dietary Intake Improve Mental Health in Chinese Adolescence Aged 12–13

Wenjie Liang[1], Jian Fu[1], Xin Tian[1], Jiaxue Tian[1], Yu Yang[1], Wencui Fan[1], Zijuan Du[2] and Zheyu Jin[1]*

[1] College of Physical Education, Yangzhou University, Yangzhou, China, [2] Xi'an International Studies University, Xi'an, China

Background: Mental health has become a major public health issue worldwide. Biological and epidemiological studies have suggested that diet and physical fitness play a role in the prevention or cure of mental disorders. However, further research is required to elucidate the relationship between diet, physical fitness, and mental health. The study aims to provide a theoretical basis for promoting an adolescent healthy lifestyle and preventing mental problems by exploring the relationship between physical fitness, calcium intake, calorie intake, and adolescent mental health.

Methods: A cross-sectional study of a sample of adolescents (N = 253, 12–13 years) was conducted. The study involved adolescents from three middle schools in Central Jiangsu Province, including 136 boys and 117 girls. Weight, height, and body mass index were measured. Physical fitness was scored using the Chinese National Student Physical Fitness Standard. Diet data were collected using a weighed 7-day food diary to estimate energy intake and dietary calcium intake. The mental health status of the participants was assessed using the Chinese Middle School Student Mental Health Scale. A T-test and analysis of variance were used to analyze the differences of variables between different genders and body mass index, and Pearson correlation and stepwise multiple regression were used to explore the relationship between physical fitness, dietary intake, and mental health.

Results: The height (165.13 ± 8.07), weight (55.24 ± 13.00), and strength quality (64.93 ± 21.66) of boys are higher than those of girls (161.67 ± 6.44,48.99 ± 8.97, 58.40 ± 23.75, $P < 0.05$), and the flexibility quality (74.59 ± 14.75) of girls is higher than that of boys (68.30 ± 20.84) ($P < 0.05$). There were significant differences in the total scores of speed and physical fitness (F values were 4.02187.73, 3.07, 5.95, 10.33, and 9.52, respectively, $P < 0.05$). There was a significant positive correlation between calcium intake, cardiopulmonary fitness, and mental health ($r = 0.276$, $P < 0.01$; $r = 0.159$, $P < 0.05$). Calcium intake and cardiopulmonary fitness could explain 8.4% of the changes in the mental health of adolescents aged 12–13($\Delta R_2 = 0.084$, $P < 0.05$).

Conclusion: Adequate calcium intake and the improvement of cardiopulmonary fitness in adolescents aged 12–13 are essential for the good development of their mental

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***Correspondence:**
Jian Fu
fujian@yzu.edu.cn

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health. Future research in this field should examine the prospective associations between multiple measures of physical fitness composition and other nutrients ingested and mental health outcomes, as well as intervention studies that seek to provide evidence of causality.

Keywords: cardiorespiratory fitness, calcium intake, mental health, adolescents, physical fitness

BACKGROUND

Mental health problems affect 10–20% of children and adolescents worldwide (Kieling et al., 2011). Childhood and adolescence represent periods of rapid growth and brain development characterized by neuronal plasticity, formulation of self-concept, and the establishment of behavior patterns that may influence mental health (Lubans et al., 2016). Good physical fitness and a reasonable and balanced dietary structure are the implicit and explicit resources to form a healthy lifestyle and behavior, and they are also the main risk factors to determine current and future mental health. Considering the negative consequences of adolescent mental health problems, it is very important to find effective prevention methods to improve adolescent mental health.

Physical activity is an effective tool to improve health. Many scholars have discussed the mode, time, intensity, and mental health of physical activity from several points of view. There is evidence suggesting that physical activity is a protective factor against mental health problems such as depression (Mammen and Faulkner, 2013). Although there is no clear consensus, neurobiological, psychosocial, and behavioral mechanisms have all been hypothesized to explain the relationship between physical activity and mental health (Lubans et al., 2016). However, the level of physical activity of each person fluctuates at any time under the influence of society, family, and individual motivation. Physical fitness is the ability of the body to perform physical activity (Rodriguez-Ayllon et al., 2018). Although physical fitness is influenced by genetics (Fisher et al., 2015) to a certain extent, it represents the type, frequency, intensity, and duration of physical activity over time (Blair et al., 2001). Therefore, physical fitness is a symbol of the aftereffect of physical activity, and also provides a more stable measurement standard for the level of regular physical activity. Also, compared with physical activity, physical fitness is more predictive of health outcomes in adolescents (Bovet et al., 2007). Given the relationship between physical activity and physical fitness, the mechanisms proposed to explain the relationship between physical activity and mental health might also apply for physical fitness and mental health (Silverman and Deuster, 2014). The health-related components of physical fitness are commonly classified as cardiorespiratory fitness, muscular strength and endurance, flexibility, and speed (Ministry of Education of the People's Republic of China, 2012). Many studies have been conducted from one or a combination of two aspects of physical fitness. Cardiorespiratory fitness refers to the capacity of the circulatory and respiratory systems to supply oxygen to the skeletal muscle mitochondria for energy production during physical activity (Pillsbury et al., 2013). Cardiorespiratory fitness can influence mental health outcomes through neurobiological processes (Silverman and Deuster, 2014). Studies have shown that cardiopulmonary health is positively correlated with the mental health of adolescents, (Greenleaf et al., 2010; Martin et al., 2011) and lower cardiorespiratory fitness shows higher levels of depression. Likewise, adequate muscular fitness has been shown to be associated with high self-esteem (Kalogiannis and Papaioannou, 2007; Lubans and Cliff, 2011) and low levels of anxiety. Muscular fitness is the ability of the body to exert maximal force against an external resistance (i.e., muscular strength) (Raghuveer et al., 2020). Muscular strength may also depend on cultural norms (Rodgers et al., 2012), thereby possibly affecting mental health through sociocultural mechanisms. Many researchers have explored the relationship between physical fitness and mental health, but they still have no clear consensus. The importance of speed to teenagers' mental health has not been paid attention to in previous literature. We also do not know whether one component of physical fitness is more important than others, and the correlation intensity between various physical fitness and different dimensions of adolescent mental health is different, which still needs to be further discussed.

Diet, as an important variable to intervene in mental health, is another focus of this study. There is increasing evidence that certain dietary patterns have a positive impact on health. A healthy, balanced diet includes a variety of vegetables and fruits, whole grains, seafood and nuts, moderate amounts of low-fat dairy, red meat, and saturated and *trans* fats, all of which have been associated with good mental health (Hosker et al., 2019). The more western fast-food or highly processed food you eat, the more likely you are to develop psychological symptoms such as depression and anxiety (Dimov et al., 2019). There is consistent evidence of an association between unhealthy diets and worse mental health in children and adolescents, but more research is needed for better conclusions (O'Neil et al., 2014). Recently, more attention has been paid to the association between trace mineral intake and mental health. Studies have shown that low intake of zinc, copper, and manganese was associated with depression and anxiety symptoms (Nakamura et al., 2019). Similarly, calcium supplementation is more effective in reducing the risk of depressive symptoms (Wu et al., 2020). Calcium has the biological function of regulating the synthesis and release of neurotransmitters in the nervous system and plays an important role in activating neurons and regulating moods (Marambaud et al., 2009; Pal, 2021). Additionally, calcium is required to produce serotonin, which is the precursor of melatonin (Nongonierma and FitzGerald, 2015). Melatonin plays a fundamental role in sleep regulation and the maintenance

of emotional health (Zisapel, 2018). These tiny improvements in dietary habits and nutrient intake lead to major benefits for adolescent mental health and development. Many research reports have explored the relationship between dietary patterns, frequency of intake of vegetables and fruits, intake of minerals and vitamins, and mental health at different levels, but the unavoidable question of studying the relationship between diet and mental health in children and adolescents is how to apply better dietary survey methods. Whether it is a 24-h review method, 3-day weighing record method, or food frequency questionnaire method, each has its own advantages and disadvantages, and there are still inconsistencies and gaps in the evidence obtained. Due to synergistic effects between nutrients (Hu, 2002), some scholars suggested a measure of overall diet as a better indicator in studies of the effects of diet quality on mental health. Taking advantage of the particularity of students' unified eating, our study investigates and calculates the calorie and calcium intake of diet by combining the recording and weighing method. The purpose is to understand the dietary patterns and habits of the respondents without reducing the reliability of information, so as to better reveal the relationship with mental health.

Childhood and adolescence are likely to be critical times for establishing good mental health but there is still much to be learned about factors that may have a positive impact on psychological health in childhood (Sawyer et al., 2012; Lubans et al., 2016). Diet and physical fitness have been paid special attention as important factors affecting mental health, but the underlying mechanism of their interaction is still unclear. Based on the above analysis, our research will further clarify and discuss the relationship between the three and provide methods and theoretical basis for adopting reasonable dietary behaviors and physical exercise to control and prevent adolescents' mental health problems. We hypothesized that: (1) different components of physical fitness are differently associated with mental health and (2) lower calcium intake and cardiorespiratory fitness both predict lower levels of mental health.

MATERIALS AND METHODS

Design and Participants

The current study selected participants based on relevant research and adopted stratified random sampling from three middle schools in Central Jiangsu Province (China). Schools were selected for their representativeness, accessibility to our research team, and availability of the teachers to assist with logistics. Only students aged 12 and 13 were invited to participate in the study (n = 302). A written informed consent from their parents or guardians was received. All participants received comprehensive medical screening, and students with the following diseases are excluded: (1) cardiovascular or respiratory diseases; (2) bone, muscle, and ligament injuries or a history of such injuries; (3) surgical history of major diseases; (4) history of mental disorder or nervous system disease. A total of 277 adolescents were eligible for the study. Before data collection, all participants were informed about the purpose of the study and that they could withdraw at any time. Each school has 2 research assistants who provide guidance on the completion of questionnaires and conduct physical fitness testing. The participants were tested at their respective schools in the winter of 2020 during school time. All the testing personnel received the same training beforehand to make sure there were no discrepancies in how the tests were carried out. Among these participants, 24 did not complete the testing protocol. Eventually, only 253 adolescents (136 boys and 117 girls) were included in the data assessment. The study was conducted in accordance with the recommendations of the World Medical Association's Declaration of Helsinki and approved by the Institutional Review Committee of Jinhu Hospital of Traditional Chinese Medicine (JHZYY202010).

Measurements

Anthropometry

The body height and weight of the subjects were measured through a height and weight tester (HK6800-ST, China). During the test, the subjects were barefooted and wearing only thin clothing. Body mass index (BMI) was measured as a covariate because it is correlated with both dietary intake and mental health measures included in the analyses. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and "School-age Children and Adolescents Screening Standards for Overweight and Obesity" (WS/T 586-2018) (National Health and Family Planning Commission of the People's Republic of China, 2018) was adopted to divide the body mass index into four grades: low weight, normal weight, overweight, and obesity.

Physical Fitness Assessment

Physical fitness was measured using the Chinese National Student Physical Fitness Standard (Zhu et al., 2017). Primary outcome measures the following: the cardiorespiratory fitness test, which measured an individual's aerobic capacity, vital capacity, and mid-distance running (800 m for girls and 1,000 m for boys), was used to measure cardiorespiratory fitness. Muscle fitness assessment adopted lower extremity muscle strength (standing long jump) to test the body's ability to exert maximum force against external resistance. Speed was assessed by the 50-m run test, which reflected the ability to move quickly on the ground or move the limbs quickly. Flexibility refers to an individual's range of motion around a joint or group of joints, and the flexibility test used in this research was the sitting forward flexion test.

Vital capacity was assessed by the FHL-II spirometer (Xindong Huateng Inc., Beijing, China). After the first maximum exhalation, participants rested for a minute before the second test, and the best performance was recorded.

Men's 1,000-m/women's 800-m tests were conducted on the 400-m track. Before the test, students are required to do a full warm-up and then they started in a group of 10–12 people by using a standing start.

The standing long jump was tested on a bunker with the sand surface level with the ground or on a flat ground with soft soil using a measuring ruler. The subject's feet were naturally separated, and after standing on the jumping line, both feet took off at the same time. Records were in centimeters to one

decimal place. The test was taken three times and the best score was considered.

The 50-m running test was conducted on the track and field. The subjects were in groups of 2-3 and started standing up; when they heard the start signal, they immediately started and ran to the finish line with all their strength. Test equipment: starting flag, starting whistle, and stopwatch.

The sitting body flexion test was performed with an electronic sitting flexion tester (Wanqing WTS-600, Shanghai, China). The test subjects were asked to sit on the test plate, with their legs straight, their feet flat on the test longitudinal plate, their upper bodies flexing forward, their arms stretching forward, and the Vernier was gradually pushed forward with their middle fingertips until they could not be pushed forward. Records were in centimeters to one decimal place.

Finally, according to the "National Student Physical Health Standards" promulgated by the Ministry of Education and the General Administration of Sports of the People's Republic of China, the students' scores were converted into corresponding scores.

Mental Health Assessment

Mental health was tested by the mental health scale for middle school students (Su and Huang, 2007) prepared by Sudan and Huang Xiting. It has high reliability (retest reliability is 0.82) and is widely used in China. The scale was a multi-dimensional measuring tool. It evaluated the mental health of middle school students from five aspects: life, study, interpersonal communication, examination, and emotion. There were 25 items in total, and the 5-level score was adopted. The higher the score, the better the mental health. We took the school as a unit for group measurement, and the testers in the classroom uniformly distributed the mental health scale. At the beginning of the test, the test subjects were instructed to fill in the questionnaire with unified and clear instructions, and the questionnaire was collected immediately after completion.

Dietary Intake Assessment

The study used a dietary survey method combining the food recording method and the weighing method. The daily dietary situation was reflected through a cross-sectional dietary survey, and the dietary intake of the participants was recorded for 7 consecutive days, including 5 days on-campus and 2 days off-campus. The research subjects filled in the name, category, quantity, and weight of the food they ingested according to the "Daily Diet Log" (Egger and Flueck, 2020; Tian et al., 2021). A 2-day pre-investigation was conducted before the formal investigation. The investigator explained the filling requirements to the students according to the school's fixed recipes and quantitative cutlery and promptly corrected and answered the questions that the subjects had during the recording process. During the formal investigation, each class was assigned an investigator for timely observation and guidance. After the end of the day's investigation, the investigator collected the information, checked and corrected the information, and distributed the information the next day. It could well make up for the inaccurate estimation of food intake caused by the 24-h review method for recalling information. Finally, the different meals provided by the respondents were weighed and recorded. On rest days, the respondents and their guardians would record the dietary intake for the 2 days, and the investigator would provide online Q&A to ensure the reliability of the survey. A total of 253 valid questionnaires were returned. The calcium intake and calorie intake in the diet were calculated according to the "Chinese Food Composition Table (2019 Edition)."

Statistical Analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, United States) was used to analyze the data. The general demographic data, factors of physical fitness, dietary intake, and mental health levels of the research subjects were analyzed by descriptive statistics, the quantitative data were described by the mean ± standard deviation, and the data were tested for normality. The binary variable sex and each variable were used for *t*-test, the multi-category variable was used to replace the continuous variable, and ANOVA was used to analyze whether there was a difference between the different body mass indexes of adolescents and each variable. The study also used Pearson correlation and stepwise multiple regression for statistical analysis. The level of statistical significance was set at $P < 0.05$ (two-tailed). Graphpad Prism8.0.2 software was used for graphics processing.

RESULTS

Comparison of Mental Health, Diet, and Physical Quality in Different Genders and BMI

Among the 253 adolescents aged 12–13 who participated in the survey from November 2020, the average mental health score was (72.7 ± 9.05), the average calcium intake was 2,241.87 ± 694.17 mg, and the average caloric intake was 36,528.18 ± 7,956.8 KJ. The average scores of cardiorespiratory fitness, muscle fitness, flexibility, speed, and total physical fitness were (131.44 ± 33.11), (61.91 ± 22.84), (71.01 ± 20.38), (75.95 ± 17.53), and (340.30 ± 62.10), respectively. Boys' height, weight, BMI, and muscle fitness were higher than girls' ($P < 0.05$), and girls' flexibility was higher than boys' ($P < 0.05$), and other variables had no significant differences between genders. There was no significant difference in mental health scores among different BMIs, while the differences in total scores of height, weight, BMI, calorie intake, muscle fitness, speed, and physical fitness were statistically significant ($p < 0.05$). The calcium intake, calorie intake, cardiorespiratory fitness, and muscle fitness of low-weight adolescents were higher than those of normal adolescents. **Table 1** showed the comparison of psychological quality, diet, and physical fitness under different gender and BMI.

Correlation Analysis of Physical Fitness, Dietary Intake, and Mental Health

First of all, as shown in **Table 2**, the psychological health of the research subjects was significantly positively correlated with calcium intake and cardiorespiratory fitness (**Figure 1**), and the

TABLE 1 | Comparison of mental health, diet and physical fitness under different gender and BMI (mean ± SD).

Variable	Gender (x ± s)				BMI (x ± s)					
	Total (*n* = 253)	Male (*n* = 136)	Female (*n* = 117)	*P*	Low Weight (*n* = 23)	Normal (*n* = 168)	Overweight (*n* = 38)	Obesity (*n* = 24)	P	F
Mental health	72.70 ± 9.05	71.71 ± 9.66	73.85 ± 8.17	0.056	74.61 ± 9.61	73.03 ± 9.04	71.05 ± 8.64	71.17 ± 9.12	0.364	1.07
Height (cm)	163.53 ± 7.55	165.13 ± 8.07	161.67 ± 6.44	0.001	161.87 ± 8.26	162.76 ± 7.41	165.61 ± 6.39	167.27 ± 8.11	0.008	4.02
Weight (kg)	52.35 ± 11.71	55.24 ± 13.00	48.99 ± 8.97	0.001	38.96 ± 4.14	48.45 ± 6.34	62.99 ± 4.61	75.63 ± 10.89	0.001	187.73
BMI (kg/m^2)	19.46 ± 3.50	20.11 ± 3.79	18.69 ± 1.97	0.001	14.83 ± 0.53	18.24 ± 1.57	22.95 ± 0.81	26.91 ± 2.16	0.001	383.42
Calcium intake (mg/week)	2,241.87 ± 694.17	2,313.59 ± 720.24	2,158.50 ± 655.81	0.074	2,371.20 ± 655.36	2,205.20 ± 670.10	2,278.19 ± 757.12	2,317.09 ± 807.28	0.650	0.55
Caloric intake (KJ/week)	36,528.18 ± 7,956.80	37,090.43 ± 8,328.52	35,874.62 ± 7,599.01	0.226	37,765.24 ± 8,164.55	35,743.79 ± 7,662.03	36,574.13 ± 7,933.80	40,760.68 ± 8,812.48	0.029	3.07
Cardiorespiratory fitness	131.44 ± 33.11	129.29 ± 32.87	133.94 ± 33.34	0.266	134.71 ± 24.51	132.88 ± 33.60	134.14 ± 31.94	113.87 ± 35.18	0.055	2.57
Muscle fitness	61.91 ± 22.84	64.93 ± 21.66	58.40 ± 23.75	0.024	67.09 ± 17.44	64.73 ± 21.60	55.75 ± 24.23	46.92 ± 26.66	0.001	5.95
Flexibility	71.01 ± 20.38	68.30 ± 20.84	74.59 ± 14.75	0.022	71.43 ± 16.22	72.75 ± 19.96	68.83 ± 18.11	61.83 ± 27.56	0.087	2.21
Speed	75.95 ± 17.53	77.12 ± 19.58	74.59 ± 14.75	0.244	75.22 ± 18.47	78.76 ± 15.50	74.87 ± 10.68	58.65 ± 27.18	0.001	10.33
Physical fitness	340.30 ± 62.10	339.63 ± 66.71	341.09 ± 56.55	0.851	348.45 ± 48.15	349.14 ± 57.78	333.59 ± 55.03	281.27 ± 81.11	0.001	9.52

correlation with calcium intake was the greatest ($p < 0.01$). Secondly, there was a low correlation between physical fitness and mental health ($r = 0.114$), but it was not significant. Among the independent variables, there was a significant low correlation between calcium intake and cardiorespiratory fitness ($r = 0.126$, $P < 0.05$), and cardiorespiratory fitness was moderately positively correlated with muscle fitness and speed ($P < 0.01$).

Regression Analysis of Mental Health, Calcium Intake, and Cardiopulmonary Fitness

In order to further understand the relationship between adolescents' physical fitness, dietary intake, and mental health with mental health as the dependent variable, a stepwise multiple regression analysis was performed on calcium intake and cardiorespiratory fitness (**Table 3** and **Figure 2**). The two independent variables of calcium intake and cardiopulmonary fitness entered the final model. Calcium intake and cardiorespiratory fitness had a significant positive predictive effect on mental health, and they could explain 8.4% of the variation in mental health ($P < 0.01$).

DISCUSSION

Physical fitness is widely recognized as a power marker of health-related outcomes and an important determinant of current and future mental health. Numerous studies have shown a positive correlation between physical fitness and mental health (Loprinzi et al., 2017; Oliveira et al., 2019). Based on the cross-sectional study, we observed that there was a low correlation between total physical fitness and mental health in youth, and there was no significant level. However, the survey lacks information related to sensitive quality, which is not enough to draw powerful and clear conclusions. In the follow-up study, it is necessary to increase the sample size and investigate all physical fitness indicators so as to better evaluate the relationship between the two. But there is a significant positive correlation between cardiorespiratory fitness and the overall mental health of adolescents. The study also complements previous findings, suggesting that good cardiorespiratory fitness in adolescents leads to better mental health (Reddon et al., 2017). Although, longitudinal studies are lacking, cardiorespiratory fitness appears to be an important predictor of current and future mental health status. The relationship between cardiorespiratory fitness and mental health has been investigated in most studies. In recent years, more and more attention has been paid to investigate the relationship between muscle strength and mental health in adolescents (Smith et al., 2014; Appelqvist-Schmidlechner et al., 2020). Our study did not find a significant correlation between muscular strength and mental health. One possible explanation is that there are few and incomplete indicators for measuring muscular strength. Comprehensive and detailed measurements of core strength, upper body strength, and grip strength of

TABLE 2 | Correlation between physical fitness, dietary intake, and mental health (r).

Variable	Mental health	Caloric intake	Calcium intake	Cardiorespiratory fitness	Muscle fitness	Flexibility	Speed	Physical fitness
Mental health	1							
Caloric intake	0.004	1						
Calcium intake	0.276**	0.436**	1					
Cardiorespiratory fitness	0.159*	−0.040	0.126*	1				
Muscle fitness	0.054	−0.026	0.096	0.340**	1			
Flexibility	−0.04	0.060	−0.080	0.049	0.018	1		
Speed	0.081	−0.011	0.043	0.346**	0.545**	0.113	1	
Physical fitness	0.114	−0.014	0.089	0.772**	0.709**	0.393**	0.705**	1

***P < 0.001, *P < 0.05, the results are rounded to 3 decimal places.*

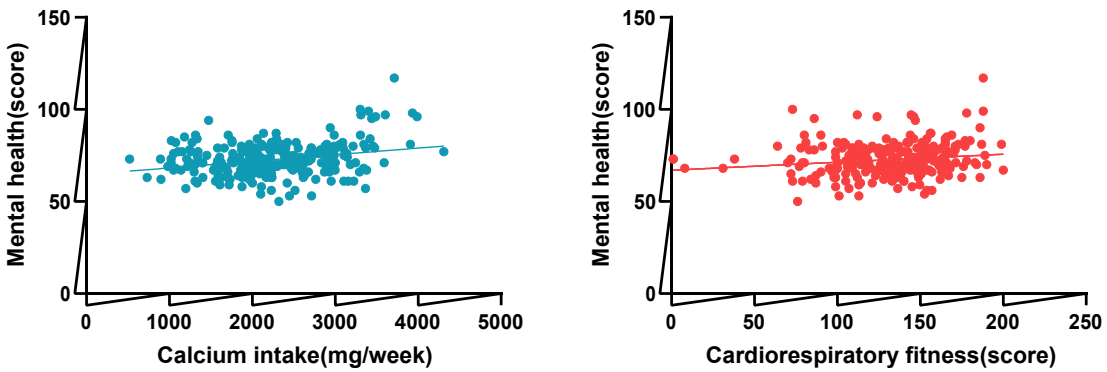

FIGURE 1 | The correlation between dietary calcium intake, cardiopulmonary quality and mental health.

TABLE 3 | Regression analysis of mental health, calcium intake, and cardiopulmonary fitness.

Dependent variable	Constants and variables	B	Beta	t	F	R^2	Δ R^2	P
Mental health	(Constant)	64.639	0.276	34.842	20.682	0.076	0.072	0.000**
	Calcium intake	0.004		4.548				
	(Constant)	60.578		22.528				
	Cardiopulmonary fitness	0.034	0.126	2.074	12.627	0.092	0.084	0.039*
	Calcium intake	0.003	0.260	4.279				0.000**

***P < 0.001, *P < 0.05, the results are rounded to 3 decimal places.*

adolescents are required. In adolescents, however, muscular strength and speed are mainly associated with appearance-related mental health outcomes, such as self-perception, perceived physical appearance, or physical self-worth (Cadenas-Sanchez et al., 2021). Differences in psychometric tools also make it difficult to compare research results horizontally. Of note, although no significant correlation was found between speed quality and mental health, the correlation coefficient of speed quality was more closely related to mental health than strength and flexibility. Therefore, future research on the relationship between physical fitness and mental health should include different measures of mental health factors to better understand whether components of physical fitness are associated with specific outcomes of mental health. In addition, there are few studies on the relationship between flexibility and mental health. Some studies believe that the improvement of flexibility can help patients with developmental delays to improve their psychological state (Shell et al., 2018). Our results show that flexibility cannot predict the mental health of adolescents aged 12–13, and the relationship between flexibility and mental health of different ages and specific populations is not well defined.

With changes in lifestyle, the number of overweight and obese children and adolescents increases substantially. The impact of obesity and diet quality on mental health has been of concern and supported by a diverse evidence base (Adan et al., 2019). It is logical that food intake and food quality can have an impact on brain function, which makes diet an adjustable variable for mental health, mood, and cognitive function (Dinan et al., 2018).

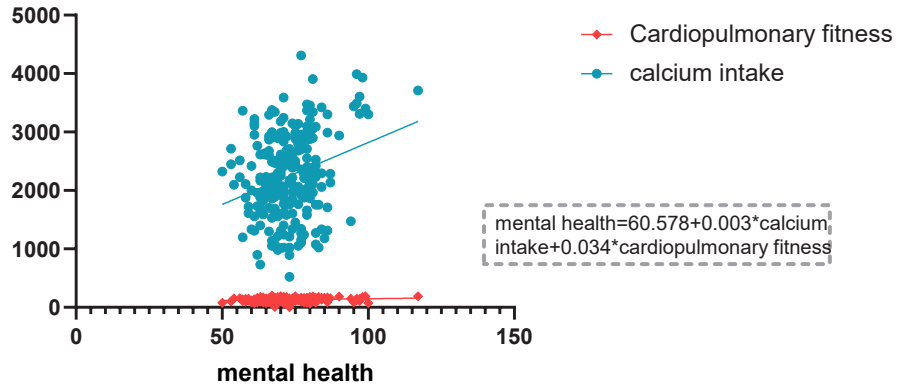

FIGURE 2 | Regression curves and equations of dietary calcium intake, cardiorespiratory fitness, and mental health.

The relationship between calcium intake and mental health in the literature is rarely studied and controversial. The significant positive association between calcium intake and mental health in adolescents observed in the present study is broadly similar to the results of previous studies (Miki et al., 2015; Wu et al., 2020). A previous Korean study (Kim et al., 2015) that investigated the relationship between calcium intake and mental health showed controversial results that increasing the frequency of calcium intake did not reduce the risk of mental illness. The inconsistent results of the study may be attributed to the methods in the study and the differences in gender, age, and race, which are related to the control variables. But our results provided positive evidence for an association between supplemental calcium intake and mental health in adolescents. In addition, we also observed that there was no correlation between BMI and mental health, and the change in adolescent BMI after classified adjustment of BMI did not have a significant impact on mental health. This is because overweight and obesity may be an important confounder in the relationship between diet and mental health (Halfon et al., 2013). Luppino et al. (2010) found an association between overweight and depression in adults, but not in those under 20. The results of this study showed no association between BMI and mental health in 12- to 13-year-olds, so this suggests that different relationships may emerge between different age groups. The imbalance between energy intake and energy expenditure is the direct cause of individual overweight or obesity. There are significant differences in caloric intake among different body mass indices in the study results, but there is no correlation between caloric intake and mental health, which better increases the reliability of the results of this study. Essential nutrients that have the potential to have beneficial effects on mental health must be obtained from the diet. Our study used the overall diet as a better indicator to investigate calcium intake and calorie intake from food sources. In the future, it is necessary to increase the frequency of different food intake and information on other nutrients and trace elements, and investigate people of different ages more accurately explain the relationship between diet and mental health.

Overall, our findings suggested that cardiorespiratory fitness and calcium intake were positively associated with better mental health. Further, stepwise multiple regression analysis showed that cardiorespiratory fitness and calcium intake could jointly explain 8.4% of the variation in mental health among adolescents aged 12–13. This study highlighted the importance of dietary calcium intake and cardiorespiratory fitness in adolescence and its potential role in modifying mental health over the life course.

Several limitations in this study should be discussed. First, there are significant gender differences in the development of adolescent physical fitness. We found that the strength and BMI of 12- to 13-year-old boys were greater than that of girls, and the flexibility of girls was better than that of boys. However, we did not highlight the relationship between gender and individual variables. In studies of specific components of physical fitness and mental health, the respective relational effects of adolescent boys and girls need to be considered. Secondly, in the dietary survey, we only analyzed the dietary calcium intake of one nutrient, thus lacking a comprehensive evaluation of the synergistic effect of other nutrients and calcium. Given the prevention of mental health problems and the critical period of growth and development, it is essential for adolescents to supplement dietary calcium intake and improve cardiopulmonary fitness. However, care is needed with calcium supplementation as it may be a risk factor for vascular disease (Tankeu et al., 2017). Consistent adverse effects on cardiovascular health have not been demonstrated for dietary calcium (Reid et al., 2017), and dietary calcium intake was lower in the survey sample. Therefore, we encourage getting calcium from the diet. In addition, it is worth noting that as a cross-sectional study, we do not know whether insufficient calcium intake leads to poor mental health, whether adolescents with poor mental health consume less calcium-rich foods, or whether the effect of cardiorespiratory fitness is an innate condition-determined, all of which imply that genetics and family environment may play a role. Therefore, there is an urgent need for longitudinal studies and randomized controlled trials investigating the explanatory mechanisms between physical fitness, diet, and mental health outcomes, especially in adolescent populations. As most mental health problems first manifest

in adolescence and early adulthood, it is necessary to fully understand the relationship between relevant variables and determine the short-term and long-term effects of physical fitness and diet on adolescents' mental health so as to provide a more accurate theoretical basis for adolescents' good mental health and healthy lifestyle in China.

CONCLUSION

The cross-sectional analysis showed gender differences in muscular strength and flexibility, and differences in caloric intake, muscular strength, speed, and overall physical fitness between BMIs among adolescents aged 12 and 13. Through the analysis of the correlation between dietary intake, physical fitness, and mental health of adolescents, the following conclusion was reached in this study. There was a positive correlation between cardiorespiratory fitness and calcium intake, and higher cardiorespiratory fitness and adequate calcium intake were significantly associated with lower levels of psychological distress. Strength, speed, flexibility, and mental health were not significantly associated. These findings suggested that adequate dietary calcium intake and improved cardiorespiratory fitness may lead to better mental health among teenagers aged 12 and 13 in China.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Jinhu Hospital of Traditional Chinese Medicine. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WL and JF: conceptualization and methodology. JT: software. JT, YY, and WL: validation. WL: formal analysis, resources, and writing—original draft preparation. WL, XT, JT, and YY: investigation. WF: data curation. ZJ: graphical processing of data. ZD: writing—review and editing. WL and XT: visualization. JF and WL: supervision and project administration. All authors have read and agreed to the published version of the manuscript.

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REVIEW
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The BERN Framework of Mind-Body Medicine: Integrating Self-Care, Health Promotion, Resilience, and Applied Neuroscience

Tobias Esch[1]*† *and George B. Stefano*[2†]

[1]*Institute for Integrative Health Care and Health Promotion, School of Medicine, Witten/Herdecke University, Witten, Germany,* [2]*Center for Cognitive and Molecular Neuroscience, First Faculty of Medicine, Charles University, Prague, Czechia*

Background: Mind-body medicine (MBM) focuses on improving our understanding of how the interactions between the brain, mind, body, and behavior can be used to promote health. In this narrative review, we present the basic principles of MBM, including the introduction of a rational framework for the implementation of MBM-based interventions. We also discuss the contributions of MBM to motivation and reward systems in the brain including those that may specifically involve the mitochondria.

Results: MBM can be used to promote health in patients with chronic diseases, especially conditions identified as lifestyle-related. MBM builds on salutogenesis, which is a paradigm that focuses on health (as opposed to disease) determinants and the development of individual resilience and coherence factors as a means to reduce stress, decrease the burden of disease, and improve the quality of life. This approach involves several well-known principles of self-healing and self-care. MBM interventions typically include behavioral modification techniques in conjunction with cognitive work focused on stress regulation, exercise, relaxation, meditation, and nutrition. We suggest the use of the acronym "BERN" (Behavior, Exercise, Relaxation, and Nutrition) to summarize the operational framework of this approach.

Discussion: Different BERN techniques act *via* shared autoregulatory central nervous system (CNS) reward and motivation circuitries. These systems rely on numerous neurobiological signaling pathways with overlapping effector molecules that converge, e.g., on nitric oxide (NO) as a common effector molecule. NO is critically coupled to reward physiology, stress reduction, and self-regulation as it modulates the responses of various mitochondrial, nuclear, and chromosomal processes within brain cells. NO has also been implicated in relevant outcomes (e.g., the placebo response).

Conclusions: MBM interventions typically follow the BERN model and aim to strengthen health and resilience, and reduce stress. The mechanisms of action of these processes involve the CNS reward systems and correlate with placebo and self-healing pathways.

Keywords: stress management, meditation, integrative medicine, behavioral medicine, salutogenesis, self-healing, placebo, mitochondria

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***Correspondence:**
Tobias Esch
tobias.esch@uni-wh.de

†ORCID:
Tobias Esch
orcid.org/0000-0001-5176-4367
George B. Stefano
orcid.org/0000-0002-8146-0740

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BACKGROUND: MIND-BODY MEDICINE

Historical Perspective

Mind-body medicine (MBM) was founded by late Harvard cardiologist Herbert Benson in the context of modern meditation research that emerged in the 1970s (Benson and Klipper, 2000). Right from the start, there was the observation that connections and interactions between the brain, mind, body, and behavior can activate psychophysiological changes and a health-promoting potential in the individual—paths towards better health. As a generic term, mind-body medicine, from the start, included mental or behavioral medicine approaches and other techniques from the areas of exercise, relaxation, stress regulation, and nutrition (see below).

From the beginning, there was a close connection between the scientific investigation of meditation and relaxation mechanisms on the one hand and the exploration of individual self-healing and self-regulation potential on the other (Esch, 2014). After initial expeditions to the Himalayas and early research, e.g., on temperature regulation under meditation conditions in Buddhist monks, Herbert Benson founded the Mind-Body Medical Institute at Harvard Medical School in Boston in 1988 (today: Benson-Henry Institute for Mind Body Medicine). What Benson noticed early on was the observation that self-healing was a "mind thing" (Benson, 1987).

Meanwhile, mind-body and meditation phenomena such as self-induced blood pressure reductions or changes in peripheral body temperature, as well as changes in skin resistance or heart rate or heart rate variability in the context of relaxation, are known in many areas, including in biofeedback or autogenic training, as well as in self-hypnosis. Benson adopted this recurring physiological pattern in his concept of the relaxation response (Benson and Klipper, 2000)—the physiological antagonist of the biological stress response (Stefano et al., 2005), elicited and controlled by the central nervous system (CNS), i.e., its self-regulation and stress-relaxation axes.

The insights into the basic mechanisms and potential of self-regulation were not new at the beginning of mind-body medicine either, as this was based, among other things, on the research of the physiologist Walter B. Cannon, who decades earlier in the same laboratory (Cannon, 1933), in which Benson also worked, had done research on stress and regulation. What was new, indeed, was that people should be able to use mental techniques to influence the "involuntary" (i.e., autonomic) regulation in a targeted (i.e., conscious, focused) way. Therefore, Benson set out to make the study of such mind-body phenomena—and their possible significance for medicine—his life's work under the new label of mind-body medicine (Komaroff, 2001). However, there was still a long way to go from the first investigations in the Himalayas to in-depth studies according to Western standards—including experimental human biological studies under laboratory conditions (e.g., Dusek et al., 2008).

The Current State

Today, MBM has been widely implemented as an important component of general health care and medical practice in the United States, typically within the framework of behavioral medicine practices. MBM includes numerous straightforward and effective approaches that can be used to promote patient-centered health care (Esch, 2020). These approaches are conceptually and practically compatible with many current trends and disciplines in both clinical medicine and research (Dobos and Paul, 2019; Esch, 2020). Of note, MBM expands the outlook of somatically-oriented general medicine practices because it encourages healthcare providers to focus on behavioral and lifestyle orientation as a means to promote health (i.e., salutogenesis—see below) *via* self-help and self-healing skills (Esch, 2014, 2020).

National Institutes of Health (NIH), U.S. Department of Health and Human Services (2019) of the U.S. Department of Health and Human Services describe MBM as a discipline that focuses on:

- The nature of the interactions that link the brain, the body, the mind, and behavior to one another.
- How emotional, mental, social, spiritual, experiential, and behavioral factors can directly influence health.

National Center for Complementary and Integrative Health (NCCIH), National Institutes of Health (NIH), U.S. Department of Health and Human Services (2019) defines MBM techniques as those that:

- Focus on the mind as a means to influence physical functioning and promote health.
- Enhance individual capacity for self-knowledge and self-care.

MBM is thus based on the recognition of a central mind-body axis, which is a concept that encompasses consciousness, behavior, and the interactions between the brain and the body. A central principle of MBM focuses on how psychological, emotional, spiritual, social, experiential, and/or behavioral factors influence human health. Effective MBM techniques are those that support individual self-regulation of the mind-body connection based on these observations.

In this narrative review, we discuss underlying factors and overarching mechanisms associated with MBM, including a general consideration of motivation and reward systems in the CNS. We also present a rational framework for the various therapeutically-effective interventions that are typically used in MBM practice.

HEALTH PROMOTION AND SALUTOGENESIS

MBM is currently used clinically for primary prevention and health promotion as well as for the treatment of lifestyle-associated chronic diseases (Dobos et al., 2006). MBM can be used to address many of the problems that are most frequently presented to general practitioners (Laux et al., 2010), including, musculoskeletal complaints (e.g., pain disorders and chronic inflammatory/rheumatic diseases), lipid metabolism disorders, endocrine, metabolic, or nutrition-related diseases (including type 2 diabetes mellitus), high blood pressure, depressive symptoms, and/or gastrointestinal dysfunction (reviewed in

Esch, 2020). MBM can also be used to support cancer treatment (Jeitler et al., 2017; Voiss et al., 2019), as an adjunct therapy for addiction treatment, strengthening resilience, and stress reduction (Esch, 2008).

In contrast to psychosomatic medicine (Fava and Sonino, 2010), MBM is not primarily linked to psychopathology or the presence of a specific disorder. While MBM techniques can be used to address a specific indication, they can also be applied more generally as a means to promote health and well-being. Similarly, and unlike conventional psychotherapy, the primary goal of MBM is not the uncovering and clarification of psychological conflicts; no psychodynamic explanations are typically sought for behaviors that need to be addressed (Paul and Altner, 2019). MBM interventions are primarily aimed at developing health-promoting attitudes and healthy, sustainable behaviors in everyday life. This approach is based on the concept of salutogenesis, which is the assumption that, in addition to factors that trigger or sustain disease processes, one can also focus on factors that generate and/or maintain human health. These "health protection factors" or "resistance resources" include those focused on stress reduction (Antonovsky, 1979, 1996).

THE BERN FRAMEWORK

MBM is based on the principle that all individuals have the potential for self-healing and can be trained to accomplish this within the framework of a resource-oriented and integrative (i.e., salutogenic) medicine program (Esch, 2002; Dobos et al., 2006; McClafferty, 2011; Brinkhaus and Esch, 2021). MBM interventions focus on the individual and consider individual competencies. The terms "auto-" or "self-regulation" or "self-regulatory medicine" are often used to describe the underlying mechanisms and active factors involved in this process (Esch, 2003, 2014, 2017, 2020).

MBM-based interventions have been established that follow the "BERN" framework (**Figure 1**). As a group, these are strategies that have an impact on behavior (B), exercise (E), relaxation (R), and (N) nutrition (Esch, 2008). Within this context, it is important to note that BERN is not a distinct program or a single example of a set of mind-body interventions (MBIs), but rather a description of a framework that encompasses numerous multimodal interventions. BERN represents a practical set of tools that are based on the individual therapeutic pillars that define MBM and MBIs.

Other important components of the multifactorial BERN approach include social support, which is usually included in the behavior column, and spirituality, faith/belief, meditation, or mindfulness techniques, which are usually associated with relaxation (Esch, 2008; Jeitler et al., 2017). Additional behavioral aspects enclose resilience factors (Ludolph et al., 2019) and instruments that promote "positive psychology" (Seligman and Csikszentmihalyi, 2000; Siegel, 2009; Esch, 2017). Likewise, other elements used to promote relaxation include formal meditation and mindfulness exercises.

Although MBM is still relatively young and the framework presented here was developed in a modern medical-scientific context, it must not be forgotten that individual components (columns, pillars, specific techniques) have a very long tradition in medicine. Hence, we can already find essential parts of them in Hippocrates and Galen (van der Eijk, 2011; Esch, 2014). The combination—practically the whole package of complete BERN-MBIs—has been around for a long time: in yoga, for example, the multifactorial practice of posture, movement, relaxation (meditation, breathing exercises), nutrition and even cognitive-mental techniques (visualizations, affirmations, etc.) was implemented long ago, and this "BERN" framework is also showing impressive effectiveness in modern medicine (Cramer et al., 2017; Shin, 2021; Wibowo et al., 2022).

BERN AND THE "TWO-DOOR MODEL" OF BEHAVIORAL AND MIND-BODY MEDICINE

The BERN framework of MBM promotes the general principles of resilience and health maintenance (see also below). The behavior-related health and lifestyle modification programs are typically introduced as components of a preventive, behavioral, or complementary medical intervention. However, the actual implementation of BERN is frequently handled not by a physician, but by health-wellness coaches, MBM instructors, behavior therapists (frequently psychologists), or specifically-trained individuals with expertise in health promotion strategies (Werdecker and Esch, 2021). In other words, these strategies are typically implemented *via* a "two-door" model (Werdecker and Esch, 2021; Esch, 2021a). Patients are initially seen in an outpatient facility where a physician provides advice and treatment for a disease process, and an allied therapist or MBM trainer then discusses—and performs—health promotion and potential behavioral changes designed to target individual health and self-healing potentials (Werdecker and Esch, 2021).

This dichotomy is not just for pragmatic and capacitive reasons, e.g., to preserve resources. Irrespective of the need for the MBM instructors to demonstrate their own professionalism, training, and qualifications for the effective implementation of BERN/MBM coaching, there is also a paradigmatic reason for the "two-door" model: doctors are well-trained experts for detecting and treating pathologies, risks, and diseases. Indeed, the external doctor (the "medicus") should be able to carry out and implement the best possible diagnostics and therapy as well as preventive measures. However, this pathogenetic view differs fundamentally—i.e., paradigmatically—from the perspective of the inner doctor (the "archaeus"), which addresses the inner potential for self-healing and salutogenesis: BERN and MBM as frameworks and set of techniques or practical programs for health promotion and empowerment of the inner doctor are intended, as outlined, to increase individual health potentials, i.e., to generally activate health protection factors, increase resistance resources, and reduce allostatic loads, i.e., stress (McEwen, 1998; Esch, 2002, 2014). This salutogenetic perspective is complementary—not alternative or exclusive—to the pathogenetic approach as it prevails in conventional medicine (Esch and Brinkhaus, 2021). The combination of both perspectives—in theory, and practice—may also be called "integrative medicine" (Brinkhaus and Esch, 2021).

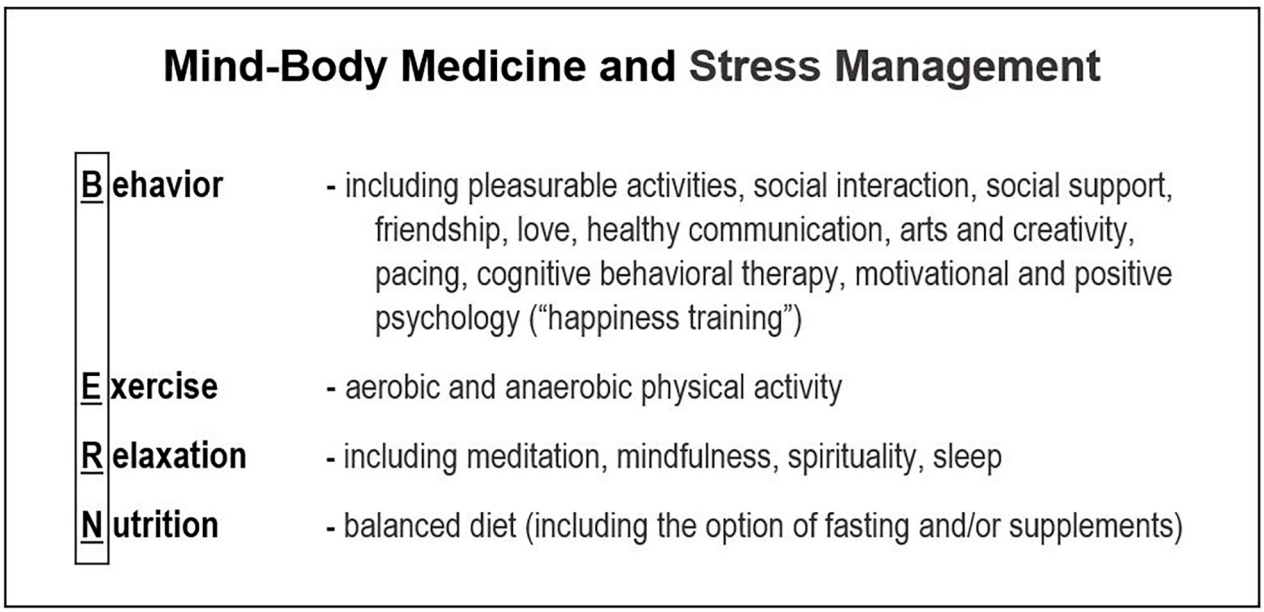

FIGURE 1 | The BERN framework of mind-body medicine (MBM). The four principles of integrative multimodal MBM and stress management programs include Behavior, Exercise, Relaxation, and Nutrition.

BERN AND RESILIENCE

There has been a sizable increase in the amount of evidence available that supports the use of MBM in health promotion as well as in the prevention and therapy of various diseases, especially in primary care settings (Esch and Brinkhaus, 2021). There are now numerous publications and systematic reviews that support the efficacy of MBM-based interventions (e.g., Astin et al., 2003; Anderson and Taylor, 2011; Prochaska and Prochaska, 2011; Cramer et al., 2015). However, while robust evidence is available to support the four BERN pillars (see below), several issues remain unclear. For example, additional evidence will be needed for an effective evaluation of MBM and its role in preventing or promoting more favorable outcomes in diseases with high mortality.

Resiliency (or: resilience) is the ability to maintain adaptive functioning in response to the ongoing stress of daily living (Park et al., 2021). Hence, resiliency training is a core element of MBM (Stahl et al., 2015; Esch and Esch, 2021; Park et al., 2021), and here, it typically refers to practicing a set of core coping skills (i.e., relaxation, stress awareness and management, and adaptive/behavioral strategies). However, evaluating the overall health outcomes of MBM-resilience practice in specific diseases and patient populations remains a challenge, e.g., due to a significant lack of longitudinal and controlled studies.

Among the issues associated with these assessments, the classifications (i.e., the assignment of a given attribute to a specific BERN pillar) are frequently not uniform. For example, some researchers assign the resilience factors solely to the areas associated with cognition and behavior (B) vs. relaxation (R) and mindfulness (Stahl et al., 2015). However, some combine B and R into their own synoptic resilience framework (Ludolph et al., 2019). Others see physical training and sport as a formal reference for resilience training, and thus assigned to Exercise (E), or the entire BERN framework (Komaroff, 2001; Stahl et al., 2015).

Moreover, it is not yet clear whether individual BERN or lifestyle factors can be fundamentally influenced by therapy; this remains a subject of intensive research with sometimes controversial results. At this time, there is strong evidence supporting the positive impact of exercise (E) or physical activity (e.g., Miko et al., 2020; Posadzki et al., 2020) and nutrition-related (N) interventions (e.g., Rees et al., 2013; Naude et al., 2017), such as in cardiovascular health (e.g., Casas et al., 2018; Fiuza-Luces et al., 2018), sometimes also used in combination (e.g., Nitschke et al., 2022). Likewise, the evidence supporting a role for primarily cognitive or psychological techniques (B) has improved significantly in recent years, despite methodological weaknesses and the substantial heterogeneity associated with this field of study (reviewed in Esch, 2002, 2017, 2020). Recent meta-analyses that focus on positive psychology, resilience, and optimism have generated an overall positive picture (Bolier et al., 2013; Chakhssi et al., 2018; Joyce et al., 2018; Rozanski et al., 2019). These findings also include studies on risk stratification in which the results associated with different pillars are combined (e.g., Chomistek et al., 2015). For the relaxation (R) or meditation pillar, too, the evidence appears rather robust, although weaker overall (e.g., Astin et al., 2003; Ospina et al., 2007; Goyal et al., 2014; Stahl et al., 2015; Long et al., 2017; Flynn, 2018; Michaelsen et al., 2021). Current knowledge that addresses

molecular mechanisms and active factors (e.g., Esch and Stefano, 2004, 2010; Esch et al., 2004, Stefano and Esch, 2005; Salamon et al., 2006; Stefano et al., 2006, 2019a; Esch, 2013; Esch et al., 2018, 2020a; also see below), as well as its inherent cost-efficiency (Sobel, 2000), has also promoted a more widespread acceptance of MBM in the healthcare systems in many countries.

THE NEUROBIOLOGICAL BASIS OF MIND-BODY MEDICINE

Current research on the neurobiological basis of MBM, including the molecular and autoregulatory pathways underlying the positive responses to relaxation and meditation, has shown relevant parallels to physiologic activation patterns that are similar to those associated with, for example, placebo mechanisms (Moss et al., 2022; Sezer et al., 2022). This applies in particular to the involvement of neurobiological reward processes, including the specific reward and motivation systems that are initiated in the three limbic levels of the CNS (Esch and Stefano, 2004, 2010; Esch et al., 2004, 2017; Esch, 2013, 2017; Esch, 2020).

Interestingly, the existence of a placebo effect was disputed for a long time or, alternatively, dismissed as a methodological error (Esch, 2014, 2020). Today, the placebo effect is widely recognized and accepted, although it is not yet fully understood. The results from studies published by Kam-Hansen et al. (2014) and Kaptchuk et al. (2010) suggested that the placebo effect exists even in studies involving "open-label treatments" (i.e., when the patient is informed that he or she will be taking a drug with no active ingredients). This study design virtually eliminates concerns regarding deception. However, it is critical to note that these actions may have a positive influence on self-healing, as the possibility of self-regulation remains functional under these circumstances. Perhaps equally interesting, as predicted earlier by anthropologists (as described in Esch, 2014, 2020), recent research has uncovered genetic factors that contribute to the susceptibility to the placebo effect (e.g., Hall et al., 2012).

Accordingly, the placebo effect also works if it is not based on deception or "blind belief". The intentional directing of attention to a previously learned (conditioned)—and positively anticipated (expected), in a suitable situation—favorable outcome activates self-healing processes (Esch, 2014). It is undisputed that there can also be specific effects within the framework of MBM and MBIs, just as the individual pillars of the BERN framework also present specific components in addition to overlapping signaling paths (see Esch and Stefano, 2010; **Figure 2**). In addition to the anticipation and motivation systems involved, other CNS networks also come into play, such as the salience network, which is closely linked to the reward system, the resting state network (default mode network), or parts for self-processing and self-reference, and finally, frontal CNS networks for executive functions (Lee et al., 2018; Gothe et al., 2019; Esch, 2021b; Michaelsen and Esch, 2021, 2022; Zhang et al., 2021). The feeling of non-wanting or of relief (i.e., stress reduction), as for "happiness", is also embedded here (Esch, 2022). However, placebo effects may account for and serve as blueprints (or "relay stations") for the most relevant CNS networks and functions involved in MBIs and BERN practices and their reported health outcomes.

Hence, as suggested, also by the results of modern analysis and imaging methods, the brain is the most likely source of all self-regulatory responses. The activation of these phenomena is accompanied by the release of characteristic CNS messengers (e.g., dopamine). The regions and networks activated are located in phylogenetically old areas of the CNS, including the limbic reward regions (**Figure 2**; Esch et al., 2004; Esch and Stefano, 2004, 2010; Michaelsen and Esch, 2021). Many self-healing techniques have been associated with these same processes; while the factors that activate each mechanism may be specific to each individual based on strong genetic and/or cultural influences, the overall mechanism may rely on more universal biological principles (Esch, 2014, 2020).

Thus, it is not surprising to find overlap or convergence of many different self-healing properties on a central autoregulatory center, ultimately leading to a reduction of inflammation and stress (Esch and Stefano, 2004, 2010; Stefano et al., 2005). Both, BERN and the placebo effect, seem to engage reward and motivation centers in the CNS (**Figure 2**; Stefano et al., 2001; Esch and Stefano, 2004; Esch et al., 2004; Fricchione and Stefano, 2005; Esch, 2014, 2020).

Overall, we can conclude that both MBM and the placebo effect are based on a system of self-regulation, and require the activation and functioning of a corresponding biological CNS reward-motivation system. Effective activation of this system relies on the convergence of factors associated with an "embedded" (individually memorized or culturally learned) positive experience. This experience leads to positive expectations for the future (i.e., anticipation) based on a "suitable opportunity" that depends directly on concrete conditioning and also on the specific context. *Via* this mechanism, a positive outcome is anticipated and the regulatory processes are focused in this direction. Correspondingly, the newly-focused attention frame does not anticipate other outcomes. In other words, one "trusts" that there will be a repetition of the positive result that has already been experienced in the past.

In principle, these outcomes can be achieved *via* the actions of brain regions or networks that represent a systemic or functional unit (Esch and Stefano, 2004; Esch, 2017). With respect to the person affected (i.e., the "regulator"), this implies that healing is possible and lies within the intentional window of perception and probability. While specific methodologies, for example, the BERN framework, provide context for these phenomena, these are frequently determined by cultural and/or situational attributes. In these cases, positive conditioning can provide self-assurance and may lead to an expectation of positive self-efficacy. Once complete, the result is that one can experience oneself as competent and effective (Esch, 2003).

In a sense, we can understand MBM and related behavioral self-healing rituals as practical anchors of the neurobiological and psychological connections presented (Esch and Stefano, 2010). Thus, MBM can be viewed as an "applied placebo effect", and self-healing as a type of "placebo medicine" (Stefano et al., 2001). As described above, results from several recent neurobiological studies stand in strong support of the involvement of relevant

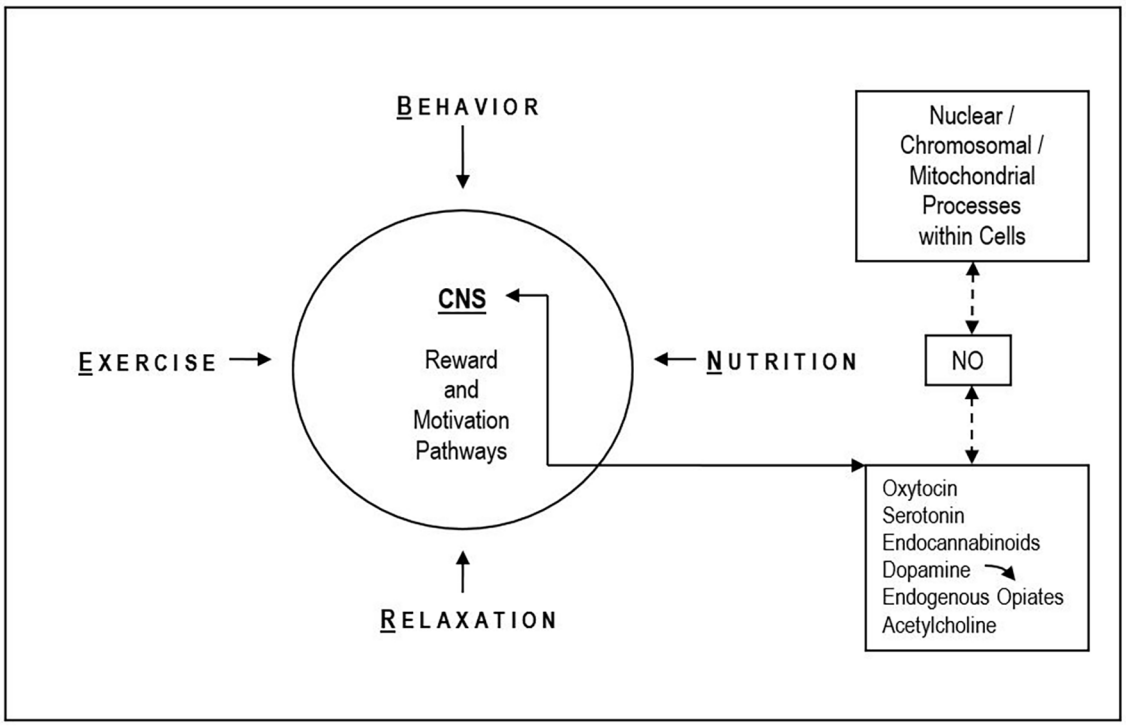

FIGURE 2 | The shared neurobiology of BERN approaches. Different BERN techniques and MBM (self-care) practices may have a direct impact on physiologic regulatory reward and motivation circuitries in the central nervous system (CNS). This commonality may represent overlapping functions associated with the general neurobiological principles of autoregulation (i.e., the potential for self-healing). MBM engages numerous CNS signaling pathways and effector molecules to promote healing, many of which converge on nitric oxide (NO) as an example for a common effector (i.e., a secondary or tertiary messenger). NO is critically coupled to the reward physiology and stress reduction/self-regulation and has a decisive impact on various processes within the cells and their organelles (i.e., chromosomes, nucleus, mitochondria). NO has also been specifically implicated in pathways leading to the placebo response (for further information and references: see text).

brain regions for limbic and reward regulation in self-healing and MBM practices (Moss et al., 2022; Sezer et al., 2022).

In summary, the concepts and phenomena associated with self-regulation, BERN, and MBM are of great relevance to medicine (Esch, 2014). The benefits of these phenomena will be revealed by additional research, self-understanding, and clinical application.

HYPOTHESIS FOR FUTURE RESEARCH: ADDITIONAL PATHWAYS AND MITOCHONDRIAL INVOLVEMENT

Stress management and self-regulation training usually consist of one to all of the following instruments and activities: behavioral or cognitive, exercise, relaxation, and nutritional or food interventions (BERN), including social support and spirituality. Some of the relevant molecular regulatory pathways involved are already known, while others remain to be described.

Based on the observed physiological and molecular mechanisms underlying the known responses to MBM, we further hypothesize that interventions involving relaxation and other modalities act by modulating autonomic responses (Stefano et al., 2019a,b). This hypothesis also suggests that MBM behavioral training programs such as BERN have an overall positive impact on mitochondrial bioenergetics and insulin secretion and can reduce the activation of pro-inflammatory and stress-related pathways. We surmise that a plausible model of behaviorally-mediated regulation of whole-body metabolic processes must be intrinsically broad-based and multifaceted, and this will require the integration of numerous contributions from functionally interactive organs associated with both the peripheral and CNS (Stefano et al., 2019a,b).

Beneficial behaviors and strategies to overcome stress are, as a more general principle, neurobiologically rewarded by pleasure ("happiness") induction, yet positively and physiologically amplified and reinforced (Esch et al., 2003; Michaelsen and Esch, 2021; Esch, 2022). The underlying physiology (i.e., self-/autoregulation) seems to work *via* dopamine, endocannabinoid, endorphin, and morphine release, as well as stress hormone (adrenaline/noradrenaline, cortisol) modulation, oxytocin and serotonin signaling pathways (Esch et al., 2002, 2004; Esch and Stefano, 2004, 2010; Esch, 2022), many of which act *via* nitric oxide (NO) release—apart from other messenger molecules (**Figure 2**). These latter effects are unspecific, however, downregulatory and clearly stress-reducing by their nature, acting *via* local CNS networks.

States of persistent activity within local circuits of cortical neurons are tonically modified by inhibitory synaptic depression. Importantly, gamma-aminobutyric acid (GABA) CNS systems, exemplified in this regard, are well established to represent the major source of regulatory neural inhibition on chronically active local circuit cortical neurons (Mann et al., 2009). The inhibitory/suppressive effects of GABA are pharmacologically mediated by differential activation of GABAA and GABAB receptor subtypes (Mann et al., 2009). Hence, the clinical importance of restorative GABAergic transmission in anesthesia, pain and analgesia, cardiovascular function, and psychiatry is supported by the wide variety of pharmaceutical agents designed to selectively target GABAA and GABAB receptor subtypes (e.g., Hepsomali et al., 2020). The essential regulatory effects of GABA on patterns of excitatory activity across cortical microcircuitry extend to GABAergic modulation of brainstem neurons involved in CNS mediation of autonomic control of cardiovascular function within the nucleus tractus solitaries (Tjen-A-Looi et al., 2014). In sum, the putative regulatory effects of GABAergic transmission on multiple physiological aspects of the relaxation response are compelling and most likely extend to integrated patterns of neuronal activities throughout sensory, cognitive, and autonomic regulatory neuronal groupings throughout the CNS (Stefano et al., 2019a; Hepsomali et al., 2020; Büttiker et al., 2021; Namgung et al., 2021).

In addition, we further speculate that the activation of numerous protective and anti-bio-senescence processes may have emerged during evolutionary development to ensure the survival of hybrid prokaryotic/eukaryotic progenitor cells (i.e., the precursors of mitochondria) and protect them from the harmful byproducts of oxidative metabolism (Stefano et al., 2019a,b; Esch et al., 2020b). Preservation and adaptation of multifaceted regulatory molecules, notably NO, most likely paralleled the development of eukaryotic cells *via* multifaceted stereo-selective recognition and conformational matching executed by complex biochemical and enzyme systems.

Hence, the relaxation response may be a manifestation of a synchronized process of molecular metabolic corrective responses that also include cognition (i.e., "awareness"; see Stefano et al., 2019a,b). In fact, cognitive-behavioral, as well as relaxation, meditation, and other BERN practices can show an intimate connection to intracellular processes and signaling, including mitochondrial and chromosomal activation (**Figure 2**; also see Esch et al., 2018, 2020b; Stefano et al., 2019a,b). In this regard, as stated earlier, complex BERN and other mind-body techniques such as yoga have already demonstrated their neurobiological, psychoneuroendocrinological, and -immunological as well as physiological stress-reducing and health-promoting potential (Michalsen et al., 2005; Wolever et al., 2012; Posadzki et al., 2014; Cramer et al., 2015, 2017; Pascoe et al., 2017; Shin, 2021; Koch et al., 2022; Wibowo et al., 2022).

CONCLUSIONS

MBM is a field that focuses on health promotion, prevention, and treatment of lifestyle-related diseases. It builds on the concepts of salutogenesis and resilience, based on principles that include general self-healing or self-care. MBM interventions follow the BERN framework (behavior, exercise, relaxation, and nutrition). The responses to various BERN techniques converge on shared mechanisms of CNS autoregulation involving limbic reward and motivation systems. Various neurobiological signaling pathways and effector molecules within these systems overlap and converge on constitutive NO as a common effector molecule. Other key regulators—such as GABA—are modulated as well, resulting in an overall downregulating potential for MBM and BERN. Thus, NO—and related messenger substances—are critically coupled to the reward physiology as well as stress reduction and self-regulation, and they may have an impact on mitochondrial, nuclear, and/or chromosomal processes as well as the placebo response.

AUTHOR CONTRIBUTIONS

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Research in Mindfulness Interventions for Patients With Fibromyalgia: A Critical Review

Salomé Leça[1] *and Isaura Tavares*[1,2,3]*

[1] Unit of Experimental Biology, Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal, [2] Institute of Molecular and Cell Biology, University of Porto, Porto, Portugal, [3] I3S–Institute of Investigation and Innovation in Health, University of Porto, Porto, Portugal

Fibromyalgia is one of the most common causes of widespread chronic pain. It has a huge impact on the quality of life, namely because it appears earlier in life than most of the chronic pain conditions. Furthermore, emotional-cognitive distress factors, such as depression and anxiety, are a common feature in patients with fibromyalgia. The neurobiological mechanisms underlying fibromyalgia remain mostly unknown. Among non-pharmacological treatments, cognitive-behavioral therapy has been used during the last decade, namely with the enrolment of patients in programs of mindfulness-based stress reduction (MBSR) and in mindfulness-based interventions (MBI). We critically analyzed the literature to search for scientific evidence for the use of MBI in fibromyalgia. The studies were evaluated as to several outcomes of fibromyalgia improvement along with aspects of the study design which are currently considered relevant for research in mindfulness. We conclude that despite the sparsity of well-structured longitudinal studies, there are some promising results showing that the MBI are effective in reducing the negative aspects of the disease. Future design of studies using MBI in fibromyalgia management should be critically discussed. The importance of active controls, evaluation of sustained effects along with investigation of the subserving neurobiological mechanisms and detailed reports of possible adverse effects should be considered.

Keywords: chronic pain, mind-body interventions, meditation, emotional-regulation, selfregulation, clinical trials, oriented review

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Emem Laguda, Health Strategy and Delivery Foundation, Nigeria

***Correspondence:**
Isaura Tavares
isatav@med.up.pt

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INTRODUCTION

Fibromyalgia is a complex and debilitating disease. Its main symptoms are chronic widespread pain, sleep problems, physical exhaustion, and cognitive difficulties (Hauser et al., 2015). Patients suffering from this condition also have a high variety of somatic symptoms, psychological distress and present a higher prevalence of depression and anxiety-related disorders (Fietta et al., 2007).

There is no gold standard test for fibromyalgia diagnosis. The more recent criteria of the American College of Rheumatology (ACR) to identify fibromyalgia postulate that the diagnosis in adults should meet the following criteria (Wolfe et al., 2016):

1. Generalized pain, defined as pain in at least 4 of 5 regions;
2. Symptoms present at a similar level for at least 3 months;

3. Widespread pain index (WPI) $\geq$ 7 and symptom severity scale (SSS) score $\geq$ 5 OR WPI of 4–6 and SSS score $\geq$ 9;
4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

Most studies show that fibromyalgia prevalence is approximately 2% in the general population, having a higher impact in women. However, one systematic review in the world using meta-analyses (Heidari et al., 2017) showed that this general population prevalence is much lower than the prevalence of fibromyalgia among patients with specific disorders, such as irritable bowel syndrome (12.9%), hemodialysis (6.3%), and type 2 diabetes mellitus (14.80%).

The pathophysiology of the disease is under active research but remains unknown. Two main neurobiological mechanisms have been proposed. The first is an alteration of the immune-inflammatory connection which may lead to sensitization of the peripheral and central nervous system. Patients with fibromyalgia present an imbalance of pro-inflammatory and anti-inflammatory cytokines, with an increase in the former and a decrease in the later (Uceyler et al., 2011; Rodriguez-Pinto et al., 2014; Littlejohn, 2015; Backryd et al., 2017).The second mechanism derives from the strong link between pain complaints and emotional/cognitive distress consistently reported in patients with fibromyalgia and proposes that peripheral causes are less relevant than central consequences. This so-called "brain hypotheses" (Ceko et al., 2013; Hubbard et al., 2020) considers that fibromyalgia is a central sensitivity syndrome characterized by sensitization of the somatosensory system, a condition common to chronic pain situations, in which a signal amplification occurs during the transmission of nociceptive input, which leads to exacerbation of pain perception (Vierck, 2006). Besides this somatic sensitization, fibromyalgia patients also present "cognitive-emotional sensitization," a cognitive bias toward the negative events accompanied with perseverative negative thoughts, rumination and catastrophizing (Brosschot, 2002). A recent imaging study proposed that fibromyalgia patients with more severe pathology in the peripheral nervous system presents higher alterations in morphology, structural and functional connectivity at the encephalon, which allows to connect the peripheral and brain mechanism reviewed above (Aster et al., 2022).

Pain is modulated from the brain, and several chronic pain conditions have been ascribed to deficient top-down pain modulation that is unable to block the transmission of input from the spinal cord or may even increase neuronal transmission through the somatosensory system (Heinricher et al., 2009). A meta-analysis of neuroimaging studies showed that in fibromyalgia there is an increased neuronal activation in pain processing areas, such as the posterior insula and secondary somatosensory cortices, along with altered functional connectivity in brain areas included in the pain matrix related to central sensitization (O'Brien et al., 2018). Also, in fibromyalgia patients, increased connectivity was detected between the insula (a pronociceptive region) and the "default mode network," which is active when the brain is at rest (Napadow et al., 2010; Jensen et al., 2012). The opposite, decreased connectivity, occurs between brain areas involved in pain inhibition (Napadow et al., 2010; Jensen et al., 2012). These results are in accordance with other studies and indicate impaired top-down pain modulation during fibromyalgia.

Because of its multifactorial and poorly understood etiopathogenesis, fibromyalgia has no curative treatment. The current modalities aim to target the main symptoms of the disease and improve the quality of life (QoL). However, because of the high variability in patient-to-patient symptoms' predominance and severity, the approach needs to be empirical, individualized, and based upon a strong therapeutic alliance between clinician and patient with realistic treatment goals.

The European League Against Rheumatism (EULAR) revised recommendations for managing fibromyalgia, separates the specific recommendations in non-pharmacological and pharmacological therapies (Macfarlane et al., 2017). It recommends starting the treatment with non-pharmacological modalities, namely, physical exercise, the only "strong for" recommendation, with effects on pain, physical function and wellbeing. Additional non-pharmacological therapies can be combined, such as meditative movement therapies (qigong, yoga, tai chi $\rightarrow$ effects on sleep, fatigue, and QoL), mindfulness-based stress reduction (pain and QoL), acupuncture (pain and fatigue), and hydrotherapy (pain and QoL).

If therapeutic failure within this first step, an additional individualized treatment is recommended. For those with mood disorders or unhelpful coping strategies, cognitive behavioral therapy should be considered. Patients with severe pain or severe sleep disturbance should be considered for pharmacotherapies, specifically duloxetine, pregabalin and tramadol for pain and amitriptyline, cyclobenzaprine and pregabalin for sleep (Macfarlane et al., 2017). However, some "transatlantic" differences emerged namely as to the use of duloxetine and pregabalin namely given the small effect sizes and the associated adverse effects (Briley, 2010). Ultimately, multimodal rehabilitation programs will be necessary for patients with severe disability, with stronger improvements than individual therapies alone.

MIND-BODY INTERVENTIONS: MINDFULNESS

The use of mind-body interventions has increased dramatically in the last two decades in Western countries with the huge challenge of conciliating evidence-based medicine with traditions and practices that are common for centuries in the East.

Departing from the Buddhist philosophy, mindfulness has reached the Western mainly by the structured programs of mindfulness-based stress reduction (MBSR) implemented in 1979 by Kabat-Zinn (1982). Departing from MBSR programs, other mindfulness approaches such as mindfulness-based cognitive therapy (MBCT) and mindful-self compassion (MSC) have been applied for the treatment of clinical disorders such as anxiety, depression and stress along with diseases with a huge psychological burden and impact in the QoL,

such as chronic pain (Khoury et al., 2013; Goyal et al., 2014; Creswell, 2017).

These programs typically last 8 weeks and its primary theoretical premise is that, by practicing mindfulness, individuals will become less reactive to unpleasant phenomena and more contemplative and reflective, leading to increased self-awareness and self-emotional regulation (Creswell, 2017). Mindfulness is an active and intentional practice that may lead to a mental condition characterized by non-judgmental awareness of the experience in the present moment, including one's sensations, thoughts, bodily states, consciousness, and the environment, while encouraging openness, curiosity, and acceptance (Bishop et al., 2004).

Mindfulness involves two components: self-regulation of attention and orientation toward the present moment with curiosity, openness, and acceptance (Bishop et al., 2004). Although they are not mindfulness-structured programs, mindfulness is present in other evidence-based cognitive-behavioral therapies, such as dialectical behavior therapy (DBT) and acceptance and commitment therapy (ACT). Despite the exponential increase in the number of published studies with the application of Mindfulness Based Interventions (MBI) in the last decades, a considerable bulk of research comes from cross-sectional studies, waitlist-controlled trials, and other methodological shortcomings that reduce the strength of the conclusions. A continuous monitoring of the quality of research using MBI has been proposed by several researchers.

MIND-BODY APPROACHES IN FIBROMYALGIA: MINDFULNESS BASED INTERVENTIONS

There are at least four major challenges in fibromyalgia treatment. The first derives from the fact that fibromyalgia is hard to diagnose. After lombalgia and osteoarthritis, fibromyalgia is usually considered the third most prevalent musculoskeletal pain-associated condition, but it remains underdiagnosed and is considered a "mysterious syndrome" (Sarzi-Puttini et al., 2020). The second challenge derives from its unclear etiopathogenesis which precludes a fully based mechanistic treatment (Perrot, 2019). The third and fourth challenges are common to some pain conditions, namely the lack of standard biomarkers (signatures) and interindividual variability of complaints and responses to treatment. Both challenges may be due to the concept of pain.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Pain is not only a sensory experience, and its cognitive and emotional components demand a multifactorial approach which is far beyond pharmacological management and frequently requires psychological interventions aimed to promote coping strategies and emotional regulation. These psychological approaches represent a possibility for individually tailored interventions, where pharmacological treatments are insufficient.

Also demonstrating the importance of psychological factors, expectations are important in clinical management of fibromyalgia. One systematic review and meta-analysis of randomized controlled trials showed that the size effect of placebo for pain relief was clinically moderate (0.53, 95% CI 0.48–0.57). The same review concludes that placebo treatment was shown to also reduce fatigue and improve non-restorative sleep and increase the QoL mainly in women and initial phases of the disease (Chen et al., 2017).

Mindfulness may be defined as "the awareness that arises through paying attention, on purpose, in the present moment, non-judgmentally" (Kabat-Zinn, 1982). By promoting acceptance and fostering emotional self-regulation, MBI may theoretically be suitable for managing distress events in patients with fibromyalgia. From the multiple studies using MBI in those patients, the majority have used MBSR programs.

Based on the critical perspectives and concerns about research in mindfulness (Davidson and Kaszniak, 2015; Van Dam et al., 2018), we conducted a critical review of the literature with two aims 1. Analyze the evidences of benefits of MBI in patients with fibromyalgia and 2. Establish if the available papers used the directives of research in this field, namely the existence of active controls, reports of previous experience of participants in mind-body approaches, evaluation of expectations of the participants and meditation experience of the teachers. The purpose of this critical review was not to perform a systematic review of the literature since there are several studies that evaluated the effects of MBI interventions for fibromyalgia (Lauche et al., 2013; Haugmark et al., 2019; Khoo et al., 2019; Pei et al., 2021).

We conducted a research on database PubMed, using the terms "(mindfulness or meditation) and fibromyalgia". Our inclusion criteria were:

1. Randomized controlled trials and non-randomized controlled trials.
2. Studies of patients diagnosed with fibromyalgia (no other chronic pain conditions).
3. Studies that compared well-structured MBI programs with any active treatment.
4. Studies that assessed at least one patient-centered outcome, with no restrictions applied.

From the 160 initial results, we first removed all duplicates. Then, titles and abstracts were individually screened for potentially eligible studies. The remaining 30 studies passed through a full text assessment and 11 were excluded for not being controlled trials, seven for not having an active intervention for comparison, four for not having well-structured MBI programs within the intervention group and one for not assessing patient-centered outcomes. This resulted in seven eligible studies, which are listed in **Table 1**, in chronological order of publication.

Table 1 summaries the results regarding the evidences of benefits of MBI in patients with fibromyalgia (our first aim). We clustered the outcomes as being related to either Fibromyalgia Functional Impact and Symptomatology, Pain, Mental Health, or QoL. We highlight positive findings and outcomes measured through a validated scale. Two studies

TABLE 1 | Overview of included studies'characteristics and main findings.

Author, year, (reference)	Participants (N, age, gender, drop-out rate)	Co-occurring therapies	Intervention	Comparison (control)	Outcome measures	Measurement time point	Results		Self-reported study limitations
							Short-term	Long-term	
Grossman et al. (2007)	58 fibromyalgia patients Mean age MBSR group: 54.40 ± 8.30 years Control group: 48.80 ± 9.10 years Gender: female only Drop-out: 10,30%	Not detailed	MBSR (n= 39) Kabat-Zinn adapted program 8 weeks total One 2.5h weekly group-session + all-day retreat (7h) + 45-min daily self- practice	Social support, relaxation, stretching. (n=13) 8 weeks total One 2.5h weekly session + 45 min daily self-practice	1) Pain severity (VAS) 2) Pain perception (PPS) 3) Pain regulation (l PR) 4) Quality of life (PLC) 5) Anxiety and Depression (HADS) 6) Physical symptoms	Baseline Post-treatment 3 years follow-up (only for MBSR group)	No between-groups comparisons made. MBSR: Control group: 1) Sign, improvement 1) No sign.imp. 2) Sign, improvement 2) No sign.imp. 3) Sign, improvement 3) No sign.imp. 4) Sign, improvement 4) No sign.imp. 5) Sign, improvement 5) No sign.imp. 6) Sign, improvement 6) No sign.imp.	MBSR only (n=26): 1) Sign. improvement 2) No sign. improvement 3) Sign. improvement 4) Sign. improvement 5) Sign. improvement 6) Sign. improvement	Not randomized Female patients only Small control group Baseline differences between experimental groups No medical utilization Assessed Follow-up did not include the control group
Schmidt et al. (2011)	177 fibromyalgia patients Mean age: 52.50 ± 9.60 years Gender: female only Drop-out: 5,10%	Usual care Not detailed	MBSR (*n*= 53) Kabat-Zinn based program 8 weeks total One 2.5h weekly group-session + all-day retreat + 45-60 min daily self-practice.	Wait-list (n=59) No-treatment Active intervention (N=56) Support, education, relaxation, stretching. 8 weeks One 2.5 h weekly session + 45–60 min daily self practice	1) Pain perception (PPS) 2) Quality of life (PLC, FIQ) 3) Quality of sleep (PSQI) 4) Depression (CES-D) 5) Anxiety (STAI) 6) Physical symptoms (GCQ)	Baseline Post-treatment 2 months follow- up	1) No sign, group differences 2) No sign, group differences 3) No sign, group differences 4) No sign, group differences 5) No sign, group differences	1) No sign. group differences 2) No sign. group differences 3) No sign. group differences 4) No sign. Group differences 5) No sign. Group differences	Excessive patient burden Recruitment and assignment Treatment fidelity

(Continued)

TABLE 1 | (Continued)

Author, year, (reference)	Participants (N, age, gender, drop-out rate)	Co-occurring therapies	Intervention	Comparison (control)	Outcome measures	Measurement time point	Results		Self-reported study limitations
							Short-term	Long-term	
Davis and Zautra (2013)	79 fibromyalgia patients Mean age: 46.14 years Gender: 77 female (97,50%) 3 male (2,50%) Drop-out: 0,00%	Not detailed	MSER (n=39) Online. Up to 6 weeks duration. 12 modules, self-paced. One Adobe Presentation lasting 15 min for each module. + Encouragement to use the skills discussed in each module. + Audio-recording of 1 mindfulness meditation relevant for each module plus encouragement to access it daily + Daily reports	Health tips (n=40) Information regarding health-promoting behaviors. Online. Up to 6 weeks duration. 12 modules, self-paced. One Adobe Presentation lasting 15 min for each module + Daily reports	1) Pain 2) Pain Coping Efficacy 3) Positive and Negative Affect (PANAS) 4) Perceived Social Relations (Social activity engagement, Loneliness, Family stress, Family enjoyment)	Baseline Post-treatment	1) No sign, group differences 2) Sign, group differences favoring MBI 3) PA: Sign, group differences favoring MBI NA: No sign, group differences 4) Sign, group differences favoring MBI		No confirmation of Fibromyalgia diagnosis Untested generalizability of findings Self-reported outcome measures No evaluation of treatment effects mechanisms No follow-up Preliminary findings
Grossman et al. (2017)	168 fibromyalgia patients Mean age: 52.50 ± 9.60 years Gender: female only Drop-out: 16,70%	Usual care 46% taking antidepressants (no group differences)	MBSR Kabat-Zinn based program 8 weeks total One 2.5h weekly group-session + all-day retreat + 45-60 min daily self-practice.	Wait-list No-treatment Active intervention (N= 59) Support, education, relaxation, stretching. 8 weeks One 2.5h weekly session + 45-60 min daily self-practice	1) Cardiac autonomic regulation (HR, RSA) 2) Respiratory function (Fb, Vt, V) 3) Physical activity (accelerometer) 4) Association between 1),2),3) and Patient-reported clinical improvement (PPS, PLC, FIQ, PSIQI, CES-D, ST AI, GCQ)	Baseline Post-treatment 2 months follow-up	1) No sign, group differences 2) No sign, group differences 3) No sign, group differences 4) No sign, association despite sign. Patient-Reported clinical improvement	1) No sign, group differences 2) No sign, group differences 3) No sign, group differences 4) No sign, association	Small period of monitoring Excessive patient burden High drop-out rate Co-occurring psychopharmacologic al medication

(Continued)

TABLE 1 | (Continued)

Author, year, (reference)	Participants (N, age, gender, drop-out rate)	Co-occurring therapies	Intervention	Comparison (control)	Outcome measures	Measurement time point	Results		Self-reported study limitations
							Short-term	Long-term	
Van Gordon et al. (2017)	148 fibromyalgia patients Mean age MAT group: 46.41 ± 9.06 years Control group: 47.34 ± 9.83 Gender 123 female (83,10%) 25 male (16,90%) Drop-out: 28,40%	Not detailed	MAT (n=54) 8 weeks total One 2h group weekly group-session (with 5-min break) + 50-min one-to-one support sessions + daily self-practice (dynamic and individualized routine)	CGBT (n=52) Education-focused 8 weeks total One 2h group weekly group-session (with 5- min break) + 50-min one-to- one support sessions + at-home practice	1) Functional Impact (FIQR) 2) Pain perception (SF-MPQ) 3) Sleep quality (PSIQI) 4) Psychological distress (DASS) 5) Non-attachment (NAS) 6) Civic engagement	Baseline Post-treatment 6 months followup	1) Sign, group differences favoring MAT 2) Sign, group differences favoring MAT 3) Sign, group differences favoring MAT 4) Sign, group differences favoring MAT 5) Sign, group differences favoring MAT 6) Sign, group differences favoring MAT	1) Sign, group differences favoring MAT 2) Sign, group differences favoring MAT 3) Sign, group differences favoring MAT 4) Sign, group differences favoring MAT 5) Sign, group differences favoring MAT 6) Sign, group differences favoring MAT	Self-referring participants Reliance on selfreport measures Only three-time points assessments "Popularity Effect' phenomenon
Cejudo et al. (2019)	117 fibromyalgia patients Mean age 47.59 ± 5.93 years Gender: female only Drop-out: 11,10%	Pharmacological treatment for pain Not detailed	MBI (n= 53) MBSR-adapted: 20 weeks total One 1 h weekly group- session + daily self-practice (audio-guide support + 5 min body scan + 15 min attention focused on breathing)	Psychoeducation (n= 51) Information on common symptoms and advice on self-care	1) Subjective wellbeing (SWLS, PANAS) 2) Trait emotional intelligence (TEIQue- SF) 3) Mental health (MH5) 4) Resilience (ER-14)	Baseline Post-treatment 6 months followup	1) SWLS: Sign, group differences favoring MBI PANAS:Sign. group differences favoring MBI in PA (not in NA) 2) No sign, group differences 3) Sign, group differences favoring MBI 4) Sign, group differences favoring MBI	1) SWLS: Sign, group differences favoring MBI PANAS: Sign, group differences favoring MBI in PA (not in NA) 2) Sign, group differences favoring MBI 3) Sign, group differences favoring MBI 4) Sign, group differences favoring MBI	Sample composed with female only Not objective measures (self-report only) Different MBI structure from other studies

(Continued)

TABLE 1 | (Continued)

Author, year, (reference)	Participants (N, age, gender, drop-out rate)	Co-occurring therapies	Intervention	Comparison (control)	Outcome measures	Measurement time point	Results		Self-reported study limitations
							Short-term	Long-term	
Pérez-Aranda et al. (2019b)	225 fibromyalgia patients Mean age: 52.50 ± 9.60 years Gender: 221 female -98.20% 4 male (1,80%) Drop-out 23,10%	T reatment-as-usual (TAU) Anxiolytics, antidepressant s, opioids, antiinflammatories, and analgesics. (No group differences)	MBSR (n=58) University of Massachusetts Medical School (USA) MBSR protocol: 8 weeks total One 2h weekly group- session + optional 6h retreat + 45 min daily selfpractice.	TAU alone (n=55) No-treatment FibroQoL (n=60) Psychoeducation, selfhypnosis. 8 weeks One 2h weekly session + 45-60 min daily selfpractice	1) Functional impact (FIQR) 2) "Fibromyalginess" (FSDC) 3) Anxiety and Depression (HADS) 4) Pain catastrophizing (PCS) 5) Perceived stress (PSS-10) 6) Cognitive disfunction (MISCI)	Baseline Post-treatment 12 months follow-up	1) Sign, group differences favoring MBSR over FibroQoL and TAU. 2) Sign, group differences favoring MBSR over TAU (not FibroQoL) 3) Sign, group differences favoring MBSR over TAU and FibroQoL 4) Sign, group differences favoring MBSR over TAU and FibroQoL 5) Sign, group differences favoring MBSR over TAU and FibroQoL 6) Sign, group differences favoring MBSR over TAU and FibroQoL	1) Sign, group differences favoring MBSR over TAU (not FibroQoL). 2) Sign, group differences favoring MBSR over TAU and FibroQoL. 3) Sign, group differences favoring MBSR over TAU (not FibroQoL). 4) Sign, group differences favoring MBSR over TAU and FibroQoL. 5) Sign, group differences favoring MBSR over TAU (not FibroQoL). 6) Sign, group differences favoring MBSR over TAU (not FibroQoL).	Practice frequencydependent outcomes Randomization issues Low follow-up rates (65%) MBSR and FibroQoL differences in therapy time and patient expectations Not optimal adherence to intervention protocols High-time demanding training

CES-D, Center for epidemiological studies; CGBT, Cognitive behavioral theory for groups; DASS, Depression, Anxiety, and Stress Scale; ER-14, Resilience Scale; Fb, Breathing frequency; FIQ, Fibromyalgia Impact Questionnaire; FIQR, Revised Fibromyalgia Impact Questionnaire; FSDC, Fibromyalgia Survey Diagnostic Criteria; GCQ, Giessen Complaint Questionnaire; HADS, Hospital Anxiety and Depression Scale; HR, Heart Rate; IPR, Inventory of Pain Regulation; MAT, Meditation awareness training; MBSR, Mindfulness-based stress reduction; MH-5, Mental Health Questionnaire; MISCI, Multidimensional Inventory of Subjective Cognitive Impairment; MS ER, Mindful socioemotional regulation; NAS, N on-Attachment Scale; PANAS, Positive and Negative Affection Scale (division in to PA, Positive Affection, and NA, Negative Affection, subscales); NRS-101, 101-point Numerical Rating Scale; PCS, Pain Catastrophizing Scale; PLC, Quality of life Profile for the Chronically Ill; PPS, Pain Perception Scale; PSQI, Pittsburgh Sleep Quality Index; PSS-10, Perceived Stress Scale; RSA, Respiratory sinus arrhythmia; SF-MPQ, Short-form McGill Pain Questionnaire; STAI, State-Trait-Anxiety-Inventory; SWLS, Satisfaction with Life Scale; TEIQue-SF, Trait Emotional Intelligence Questionnaire Short FormjV, Ventilation; VAS, Visual Analog Scale; $V_{t,}$ Tidal volume.

(Van Gordon et al., 2017; Pérez-Aranda et al., 2019b) assessed Fibromyalgia Functional Impact and Symptomatology-related outcomes (FIQR and FSDC) in which effect sizes in the medium-large range were reported favoring the mindfulness-based intervention (Cohen's d from 0.35 to 0.86). Three studies (Grossman et al., 2007; Van Gordon et al., 2017; Pérez-Aranda et al., 2019b) specifically assessed Pain-related outcomes, either its objective (pain severity) or subjective (pain perception, regulation, and catastrophizing) experience, with medium-large size effects reported in MBI over control group (Cohen's d from 0.34 to 1.10). Mental Health-related outcomes, such as anxiety and depression (HADS), mental health (MH5), psychological distress (DASS) and perceived stress (PSS-10) were measured by four studies, showing small-medium effect sizes favoring MBI (Cohen's d from 0.39 to 0.77; Eta squared h2 0.022) (Grossman et al., 2007; Van Gordon et al., 2017; Cejudo et al., 2019; Pérez-Aranda et al., 2019b). Quality of life-related outcomes included subjective well-being (SWLS), positive and negative affect (PANAS), resilience (ER-14), Sleep quality (PSIQI), non-attachment (NAS), and cognitive dysfunction (MISCI). Effect sizes in the small-big range were reported favoring the MBI (Cohen's d from 0.52 to 1.12; Eta squared h2 from 0.015 to 0.143) (Grossman et al., 2007; Davis and Zautra, 2013; Van Gordon et al., 2017; Cejudo et al., 2019; Pérez-Aranda et al., 2019b). In conclusion, and regarding our first aim, the global evaluation of the results in **Table 1** shows that there is some evidence that MBI are effective in reducing several fibromyalgia outcomes.

As to the second aim of this manuscript namely to analyze if the current literature considered the recommendations for research in Mindfulness (Davidson and Kaszniak, 2015; Van Dam et al., 2018) several conclusions can be outlined. The overall analysis of the published studies shows that only 4.38% had inclusion criteria such as active control groups and randomized controlled trials which lead us to include only seven studies in this critical review. Furthermore, none of the considered studies for analysis reported information which is considered relevant in mindfulness research (Davidson and Kaszniak, 2015; Van Dam et al., 2018), namely detailed the previous mindfulness experience of the enrolled participants and the participants' interests for medical approaches only or for integrative ones as well. Regarding the teachers' experience (e.g., "number and type of retreats attended," "blindness to the research hypothesis", "conflicts of interest"), the information is scarce or even nil. The type of meditation practiced by the teachers was also not referred. The occurrence of adverse or unpleasant effects of MBI, an issue to consider (Britton et al., 2021), was only reported by Pérez-Aranda et al. (2019b).

DISCUSSION AND FUTURE PERSPECTIVES

Several systematic reviews and meta-analysis evaluated the evidences for the use of MBI in fibromyalgia (Lauche et al., 2013; Haugmark et al., 2019; Khoo et al., 2019; Pei et al., 2021).Therefore, the current study did not intend to perform a systematic review but rather a critical analysis of some of the available literature, considering the outcomes of the studies but taking into account the alerts recently raised by researchers in Mindfulness (Davidson and Kaszniak, 2015; Van Dam et al., 2018). The analyzed studies used a wide diversity of outcomes and showed moderate evidence for the use of MBI in fibromyalgia. Considering the limitations of the current analysis, this critical review is in line with the results of the systematic reviews in this field (Lauche et al., 2013; Haugmark et al., 2019; Khoo et al., 2019; Pei et al., 2021).

As to the critical analysis of the methodology used in the studies and taking into account some of the current recommendations regarding research in Mindfulness (Davidson and Kaszniak, 2015; Van Dam et al., 2018), a relevant issue is the inclusion of active controls. The inclusion of active controls is important in what concerns study design namely because it helps to solve the question of double-blinding (Davidson and Kaszniak, 2015). A recent study analyzed the effects of including a validated well-matched active control group with a large sample size and defined in a randomized manner in the effects of MBSR in brain structure (Kral et al., 2022). This study failed to confirm previous results showing neuroplastic changes induced by MBSR groups in comparison to active controls, which reinforces the importance of defining the best control groups for each MBI intervention which may probably require both active and waiting list groups (Kral et al., 2022). As to fibromyalgia, it was never evaluated the importance of defining control groups in MBI research. The complexity which may be introduced by not defining in detail what the active control group is enrolled in, namely if there is a validated and matched structured program or if the waiting list participants spontaneously changed their activities during the participation in the study. As to the studies excluded of the current analysis due to the lack of a control group (Kaplan et al., 1993; Sephton et al., 2007; Amutio et al., 2014, 2018; Cash et al., 2015; Andres-Rodriguez et al., 2019) it should be noted that they were also excluded because of other factors namely because in some of them the interventions could not be considered a MBI or they were just evaluating Mindfulness scores without intervention. Since we were not performing a systematic review of the literature, we consider that the exclusion of those studies from **Table 1** is not relevant.

Real life adaptation may be considered in MBI research for fibromyalgia, in agreement to other authors (Mantzios and Giannou, 2019). High drop-out rates and/or low adherence to total completion of intervention is a common feature in the analyzed studies, which was also reported in MBI for health conditions other than fibromyalgia (Zhou et al., 2020). Multiple causes can be appointed to this situation. We first highlight that three of the analyzed studies using MBSR programs as intervention reported limitations such as excessive patient burden (Schmidt et al., 2011; Grossman et al., 2017), no optimal adherence to intervention and high-time demanding training (Pérez-Aranda et al., 2019b). The basic program requires 45 min per day of formal home practice, plus one weekly 2–2.5 h group session and one all-day retreat over the course of 8 weeks. A high and condensed time requirement approach like this may limit the intervention efficiency, considering that fibromyalgia patients will encounter resistance in adapting it to their real life routine

and own obstacles—in fact, such a schedule is challenging for anyone to accomplish. There are possible solutions to overcome the problem, such as, providing (1) MBI programs with longer intervention time intervals but with less week load, with shorter daily practices (Cejudo et al., 2019), (2) MBI online-adapted programs, potentiating patient-freedom in time-scheduling their own self-paced sessions (Davis and Zautra, 2013), and (3) an enhancement of group-support sessions to improve adherence. The value of these adaptations may be considered inasmuch that several studies showed that decreasing the duration of the intervention does not preclude efficacy in pain responses (Zeidan et al., 2010). Future research considering the need of MBI programs adaptation to real-life routine, could provide more efficient results among fibromyalgia patients. This may also be important to the continuation of the practice of mindfulness after completion of the interventions which is a problem that can impair long term effects of MBI.

Also regarding adherence to MBI, patient motivation for the intervention is frequently under evaluated. Two of the analyzed studies (Grossman et al., 2007; Schmidt et al., 2011) are from the same research group, and the former is a forerunner study of the latter. Despite sharing similar design, intervention groups (including actual MBSR instructors) and outcome variables, they show different results. Possible reasons for the discrepancies could be the recruitment and assignment of patients to intervention, according to their motivations (Schmidt et al., 2011). While study 27 was based upon patients' preferences, who were allowed to actively choose the MBSR intervention, study 26 was a randomized assignment. Despite being considered a study with better design quality, due to its randomization, it may diminish the effect that patients' preference, and consequent motivation for intervention-adherence has on enhancing the effect of the treatment itself. Even if patient motivations are not considered in allocation of the patients to the interventions, it is important to evaluate these parameters for a better analysis of the intervention's impact.

Along with patient preferences and motivation, patient expectations are also a factor to consider. Pérez-Aranda et al. (2019b) addresses this topic, describing MBSR receiving higher ratings on treatment-expectations compared to FibroQoL, with significant group differences but with no association with treatment outcomes. Since placebo interventions were shown to have some efficacy in fibromyalgia (Chen et al., 2017), we hypothesize that fibromyalgia patients' preferences, expectations and motivation for MBI programs integration are enhancers to its beneficial effects. It was recently demonstrated that expectancies and believes of participants play a stronger role in attenuating acute pain in novices following brief mindfulness interventions than the actual mindfulness-specific processes or instructions delivered (Davies et al., 2022). Future research in this promising topic may help develop more tailored indications for MBI treatments in fibromyalgia.

As referred above, the seven analyzed studies used a large diversity of outcomes, most of which were only based in self-reports of the participants. The discovery of biomarkers of the disease may allow to more objectively understand how MBI acts in fibromyalgia. The investigation of the mechanisms of fibromyalgia is expected to provide important results in the next years. In fact, as to the neurobiological mechanisms referred in the Introduction, namely the immune-inflammatory connection, recent studies indicated that MBSR has regulatory effects of the immune response since it partially corrected the imbalance in the ration of pro- and anti-inflammatory cytokines, along with Brain-Derived Neurotrophic Factor (BDNF) (Andres-Rodriguez et al., 2019; Sanabria-Mazo et al., 2020). As to the "brain hypothesis," and considering that impaired endogenous pain modulation was detected by imaging studies in fibromyalgia patients (Staud, 2011), an interesting study showed that the regional cerebral blood flow is altered in patients with fibromyalgia subjected to mindfulness interventions (Medina et al., 2022). Although we consider that objective biomarkers are necessary for research in MBI for fibromyalgia, we expected that they will be evaluated along with self-reports. Approaches based in cost-utility evaluations of the effects of MBI in fibromyalgia which also include self-reports have shown to be useful (Pérez-Aranda et al., 2019a) and in what concerns pain it is "always a personal experience that is influenced to varying degrees by biological, psychological, and social factors" and "a person's report of an experience as pain should be respected" (Raja et al., 2020).

In conclusion, research in mindfulness for fibromyalgia needs to be optimized to provide more grounded results (Davidson and Kaszniak, 2015; Van Dam et al., 2018). The specificities of fibromyalgia, the challenges in disease detection and the lack of biomarkers, add to the limitations of mindfulness interventions' research for these patients. Research in mindfulness effects for fibromyalgia should continue taking into account the conceptual and methodological specificities inherent to research in mindfulness interventions itself.

AUTHOR CONTRIBUTIONS

Both authors have contributed equally to the research, design, analysis, and writing and approved the submitted version.

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EDITED BY
Steffen Schulz,
Charité Universitätsmedizin
Berlin, Germany

REVIEWED BY
Mohamed Hassan Elnaem,
International Islamic University
Malaysia, Malaysia
Leila Itani,
Beirut Arab University, Lebanon
Milena Peruhova,
Lozenetz Hospital, Bulgaria

*CORRESPONDENCE
Jost Langhorst
jost.langhorst@sozialstiftung-bamberg.de

†These authors have contributed equally to this work and share first authorship

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Mind-body-medicine and comprehensive lifestyle-modification in patients with Crohn's disease—Feasibility of a randomized controlled trial under pandemic circumstances

Nina Bauer[1,2†], Claudia Löffler[3†], Özlem Öznur[1,2], Christine Uecker[1,2], Thomas Keil[4,5,6] and Jost Langhorst[1,2*]

[1]Department of Internal and Integrative Medicine, Sozialstiftung Bamberg, Bamberg, Germany, [2]Department of Integrative Medicine, Medical Faculty, University of Duisburg-Essen, Bamberg, Germany, [3]Department of Internal Medicine II, University Hospital of Würzburg, Würzburg, Germany, [4]Institute of Clinical Epidemiology and Biometry, Julius Maximilians University of Würzburg, Würzburg, Germany, [5]State Institute of Health, Bavarian Health and Food Safety Authority, Erlangen, Germany, [6]Institute of Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Berlin, Germany

Introduction: Mind-body medicine (MBM) focuses on stress reduction and lifestyle changes. The primary objective of this pilot trial was to test study feasibility of a complex integrative MBM program for patients with Crohn's disease (CD), especially in rural regions, and under pandemic conditions.

Methods: Patients were stratified and randomized to the intervention group (IG) or the control group (CG). The intervention included a weekly 6-h session for 10 weeks. The CG (waiting list) received an initial 90-min workshop and started the intervention 9 months later. The primary outcome for study feasibility was recruitment and retention rates, as well as reasons for drop-out. The trial took place in Bamberg, Germany (September 2020 to December 2021).

Results: Totally 700 members of the German Crohn's and Colitis Organization—DCCV—were contacted. A total of 15% (102/700; 95% CI 12–17%) expressed interest to participate. Following screening, 41% (95% CI 32–50) were randomized to IG ($n = 22$) and CG ($n = 20$). The patients were on average (±standard deviation) 48 ± 13 years old, 67% were female, and have been suffering from CD for 20 ± 12 years. Patients traveled 71.5 ± 48.7 km (range: 9–227 km) to the intervention with no differences between IG and CG. At the 6-month follow-up, 36/42 (86%, 95% CI 74–95%) participants completed final assessment and 19/22 (86%, 95% CI 70–100%) the intervention. The most important reasons for non-responding were work-related (12/60; 20%) and for or drop-out pandemic-related anxiety (3/6). No patient and staff member became infected with SARS-CoV-2 during the study.

Conclusion: The feasibility of the MBM study was confirmed in terms of predefined recruitment and retention criteria, both despite difficult conditions (including the rural setting) and patients' fears associated with the pandemic.

It was crucial to develop appropriate hygiene and safety concepts that enable chronically ill patients to participate in helpful group-based interventions even under pandemic conditions.

Clinical trial registration: ClinicalTrials.gov, identifier: NCT05182645.

KEYWORDS

Crohn's disease, lifestyle modification, mind-body medicine, pandemic, inflammatory bowel disease, stress management, rural conditions, feasibility

Introduction

The global prevalence of inflammatory bowel disease has steadily increased within the last two decades, with an average of 1 in 200 people affected (Ng et al., 2017). Crohn's disease (CD) has an overall incidence in Germany of 6.6 new cases per 100,000 inhabitants per year, with ∼25,500 patients per year who require inpatient treatment (Preiß et al., 2014; Ng et al., 2017; Sturm et al., 2022). Due to a large number of symptoms, the health-related quality of life (HRQOL) of many patients with CD is comprehensibly impaired in the most productive years of their lives. The most frequently reported symptoms with an impact on HRQOL are diarrhea, abdominal pain, fatigue, anemia, weight loss, recurrent fistulas, and extraintestinal manifestations (Romberg-Camps et al., 2010; Schirbel et al., 2010; Danese et al., 2015; Gomollón et al., 2017). Accordingly, studies have shown a statistically significant correlation between disease activity, need for retreatment, and quality of life (Casellas et al., 2000; Blondel-Kucharski et al., 2001; Bernklev et al., 2005). In addition to physical functions, emotional wellbeing, as well as social and interpersonal interactions, also play an important role in individual HRQOL. A stable social network is perceived as helpful by patients (López Blanco et al., 2005; Katz et al., 2016), while anxiety and depression, as well as dysfunctional coping with the disease, can have a negative impact on HRQOL (van der Eijk et al., 2004; Mawdsley and Rampton, 2005; Tomazoni and Benvegnú, 2018). Consequently, patients' quality of life has increasingly become focused in research on Crohn's disease and other gastrointestinal disorders (Borgaonkar and Irvine, 2000).

In line with these observations, randomized studies have shown that mind-body therapies, meditation, mindfulness, relaxation, stress management programs, and yoga may improve disease-specific quality of life and can even reduce disease-related pain in patients with IBD (Boye et al., 2011; Langhorst et al., 2013, 2015; Gerbarg et al., 2015; Neilson et al., 2016; Norton et al., 2017; Ewais et al., 2019; Torres et al., 2019). Furthermore, preliminary results from small studies suggest that patients with CD may benefit from a moderate exercise program in terms of quality of life (Ng et al., 2007), while a survey substantiated additional beneficial effects on perceived stress by exercise therapies (Torres et al., 2019). There is also some evidence that stress is associated with a higher risk of relapse in IBD (Bitton et al., 2003). In addition, Cognitive behavioral therapy (CBT) has a short-term beneficial effect on QoL in adults with IBD (Gracie et al., 2017). These first promising approaches try to explore possible psychoneuroimmunological connections between the nervous system and the immune system up to gut mucosal levels. Moreover, initial evidence also exists for further lifestyle modifications in the context of IBD (Gracie et al., 2018, 2019; Torres et al., 2019). Of particular interest is the topic of nutrition (Roda et al., 2020). Initial prospective studies have shown a substantially lower risk of later-onset CD in people following a Mediterranean diet (Khalili et al., 2020). In addition, herbal remedies are frequently used by patients as an adjunct to therapy, especially in patients with increased disease activity (Elsenbruch et al., 2005; Langhorst et al., 2005, 2007, 2015, 2020). A survey concluded that certain herbal remedies and acupuncture may reduce disease activity (Langhorst et al., 2015).

Based on these data, it is highly probable that multimodal concepts, which include mindfulness, relaxation methods, exercise, and nutrition, as well as herbal remedies, could be effective. The efficacy of such a multimodal program has already been demonstrated for patients with ulcerative colitis. In particular, there was a significant improvement in the short- and long-term quality of life and mental health (Elsenbruch et al., 2005; Langhorst et al., 2007, 2020; Labanski et al., 2020; Koch et al., 2021; Schlee et al., 2022).

However, the data available to date for patients with CD are still insufficient and some of the available studies have methodological limitations such as missing control groups, small sample size, or a too short follow-up period.

Consequently, there is a need for high-quality studies on multimodal integrative interventions. In January 2020, when recruitment was supposed to start, the first corona cases were reported in Germany.

It quickly became evident that patients with chronic diseases, in particular, that is, at higher risk for a severe COVID course, were increasingly hesitant to utilize medical treatments (Musche et al., 2020). Grunert et al. (2020) reported that patients with IBD were significantly more affected by the COVID-19 pandemic than their non-IBD peers.

Moreover, it was not until 2021 that a cross-sectional study revealed that generalized anxiety is more prevalent in rural communities, whereas COVID-19-related fear is elevated in metropoles (Diala and Muntaner, 2003; Probst et al., 2006; Schweda et al., 2021).

Taken together, we hypothesize that a holistic, comprehensive mind-body lifestyle modification program is a feasible intervention for patients with Crohn's disease even under pandemic circumstances. Therefore, the evaluation of a multimodal integrative program within the framework of this feasibility study aims on one hand to close gaps in care and on the other hand to contribute to the expansion of evidence with high methodological quality to continuously improve the treatment strategies for patients with Crohn's disease.

Materials and methods

Recruitment and patient characteristics

In addition to a call for studies in social and print media, we contacted a total of 700 members of the German Crohn's Disease/Ulcerative Colitis Association (DCCV e.V.)—a patient self-help association—from July 2020 to January 2021. Therefore, we considered a radius of 100 km from the study center to account for the population density in northern Bavaria (Upper Franconia) of 147 inhabitants per km² (Bayerisches Landesamt für Statistik und Datenverarbeitung, 2014).

Patients who returned received detailed information about the study. The following inclusion criteria were considered: (a) patients between 18 and 75 years, (b) with a confirmed diagnosis of Crohn's disease, (c) stable medication for at least 3 months, and (d) signed informed consent. In contrast, patients with (a) a current highly acute course, (b) complete colectomy, (c) severe mental illness (e.g., major depression, addiction, and schizophrenia), (d) severe comorbid somatic diseases (e.g., diabetes mellitus, and oncological diseases), (e) pregnant women, and (f) participants of stress reduction programs or clinical studies on psychological interventions during the time of study were not eligible to participate in the study.

Study design

To investigate the feasibility of a comprehensive mind-body lifestyle modification program in patients with Crohn's disease, we chose a prospective controlled randomized study design with four data collection points, using different data collection methods. The study was approved by the Ethics Committee of the Bavarian Medical Association (No. 19096), registered at clinicalTrials.gov (NCT05182645), conducted according to the Declaration of Helsinki, and reported according to the CONSORT statements.

After written informed consent and baseline assessment, patients were randomized in a ratio of 1:1 to the intervention group or the control group stratified by gender, disease severity (clinical remission: mean Harvey Bradshaw Index HBI $\leq$ 5; mild disease HBI $\geq$ 6), and medication (immunomodulator yes/no) by de-aging sealed envelopes by the study management at Bamberg Hospital (out-patient department for integrative medicine) at two time points (September 2020 and January 2021). While the intervention group attended the program immediately after the first data collection point (week 0), the control group received a single psychoeducation workshop with information for self-directed application and started the full intervention 9 months later (week 36).

Following the intervention (week 12) and after 6 months (week 36), the questionnaires were again administered and laboratory parameters were collected by independent members of the research department trained in good clinical practice. In addition, the Trier Social Stress Test (TSST), which is a highly reliable method of inducing acute stress, was administered at week 12. Three months after the intervention, subjects in the intervention group were asked to participate in a partially standardized guideline-based telephone interview. Subsequently, subjects in the control group had the opportunity to participate in the intervention (Figure 1). The intervention took place on the premises of the out-patient department and the study visits on the premises of the research team, both from the Department of Internal and Integrative Medicine, Sozialstiftung Bamberg, Bamberg, Germany.

Intervention

As part of the group intervention, five to seven patients per group participated in a 60-h mind-body medicine and comprehensive lifestyle modification training program over a 10-week-period (i.e., 6 h 1 day a week for 10 weeks) from 11 a.m. to 5 p.m. An experienced mind-body instructor and an experienced gastroenterologist specializing in integrative medicine guided the sessions.

Program topics focused on different procedures described above, for which scientific evidence already exists in patients with CD in an individual setting.

This includes, in particular, stress reduction and stress management, based on the Mind-Body Medical Institutes of the Harvard Medical University (Benson and Stuart, 1993) and the Mindfulness-Based Stress-Reduction (MBSR) program of the University of Massachusetts (Kabat-Zinn, 2013) as described previously in a study with CU patients (Langhorst et al., 2007; Schlee et al., 2022). Techniques taught included relaxation, mindfulness meditation, breathing, yoga, and qi gong, but also elements of cognitive behavioral therapy (CBT) and psychoeducational approaches like stress management, coping skills training, and communication. CBT techniques included perceiving and recognizing automatic thoughts and

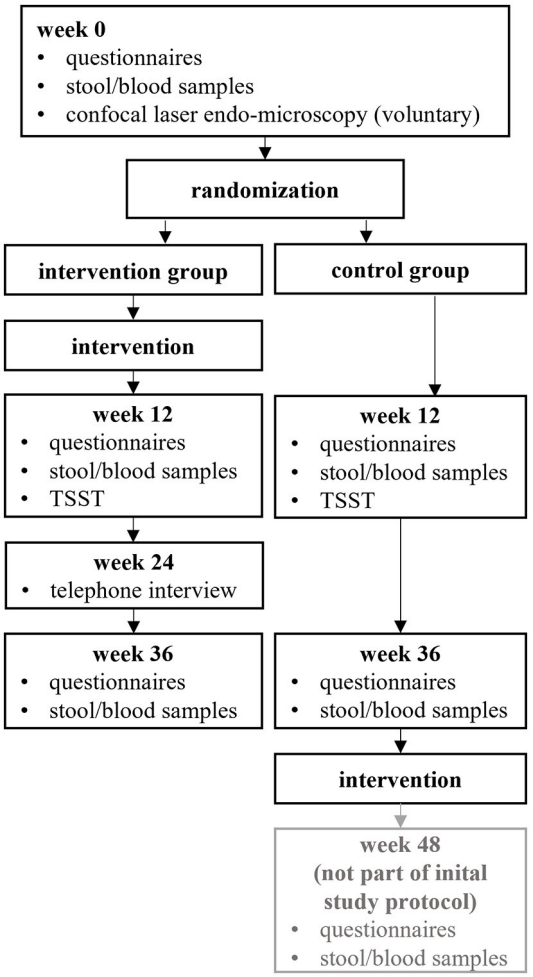

FIGURE 1
Illustration of the study design. TSST, Trier Social Stress Test.

TABLE 1 P.I.C.O. model endpoints focused on study feasibility, investigations, and intervention.

Population	- Patients with Crohn's disease
Intervention	- 10 week mind-body medicine and comprehensive lifestyle intervention
Control	- Control group: care as usual and one-time education of 90 min on naturopathic self-help strategies
Outcome	Feasibility of the study and investigations
	1. *Recruiting success*: Proportion of individuals contacted, who
	○ 1.1) reported for the study and
	○ 1.2) were enrolled.
	2. *Compliance*: Proportion of patient randomized who completed
	○ 2.1) the post-survey,
	○ 2.2) the Trier Social Stress Test,
	○ 2.3) the follow-up survey among included and randomized patients, and
	○ 2.4) the telephone interview among patients of the intervention group.
	Feasibility of the intervention
	3. Feasibility of *intervention* included
	○ 3.1) the proportion of patients who started the study and participated in the intervention,
	○ 3.2) recording of reasons for dropping out of the study, and
	○ 3.3) for non-participation in individual sessions of the intervention,
	○ 3.4) the average number of sessions attended,
	○ 3.5) satisfaction with the intervention.
	Safety
	4. Number and type of severe and mild adverse events

The outcomes 3.4 and 3.5 were not part of the initial study protocol.

mental distortions with a focus on one's own patterns of perception and evaluation to meet them with a non-judgmental and self-kind attitude. In addition, Mediterranean whole food nutrition, as suggested by the German consensus treatment guidelines (Sturm et al., 2022), light exercise, and walking were core elements. Complementary self-care strategies, such as hydrotherapy and herbal medicine for gastrointestinal symptoms were also demonstrated and trained. In the time between the out-patient appointments, patients were asked to fill in exercise diaries daily, were given a link to audio guides for relaxation/meditation, and a variety of print information and exercises as homework to encourage 60 min home practice daily.

Participants in the control group received care as usual and a one-time 90-min workshop on mind-body medicine and complementary self-care strategies (on site respectively online). Following the measurement at Week 36, this group was also given the opportunity to participate in the intervention.

At all appointments in attendance, strict adherence to a comprehensive hygiene concept (including adherence to distance rules the obligation to wear an FFP-2 mask throughout the day) was ensured.

Outcomes and research aims

The endpoints focused on feasibility, investigations, and intervention can be find in Table 1. The following definitions of successful feasibility may serve as the basis for conducting a future large-scale confirmatory study:

1. Recruiting more than 10% of eligible patients who were contacted and invited to the study center,
2. at least 67% of the recruited study participants completed the intervention phase and the final follow-up assessment.

Instrument design and questionnaire

The anonymous, self-administered questionnaire was compiled based on previous studies (Elsenbruch et al., 2005; Langhorst et al., 2007, 2020; Labanski et al., 2020) and tested for comprehension on three in-patients with CD. It consisted of 174 items covering demographic characteristics, disease-, quality of life- and psychological-related factors. While the focus of this paper is the evaluation of feasibility and compliance, possible treatment effects will be presented separately. Therefore, only questionnaires relevant to this paper are presented.

Disease-specific quality of life was measured using the validated German version of the *Inflammatory Bowel Disease Questionnaire*. This widely used and validated instrument consisting of 32 items with a 7-point-Likert-scale (1 = always to 7 = never) divided into the four subscales: bowel symptoms, systemic symptoms, social function, and emotional function. The total score can vary from 32 to 224, with higher scores indicating better quality of life (Janke et al., 2006).

The Harvey-Bradshaw Index is a simplification of the Crohn's Disease Activity Index (CDAI; correlation HBI and CDAI, $r = 0.93$, $p < 0.001$) and is composed of five items. Sum score was rated as remission (0–4), mild (5–7), moderate (8–16), and severe (>16) disease activity (Harvey and Bradshaw, 1980; Irvine et al., 1994).

Statistical analyses

Response rates and study compliance, as well as treatment adherence and drop-out rates, were calculated as the proportion of patients to whom a characteristic was applied (e.g., participation in post-survey) from the total population considered (all randomized patients) and reported as a percentage with corresponding 95% confidence interval (95% CI). Reasons for individual days of absence or study drop-out were reported qualitatively and quantitatively.

Descriptive statistics were used to report baseline characteristics, including sex, marital status, schooling, occupation, age, distance to the out-patient department, disease duration, disease activity (HBI), and quality of life (IBDQ).

The evaluation of the feasibility was not designed as a confirmatory study. We followed an exploratory approach without formal testing of hypotheses and therefore did not define a formal level of statistical significance.

Results

Sample description

The participants were on average 48 ± 13 years old and 67% were female. Most of them reported living in a stable relationship, having a medium level of education, and working part-time. Almost a quarter of the patients were retired due to age or an illness. At the start of the study, they had been suffering from a diagnosis of Crohn's disease for an average (standard deviation) of 20 ± 12 years, reported mild current disease symptoms (HBI: 6.0 ± 3.7), and a reduced quality of life (IBDQ: 147.1 ± 28.6). The distribution of sociodemographic factors was not considerably different between the two treatment groups (Table 2).

Feasibility of the study and investigations

About 102 (=15%; 95% CI 12–17%) of 700 patients, more than the predefined 10% of the contacted patients, reported back to the study center (Figure 2). Following the screening, we randomized 6% (42/700; 95% CI 4.4–8.0) of contacted patients and 41% (42/102; 95% CI 32–50%) of patients who reported back to the study center: 22 in the intervention and 20 in the control group. Eighty-six percent (95% CI 70–100%) of the patients remained in the study until the end. The compliance within the study for the investigations at defined time points was similarly high: 86% (95% CI 70–100%) and 85% (95%-CI 67–100%) of the recruited patients completed the post and follow-up surveys, and 83% (71–95%) the Trier Social Stress Test (TSST) at Week 12. Two months after the intervention, all patients in the intervention group agreed to a partially standardized guideline-based telephone interview.

Drop-out rates and feasibility of the intervention

One-third of the patients, who contacted the study center, did not meet the inclusion criteria or met one or more exclusion criteria. Reasons for non-response are listed in Figure 3. Twelve percent of the recruited patients (95% CI 2–23%) dropped out of the study within 2 weeks (IG: 3, CG: 2). Two patients (IG) had hoped to be assigned to the spring/summer waiting control group. For them, participation in a group intervention was not an option due to the high restriction of the measures related to the pandemic (e.g., lock-down) at the time of randomization. Further reasons are reported in Figure 3. The drop-out rates did not differ (*95% CI* −0.30–0.32) between IG (14%) and CG (15%). With 86% (95% CI 70–100%), the required participation rate of 67% in the intervention group was met.

The following complementary findings are made with regard to feasibility and compliance. Of the 20 patients in the control group, 14 participated in the intervention (70%, 95% CI 48–90%). Patients participated in an average of 9.1 ± 1.4 of the 10 sessions, with no differences between the two groups (*95% CI* −0.67–1.40). Symptoms of a common cold were reported more frequently in the intervention group (winter months) and

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TABLE 2 Patient characteristics at baseline of the study and intervention related factors.

	Total ($n = 42$)	Intervention ($n = 22$)	Control ($n = 20$)	p-value
Sociodemographic characteristics				
Gender				$p = 0.827$
Male	14 (33.3%)	7 (31.8%)	7 (35%)	
Female	28 (66.7%)	15 (68.2%)	13 (65%)	
Age (years)	47.6 (12.5)	49. 0 (13.6)	46.1 (11.2)	$p = 0.345$
Relationship status				$p = 0.260$
Single	6 (14.3%)	4 (18.2%)	2 (10%)	
Married/cohabitant	34 (81%)	18 (81.8%)	16 (80%)	
Divorced/separated/widowed	2 (4.8%)	0 (0%)	2 (10%)	
Education				$p = 0.450$
No qualification	1 (2.4%)	0 (0%)	1 (5%)	
Elementary school	7 (16.7%)	5 (22.7%)	2 (10%)	
Middle school	17 (40.5%)	9 (40.9%)	8 (40%)	
(Technical-) Highschool with/without (technical-) university degree	17 (40.5 %)	8 (36.4%)	9 (45%)	
Employment				$p = 0.394$
Full-time	13 (31%)	5 (22.7%)	8 (40%)	
Part-time/occasional work	16 (38.1%)	9 (40.9%)	7 (35%)	
Retired/unemployed	9 (21.4%)	7 (31.8%)	2 (10%)	
Housewife/househusband	4 (9.5%)	1 (4.5%)	3 (15%)	
Distance hospital - home (km)	68.5 (45.1)	78.0 (54.2)	58.1 (30.5)	$p = 0.146$
Disease related factors				
Years since initial diagnosis	20.1 (11.6)	20.0 (12.3)	20.3 (11.1)	$p = 0.924$
Disease activity (HBI)	6.0 (3.7)	6.5 (4.3)	5.4 (2.9)	$p = 0.363$
Quality of life (IBDQ)	147.1 (28.6)	141.4 (30.5)	153.4 (25.7)	$p = 0.178$
Erythrocyte sedimentation rate	14.9 (2.3)	17.4 (12.8)	12.1 (13.6)	$p = 0.243$
C-reactive protein	0.6 (0.2)	0.9 (1.1)	0.4 (0.9)	$p = 0.118$
Lactoferrin	33.2 (6.9)	44.0 (45.9)	21.9 (31.6)	$p = 0.109$
Intervention related factors				
Satisfaction (of 10 points)	9.1 (0.9)	9.0 (0.8)	9.3 (0.9)	$p = 0.249$
Participation (of 10 sessions)	9.1 (1.4)	9.2 (1.0)	8.9 (1.8)	$p = 0.486$

vacation more often in the control group (summer months). Patients covered an average distance of 71.5 ± 48.7 km to the intervention (25%-percentile: 37 km; 50%-percentile: 59 km, 75%-percentile: 103 km). The longest distance traveled one way was 227 km. However, patients with a further journey were more likely to skip a session (*95% CI* −0.66 to −0.04).

The satisfaction with the intervention was high at 9.1 ± 0.9 (*95% CI* −0.99–0.27), out of a possible 10 points (best score).

Safety of the study under pandemic conditions

During the entire study period, two severe (SAE) and four mild adverse events occurred, which were presumably not causally related to the study. One SAE patient in the control group developed an episode of her Crohn's disease 2 months after baseline measurement and was admitted to the hospital as an inpatient. The second SAE patient suffered pancreatitis after elective endoscopic retrograde cholangiopancreatography (ERCP) shortly after baseline measurement, which kept her from participating in the intervention for the first 2 days of intervention. The four mild adverse events all occurred in the intervention group. For safety reasons, these patients with symptoms typical of a respiratory infection remained at home to avoid infecting other group members in case of (corona) virus infection. Due to this respectful interaction of the group members in the pandemic, as well as the high hygiene standards, no patient and no member of the therapeutic or scientific team became infected with SARS-CoV-2.

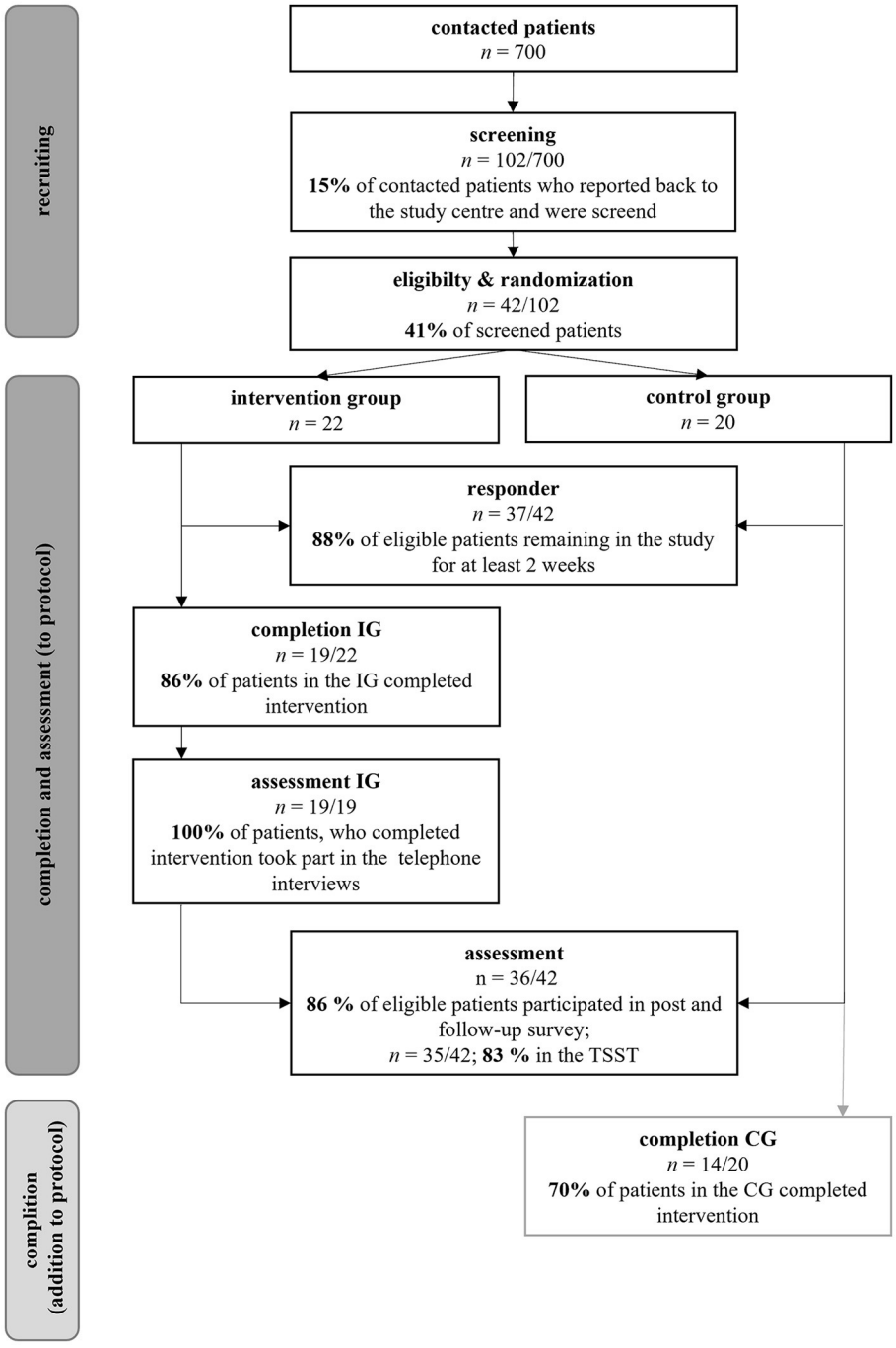

FIGURE 2
Recruitment success, compliance and feasibility of the intervention. Reasons for non-response and drop-out see Figure 3.

Discussion

This paper provides three findings we believe to be important. This study proves for the first time the feasibility of a randomized controlled trial with a long observation period and a comprehensive mind-body lifestyle modification program in patients with Crohn's disease. As the recruitment rate and compliance were achieved according to predefined criteria, the feasibility of such a trial is also given in rural regions and under pandemic conditions. Second, a high level of adherence to the program appointments could be demonstrated. Third, a high level of patient satisfaction with the multi-modal

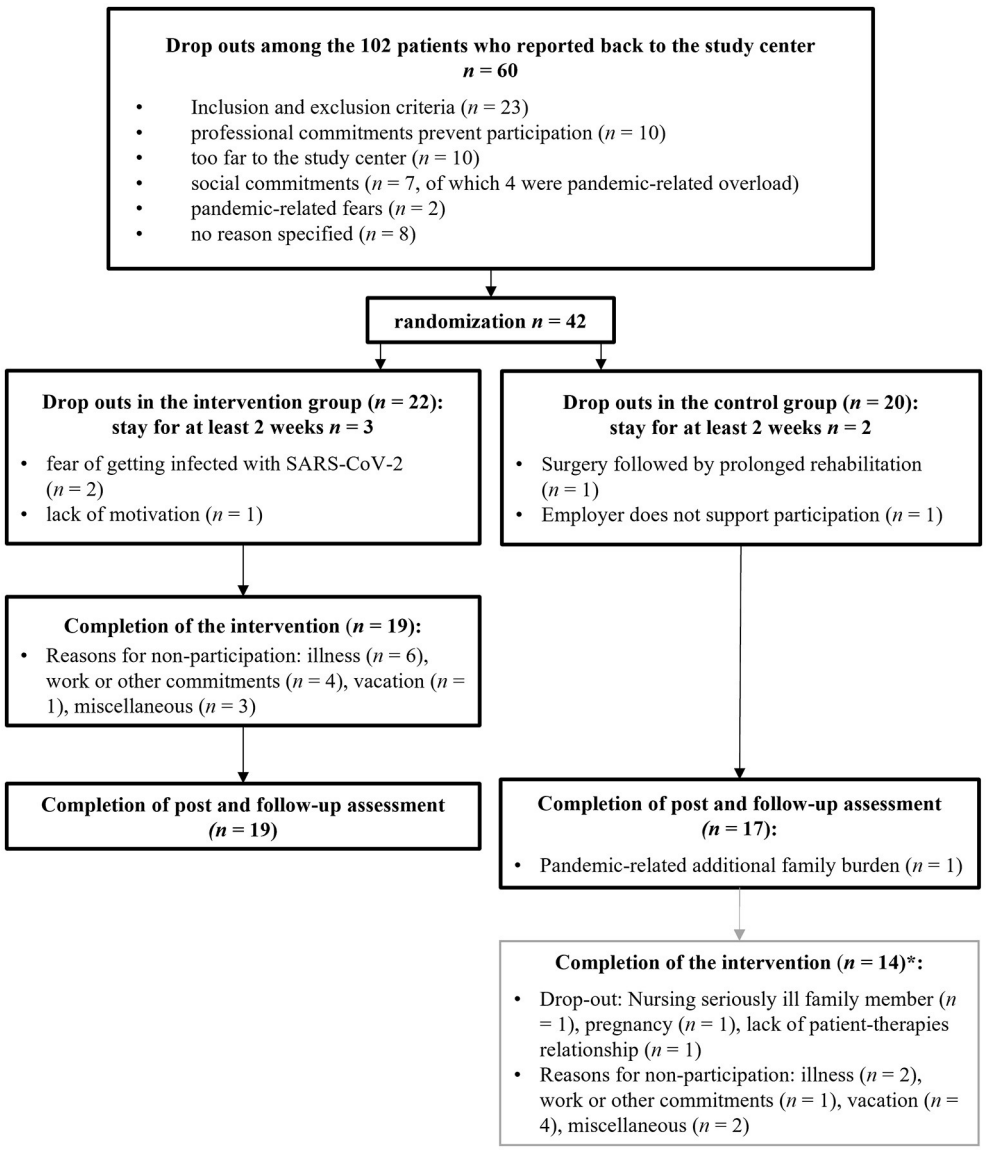

FIGURE 3
Reasons for study discontinuation. *Completion of the intervention was not part of the initial study protocol.

intervention was shown, although this required a strong and continuous commitment.

Feasibility of the study

A particular challenge with regard to the feasibility of studies for patients with chronic diseases, such as CD, is the pandemic. A large cross-sectional German study including almost 17,000 participants could demonstrate elevated levels of generalized anxiety, COVID-19-related fear, adherent/dysfunctional safety behavior, and subjective risk perception in participants with high-risk conditions, such as diabetes or conditions of immunodeficiency (Kohler et al., 2021). In consequence, rates of mental distress and disorders increased significantly (Bäuerle et al., 2020; Mehrotra et al., 2020). Until a vaccine was developed, it was therefore recommended that risk groups, in particular, isolate themselves. However, studies have clearly shown that the COVID-19 pandemic has led to a decrease in the utilization of many medical care services (Mehrotra et al., 2020). This can be reported particularly for chronic conditions (Hacker et al., 2021). For example, in the first summer of the pandemic, 4 in 10 adults surveyed reported that they had postponed or avoided routine or emergency care because of the pandemic (Czeisler

et al., 2020). Therefore, treatment teams increasingly focused on transferring face-to-face group therapy to online group chats during the early months of the COVID-19 pandemic (Scholl et al., 2021). However, since multimodal concepts can only be partially adapted to a virtual format, the next challenge was now to develop appropriate hygiene and safety concepts that enable chronically ill patients to participate in helpful programs even under pandemic conditions and to feel safe and in good hands. Even before the S-3 guideline supplement on the COVID-19 pandemic for patients with inflammatory bowel disease was published in October 2020 (Stallmach et al., 2020), the Bamberg study team, therefore, decided to start recruitment.

Against this background, the unexpectedly high interest of the contacted patients with 15% contacting the study center is remarkable. On one hand, this could be due to the many years of very good cooperation with the national patient organization for IBD ("Deutsche Morbus Crohn/Colitis Ulcerosa Vereinigung," DCCV e.V.), whose members were probably familiar with the expertise and commitment of the study center. Moreover, the role of the self-help group in studies could be very important, as members trust their patient organization, which communicates respectfully with its members and provides information to the best of its knowledge. On the other hand, it could also have played an important role to convey the mitigation efforts to ensure that this mind-body medicine program is safe [e.g., small groups ($n_{max} = 7$), large rooms, regularly ventilate, mask requirements, and social distancing] and to explain clearly how to safely access care in the invitation to participate.

If we look at the patients who contacted the study center but then decided against participation before the randomization, it is noticeable that, in particular, professional or social commitments were the most frequently cited reasons for deciding against participation, in addition to a perceived too far journey. This is in line with the results of the recently published qualitative study on patients with ulcerative colitis (Schlee et al., 2022). Less than 4% of eligible patients decided not to participate due to pandemic concerns or fears, which again may indicate that patients felt safe in the study setting presented.

The feasibility of the study was also quantified by the compliance within the study, which was determined as the proportion of subjects who completed the scheduled assessments at different time points. Eighty-six percent of randomized patients completed both the post-survey directly after the intervention and the 6-month follow-up. This figure is comparable to other studies (Berrill et al., 2014; Neilson et al., 2016). However, these studies were not conducted under pandemic conditions, which must be considered.

In addition, 83% of the participants in both study groups carried out the Trier Social Stress Test (TSST), and all patients in the intervention group agreed to a partially standardized guideline-based telephone interview 2 months after the intervention. The fact that patients were even willing to undergo a stress-triggering test, which tends to be perceived as rather unpleasant, as well as a time-intensive telephone interview, speaks for a very good identification with the study and strong patient commitments.

In the control group, only three drop-outs were recorded after randomization, most of which could not be related to study design or waiting time. The fact that, at the end of the actual study, 14 of the 17 patients remaining in the control arm also took the opportunity to participate in an intervention suggests that a multimodal comprehensive mind-body lifestyle modification program addresses the unmet needs of the patients. Moreover, the one-time 90-min workshop on mind-body medicine and complementary self-care strategies in the control group might have been a motivation to stay.

Feasibility of the intervention

To examine the feasibility of the stress-management and comprehensive lifestyle-modification program, we studied patient adherence to appointments with a focus on reasons for non-participation in individual sessions and for dropping out of the study. In addition, we asked the participants about their satisfaction with the intervention.

Three of five patients, who terminated the study early, dropped out in the first 2 weeks after randomization. Although more patients in the intervention group dropped out of the study directly, verbally reported back dissatisfaction with the outcome of randomization was higher in the control group, which may reflect patients' need for a multimodal, multi-week approach. Even though long observation periods are important from a scientific point of view and the patients in the control group received a single psychoeducation workshop, the patients' desire to be allowed to participate in a potentially helpful intervention in a timely manner is understandable.

Because studies have shown that non-compliance is a barrier to learning mindfulness, which is a key element in the investigated comprehensive mind-body lifestyle modification program, it is especially important to examine and understand the reasons for drop-outs and lack of compliance after the start of the intervention (Lymeus et al., 2019; Zhang et al., 2021). Unfortunately, drop-out rates of 25% or higher have been reported in representative studies (Abbott et al., 2014; Lamothe et al., 2016). Adherence to mindfulness-based interventions in patients with inflammatory bowel disease in randomized trials published to date ranged from 55% (Schoultz et al., 2015, 2016) to 58% (Berrill et al., 2014) and remained below the values achieved here even in a study with free group choice (82%) (Neilson et al., 2016).

Adherence from randomization to the end of the holistic integrative medicine intervention was 86%, the same as in a meta-analysis for yoga interventions in Europe (Cramer et al., 2016). However, compared to study data showing that drop-out rates increase with underlying medical conditions and even

nearly double as the number of sessions increases (under 8 vs. over 12 sessions) (Cramer et al., 2016), adherence in the context of this study appears unexpectedly high, even more so under pandemic conditions. In this study, although the number of face-to-face sessions is in the middle range at 10 weeks, individual yoga sessions, as in the meta-analysis mentioned above, were considerably shorter at 1–2 h than a duration of 6 h in the out-patient department.

Despite the comprehensive hygiene concept of the hospital, SARS-CoV-2-related fears or anticipated pandemic-related challenges were a major issue for patients already in the recruitment phase and were responsible for half of the study drop-outs in the further course ($n = 3$ out of 6). On the other hand, this study showed that Crohn's disease patients are motivated to participate in a comprehensive mind-body lifestyle modification program even under pandemic conditions and that its implementation is possible under high hygiene standards without endangering the health of the partly immunosuppressed participants. Not a single SARS-CoV-2 positive patient or therapist during the intervention periods was recorded. In addition, virtual sessions may not appear to be an equivalent alternative to face-to-face sessions. In a systematic review of Internet-based interventions focusing on mindfulness, adherence ranged from 38 to 78% (mean 40%) (Christensen et al., 2009), well below the adherence in the present study.

The patients participated very regularly in the group intervention itself and were extremely satisfied, although a high degree of cooperation (including no sick leave possible) was also required outside the program. The high participation rate is particularly remarkable because many patients travel long distances to take part. To relieve the patients and to make it easier to reconcile the intervention with work, it would be of central importance here to have the intervention recognized as a health insurance benefit with the consequence of the possibility of issuing a certificate of incapacity for work. This is particularly important because a program for building-up personal health competence could be interesting not only for the patients' quality of life but also from an economic point of view.

The results must be interpreted carefully considering several potential limitations. First, a weakness is the small case number, although this is in the nature of feasibility studies. Second, a self-selection bias is likely due to the voluntary character of the intervention and the overrepresentation of women. For example, studies concluded that women use different coping strategies than men and that emotional coping strategies, in particular, may play a greater role. Women might therefore have felt more addressed by the holistic approach (Sarid et al., 2017). Furthermore, it is possible that individuals with an interest in integrative medicine, naturopathy, and/or mindfulness-based exercises, as well as patients who are motivated for group interventions, in general, were more likely to contact the study center. The strengths of the study are the high-quality study design, the data assessment by "good-clinical-practice" certified researcher, and the discussion of drop-out rates and reasons against the background of planning and feasibility of studies under challenging conditions (rural region and pandemic). Where appropriate and necessary (e.g., assessment of disease activity and quality of life), standardized, established, and validated questionnaires were used to allow meaningful classification and, if necessary, subsequent comparison of results in reviews and meta-analyses. Both survey waves, starting September 2020 and January 2021, were conducted identically and strictly according to the study protocol.

Conclusion

In summary, an expansion of the offer of comprehensive mind-body lifestyle modification programs is desirable for patients with Crohn's disease, since this offer is very well accepted by the patients even under rural and pandemic circumstances. Patients showed high adherence, were highly satisfied with the intervention, traveled long distances to the out-patient department, and even participated without a sick leave certificate for the days of the study.

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 human participants were reviewed and approved by Ethics Committee of the Bavarian Medical Association: No. 19096. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JL and TK contributed to the conception and design of the study. NB, CU, ÖÖ, and JL managed the project administration and the data collection. NB performed the statistical analysis. NB and CL wrote the first draft of the manuscript. All authors have reviewed and edited the manuscript and agreed to the submitted version.

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Conflict of interest

CL received lecture fees from Celgene GmbH, Roche GmbH, Novartis Pharma GmbH, BMS GmbH & Co. KGaA, Mundipharma GmbH Co. KG, Merck KGaA. JL was a speaker for Repha GmbH, Techlab Inc., Falk Foundation, Takeda, Celegene GmbH and Willmar Schwabe and received research funding from Repha GmbH, Techlab Inc., Falk Foundation and Willmar Schwabe.

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.

The handling editor SS declared a shared affiliation with the author TK at the time of review.

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EDITED BY
Steffen Schulz,
Charité – Universitätsmedizin Berlin, Germany

REVIEWED BY
Richard Gevirtz,
Alliant International University, United States
Herbert F. Jelinek,
Khalifa University, United Arab Emirates
Martin Siepmann,
Technical University Dresden, Germany

*CORRESPONDENCE
Andy Schumann
andy.schumann@med.uni-jena.de

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Depressive rumination and heart rate variability: A pilot study on the effect of biofeedback on rumination and its physiological concomitants

Andy Schumann[1,2]*, Nadin Helbing[1], Katrin Rieger[1], Stefanie Suttkus[1] and Karl-Jürgen Bär[1]

[1]Lab for Autonomic Neuroscience, Imaging and Cognition (LANIC), Department of Psychosomatic Medicine and Psychotherapy, Jena University Hospital, Jena, Germany, [2]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Objective: Recent studies suggest that lower resting heart rate variability (HRV) is associated with elevated vulnerability to depressive rumination. In this study, we tested whether increases in HRV after HRV-biofeedback training are accompanied by reductions in rumination levels.

Materials and methods: Sixteen patients suffering from depression completed a 6-week HRV-biofeedback training and fourteen patients completed a control condition in which there was no intervention (waitlist). The training included five sessions per week at home using a smartphone application and an ECG belt. Depressive symptoms and autonomic function at rest and during induced rumination were assessed before and after each of the two conditions. We used a well-established rumination induction task to provoke a state of pervasive rumination while recording various physiological signals simultaneously. Changes in HRV, respiration rate, skin conductance, and pupil diameter were compared between conditions and time points.

Results: A significant correlation was found between resting HRV and rumination levels, both assessed at the first laboratory session (r = -0.43, $p < 0.05$). Induction of rumination led to an acceleration of heart rate and skin conductance increases. After biofeedback training, resting vagal HRV was increased ($p < 0.01$) and self-ratings of state anxiety ($p < 0.05$), rumination ($p < 0.05$), perceived stress ($p < 0.05$), and depressive symptoms (QIDS, BDI; both $p < 0.05$) were decreased. In the control condition, there were no changes in autonomic indices or depressive symptomatology. A significant interaction effect group x time on HRV was observed.

Conclusion: Our results indicate that a smartphone-based HRV-biofeedback intervention can be applied to improve cardiovagal function and to reduce depressive symptoms including self-rated rumination tendencies.

KEYWORDS

depression, rumination, heart rate variability, pupil diameter, skin conductance

Introduction

Impaired mood, reduced energy, repetitive negative thinking and general loss of interest are key characteristics of depression. Depression is one of the most common diseases with a rising prevalence (1, 2). And the most relevant cause of disability worldwide (3). Depression is closely linked to heart disease, with significant clinical and economic consequences (4). Longitudinal cohort studies show that depression subsequently increases the risk of cardiovascular morbidity and mortality (5, 6).

Heart rate variability (HRV) quantifies cardiac vagal control and is a robust and independent marker of cardiac mortality. Several studies reported low vagal function in unmedicated patients (7–9). Meta-analyses by Rottenberg (10) or Kemp et al. (11) demonstrated a significant relation between depression and HRV decrease. This effect becomes larger when patients suffer comorbid from generalized anxiety disorder (12). Antidepressant treatment has been reported to further decrease vagal modulation (13, 14). In a longitudinal study, Licht et al. (15) showed that tricyclic, serotonergic as well as noradrenergic antidepressants are associated with a decrease in cardiac vagal function (15).

Perception, cognition, and emotions are closely tied to autonomic regulation in specific ways and at various levels of the neuraxis. As part of the autonomic response, heart rate accelerates when an individual is confronted with physical or psychological stress. Beat-to-beat variations of heart rate are characterized by HRV. HRV is considered a non-invasive marker of autonomic function that predicts of all-cause mortality (16). It has been shown that people with higher resting HRV exhibit effective regulation of negative affect, more adaptive emotion regulatory strategies, and more flexible emotional responding (17). The higher an individual's HRV, the better their performance was found in response inhibition and emotion regulation tasks (18–20). Thayer (21) showed that low HRV marks increased risk to stress exposure. Thus, low parasympathetic activity is associated with deficits in stress-related behavior, high negative affect and general negative health consequences.

This seems to facilitate depressive rumination, the habit of pondering over one's own negative thoughts and feelings. It is a central feature of depression that even remains elevated after both partial and full remission (22, 23). The amount of rumination is associated with diminished responsiveness to anti-depressant medication and cognitive therapy and rumination has been demonstrated as a crucial factor in vulnerability to depression, predicting the onset, severity, and duration of future depressive episodes (24–26). Moreover, rumination involves the repetitive focusing on one's distress symptoms or negative emotions, and strong self-referential attention (27, 28). Thus, depressed patients find it difficult to disengage from self-focusing even though it might be irrelevant in the present moment (29, 30).

Several studies have reported that rumination and worry are associated with elevated sympathetic arousal and decreased parasympathetic heart rate modulation (31–35). After experimental induction as well as spontaneous onset of rumination, a decline in HRV was reported (36–38). In a meta-analysis, Ottaviani et al. (39) summarized that rumination and perseverative cognition are accompanied by increases in heart rate, blood pressure and cortisol levels as well as by HRV withdrawal. These results indicate that rumination is a form of chronic stress that is associated with a shift in sympathovagal balance toward sympathetic predominance.

Interestingly, the close relationship of altered heart rate regulation and rumination (36, 40) might be due to the loss of inhibitory control over important subcortical regions (41). Self-referential processing in depression was associated with abnormally increased activity of medial frontal and emotion-regulating structures (42–44). Several studies found a disconnection of the medial prefrontal cortex (45–48), especially, to limbic regions such as the amygdala and insula seem to be related to deficits in affective processing and emotional evaluation (49–52).

Heart rate variability biofeedback has been demonstrated to improve clinical symptoms in patients suffering from depression (53–57). A recent meta-analysis of randomized controlled studies including a total number of 794 participants yielded a significant medium size effect (Hedges' g = 0.38) of HRV biofeedback on depressive symptoms (58). Physiological effects seem to be primarily mediated *via* enhanced baroreflex function and cardiovagal activity (59–61). In a previous study, we found increased resting HRV and baroreflex sensitivity after an 8-week HRV biofeedback intervention in healthy volunteers (62).

In this study, we aimed to investigate whether HRV biofeedback has a specific positive effect on rumination in depressed patients. We hypothesized a correlation of resting HRV and self-reported tendencies to engage in ruminative thoughts. After a 6-week HRV biofeedback intervention, we assumed that patients report lower levels of rumination.

Materials and methods

Patients

We recruited 25 patients (19 women, six men; age: 41 ± 15 years; BMI: 25.5 ± 5.5 kg/m^2) from ambulatory care either in the psychiatric outpatient ward of the Jena University Hospital or nearby resident practitioners. All participants gave written informed consent to a protocol approved by the Ethics Committee of the medical faculty of the Friedrich-Schiller University Jena (# 5423-02/18) in accordance with the Declaration of Helsinki.

Inclusion criteria were ICD-10 diagnosis of depression, age between 18 and 55, male or female, period, ability to give written informed consent to the study, stable psychopathology and constant antidepressant treatment over a 2-week screening, minimum rating of 30 on the rumination scale RRQ, unremarkable results of physical examination, ECG, laboratory investigations. Patients were instructed to refrain from smoking, heavy meals, exercise and alcohol 2 h before laboratory session.

Patients have been diagnosed with a minor (N = 8), moderate (N = 11) or severe (N = 2) recurrent depressive disorder, major depression (N = 2) or dysthymic disorder (N = 2). The majority of patients were treated with one or more types of antidepressant medication, including serotonergic (N = 13) and noradrenergic reuptake inhibitors (N = 1), tricyclic and tetracyclic antidepressants (N = 5, N = 1), Atypical antidepressant (N = 2) and antipsychotic medication (N = 2). Seven patients were currently not treated with antidepressants. Two weeks before and the time during the control and intervention condition, type and dose of pharmacological treatment and the frequency of psychotherapy sessions had to remain constant. Additionally, we ensured no severe changes in daily life such as job change, relocation, vacations, or study exams took place during this period.

All 25 patients started the procedure with an initial laboratory session, before starting a 6-week control condition (waitlist) or a biofeedback intervention for 6 weeks. Two patients dropped out due to stationary admission (N = 1) and changes in medication status during the course of the experiment (N = 1). Finally, 14 patients completed the control condition, and 16 patients finished the biofeedback intervention. Seven patients first completed the control condition and then conducted the biofeedback training (not randomized cross-over design). An overview of patients' characteristics included in the control and intervention group are given in **Table 1**.

The psychopathological state was assessed by the Beck's Depression Inventory (BDI-II) (63), the Quick Inventory of Depressive Symptomatology (QIDS-SR16) (64), the State-Trait Anxiety Inventory (STAI) (65), and the Perceived Stress Scale (PSS-10) (66). State rumination and current tendencies for perseverative cognition were assessed by the German version of the Rumination-Reflection Questionnaire (RRQ) (67), and the rumination response style (RRS) (28).

Timing schedule

After the recruitment interview, a first appointment was arranged in which participants had an initial laboratory assessment. During the control condition, patients waited for 6 weeks to undergo another laboratory session (waitlist). In the intervention condition, patients were instructed on how to use the training instruments [App(s) and add-on devices] and go for a test run. The training was then conducted at home (see Biofeedback intervention). After 6 weeks the intervention ends and participants underwent laboratory investigations again. At all laboratory sessions, patients performed the rumination induction paradigm and filled out all questionnaires. Repeated sessions were scheduled individually at a similar time of day in each participant between noon and early evening (12 a.m.–5 p.m.). We have ensured beforehand that no serious events were scheduled within the period of the control condition and intervention.

Laboratory session

Resting recordings were conducted in a supine position for 15 min. The first 5 min were not analyzed, to exclude the adjustment period to the environment. The examination room was quiet and fully shaded with a low intensity ambient light source. Additionally, participants wore headphones to be

TABLE 1 Sample characteristics.

	Control	Intervention
Men/women	N = 3/N = 11	N = 4/N = 12
Age (years)	38 ± 13	42 ± 17
BMI (kg/m^2)	24 ± 5	25 ± 5
Smoker/Non-smoker	N = 1/N = 13	N = 2/N = 14
Years of education	11 ± 1	11 ± 1
BDI	20.2 ± 7.9	21.6 ± 10.7
QIDS	13.8 ± 3.3	13.3 ± 5.6
RRS	25.1 ± 2.7	25.3 ± 6.5

BDI, Beck depression inventory; QIDS, quick inventory of depressive symptoms; RRS, rumination response scale. All data assessed at the first session.

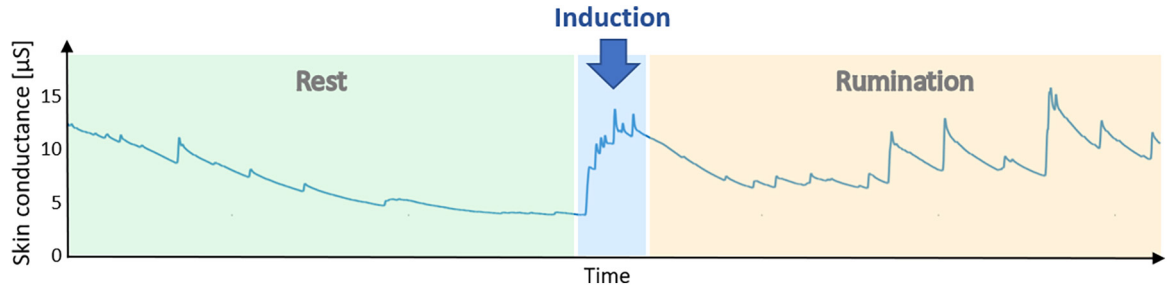

FIGURE 1
Example time course of skin conductance during a laboratory session. After 10 min of resting state, instructions to engage in rumination were displayed. The rumination phase lasted another 10 min. An elevation of skin conductance during the rumination phase indicates sympathetic activation elicited by ruminative thoughts.

isolated from a potential surrounding noise. Through a monitor fixed over the couch a dark gray ellipse was displayed on light gray background as a fixation anchor. Room temperature was controlled to 22°C.

We used the well-established rumination induction paradigm (68, 69). Patients are instructed to think of a situation that makes them feel sad or anxious. The episode may have happened in the past or may happen in the future. They are asked to think about this situation in detail especially possible causes, consequences, and their feelings. The rumination phase lasted another 10 min while all physiological signals were continuously recorded.

Physiological recordings

Simultaneous multi-channel recordings of autonomic function were performed at rest and during rumination using a polygraph MP150 system (BIOPAC Systems Inc., Goleta, CA, United States) at 1 kHz sampling frequency. ECG was acquired by arranging three electrodes on the chest. Abdominal and thoracic respiratory movements were recorded by two individual strain gauge transducers. Skin conductance was measured continuously by the constant voltage technique on the left hands' palm with electrodes placed at the thenar and hypothenar eminence. Pupil size changes were assessed every 4 ms by the infrared camera system RED 250 (SensoMotoric Inc., Boston, MA, United States).

Indices of autonomic function

Artifacts and ectopic beats in the beat-to-beat interval series (BBI) were detected and removed using an adaptive filtering technique (70). The mean heart rate HR and standard deviation of BBI (SDNN) around the mean were estimated according to the established standard procedures (71). In each BBI, systolic blood pressure (SBP) was extracted as the maximum blood pressure in one cardiac cycle. We report the mean SBP over the recording. The mean breathing rate (BR) was derived from the respiration signal. Skin conductance level (SCL) and pupil diameter were estimated by averaging the whole skin conductance signal and pupil diameter values.

Biofeedback intervention

Participants performed a biofeedback training for 6 weeks, in order to elevate heart rate variability (HRVBF). Five sessions per week were done at home, using a smartphone and an HR belt (H10 POLAR, Polar Electro Oy, Kempele, Finland).

At the start of the intervention, the resonant frequency (RF), at which HRV is highest, was estimated in the laboratory. In the first 2 weeks participants train to breath at their individual RF as a preparation for the subsequent biofeedback of heart rate. To determine RF, participants were asked to breathe according to a given rhythm (7, 6, 5, 4.5, and 4 bpm) for 2 min each, while ECG and respiration were recorded. A visual pacer was displayed on the screen above the participants lying on the couch. The respiratory trace was used to ensure that patients followed the presented rhythm. SDNN was estimated in each 2-min segment. At the breathing rate where SDNN was highest the optimal RF was extracted (62).

From week three to six, participants were asked to concentrate on the HR-curve. Their target is to synchronize their breathing rhythm with this curve by inhaling when HR increases and exhaling when HR decreases, trying to progressively expand the amplitudes of HR oscillations.

Participants trained five times a week at home. Each session comprised a 5-min resting recording and two 11-min training blocks with a break between them. At least once a week, we got in touch with each participant to discuss problems, give advice and keep motivation high.

TABLE 2 Changes in autonomic function during rumination compared to rest.

Parameter	Resting state	Rumination	*P*-value
HR [1/min]	75.3 ± 10.7	76.9 ± 10.8	0.046
HRV [ms]	34.5 ± 25	34.1 ± 22.4	0.850
SBP [mmHg]	129.8 ± 24.1	134.3 ± 22.6	0.076
SCL [μS]	2.1 ± 5.5	2.6 ± 6.5	0.043
BR [1/min]	12.6 ± 3.5	14.5 ± 5.1	0.107
DIA [mm]	4.5 ± 0.9	4.6 ± 0.8	0.394

HR, mean heart rate; HRV, heart rate variability; SBP, systolic blood pressure; SCL, skin conductance level; BR, breathing rate; DIA, mean pupil diameter.

Statistical analysis

The effect of rumination on autonomic function was assessed based on data of all patients acquired during the first laboratory session—before the start of the intervention or control condition. We compared autonomic indices estimated during resting state and induced rumination via a paired *t*-test. According to our hypothesis, we analyzed the relationships between resting HRV with psychopathological ratings; i.e., depressive symptoms (QIDS and BDI), perceived stress (PSS), state anxiety (STAI), and rumination levels (RRQ, RRS) also assessed at the first visit using Pearson correlation coefficients.

Differential effects of the biofeedback intervention and control condition were investigated by comparing changes of resting HRV and psychopathologic ratings before (T1) and after the intervention (T2) using a general linear model with the between-subjects factor group and the within-subject factor time. Simple effects of factor time were tested in each group. Significant differences over time in psychopathological scales and HRV were then correlated with each other in an exploratory manner.

Results

Analyzing all patients at their first laboratory session, we found a significant correlation of HRV with rumination levels RRS (r = -0.43, $p < 0.05$). Ruminative thoughts, we than triggered during the induction paradigm. Figure 1 shows an exemplary skin conductance (SC) time course of one patient that indicates sympathetic arousal. During the resting condition there is a decreasing trend with only a few unspecific fluctuations in SC. Reading the rumination instructions already increased skin conductance substantially. Throughout the induction period, skin conductance level (SCL) remained elevated and showed multiple fluctuations that are most probably elicited by negative emotions and stress due to induced rumination.

In Table 2, all autonomic indices assessed in our study were compared between resting state and rumination induction. A paired t-test revealed significant increases in HR (T = 2.1, $p < 0.05$) and skin conductance levels (T = 2.15, p = 0.04).

Changes in autonomic function and psychopathology from before (T1) to after (T2) the control and intervention condition are listed in Table 3. There was one significant interaction effect group x time on HRV (F = 7.36, p = 0.011) that was driven by a significant increase of HRV in the intervention group (p = 0.005, Figure 2E). Simple effects analyses revealed that patients showed a significantly reduced breathing rate after biofeedback (p = 0.026, Figure 2F). Although, there was a significant reduction in self-ratings of state anxiety (STAI: p = 0.043, Figure 2C), rumination (RRQ: p = 0.032, Figure 2D), perceived

TABLE 3 Changes in autonomic function and psychopathological state after biofeedback intervention and control condition.

Parameter	Control			Intervention		
	T1	T2	Significance	T1	T2	Significance
HR [1/min]	74.6 ± 10.2	73.2 ± 10	0.383	76.7 ± 12	74.6 ± 11.5	0.261
HRV [ms]	42 ± 27.6	38.2 ± 26.7	0.429	30.7 ± 20.9	49 ± 31.5	0.005
SBP [mmHg]	143.5 ± 25.4	140.2 ± 16.6	0.328	126.8 ± 24.6	122 ± 23.4	0.091
SCL [μS]	3.1 ± 8	2.3 ± 5.2	0.127	3.6 ± 7.8	3.3 ± 7.5	0.792
BR [1/min]	12 ± 3.3	12.8 ± 3.7	0.327	12.5 ± 3.5	10.8 ± 4.6	0.049
DIA [mm]	4.6 ± 0.9	4.3 ± 0.8	0.261	4.3 ± 1.0	4.0 ± 0.8	0.05
STAI-s	55.8 ± 10.9	51.1 ± 12.7	0.164	48.9 ± 9.8	41.4 ± 11.5	0.017
PSS	24.4 ± 7.2	22.6 ± 7.7	0.541	23.2 ± 9.2	16.8 ± 8.5	0.021
QIDS	13.8 ± 3.3	11.7 ± 5.3	0.129	13.3 ± 5.6	9.5 ± 5.2	0.016
BDI	20.2 ± 7.9	18.8 ± 8.7	0.536	21.6 ± 10.7	14.2 ± 10.5	0.001
RRS	25.1 ± 2.7	24 ± 4.1	0.484	25.3 ± 6.5	22.6 ± 6.3	0.057
RRQ	90.6 ± 7.7	90.1 ± 9.2	0.909	92.5 ± 10	85.0 ± 12.4	0.032

HR, mean heart rate; HRV, heart rate variability; SBP, systolic blood pressure; SCL, skin conductance level; BR, breathing rate; DIA, mean pupil diameter; STAI-s, state anxiety inventory; PSS, perceived stress scale; BDI, Beck depression inventory; QIDS, quick inventory of depressive symptoms; RRS, rumination response scale; RRQ, rumination reflection questionnaire.

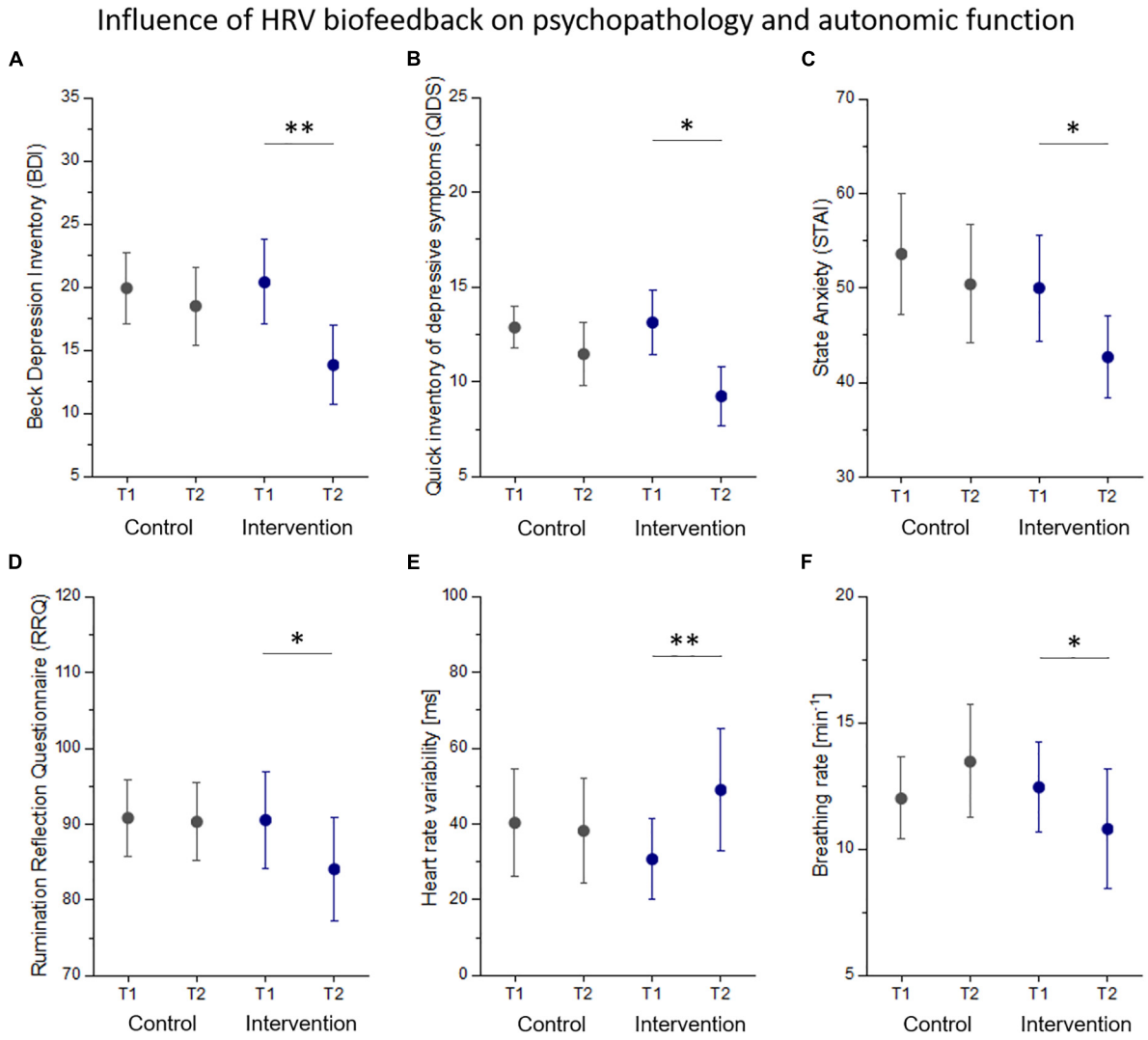

FIGURE 2
Changes in psychopathology **(A–D)** and autonomic function **(E,F)** from before (T1) to after (T2) the control and intervention condition. Statistical thresholds: $*p < 0.05$, $**p < 0.01$.

stress (PSS: $p = 0.021$), and depressive symptoms (BDI: $p = 0.001$, QIDS: $p = 0.016$, **Figures 2A,B**) in the intervention group, we found no interaction effect on any psychopathological scale. In an exploratory approach, we correlated changes in HRV with changes in those psychopathological scales that were influenced by HRVBF and found a significant correlation between HRV and BDI ($r = 0.4$, $p < 0.05$).

Discussion

In this study, we applied a smartphone-based HRV-biofeedback intervention over 6 weeks and assessed its influence on depressive symptoms with a special focus on rumination. We corroborated a link between resting HRV and rumination levels reported at the first visit. A rumination induction paradigm led to an accelerated heart rate and increased skin conductance when compared to rest. We found improved cardiovagal function and reduced severity of symptoms, including self-rated rumination levels after the biofeedback intervention.

Rumination has vastly adverse consequences for patients suffering from depression. As patients struggle to shift their attention away from negative self-related stimuli, those feelings determine their emotional state. The physiological arousal accompanying rumination might compromise patients' cardiovascular health. Cardiac sympathetic activation and withdrawal of vagal HRV seem to be a consequence of rumination (69). In this study, we especially observed activation

of the sympathetic nervous system during rumination, as indicated by increases in heart rate and skin conductance (72). In contrast, rumination induction did not affect HRV in our study. That was surprising since it is well-documented that experimentally and spontaneously induced rumination reduces HRV (36–38). One reason, might be that recurring negative thoughts elicit phasic heart rate reactions in a similar manner as they can be observed in the time course of skin conductance (73). Therefore, the rumination condition can hardly be considered a constant state that can be described by an HRV average over the entire phase. Additionally, it is likely that repetitive negative thoughts also occur spontaneously during the resting condition, obscuring the influence of rumination induction. Interestingly, our results corroborated the association between resting HRV and rumination as we observed a linear correlation of self-reported rumination tendencies and HRV estimated at rest. Resting HRV indicates the flexibility of the cardiac system as well as the adaptivity of cognitive processes (74).

Longitudinal studies have suggested HRV to mediate how rumination influences the progression of depressive psychopathology over time (40, 75). Increasing HRV seems to be a suitable way to alleviate depressive symptoms in the long run making *via* HRV biofeedback a valuable add-on to standard therapy (76). In a large study, HRV biofeedback led to reduced depressive symptoms over 1 year (77).

Our results suggest that an intensive biofeedback intervention over 6 weeks reduces depressive symptoms. The reduction in BDI scores was proportional to increases of HRV. Previous studies have indicated that HRV biofeedback enhances inhibitory control of the prefrontal cortex by augmenting functional brain connectivity to other regions such as the insula and amygdala (78, 79), which has a beneficial impact on emotion regulation and stress resilience (80). However, most neuroimaging studies have focused on heart rate as a target of top-down central control (78, 81). How autonomic reactions shape the experience and regulation of emotions has long been a matter of debate [see review by Pace-Schott et al. (82)]. A very recent study by Candia-Rivera et al. (83) gave experimental support to the "causation theory" by demonstrating a causal role of sympathovagal activity in the initiation (bottom-up) of emotional responses. Processing of these initiated emotions involves bidirectional communication between the heart and the brain (83). Thus, successful regulation and interpretation of physiological arousal seem to facilitate adaptive emotion regulation (84). Depressive rumination and negative affect have been linked to low interoceptive abilities that seem to be enhanced by interventions such as biofeedback (85, 86). This in turn might improve the brain-heart-connection during these emotion regulatory processes with a beneficial impact on worry, depressive symptoms, and negative affect (87).

As a main limitation of the current study, the rather small sample size needs to be highlighted. In consequence, the findings should be generalized with care. Additionally, the two groups are not well-matched with respect to age. Aging decreases resting HRV (88–90), and to reduce the effect of physical exercise on HRV (91–93). Although the difference between groups was not statistically significant, an effect of age on the effects within the groups cannot be excluded. To limit the impact of other factors, such as sex, body mass, eating, drinking, smoking, circadian rhythms, and antidepressant medication, we tried keeping conditions of the laboratory measurements as comparable as possible. However, all these factors might introduce additional variance to our statistical models. The reader has to keep in mind that we did not call patients in the control condition weekly as we did during the intervention. This social interaction and the feeling that someone cares may be also a beneficial factor for patients that is not related to biofeedback itself.

In conclusion, smartphone-based HRV biofeedback seems to alleviate depressive symptoms and self-reported rumination levels. Modern technology and smart mobile devices enable remote training, which is particularly advantageous when personal contact is limited. HRV biofeedback has even been suggested as a preventive strategy for people who exhibit an especially high psychological burden during the pandemic, such as healthcare workers, before they develop mental disorders (94). This study provides further evidence for the positive influence of HRV biofeedback on mental and cardiovascular health.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission FSU Jena. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AS contributed to analysis and interpretation of the data and preparing the manuscript. KR and NH contributed to acquisition of the data, quality control, and preprocessing of the data. SS contributed to study conception and critical revision. K-JB contributed to study conception, preparing the

manuscript, and critical revision. All authors contributed to the article and approved the submitted version.

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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/fpsyt.2022.961294/full#supplementary-material

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EDITED BY
Steffen Schulz,
Charité Universitätsmedizin Berlin, Germany

REVIEWED BY
Gianluca Serafini,
San Martino Hospital (IRCCS), Italy
Saul Neves Jesus,
University of Algarve, Portugal

*CORRESPONDENCE
Thomas Ostermann
thomas.ostermann@uni-wh.de

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The influence of mindfulness-based interventions on the academic performance of students measured by their GPA. A systematic review and meta-analysis

Thomas Ostermann[1]*, Martin Pawelkiwitz[1] and Holger Cramer[2,3,4]

[1]Department of Psychology, Faculty of Health, University Witten/Herdecke, Witten, Germany, [2]Department of Internal and Integrative Medicine, Evang. Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany, [3]Institute for General Practice and Interprofessional Care, University Hospital Tuebingen, Tuebingen, Germany, [4]Bosch Health Campus, Stuttgart, Germany

Objective: Mindfulness-based interventions are increasingly used in health, economic and educational systems. There are numerous studies demonstrating the effectiveness of mindfulness-based interventions in the educational sectors (primary, secondary, and tertiary). This systematic review and meta-analysis assessed the current state of research on the effectiveness of mindfulness-based interventions on the academic performance of students as measured by their grade point average (GPA).

Methods: Literature search was conducted in Psychology and Behavioral Sciences Collection, PsycARTICLES, PubMed, and Google Scholar through March 2022. The inclusion criteria were: (1) the use of GPA as a measure of students' academic performance, (2) a sample that was subjected to a mindfulness-based intervention without medical indication, (3) the student status of the subjects. Meta-analysis was conducted using a random effects model with the generic inverse variance method.

Results: The search included a total of 759 studies, of which six randomized controlled trials met the inclusion criteria. In these trials, significant group differences for GPA were found with effect sizes ranging from d = 0.16–1.62 yielding a significant overall effect of d = 0.42 (95% CI: 0.15–0.69) and a low magnitude of heterogeneity of I^2 = 37%.

Discussion: In conclusion, the first results of this emerging research field seem promising. However, the exact mechanisms of action are still unclear.

KEYWORDS

academic performance, mindfulness, meta analysis, grade point average, students

Background

One of the strongest predictors of students continuing their studies at university is the Grade Point Average (GPA; DeBerard et al., 2004). As an objective measure of the academic performance of students, by which they are measured even after graduation during their career entry, the average grade is a manageable and, through the documentation of the universities, easily accessible operationalization of academic performance for research.

In many societies, the average grade is used to measure and document the previous school and university performance of pupils and students and is used as a predictor of future performance (Tatar and Düştegör, 2020; Koropanovski et al., 2022) and job satisfaction (Al-Asmar et al., 2021). One reason for this is that one of the best predictors of future performance is past performance. The average grade is also one of the best predictors of the performance of students, which is crystallized in their GPA (Wolfe and Johnson, 1995; McKenzie and Schweitzer, 2001). Besides a person's intelligence (Duckworth and Seligman, 2005), GPA is also associated with the personality traits like conscientiousness or openness to experience (Mammadov, 2022). Student motivation has a moderating effect on the relationship of openness to experience and conscientiousness with the GPA (Komarraju et al., 2009; Hazrati-Viari et al., 2012). In addition, self-control (Wolfe and Johnson, 1995; Tangney et al., 2018) and self-discipline explain a large proportion of variance in the GPA (Duckworth and Seligman, 2005, 2006). Sleep quality (Trockel et al., 2000; Önder et al., 2014; Nagane et al., 2016), and socioeconomic status are further associated with GPA (White, 1982; Sirin, 2005; Burbidge et al., 2018).

The concept of mindfulness has its historical origin primarily in Buddhism. Mindfulness is often described as a state of consciousness when attention is non-judgmental and is directed to the present moment and the constant development of the phenomena of the present moment. Phenomena can be understood as thoughts, feelings, and body sensations that are allowed to pass without attachment (Kabat-Zinn, 2003). Mindfulness-based interventions thus can be seen as interventions that have internalized this basic idea in their underlying axioms and apply it in its specific form. Yoga, Qi Gong, Tai-Chi, and meditation can be understood as mindfulness-based interventions. The interventions often differ regarding the focus of attention in the exercises. There are systems that focus more on the body (e.g., Yoga and Qi Gong), and there are systems where the mind plays a central role (as in classical sitting meditation).

A currently very popular form of mindfulness-based intervention is the Mindfulness-based stress reduction (MBSR) program by John Kabat-Zinn. The effectiveness of the program, which spans 8 weeks and includes a variety of formal and informal mindfulness-based interventions such as yoga exercises and sitting meditation, has been demonstrated in numerous studies. Its effectiveness covers a wide range of mental and physical illnesses. There are a large number of studies that prove its effectiveness in chronic pain, cancer, heart disease, depression, and anxiety disorder (Grossman et al., 2004). Dispositional mindfulness has e.g., been shown to be negatively associated with suicidal ideation (Lamis and Dvorak, 2014). Moreover, mindfulness moderates the association between affective temperaments and psychiatric symptoms (Barnhofer et al., 2011). This is important, because, affective temperaments are independently and more strongly associated with negative clinical outcomes than a diagnosis of a major affective disorder (Baldessarini et al., 2017).

Mindfulness has also found its way into the educational system, its application can be found in primary, secondary, and tertiary education (Reber, 2014). Outcomes include social, health, and work/performance (Shapiro et al., 1998; Beauchemin et al., 2008). Although further studies are needed in this field, it seems that the effects of mindfulness-based interventions in pupils and students differ during their development span (Reber, 2014).

This systematic review and meta-analysis aimed to assess the current state of research on the effectiveness of mindfulness-based interventions on the academic performance of students as measured by their grade point average (GPA). Thus, the main hypothesis was that students' GPA will be higher after mindfulness interventions compared to a non-mindfulness control group.

Methods

The review was planned and conducted in accordance with PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009) and the recommendations of Cochrane (Higgins et al., 2019).

Eligibility criteria

The inclusion criteria of this systematic review and meta-analysis were: (1) the use of GPA as a measure of students' academic performance, (2) a randomized study design with at least one group that was subjected to a mindfulness-based intervention without medical indication, (3) the student status of the subjects. Exclusion criteria were whether: (1) the GPA was measured as an indicator for the academic performance of the students, (2) a sample of students without medical indications such as depression, ADHD, PTSD, clinically relevant anxieties, etc. was selected, and whether (3) the study was conducted with students since the English word "students" denotes both students and pupils. Exact duplicates were excluded from the results. The decision to exclude studies was made by consensus with an

external expert. No restrictions were used for the primary data search, e.g., the publication date. Due to the linguistic knowledge of the persons involved in the review, only German and English studies could be considered.

Literature search

The following electronic databases were used for the primary study search on March 08, 2022: Psychology and Behavioral Sciences Collection, PsycARTICLES, PubMed. The following search terms were used: students AND mindfulness AND (GPA or grade point average or academic achievement or academic performance).

The search terms were defined *a priori* by consensus with an external expert. In addition, a search with the search terms defined at the beginning was carried out in the Google Scholar search engine and added as an additional source. For Google Scholar the search terms "college students" mindfulness "grade point average" "student success" "control group" were used.

Web of science, Scopus, and ScienceDirect were not searched separately because Google Scholar has been shown to find nearly all citations covered by these databases (Martín-Martín et al., 2018).

The studies found in this way were checked according to the eligibility criteria for fit with the orientation of the review. The title, abstract, and full text of the retrieved studies were examined for their fit with the orientation of the review.

Risk of bias in individual studies

Two reviewers independently assessed the risk of bias in individual studies using the Cochrane risk of bias tool. This tool assesses the risk of bias on the following domains: selection bias, performance bias, attrition bias, reporting bias, and detection bias (Higgins et al., 2019). Again, discrepancies were rechecked with a third reviewer, and a consensus was achieved by discussion. If necessary, trial authors were contacted for further details.

Data analysis

Meta-analysis was conducted using Review Manager Software (Version 5.3, The Nordic Cochrane Centre, Copenhagen) by random effects model using the generic inverse variance method. Cohen's d with the standard error was calculated as the difference in post-intervention means or pre to post change scores between groups divided by the pooled standard deviation. Where no standard deviations were available, Cohen's d was calculated from t-, F- or z-statistics (Lakens, 2013). The magnitude of heterogeneity was analyzed using the I^2 statistics and categorized as (1) I^2 = 0%–24%: low; I^2 = 25%–49%: moderate; I^2 = 50%–74%: substantial; and I^2 = 75%–100%: considerable heterogeneity.

Results

Literature search

In the primary data search in the databases, PBSC and MEDLINE 86 records were found. The search in the Google Scholar database revealed 675 additional records. After examination of the exclusion criteria, seven studies were included in the qualitative, and six studies in the quantitative analysis (**Figure 1**).

Study characteristics and findings

In the following, the studies are presented in a modified form of the PICO scheme in a tabular overview (**Table 1**). The risk of bias in individual studies is reported in **Table 2**.

In addition, the studies and their results are presented alphabetically according to the name of the first author.

A recent randomized controlled trial of Baumgartner and Schneider (2021) investigated the impact of a 7-week MBSR intervention without a full day of silent mindfulness practice at the end on academic resilience and performance in 47 college students compared to an active control group of 52 students and an untreated control group of 29 students. Participants completed daily meditation or study logs. GPA was obtained for the semester prior to the study and of the study semester. Using a repeated-measures ANCOVA adjusting for pre-intervention found significant GPA improvements in the MBSR-group, while GPA remained unchanged in the control groups (d = 1.41 compared to active control; d = 1.62 compared to untreated control).

Butzer et al. (2015) conducted a study in 9th and 10th grade students on the effects of a 12-week school-based yoga intervention on changes in GPA. Participants included high school students who had registered for physical education randomized to receive either a yoga intervention (n = 44) or physical education (n = 51). The yoga intervention was designed as a 12-week school-based yoga intervention (28/29 sessions of 35–40 min) while physical education as usual consisted of 28 sessions of 35–40 min. GPA was collected *via* school records at the end of the school year. Results revealed that GPA differed between the yoga and control groups over time (d = 0.13) without being significant.

In a randomized controlled trial, 108 students from four study programs were randomized into an experimental group and a control group (Eswari, 2018). The experimental group met three times a week for 90 min to prepare for their

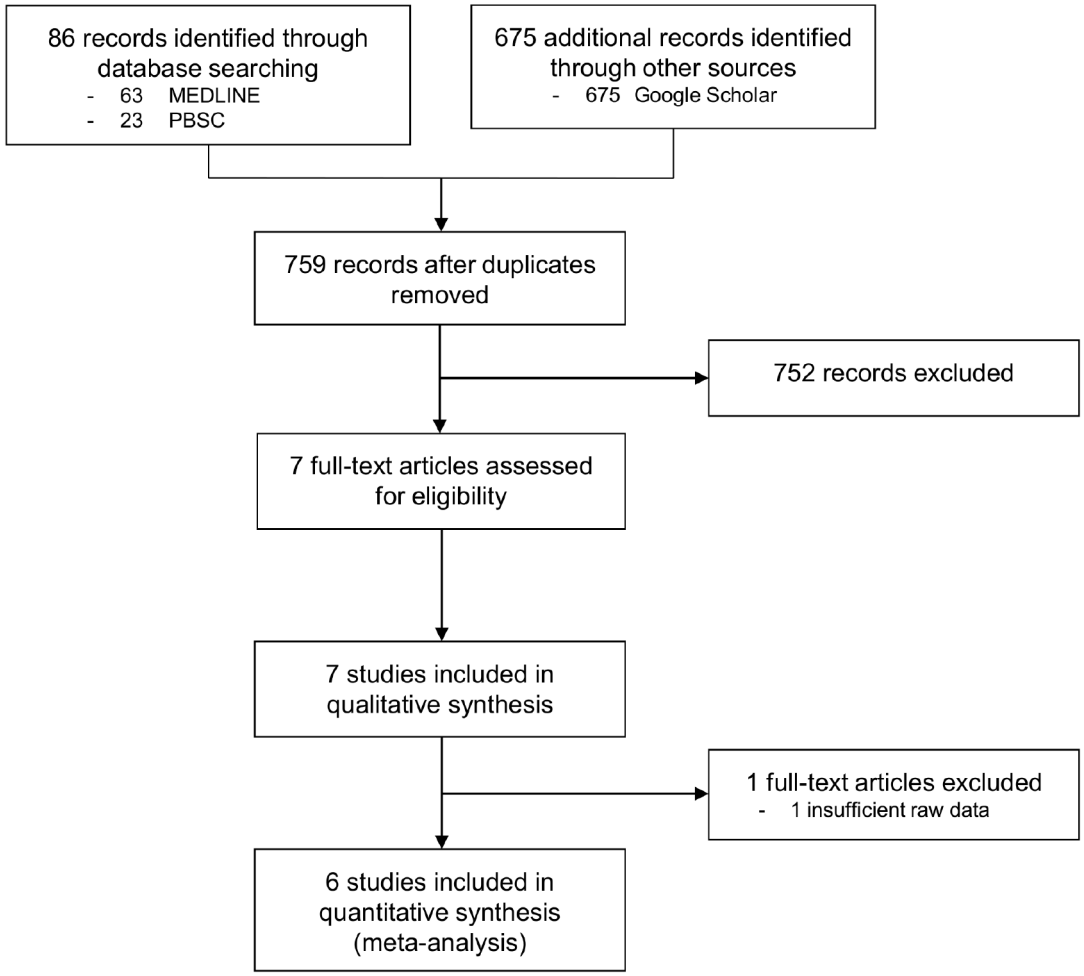

FIGURE 1
Flowchart of the results of the literature search.

studies and exam performances after a 45-min mindfulness training with physical postures, breathing techniques, and meditative exercises. The control group met for the same duration and frequency only to work towards their exams and to discuss current topics and doubts in the study subject. The subjects were obliged to maintain secrecy regarding the instructions. Significant differences in the average GPA favoring the experimental group (GPA = 8.72) over the control group (GPA = 8.51) were found after the intervention (p = 0.031; d = 0.26).

In a mixed-method research project, Güldal and Satan (2020) conducted a nested in a randomized clinical trial of a 8-week mindfulness-based psychoeducation program compared with regular guidance lessons including learning styles, study habits, and self-esteem in 20 female students of a religious high school for girls in Istanbul equally split to both groups. A difference between the test and control groups' GPA was found without being statistically significant (z = -0.378 d = 0.16).

Pamela D. Hall (1999) examined 56 African American students who had previously been randomly assigned to an introductory course in psychology at Hampton University. While the experimental group met once a week for one semester to learn 1 h after they jointly conducted a 10-min mindfulness-based intervention, the control group met to learn without the prior intervention. All subjects were obliged to not divulge to the members of the other group about what was going on in their group. The intervention was a meditation containing elements of natural breathing technique, relaxation, and attention-focusing. The subjects of the experimental group were instructed to use the same process when learning independently for an exam and before taking a test. Statistically significant differences were found between the groups in the GPA during (experimental group GPA = 2.85; control group GPA = 2.55; p = 0.041; d = 0.55) as well as after the semester were the intervention took place (experimental group GPA = 2.93; control group GPA = 2.48; (p = 0.014; d = 0.68).

TABLE 1 Tabular overview of the characteristics of the included RCTs (EG: experimental group; CG: control group).

Author (Year)	Origin	Participants	n (EG/CG)	Intervention	Control	Main results on GPA
Baumgartner and Schneider (2021)	USA	College students	27/29	7-week MBSR intervention without full day silent mindfulness practice at the end	1. No treatment 2. Study skills group	Significant difference (d = 1.62 compared to no treatment; d = 1.41 compared to study skills group).
Butzer et al. (2015)	USA	9th or 10th grade physical education class at a public high school	44;51	12-week school-based yoga intervention (28/29 sessions of 35–40 min)	Physical education as usual (28 sessions of 35–40 min)	Significant difference (d = 0.13).
Güldal and Satan (2020)	Turkey	Students of the 10th grade from a religious high school for girls	10;10	8-week mindfulness based psychoeducation program	Regular guidance lessons including learning styles, study habits, and self-esteem	No significant difference (d = 0.16).
Eswari (2018)	Bahrain	Students with an undergraduate degree in science subjects	59;59	Yoga and meditation training including physical postures, breathing techniques	No treatment	Significant difference (d = 0.26).
Hall (1999)	USA	Undergraduate students from an introductory psychology course	28;28	Meditation training including natural breathing techniques, relaxation, and attention-focusing techniques practiced for a duration of 10 min at the start and end of each study session	No treatment	Significant difference during (d = 0.55) and after the semester (d = 0.68).
Sampl et al. (2017)	Austria	Bachelor students	51; 58	Two hour group MBSLT intervention for 10–15 participants over a time period of 10 weeks	No treatment	Significant difference (d = 0.64).

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TABLE 2 Risk of bias assessment of the included studies using the Cochrane risk of bias tool.

Reference	Bias						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baumgartner and Schneider (2021)	Low risk	Unclear risk	Unclear risk	Unclear risk	High risk	Low risk	Low risk
Butzer et al. (2015)	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk
Güldal and Satan (2020)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Eswari (2018)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Hall (1999)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Sampl et al. (2017)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

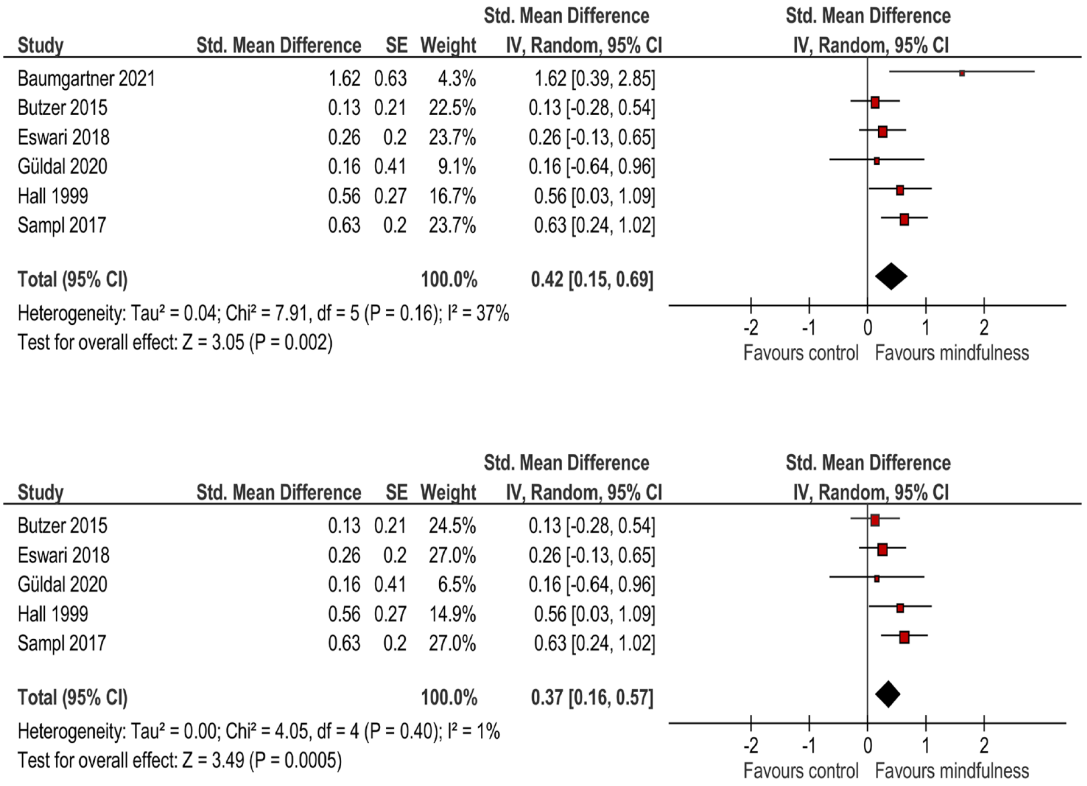

FIGURE 2
Analysis of overall effect (above) using the complete sample (above) and excluding an outlier (below).

A total of 109 students from the University of Innsbruck were examined in a longitudinal randomized control study (Sampl et al., 2017). The experimental group consisted of 51 subjects (38 women, mean age = 21.39 years), and the control group of 58 subjects (44 women, mean age = 23.07). None of the volunteers or their first-degree relatives had a psychiatric diagnosis. The intervention mindfulness-based self-leadership training (MBSLT) was developed specifically for this study and conducted in a group setting of 10–15 subjects over a period of 10 weeks for 2 h per week. The intervention itself consists of combined elements of the MBSR method (Kabat-Zinn, 1994, 2013) and training proposals for developing the ability of self-leadership (Neck and Manz, 2013). The weighted GPA of the experimental group (GPA = 2.20) was significantly higher in the intervention than in the control group (GPA = 1.78) at the end of the semester ($d = 0.64$).

Meta-analysis of these studies revealed a significant overall effect of SMD = 0.42 (95%CI = 0.16–0.88) with moderate heterogeneity. Due to the high effect size of the study of Baumgartner and Schneider (2021), this study was excluded resulting in a reduced heterogeneity without substantively changing the overall effect (**Figure 2**).

Discussion

Summary of findings

Of the 759 studies examined, six RCTs were identified as relevant for answering the question "Do mindfulness-based interventions influence the academic performance of students measured by their grade point average?". Of these, three studies revealed a statistically significant effect between the experimental group and the control group on the GPA of the subjects (Hall, 1999; Sampl et al., 2017; Baumgartner and Schneider, 2021). No significant difference between the groups was found in the remaining three studies, all of which partly found a meaningful correlation to elucidate the variance of the GPA within the group by at least one measure associated with mindfulness. Another observational study not included in the meta-analysis found a positive correlation within the group studied (Wallace et al., 1984).

Discussion of findings

The research field of mindfulness-based interventions and their influence on the academic performance of students is of growing importance. Nevertheless, there are some gaps in the study landscape. Looking at the study landscape as a whole, there are a number of contexts that should be taken into account in the evaluation: with regard to the population, a sample selection bias can be assumed. Even though the studies used a randomized design, it is not clear whether these samples are representative of the population of all students to be investigated. Research in this area faces the difficulty of examining a sample representative of the population (all students). It is questionable whether students who willingly implement a regular mindfulness practice in their lives over a longer period and use the necessary resources to do so are representative of the group of all students. Due to the spiritual background of mindfulness-based interventions, it is also unclear whether they can easily be applied to individuals without a spiritual background or from other spiritual traditions. Some studies have already pointed to the influence of these variables (Grossman and Van Dam, 2001; Napora, 2013).

The different expressions of personality traits may be another reason why a group of students that is not representative of the population as a whole tends to be more concerned with mindfulness-based interventions. Mindfulness, for example, seems to be associated primarily with the manifestations of neuroticism and conscientiousness in the Big Five model (Goldberg, 1990). Whereas the relationship between conscientiousness and mindfulness seems to be unclear—and almost unnoticed (Giluk, 2009)—so far, the literature discusses moderating and mediating influences of mindfulness on behavior and experience associated with neuroticism, such as subjective well-being (Wenzel et al., 2015) or the associated development of depressive symptoms and trait anger (Feltman et al., 2009).

Against the background that trait mindfulness has a conspicuous relationship with the personality traits neuroticism and conscientiousness—but also with a high degree of openness to experience (van den Hurk et al., 2011) , and assuming that the personality traits in the sense of the Big Five are almost normally distributed in the entire population, it is questionable that the group of students who function as a sample in the studies that either already has previous experience with (regular) mindfulness practice or are motivated to do so is representative of the total population of all students.

In reference to already expressed assumptions, such as those of Carsello and Creaser (1978), which refer to their own studies and those of Lazarus (1976), the motivation of the students—and the possibly concrete aim to improve their own grades with the intervention—as well as the personality constitution seem to have an influence on the effectiveness of mindfulness-based interventions. These interrelationships have been given little consideration in the studies to date.

Regarding the study structure, it is noticeable that the importance of the person guiding meditation in the research setting as provided in a study of Bambacus (2018) was only marginally discussed in the RCTs included in our meta-analysis. It can be assumed that the instructor in his leading function influences the results of the intervention through his previous experiences and expectations. Similarly, the use of a detailed psychometric test battery, as given in Napora 2017 was only provided in one study (Sampl et al., 2017).

Looking at the interventions, their heterogeneity is noticeable: one study used Transcendental Meditation (TM; Hall, 1999), and three used different programs with elements of MBSR (Sampl et al., 2017; Güldal and Satan, 2020; Baumgartner and Schneider, 2021), two used yoga and meditation (Butzer et al., 2015; Eswari, 2018). It is unclear to what extent the results of different forms of mindfulness-based interventions can be compared. The same is true for the density and duration of the interventions, which also clearly differed between the included studies. There does not seem to be sufficient research on what dose, i.e., what duration, frequency, and length, is necessary to achieve positive effects through mindfulness-based interventions (Lam, 2016; Bambacus, 2018). This is of particular importance given that dose is one of the most important decisions in the implementation of behavioral interventions (Voils et al., 2012).

Taking all this into consideration, the calculated effect size of the randomized controlled trials (d = 0.42), which can be understood as evidence of a small effect (Cohen, 1988), can be interpreted as the first hint of cause-effect relationships that should be researched by further studies in the future.

Limitations

First, this review is subject to the same limitations as other reviews in this field: publication bias or file drawer problem (Rosenthal, 1979; Creswell and Lindsay, 2014). Second, only one person carried out a literature search and study inclusion. Due to the small number of studies at the beginning of the literature search, it was found to be sufficient to have the process carried out carefully by one person, to discuss the process and the results with an external expert, and to evaluate them as adequate and valid for the study situation. After internal discussion, it was decided not to use an evaluation scale but to describe the studies in more detail. This nevertheless represents a limitation of the review, since such scales provide evaluation criteria of comparatively high-quality, which increase the quality of the evaluation of the studies in the review and thus increase the quality of the review.

Further directions

In future studies, researchers in this field are recommended to take a more detailed account of the demographic data of the subjects, to publish the descriptive statistics relating to the sample and thus check for possible confirmatory variables. This is important because it is essential that the gender distribution, age, and previous study length be surveyed and taken into account. Above all, it must be taken into account that students in their first year are particularly under the influence of stressors and that there will probably be a natural development of academic performance in this period, which should be differentiated from the effect of the intervention. Similarly, ethnicity should be considered (Toomey and Anhalt, 2016). In the future, it will be necessary to check whether the selected sample is representative of the population to be examined. In this sense, further studies should be carried out on the interrelationship between personality traits and mindfulness-based practices. On the other hand, the students' motivation and expectations in carrying out mindfulness-based practices and whether and in what form previous experiences exist should be taken into account. Accordingly, the health status, the embedding in a religious value system, and previous resources and obstacles in relation to one's own academic performance should be surveyed. With regard to the health status, it can be assumed that an improvement in symptomatology, which impairs performance, leads to better performance.

The investigation of the mechanisms of action should also be accelerated. Special attention should be paid to the question of type, dose, and timing of the intervention. A detailed test battery should be used that controls underlying variables (such as test anxiety), collects trait mindfulness, and correlates its developments with those of academic achievement. The research process showed that there are some studies that have collected the GPA through the students' independent data. It is recommended to use university documents instead in order to keep the probability of incorrect information small. It is also recommended to use the cumulative GPA of the second semester of the intervention. In order to adequately correlate the performance of the subjects in the experimental and control groups, it is important to weigh the grades according to the number of examinations taken and the number of credit points collected during the study period. It is recommended to take these indicators into account in the future and to publish them as well.

Conclusions

The present meta-analysis found a significant group difference in the GPA with a small but significant effect size due to mindfulness-based intervention. Thus, a preliminary indication of the effectiveness of mindfulness-based interventions on the academic performance of students measured against their GPA can be assumed. Therefore, implementing mindfulness training in students' curricula seems promising. Universities should explore ways to foster a mindful environment to maximize academic prospects for their students. However, further research is needed to support these emerging data and to clarify how this influence is structured.

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

TO and MP initiated the project and wrote the first draft. MP and HC conducted the literature search, reviewed and examined the articles. HC and TO extracted the data of the included articles and conducted the meta analysis. MP, HC, and TO wrote, edited, reviewed, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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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An Assessment of Quality of Life in Patients With Asthma Through Physical, Emotional, Social, and Occupational Aspects. A Cross-Sectional Study

*Zelal Kharaba[1,2†], Emilie Feghali[3†], Farah El Husseini[3], Hala Sacre[4], Carla Abou Selwan[4], Sylvia Saadeh[5,6], Souheil Hallit[7,8,9], Feras Jirjees[10], Hala AlObaidi[11], Pascale Salameh[4,12,13,14] and Diana Malaeb[3,15]**

[1] Department of Clinical Sciences, College of Pharmacy, Al-Ain University of Science and Technology, Abu Dhabi, United Arab Emirates, [2] Al Ain University Health and Biomedical Research Center (HBRC), Al Ain University, Abu Dhabi, United Arab Emirates, [3] School of Pharmacy, Lebanese International University, Beirut, Lebanon, [4] INSPECT-LB: Institut National de Santé Publique, Epidemiologie Clinique et Toxicologie, Beirut, Lebanon, [5] Life Sciences and Health Department, Paris-Est University, Paris, France, [6] Health and Sciences Department, American University of Health and Sciences, Beirut, Lebanon, [7] School of Medicine and Medical Sciences, Holy Spirit University of Kaslik, Jounieh, Lebanon, [8] Psychology Department, College of Humanities, Effat University, Jeddah, Saudi Arabia, [9] Research Department, Psychiatric Hospital of the Cross, Jal El Dib, Lebanon, [10] College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates, [11] College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates, [12] School of Medicine, Lebanese American University, Byblos, Lebanon, [13] Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus, [14] Faculty of Pharmacy, Lebanese University, Hadat, Lebanon, [15] College of Pharmacy, Gulf Medical University, Ajman, United Arab Emirates

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***Correspondence:**
Diana Malaeb
Dr.diana@gmu.ac.ae

†These authors have contributed equally to this work and share first authorship

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Background: Asthma is a prevalent hyperactive airway disease with physical and emotional impact. Severe asthma is associated with considerable health-related quality of life (HRQoL). The aim of this study is to assess the quality of life through physical, emotional, social and occupational aspects and evaluate the factors affecting HRQoL in patients with asthma.

Methods: This is a cross-sectional multicenter study conducted on adult asthmatic patients enrolled from community pharmacies across different Lebanese geographic areas.

Results: Having wheezing sometimes and most of the time (Beta = −0.144 and −0.552), experiencing anxiety sometimes and most of the time (Beta = −0.205 and −0.573), encountering sleep problems sometimes and most of the time (Beta = −0.270 and −0.553), having previous chest discomfort sometimes and most of the time (Beta = −0.421 and −0.713), and having depression most of the times (Beta = −0.415) were associated with higher lower quality of life scores. On the other side, holding a secondary level of education was associated with a higher quality of life score (Beta = 0.192).

Conclusion: This study highlights that asthma affects adults' quality of life through social, emotional, physical, and occupational impacts. Improved follow-up and patient education may be essential in the future to stop disease progression and achieve ideal therapeutic outcomes.

Keywords: asthma, quality of life, satisfaction, occupational aspects, patients

INTRODUCTION

Asthma is a prevalent non-communicable disease identified by chronic airway inflammation affecting children and adults worldwide (1). Differential symptoms are wheezing, dyspnea, chest discomfort, and persistent cough in addition to airflow limitation, especially at night and in the early morning. The pattern and intensity of the symptoms and airflow limitation vary over time, with exercise, allergen, exposure to irritants, weather changes, and respiratory infections, leading to exacerbation of asthma (2). Although asthma cannot be cured, exacerbations can be prevented by adequate patient counseling and proper management (3). Since it is a chronic condition, patients must utilize medications, adhere to treatment recommendations, and follow the written action for the self-control of asthma.

Even though clinical and physiological variables are used to assess asthma, they may not be enough to assess the patient's interpretation of their state of health. Thus, quality of life (QoL) is a significant endpoint as it reflects the impact of the disease from the patient's perception. Improper asthma management can have a substantial effect on the QoL, including physical, emotional, occupational, and social impacts, where the symptoms differ from one patient to another (4, 5). QoL is explained as the perception that patients have of their position in life in relation to their aims, expectations, concerns, and standards (6). The patient's wellbeing is the standard clinical outcome to assess QoL and prevent morbidity from uncontrolled disease (7).

In asthma, QoL is assessed by using the Mini asthma quality of life questionnaire (Mini AQLQ) (8); it is affected by the frequency of exacerbation, manifested through influence on daily work, deteriorated school performance, reduced social and other activities (9, 10). Other asthma-related factors that negatively affect the patient's QoL are not fully understood, and must be identified and appropriately assessed to improve the QoL (11–15). Female gender, older age, obesity, comorbid diseases such as depression, are prognostic factors associated with poor QoL (11, 16, 17). Poor QoL in asthmatic patients is associated with detrimental consequences resulting in a high prevalence of behavioral and emotional difficulties, depression, and poor academic performance (18). Moreover, avoiding triggers of asthma, and enhancing patient QoL, are effective measures to reduce morbidity and mortality (1).

In Lebanon, asthma treatment in adults falls far short of the goals specified in the international asthma guidelines, similarly to many other countries around the world. This inadequate control of the illness is associated with disease progression and poor QoL (19). In Lebanon, several studies were conducted on asthmatic patients that tackled the preschool asthma risk factor scale, evaluated association between different factors and both wheezing and asthma development, assessed asthma control, and evaluated the influence of diet and obesity on asthma (20–25). However, data on patients' QoL is still scarce, particularly among adults (26). Therefore, the purpose of this study is to assess the effect of asthma on physical, emotional, social, and occupational aspects of QoL among Lebanese adult asthmatic patients.

METHODS

Study Design

A cross-sectional multi-centered study was conducted between February and May 2019. Six Lebanese community pharmacies from all Lebanese districts gave consent to participate in the study from a total of 13 contacted pharmacies. An online software was used to randomly select different community pharmacies using the list of pharmacies provided by the Lebanese Order of Pharmacists (OPL).

Inclusion and Exclusion Criteria

Patients enrolled in the study were between 18 and 65 years, diagnosed by a physician to have asthma according to GINA criteria (27), and taking metered dose inhaler or dry powder inhaler for at least the past year. Patients excluded were those who could not fill the questionnaire appropriately because of decreased mental alertness or cognitive function (cognitive disorders, sedated patients, Alzheimer's disease, etc.).

Ethical Aspect

The Institutional Review Board of the Psychiatric Hospital of the Cross approved the study and written informed consent was acquired from all participants before study enrolment. In addition, the study followed the oxford equator guidelines for cross-sectional multi-centered studies.

Tools and Procedures

Data collection was carried out using a standardized structured questionnaire prepared in Arabic, the native language in Lebanon. A forward and backward translation was conducted for the Mini-AQLQ scale. One translator was in charge of translating the scales from English to Arabic, and another one was involved in the translation from Arabic back to English. Discrepancies between the original and translated English versions were resolved by consensus. It was administered *via* face-to-face interviews by trained researchers to ensure a higher quality of data collection. The first part of the questionnaire included patient demographics, such as gender, age, marital status, educational level (illiterate/primary, secondary, and higher education) and socioeconomic status. The second part assessed the QoL of asthmatic patients using the Mini AQLQ, a validated tool with good reliability since it is discriminates patients with different levels of impairment and validity as it measures asthma-specific quality of life (28).

This short version of the original Asthma Quality of Life Questionnaire requires a shorter time to complete (29) and includes 15 items distributed over four domains: symptoms (5 items), activity limitation (4 items), emotional function (3 items), and environmental stimuli (3 items). The symptoms field covered shortness of breath, cough, chest heaviness, sleep pattern, and wheezing. The activity limitation part assessed occupational, social, moderate, and strenuous activities. The three items evaluated by the emotional function were frustration from asthma, fear of not having the asthma medications, and concern about asthma. The fourth domain covered environmental stimuli, i.e., dust in the environment, cigarette smoking, and air pollution. The responses were scored on two 7-point Likert

scales, from "all of the time" to "none of the time," and from "severely limited" to "not limited at all." For each item, a lower score indicated higher limitation. For each domain, the mean score was calculated by adding the answers and dividing the total by the number of questions, with scores below 6 indicating that asthma had an impact on the QoL (8). The total score was computed by summing all the answers and dividing it by the total number of questions. In our study, the reliability analysis showed a Cronbach's alpha of 0.904 for the total score, 0.717 for the symptoms' domain, 0.663 for the activity limitation domain, 0.751 for emotional function, and 0.815 for environmental stimuli.

Sample Size Calculation

A minimum sample of 74 participants was calculated by The Epi Info software version 7.2 (population survey) to ensure a confidence level of 95%, based on a 66.7% expected frequency of anxiety in asthmatic adults and an odds ratio of 9 in the lack of similar studies in Lebanon. This study accounted for a possible non-response rate for this reason, oversampling is needed (30).

Data Entry and Statistical Analysis

Using Statistical Package for Social Sciences version 21.0, statistical analysis was performed. Descriptive statistics were used for patients' characteristics, with frequencies and percentages for categorical variables and means ± standard deviations for continuous variables. Bivariate associations assessed through the Pearson correlation analysis for the continuous variables along with the HRQol score, and the Student *t*-test and ANOVA F tests were used for categorical variables with two or more levels, respectively. Multivariable linear regression using the Forward method was done for patient's QoL score assessment as the dependent variable, using variables that showed a $p < 0.2$ in the bivariate analysis. All reported *p*-values are two-sided, with alpha set at a significance level of 0.05.

RESULTS

Socio-Demographic Characteristics

Data was collected from 200 participants out of whom 172 were enrolled in the study as the others had mental disorders and thus were excluded. The mean (±SD) age was 31.79 ± 20.92 years, with the majority being females 96/172 (55.8%), single 117/172 (68.0%), and with secondary level of education 86/172 (50.0%). 69/172 (46.3%) of families had a medium monthly income.

Symptoms

Patients reported frequently a discomfort affecting performance of difficult tasks (49.4%), discomfort due to coughing (48.3%) and the need to avoid going out due to weather changes (47.1%). Other asthma related symptoms reported less frequently are summarized in **Table 1**.

Quality of Life Domain Assessment

Based upon the Mini AQLQ, the majority of patients (90.1%) had poor QoL. The mean QoL scores (±standard deviation) for the four domains of the Mini AQLQ (**Figure 1**) were 3.53 ± 1.45

TABLE 1 | Demographic characteristics of study participants.

Characteristic *N* = 172	Frequency (%)
Age mean (±SD)	31.79 ± 20.92 years
Male gender	76 (44.2%)
Female gender	96 (55.8%)
Marital status	
Single/widowed/divorced	117 (68.0%)
Married	55 (32%)
Education level	
Illiterate/primary	59 (34.4%)
Secondary	86 (50.0%)
Higher education	27 (15.7%)
Monthly income	
Low	23 (15.4%)
Medium	69 (46.3%)
High	57 (38.3%)
Quality of life score mean (±standard deviation)	4.65 (±1.22)
Quality of life based upon mini-AQLQ	
Good	17 (9.9%)
Poor	155 (90.1%)
House crowding index (number of people living at home/number of rooms)	0.79 (±0.28)
Previous chest discomfort	
Never/rarely	87 (50.6%)
Few times/sometimes/quite sometimes	50 (29.1%)
Most of the time/all of the time	35 (20.3%)
Previous wheezing experience	
Never/rarely	86 (50.0%)
Few times/sometimes/quite sometimes	72 (41.9%)
Most of the time/all of the time	14 (8.1%)
Depression due to asthma	
Never/rarely	116 (67.4%)
Few times/sometimes/quite sometimes	45 (26.2%)
Most of the time/all of the time	11 (6.4%)
Feeling discomfort due to coughing	
Never/rarely	52 (30.2%)
Few times/sometimes/quite sometimes	83 (48.3%)
Most of the time/all of the time	37 (21.5%)
Feeling anxious due to asthma	
Never/rarely	97 (56.4%)
Few times/sometimes/quite sometimes	61 (35.5%)
Most of the time/all of the time	14 (8.1%)
Discomfort to avoid difficult tasks	
Never/rarely	53 (30.8%)
Few times/sometimes/quite sometimes	85 (49.4%)
Most of the time/all of the time	34 (19.8%)
Discomfort or feeling that one should avoid going out due to weather changes	
Never/rarely	59 (34.3%)
Few times/sometimes/quite sometimes	81 (47.1%)
Most of the time/all of the time	32 (18.6%)
Difficulty sleeping due to asthma	
Never/Rarely	75 (43.6%)
Few times/sometimes/quite sometimes	69 (40.1%)
Most of the time/all of the time	28 (16.3%)

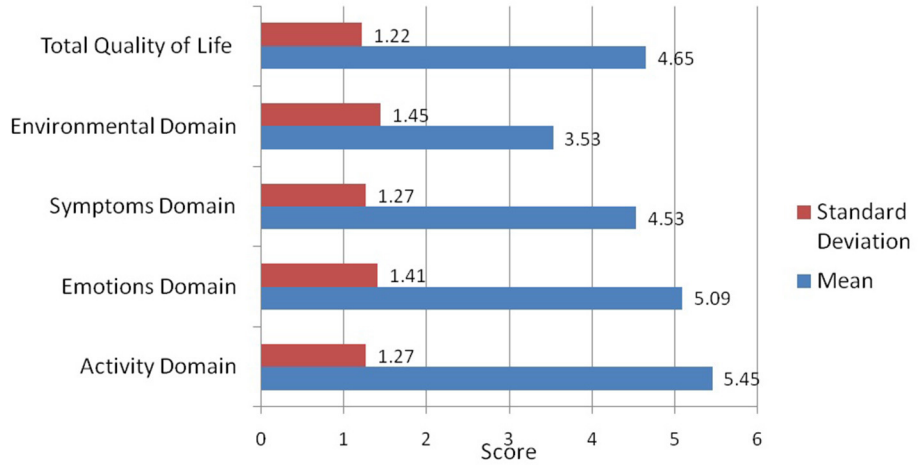

FIGURE 1 | Means and standard deviation of the Quality of life scale and subscales scores.

for the environmental stimuli, 4.53 ± 1.27 for the symptoms, 5.09 ± 1.41 for the emotional function, and 5.45 ± 1.27 for the activity limitation. The mean total score of the mini-AQLQ was 4.65 ± 1.22.

Bivariate Analysis

A meaningfully higher mean QoL score was found in males vs. females (4.88 vs. 4.50; $p = 0.020$), non-married vs. married (4.89 vs. 4.20; $p < 0.001$), high income vs. low income (4.89 vs. 4.16; $p = 0.032$) and secondary and University vs. lower levels of education (4.87 and 4.76 vs. 4.35; $p = 0.02$), and in those who had never have difficulty sleeping due to asthma (5.39 vs. 3.56; $p < 0.001$) or never had depression (5.11 vs. 2.63; $p < 0.001$) vs. most of the time. Similar results were found for feeling anxious, wheezing experience, discomfort due to coughing, discomfort related to difficult tasks and going out during weather changes. Bivariate analysis for factors associated with QoL score is summarized in **Table 2**. However, the results highlight that higher age was significantly associated with minor QoL score ($r = -0.354$, $n = 172$, $p < 0.001$) which is not illustrated in the table.

Multivariable Analysis

The results of a first linear regression, taking the quality of life score as the dependent variable and several other factors as independent variables, showed that holding a secondary level of education was associated with higher QoL scores. However, participants who had wheezing, anxiety, sleeping problems, chest discomfort, and discomfort to avoid going out, discomfort due to coughing, and avoidance of tasks performance on a frequency of "sometimes" and "most of the times" compared to "never" had lower QoL scores shown in **Table 3**. Furthermore, participants who had depression "most of the time" compared to "never," and aging were significantly associated with lower QoL scores.

DISCUSSION

The study findings support the negative effect of asthma on quality of life and show the need for continuous patient monitoring and QoL evaluation during the course of the disease. Holding a secondary educational level was associated with higher QoL score, whereas aging, depression, wheezing, chest discomfort, anxiety, sleeping problems, and avoiding discomfort related to going out, discomfort due to coughing, and avoidance of tasks performance were significantly associated with lower QoL.

Wheezing and Chest Discomfort

Wheezing and chest discomfort are critical prognostic factors in asthma (31). Indeed, wheezing is a frequent and recurrent symptom of asthma that often results in disease exacerbations and limits asthma patients' normal life. Moreover, disease severity is an essential clinical factor affecting the QoL of asthmatic patients and is associated with frequent hospitalizations and unscheduled clinic visits due to asthma exacerbation which has been documented in a previous study conducted in Germany that poorly controlled asthma is associated with a lower HRQOL in adult asthma patients (32). Consequently, wheezing and chest discomfort are associated with bad quality of life as demonstrated in our study. These findings are similar to those described in a study done in Poland on 100 asthmatic patients where high QoL scores were associated with better disease control and minimal exacerbations (11). The results emphasize on the importance of early diagnosis and management of asthma related symptoms to stop the disease progression. Our findings may be explained by the fact that patients with respiratory symptoms manifested by wheezing and chest discomfort have difficulty engaging in physical activities and daily life tasks that impair the quality of life.

TABLE 2 | Bivariate analysis for factors associated with quality of life score.

	N = 172	Quality of life score Mean ± Standard deviation	*P*-value	Statistical test used
Gender	Male	4.88 ± 0.99	0.020	Student *T*-test
	Female	4.50 ± 1.19		
Marital status	Single/widowed/divorced	4.89 ± 0.94	<0.001	Student *T*-test
	Married	4.20 ± 1.31		
Educational level	Illiterate/primary	4.35 ± 1.18	0.020	Analysis of variance
	Secondary	4.87 ± 1.08		
	Higher education	4.76 ± 0.97		
Monthly income	Low	4.16 ± 1.30	0.032	Analysis of variance
	Medium	4.62 ± 1.25		
	High	4.89 ± 0.84		
Difficulty Sleeping due to asthma	Never/rarely	5.39 ± 0.77	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.34 ± 0.91		
	Most of the time/all of the time	3.56 ± 1.11		
Depression due to asthma	Never/rarely	5.11 ± 0.88	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.05 ± 0.91		
	Most of the time/all of the time	2.63 ± 0.68		
Previous chest discomfort	Never/rarely	5.33 ± 0.65	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.37 ± 1.02		
	Most of the time/all of the time	3.47 ± 0.99		
Feeling anxious due to asthma	Never/rarely	5.27 ± 0.77	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.12 ± 0.91		
	Most of the time/all of the time	2.94 ± 0.95		
Previous wheezing experience	Never/rarely	5.26 ± 0.84	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.28 ± 0.96		
	Most of the time/all of the time	3.07 ± 0.96		
Discomfort due to coughing	Never/rarely	5.52 ± 0.80	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.61 ± 0.91		
	Most of the time/all of the time	3.61 ± 0.97		
Discomfort to avoid difficult tasks	Never/rarely	5.57 ± 0.67	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.68 ± 0.83		
	Most of the time/all of the time	3.27 ± 0.85		
Discomfort to avoid going out due to weather changes	Never/rarely	5.54 ± 0.70	<0.001	Analysis of variance
	Few times/sometimes/quite sometimes	4.61 ± 0.82		
	Most of the time/all of the time	3.24 ± 0.84		

Anxiety, Depression, Sleeping Problems

Our study findings demonstrate that insomnia is highly linked to poor QoL, consistent with the results of the study conducted by Luyster et al. (33). Sleep difficulties encountered in asthmatic patients are often the outcome of nocturnal awakenings, resulting from nighttime asthma symptoms, poor control of the trigger factors, and the regular need for rescue inhaler medication; all being symptoms of uncontrolled asthma (33). Poor QoL is also related to the daytime consequence of insomnia, namely fatigue, irritability, and impaired concentration (34).

Our results also support the previous findings in which greater depression and anxiety are associated with lower QoL among asthmatic patients (35, 36). Moreover, insomnia was associated with higher levels of depression and anxiety symptoms, poor asthma control, low QoL, and more frequent asthma-related health care utilization (37). The possible hypothesis

TABLE 3 | Linear regression taking quality of life score as the dependent variable and wheezing, anxiety, insomnia, chest discomfort, depression, asthma knowledge score, and monthly income as the independent variables.

Variables	Unstandardized beta	Standardized beta	95% confidence interval		*P*-value
			Lower	Upper	
Age	−0.640	−0.355	−0.896	−0.383	<0.001
Educational level (illiterate reference)					
Secondary education level	0.192	0.063	0.020	0.364	0.029
Wheezing (never reference)					
Few/some/quite-times	−0.144	−0.603	−0.296	0.007	0.062
Most and all of the time	−0.552	−0.137	−0.818	−0.285	<0.001
Anxiety (never reference)					
Few/some/quite-times	−0.205	−0.087	−0.370	−0.039	0.016
Most and all of the time	−0.573	−0.137	−0.854	−0.292	<0.001
Difficulty sleeping due to asthma (never reference)					
Few/some/quite-times	−0.270	−0.117	−0.429	−0.112	0.01
Most and all of the times	−0.533	−0.175	−0.751	−0.315	<0.001
Previous chest discomfort (never reference)					
Few/some/quite-times	−0.421	0.080	−0.578	−0.263	<0.001
Most and all of the times	−0.713	0.103	−0.916	−0.510	<0.001
Depression (never reference)					
Most and all of the times	−0.415	−0.905	−0.701	−0.128	0.005
Discomfort to avoid going out due to weather changes (never reference)					
Few/some/quite-times	−0.434	−0.190	−0.593	−0.276	<0.001
Most and all of the times	−0.756	−0.267	−0.983	−0.528	<0.001
Discomfort due to coughing (never reference)					
Few/some/quite-times	−0.294	−0.129	−0.458	−0.131	<0.001
Most and all of the times	−0.570	−0.209	−0.776	−0.365	<0.001
Discomfort to avoid difficult tasks (never reference)					
Few/some/quite-times	−0.389	−0.171	−0.551	−0.288	<0.001
Most and all of the times	−0.579	−0.207	−0.818	−0.340	<0.001

is that asthmatic patients may face physical limitation due to uncontrolled disease that enhances depression, and thus, decreases the QoL. A study conducted in Pennsylvania highlighted this finding and showed that severe asthma with increased symptom burden is positively highly associated with risk for co-morbid depression (33). Leander et al. also demonstrated a statistical correlation between anxiety, depression, and the asthma symptoms, including attacks of shortness of breath after activity, that all compromise the QoL (38).

Aging Process

Our findings show that older age was associated with low QoL scores, in line with previous literature (32, 39, 40). The underlying evidence that explains this effect is that elderly people have higher disease exacerbation mainly due to the poor adherence to treatment, greater physical activity limitation, and end-stage disease that leads to development of irreversible asthma (40).

Quality of Life

Quality of life is influenced by many factors, related to both the sociodemographic characteristics of the patients and comorbid disease conditions (9). This study highlights that asthma significantly affects patient's QoL as the majority of patients included in the study reported poor QoL since severe asthma has a tremendous effect on the QoL, which is an essential tool for characterizing patient populations and assessing therapeutic interventions (34). It guides healthcare professionals especially when taking care of chronic and critically ill patients. Our findings can be explained by the fact that patients with severe asthma describe poor quality of life due to excessive symptoms, frequent and life-threatening attacks, increased comorbidity burden, and high pharmacological treatment requirements (34).

The majority of the individuals endorse a poor quality of life which can be explained by the fact that many participants had secondary level of education and were of the medium socioeconomic status. According to previous literature, patients of lower socioeconomic status often report poor health behaviors that may exacerbate asthma, including higher rates of current smoking, reduced consumption of fruits and vegetables, and obesity. Also, patients with lower educational level have lower socioeconomic status and may have higher exposures to indoor and outdoor allergens, and tend to be less complaint with medication, thus increasing risk for acute asthma exacerbations which impair the quality of life (41, 42).

Limitations and Strengths

The study has some limitations. This is a cross-sectional study where the findings cannot establish a causal relationship. Moreover, this study might be also subject to selection bias as the study enrolled more females, young age participants, and single status which can influence the quality of life. The utilization of questionnaires in the general population, especially in elderly, may not always be precise and is limited by the difficulty in questions clear comprehension and influenced by recall bias which underestimates the association between different factors and quality of life. In this study, we accounted for several variables that could affect QoL; however, not all factors were accounted for as diseases, medications, and asthma severity. To remove the confounding effect of several variables, we performed a multivariate analysis; however, we could not ignore the possibility of residual confounding of the variables that we did not evaluate as cardiovascular disease, cancer, and hypertension. Accordingly, prospective studies, taking into account these limitations, are needed. The strengths of this study include the geographical distribution of participants recruited from different pharmacies across Lebanese and the use of the mini AQLQ questionnaire in the methodology, which is a validated tool utilized to assess the QoL.

CONCLUSION

The study demonstrated that asthma affects patient's QoL that was assessed through physical, emotional, occupational and social negative impacts. Patient education is an important part of treatment however, to be successful, it should not only be limited to providing knowledge, but should impact behavior and lead to a consistent change in patient's behaviors. Pharmacists and patients need to cooperate together to improve an asthma care program that targets for optimizing asthma management for a symptom-free asthma disease. During counseling, pharmacists could provide patients with adequate information about the correct use of medications and associated risks of misuse, in addition to general awareness about avoiding asthma triggers to prevent exacerbations and thus improving the QoL. In conclusion, sustained efforts are needed to optimize patients' awareness on asthma disease and its management and to dispel their myths and misconception for an improved QoL.

Implications for Practice

Health-care professionals can utilize the findings of this study to make suitable treatment strategies for asthma for the future and develop healthcare measures based on fundamental evidence. In addition to continuous medical therapy, asthmatic patients should be provided with healthcare education and psychological consultancy services. Therefore, training and psychological support should be provided to patients to ensure optimal therapeutic outcome and disease management. It is recommended that future studies assess other factors affecting QoL among asthmatic patients and methods for improving it.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The Institutional Review Board of the Psychiatric Hospital of the Cross approved the study and written informed consent was acquired from all participants before study enrolment. In addition, the study followed the oxford equator guidelines for cross-sectional multi-centered studies.

AUTHOR CONTRIBUTIONS

DM, EF, and FE analyzed and interpreted the collected data from study participants. ZK, EF, DM, HS, PS, FJ, HA, and SH contributed in idea conceptualization and study design and interpretation of data. ZK, EF, DM, FE, HS, CA, SS, SH, PS, FJ, and HA were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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EDITED BY
Steffen Schulz,
Charité Universitätsmedizin
Berlin, Germany

REVIEWED BY
Sai Sailesh Kumar Goothy,
Ruxmaniben Deepchand Gardi
Medical College, India
Feng Liu,
Tongji University, China

*CORRESPONDENCE
Li-Sheng Wang
wangls168@163.com
De-Feng Li
ldf830712@163.com
Jun Yao
YJ_1108@126.com

†These authors have contributed equally to this work

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The influence of family support during endoscopic submucosal dissection on patient's anxiety

Ruo-Yu Gao[1,2†], Ri-Yun Gan[1†], Jia-Lan Huang[1†], Ting-Ting Liu[1,3], Ben-Hua Wu[1,3], Li-Sheng Wang[1,3*], De-Feng Li[1,3*] and Jun Yao[1,3*]

[1]The Second Clinical Medical College, Jinan University, Shenzhen, China, [2]Department of Gastroenterology, Shenzhen Luohu People's Hospital, Shenzhen, China, [3]Department of Gastroenterology, Shenzhen People's Hospital, Second Clinical Medical College of Jinan University, Shenzhen, China

Background: Psychological problems may promote peptic ulcers. Ulcer-like wounds can be formed after gastric endoscopic submucosal dissection (ESD). The influence of family support on the healing of gastric ESD-induced ulcers remains largely undetermined.

Objective: In the present study, we aimed to assess the Hospital Anxiety and Depression Scale (HADS) scores and the incidence of post-ESD complications in patients with family support in the care process and those in the non-relative group.

Materials and methods: A total of 191 patients aged between 30 and 70 years who received gastric ESD were evaluated with the Chinese version of HADS. Differences in depression and anxiety between the two groups were compared using the chi-square test and *t*-test. Multivariable logistic regression models were used to examine whether anxiety and depression were the risk factors for post-ESD complications.

Results: The mean values of HADS-A (4.61 ± 2.89 vs. 5.56 ± 3.07, $p = 0.042$) and HADS-D (4.14 ± 3.03 vs. 4.97 ± 2.61, $p = 0.048$) scores were significantly lower in patients with accompanying relatives compared with those in the non-relative group. Besides, through the pre-ESD and post-ESD self-contrast, the scores of anxiety and depression in the relative-group were 0.57 and 0.56, respectively ($p < 0.001$), while those in the non-relative group were increased by 1.43 and 1.49, respectively ($p < 0.001$). Multivariable logistic regression analysis revealed that HADS-A, HADS-D scores, and age were significantly correlated with post-ESD abdominal pain ($P < 0.05$).

Conclusions: The occurrence and degree of adverse emotions such as psychological anxiety and depression in patients who received gastric ESD with accompanying relatives during hospitalization may were reduced, and the incidence of gastric post-ESD abdominal pain may was also decreased.

KEYWORDS

depression, anxiety, endoscopic submucosal dissection (ESD), complications, family

Introduction

Upper gastrointestinal cancers are the most common leading causes of cancer mortality worldwide (1), accounting for 13.7% of all cancer-related deaths (2). Every year, about 1.5 million people are diagnosed with gastric or esophageal cancers (3, 4) posing tremendous challenges to the healthcare system due to their aggressive presentation (5). As a new minimally invasive technique, endoscopic mucosal dissection (ESD) is used to treat gastrointestinal (GI) superficial neoplasias (6, 7). ESD is a technically complex process, and it removes a large area of the mucosa that may increase the risk of adverse events, such as pain, bleeding, and perforation (8–10). Delayed bleeding is the most important adverse event associated with ESD (10). Since patients may have fear of the operation, apprehension about their illness, and the ESD may cause some pain and discomfort, they are prone to psychological anxiety and depression during the perioperative period.

Health anxiety or depression is a common problem in the community (11), which imposes a huge burden on health services (12). Studies have shown that certain inflammatory diseases are associated with bad mood. Inflammation caused by anxiety and depression is the most common reason for GI mucosal injury (13). Its damage to the GI mucosa may involve a variety of different psychophysiological mechanisms, from stress stimulation of thyroid-stimulating hormone (TSH, a peptic ulcer promoter) (14) to local blood flow changes (15), leading to damage to the gastric mucosal barrier.

Peptic ulcer belongs to the category of typical psychosomatic diseases, and psycho-social factors play an important role in its pathogenesis (16). In recent years, psychological intervention can significantly reduce the degree of anxiety and depression, resulting in enhanced quality of life of patients (17). Family support is one of the important ways of psychological intervention, which can bring mental security to patients. Therefore, the production of negative emotions can be reduced accordingly, and family support plays an important role in the healing of GI mucosal injury (18, 19).

Patients planning to receive gastric ESD may experience psychological distress. We conducted a literature search of PubMed, searching the years 1990–2022,no study has evaluated the impacts of relatives on anxiety, depression, and complications in patients receiving gastric ESD. In the present study, we aimed to assess the prevalence of anxiety, depression, and ESD complications in patients.

Patients and methods

Patients

A total of 220 patients who underwent their first gastric ESD at the Shenzhen People's Hospital from January 2021 to May 2021 were enrolled in this study. The patients were divided into the relative group and non-relative group according to whether they were accompanied by relatives or not during the perioperative period. During the perioperative period, patients looked after by relatives were set up as the relative group ($n = 92$), and those looked after by non-relatives (hired caregivers) were set up as the non-relative group ($n = 89$). After the detailed screening, 29 patients were excluded from this study. The procedure and results of screening, as well as the patient classification, were shown in the flowchart (Figure 1). In the relative group, there were 43 males and 49 females aged 30–70, with an average age of 51.9 ± 9.1 years. In terms of disease type, there were four cases of high-grade intraepithelial neoplasia (HGIN), 74 cases of low-grade intraepithelial neoplasia (LGIN), one case of atrophic gastritis, three cases of superficial gastritis, and 10 cases of raised lesions. In the non-relative group, there were 48 males and 41 females aged 30–69, with an average age of 50.1 ± 7.5 years. In terms of disease type, there were three cases of HGIN, 73 cases of LGIN, four cases of superficial gastritis, and nine cases of raised lesions. The inclusion criteria were set as follows: (1) 18–80 years old; (2) diagnosed with early GI tumors or raised lesions; and (3) receiving ESD treatment and willing to provide informed consent. The exclusion criteria were as follows: (1) patients with severe systemic diseases, including kidney, liver, or heart dysfunction; (2) patients with a previous history of anxiety/depression or admission anxiety/depression score ≥ 8; and (3) patients with Mallory-Weiss syndrome, post-gastrectomy, and coagulation dysfunction. The general data on age, sex, and type of disease between the two groups were not significantly different ($p > 0.05$; Table 2). The study was approved by the Ethics Committee of Shenzhen people's Hospital (approval No. of the ethic committee: KY-LL−2020114-01) and registered at ClinicalTrials.gov with the identifier ChiCTR2000032851.

Methods

On the following day of admission, all patients were informed of the purpose and procedures of the study. If patients were willing to participate, they were asked to sign an informed consent form. Trained researchers recorded demographic and baseline clinical characteristics of each patient and then assisted the patients to perform the test using the Chinese version of the HADS. Additionally, in the family section of the survey, basic demographic information was collected on the closest family member who accompanied the patient more in the course of hospitalization. Both groups of patients underwent gastric ESD. The patients in the non-relative group were given the routine procedure as follows: the doctor introduced the surgical method to the patient and relieved the patient's tension before the operation. Postoperative proton-pump inhibitor (PPI) therapy can promote the healing of ESD-induced ulcers and reduce

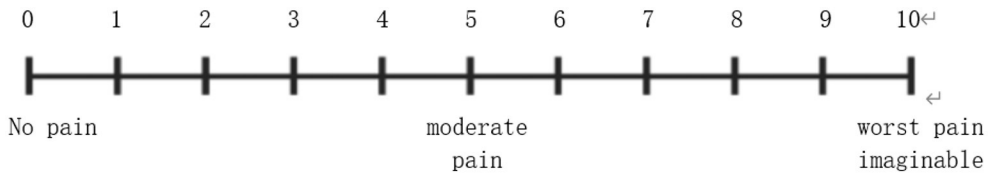

FIGURE 1
Visual analog scale for pain.

TABLE 1 HADS score.

For both scales, scores of less than 7 indicate non-cases	
8–10	Mild
11–14	Moderate
15–21	Severe

the risk of bleeding and abdominal pain. For the relative-group, besides the above-mentioned routine procedures, the accompanying family members were informed to communicate more with the patient, patiently listen to the patient's ideas and concerns, encourage the patient to relax, and provide the patient with a warm, quiet, and comfortable environment. On the first day after operation, the researchers recorded the HADS score and postoperative complications of both groups. Abdominal pain after the ESD procedure was assessed by visual analog scale (VAS) (Figure 1). The VAS consists of a 10-cm long horizontal line with its extremes marked as "no pain" and "worst pain imaginable." Each patient ticked her pain level on the line, and this self-report of pain is considered as the gold standard for pain measurement (20). It was considered that VAS score $\geq$3 was positive for postoperative abdominal pain. For the evaluation of bleeding after ESD, we think that the patients' gastric drainage tube continuously drains bright red fluid, which is ineffective after conservative drug treatment and needs further endoscopic hemostatic treatment.

Measures

The severity of the patient's anxiety and depression was scored with the Hospital Anxiety and Depression Scale (HADS) (21), which is a commonly used self-assessment scale to assess the psychological distress in non-psychiatric patients. The HADS questionnaire has been translated into many languages and applied in different countries and regions (22, 23). The rating of the HADS scale is shown in Table 1 (24). HADS is a self-report questionnaire consisting of 14 items, including seven items assessing anxiety (HADS-A) and the other seven items assessing depression (HADS-D). The total score of each subscale obtained ranges from 0 to 21 (higher scores indicate higher anxiety/depression level). In the present study, the demarcation point of 8 was used to diagnose anxiety and depression (22, 25). The HADS-A1 and HADS-D1 were defined as the anxiety and depression subscales of HADS for the relative group, respectively. HADS-A2 and HADS-D2 were defined as the anxiety and depression subscales of HADS for the non-relative group, respectively.

Statistical analysis

All data were statistically analyzed using R software (Version 3.5.3). Continuous variables were expressed as means and standard deviations (SD) and compared using the *t*-test. Categorical data were expressed as percentages and compared using the chi-square test. Normal distribution was assessed by the Kolmogorov-Smirnov test. The independent-samples *t*-test was used for normally distributed continuous variables. and the Mann-Whitney *U*-test was used for non-normally distributed continuous variables. Multivariate logistic regression analysis was performed to determine the impact of the factors on postoperative ESD complications. The regression model included the following factors: age, gender, anxiety, depression, pylori infection, type of lesion, and lesion location. Variables reaching significance, or borderline significance, on univariate analysis ($p < 0.1$) were subsequently incorporated into a multivariate model. In all tests, a $p < 0.05$ was considered statistically significant.

Result

Study population

A total of 180 patients with GI neoplasia and 30 patients with gastric raised lesions were enrolled in our cohort. Among these patients, 24 patients meeting the exclusion criteria and five patients with serious complications during gastric ESD were excluded. Therefore, there were 162 patients with GI neoplasia and 19 patients with a gastric raised lesion in the final analysis. The surgical specimens of each patient were finally diagnosed by

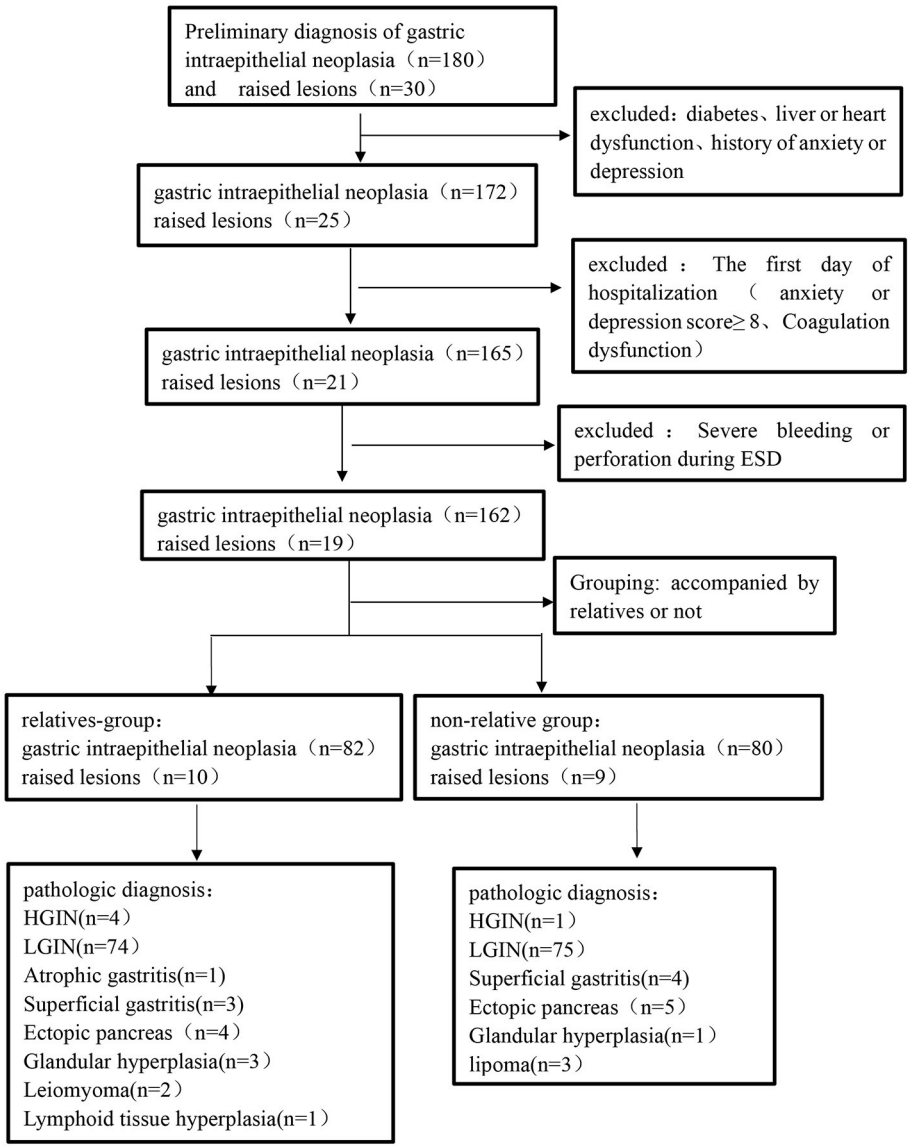

FIGURE 2
Flowchart demonstrating development of relatives-group and non-relative group.

pathology (Figure 2). Table 2 lists the demographic and clinical characteristics of the patients.

Comparison between groups: Difference in HADS scores

The anxiety and depression scores of all patients included in this study were ≤7 before gastric ESD. The baseline of HADS-A (4.04 ± 2.34 vs. 4.13 ± 2.13, $p = 0.927$) and HADS-D (3.58 ± 2.47 vs. 3.48 ± 2.02, $p = 0.801$) scores was similar between the two groups (Table 3). Figure 3 shows the distribution of differences. However, in terms of postoperative scores, the mean values of HADS-A (4.61 ± 2.89 vs. 5.56 ± 3.07, $p = 0.042$) and HADS-D (4.14 ± 3.03 vs. 4.97 ± 2.61, $p = 0.048$) scores were significantly lower in the relative group compared with the non-relative group (Table 3).

Self-contrast: Difference in HADS scores between pre-ESD and post-ESD

Besides, through the pre-ESD and post-ESD self-contrast, the scores of anxiety and depression in the relative group were 0.57 and 0.56, respectively ($p < 0.001$), while those in the non-relative group were increased by 1.43 and 1.49, respectively

TABLE 2 Baseline demographics.

Demographic and clinical variables	Relative care group ($n = 92$)	Non-relative care group ($n = 89$)	p-value
Age M (SD)	51.9 (9.1)	50.1 (7.5)	0.15
Age quartiles ≤45	24 (26.1%)	29 (32.6%)	0.34
46–53	23 (25.0%)	31 (34.8%)	0.15
54–60	24 (26.1%)	19 (21.3%)	0.45
≥61	21 (22.8%)	10 (11.2%)	0.04
Sex (% female)	49 (53.2%)	41 (46.1%)	0.33
Lesion location			
Gastric fundus	21 (22.8%)	15 (16.9%)	0.31
Gastric antrum	34 (37.0%)	45 (50.6%)	0.65
Gastric corpus	20 (21.7%)	15 (16.9%)	0.41
Gastric angle	16 (17.4%)	13 (14.6%)	0.63
Gastric cardia	1 (1.1%)	1 (1.1%)	>0.99
Type of lesion			0.76
Intraepithelial neoplasia	78 (84.8%)	76 (85.4%)	0.91
Low-grade	74 (94.5%)	75 (98.7%)	0.37
High-grade	4 (5.1%)	1 (1.3%)	0.37
Atrophic gastritis	1 (1.1%)	0 (0%)	>0.99
Superficial gastritis	3 (3.3%)	4 (4.5%)	0.72
Raised lesions	10 (10.9%)	9 (10.1%)	0.87
Pylori infection	12(13.0%)	13(14.8%)	0.74

($p < 0.001$; Table 4). Figures 4, 5 illustrate the distribution of differences.

Risk of complications following gastric ESD

After gastric ESD, we observed two types of complications as follows: abdominal pain and bleeding. Table 5 shows the scores of HADS and the incidence of complications in each group. The incidence of anxiety score ≥8 in the non-relative group was higher than that in the relative group (31.5 vs. 18.5%, $P < 0.05$), but there was no significant difference in the incidence of depression score ≥8 between the two groups (14.2 vs. 16.8%, $P > 0.05$). Apparently, the incidence of abdominal pain in the non-relative group was significantly higher compared with the relative group (19.1 vs. 8.7%, $p = 0.04$). However, there was no significant difference in the incidence of bleeding between the two groups. We conducted multivariate logistic regression analysis for the complications. The results showed that HADS-A scores ≥8 (OR, 3.664; 95% CI, 1.384 ∼ 9.701, $P = 0.009$), HADS-D scores ≥ 8 (OR, 3.064; 95% CI, 1.066 ∼ 8.801, $P = 0.038$) and individuals aged <45 years (OR, 0.276; 95% CI, 0.101 ∼ 0.755, $P = 0.012$) were significantly associated with post-ESD complications. Other factors, such as sex, H. pylori infection, type of lesion, and lesion location, were not associated with post-ESD complications ($p > 0.05$; Figure 6).

TABLE 3 Difference in anxiety and depression scores between pre-ESD and post-ESD of the patient in the relatives and non-relative groups.

	Relative care groups	Non-relative care groups	P-value
Pre-ESD			
HADS-A	4.04 ± 2.34	4.13 ± 2.13	0.927
HADS-D	3.58 ± 2.47	3.48 ± 2.02	0.801
Post-ESD			
HADS-A	4.61 ± 2.89	5.56 ± 3.07	0.042
HADS-D	4.14 ± 3.03	4.97 ± 2.61	0.048
Post-ESD complication			
Abdominal pain	8 (8.7%)	17 (19.1%)	0.04
Bleeding	3(3.2%)	3 (3.3%)	>0.99

Discussion

As one of the most studied areas of psychosomatic diseases, the relationship between negative emotions and peptic ulcers has been intensively investigated (26, 27). Similarly, negative emotions can also affect the healing of iatrogenic ulcers caused by gastric ESD. Overall, the prevalence of psychological distress in this study was about 19%, which was relatively lower compared with previous studies on patients with gastric lesions in other countries (28, 29). Such discrepancy might be attributed to the fact that the included patients in previous studies are diagnosed with different stages of gastric cancer before evaluation. Instead, we recruited only patients with dysplasia and raised lesions. Besides, on the following day of admission, patients with an abnormal value of HADS scores were excluded. When patients know that they have gastrointestinal lesions and need gastric ESD surgery, they first feel that they are on the verge of death. Because of fear of unknown diseases and operation, they may be more likely to develop psychological disorders during the perioperative period (30, 31). Some studies have pointed out that 22–58% of patients with malignant tumor have depression, anxiety and other psychological disorders (29, 32). Moreover, the suicidal tendency of these patients was 2–3 times higher than that of the general population (33).

When patients know that they need to do gastric ESD, they may be prone to psychological disorders during the perioperative period due to apprehension about unknown diseases and fear of surgery. In our observational study, we found that the HADS scores of all patients were increased in varying degrees. However, such an increase in patients in the non-relative group was more obvious. Besides, we found that the average anxiety and depression scores of the relative

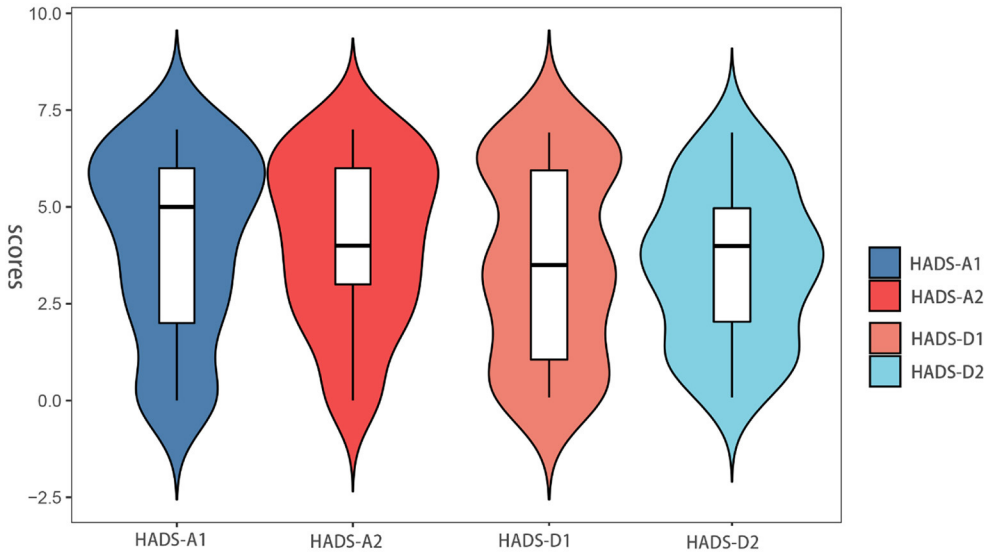

FIGURE 3
Anxiety and depression scores between pre-ESD of the patient in the relative and non-relative groups.

TABLE 4 Difference in anxiety and depression scores between post-ESD and pre-ESD of the patient in the relatives and non-relative groups.

	HADS-A				HADS-D			
	Pre-ESD	**Post-ESD**	**d**	***P*-value**	**Pre-ESD**	**Post-ESD**	**d**	***P*-value**
Relatives groups	4.04 ± 2.34	4.61 ± 2.89	0.57 ± 1.63	<0.001	3.58 ± 2.47	4.14 ± 3.03	0.56 ± 1.27	<0.001
Non-relative groups	4.13 ± 2.13	5.56 ± 3.07	1.43 ± 1.76	<0.001	3.48 ± 2.02	4.97 ± 2.61	1.49 ± 1.25	<0.001

group were lower compared with the non-relative group ($p < 0.05$). Some studies (34) have shown that patients who need gastric ESD to treat early gastric cancer were given systematic psychological intervention, and the anxiety and depression scores of patients after intervention were significantly lower than those before. However, in this study, the anxiety and depression scores increased after ESD, which may be due to some reasons: First, we recorded HADS scores on the first day after operation, when the pathological results were not yet available, which made the patient feel uneasy. Second: the intervention measures of this study are family care, while other studies are systematic psychological intervention,which include cognitive or behavioral therapies, integrative therapy, family therapy, psychodynamic therapy, humanistic therapy, interpersonal psychotherapy, and non-directive therapy (35, 36). Our finding indicated that for hospitalized patients, the accompanying of relatives could reduce the occurrence and degree of anxiety and depression to a certain extent. They could help patients with psychological counseling. Therefore, the patients could maintain a relatively positive and optimistic attitude, leading to reduced impact of psychological factors on the disease. In addition, some studies have shown that the occurrence of bad emotions is negatively correlated with family support (34, 37). Psychotherapy under the guidance of relatives can enable patients to master the relevant knowledge of gastrointestinal diseases and improve the behavior of following doctors' orders, which is similar to the health education in the relevant literature (38, 39).

Routine administration of PPI can suppress gastric acid secretion and promote ulcer healing after ESD (40–42), resulting in retarded development of post-ESD bleeding. The occurrence of anxiety, depression and other bad emotions may come from various complications after ESD, such as abdominal pain, perforation, bleeding and so on Zhao and Wang (43). In terms of complications after gastric ESD, we found six cases of bleeding and 25 cases of abdominal pain. In the relative group, abdominal pain occurred in 8 cases (8.7%) and bleeding in 3 cases (3.3%). In the non-relative group, abdominal pain occurred in 17 cases (19.1%) and bleeding in 3 cases (3.4%). A meta-analysis including 11 studies showed that the incidence of postoperative bleeding after ESD in early gastric cancer was about 6.4%. Due to the low incidence of gastric bleeding after ESD and the relatively insufficient sample size in this study, there was no significant difference in the incidence of gastric bleeding after ESD between

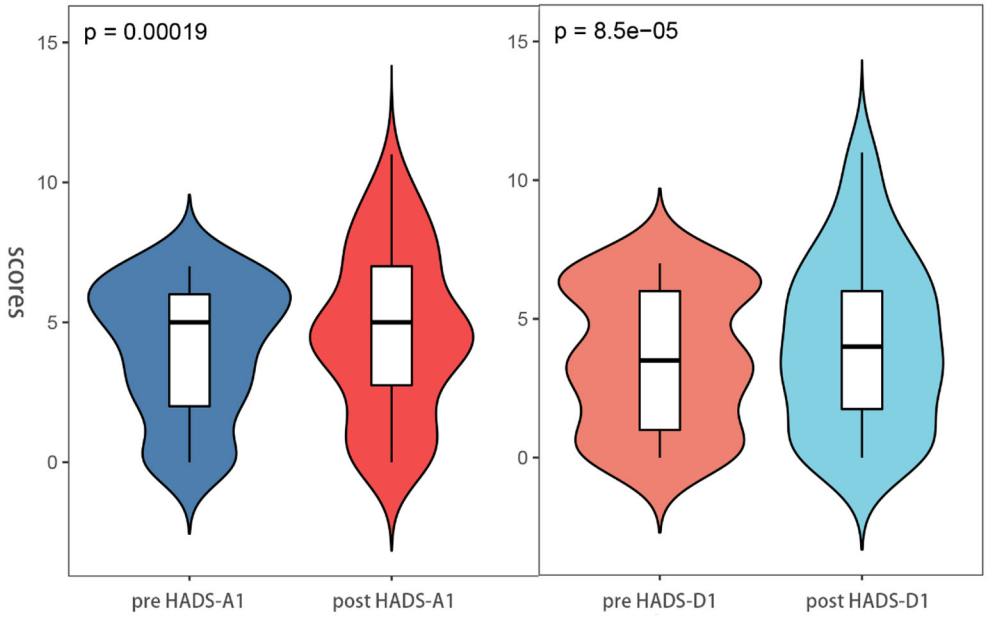

FIGURE 4
Anxiety and depression scores between post-ESD and pre-ESD of the patient in the relatives groups.

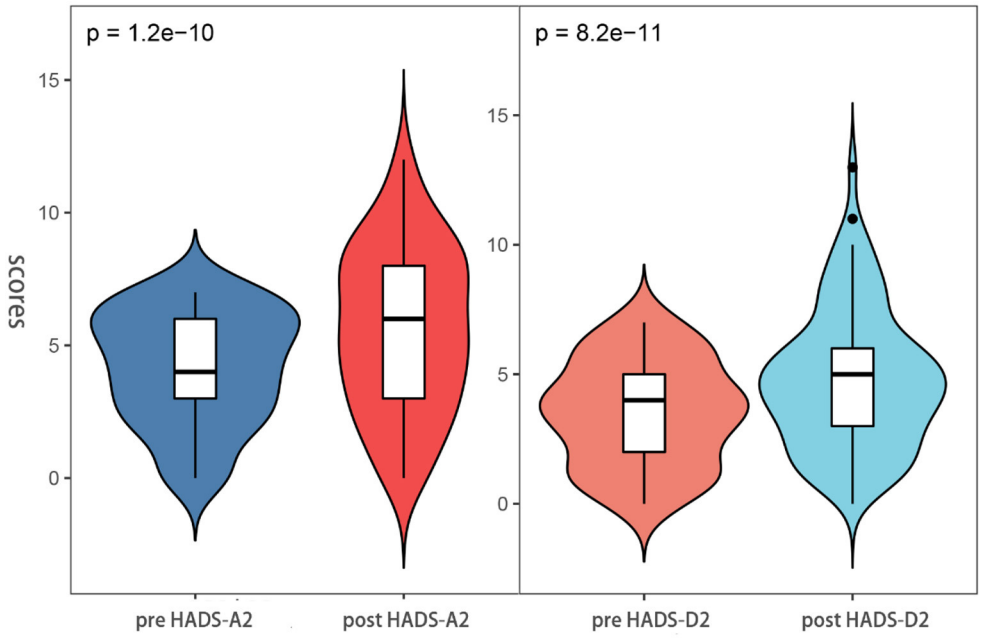

FIGURE 5
Anxiety and depression scores between pre-ESD and post-ESD of the patient in the non-relatives groups.

the two groups. However, in terms of abdominal pain after ESD, the incidence of abdominal pain in the non-relative group was significantly higher than that in the relative group (19.1 vs. 8.7%, $P < 0.05$). At the same time, the incidence of anxiety score $\geq$8 in the non-relative group was also significantly higher than that in the relative group (31.5 vs. 18.5%, $P < 0.05$), suggesting that there may be a positive correlation between abdominal pain and anxiety. Relatively speaking, patients in the non-relative

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group were more likely to undergo complications ($p < 0.05$). By multivariate logistic regression analysis, we found that the ESD complications showed a positive correlation with all subscales of HADS scores and age, while they were not associated with lesion location, type, H. pylori infection, and gender. In conclusion, the relative group had a lower HADS score and a lower incidence of post-ESD complications.

TABLE 5 post-ESD complication and HADS scores.

	Relatives groups ($n = 92$)	Non-relative groups ($n = 89$)	*P*-value
HADS-A			
≤7	75 (81.5%)	61 (68.5%)	0.04
8∼10	16 (17.4%)	24 (27.0%)	0.12
≥11	1 (1.1%)	4 (4.5%)	0.20
HADS-D			
≤7	79 (85.9%)	74 (83.1%)	0.61
8∼10	10 (10.9%)	13 (14.6%)	0.45
≥11	3 (3.3%)	2 (2.2%)	>0.99
Post-ESD complication			
Abdominal pain	8 (8.7%)	17 (19.1%)	0.04
Bleeding	3 (3.3%)	3 (3.4%)	>0.99

During the perioperative period, we should try our best to persuade family members to take care of patients, especially elderly patients. Through strengthening humanistic care, the production of bad emotions could be reduced to promote the healing of ESD-induced ulcer. Actively relieving psychological pressure in the process of family care is an effective measure to reduce anxiety, depression and postoperative complications after gastric ESD. At the same time, providing a clean, warm and comfortable hospital ward environment and establishing scientific and appropriate rest time and diet management is also a key step. In such an environment, patients' mood will appear relaxed, and high-quality sleep time can also enable patients to keep an optimistic attitude (44).

This observational study has several obvious limitations. First, this was a single-center cross-sectional study with a relatively small sample size, which might limit the reliability of the results. Second, patients with a previous history of mental disorders and an admission HADS score ≥8 were excluded. Therefore, the impact on these patients remained unknown. Third, instead of classifying patients based on the type and location of gastric lesions, we evaluated all patients together.

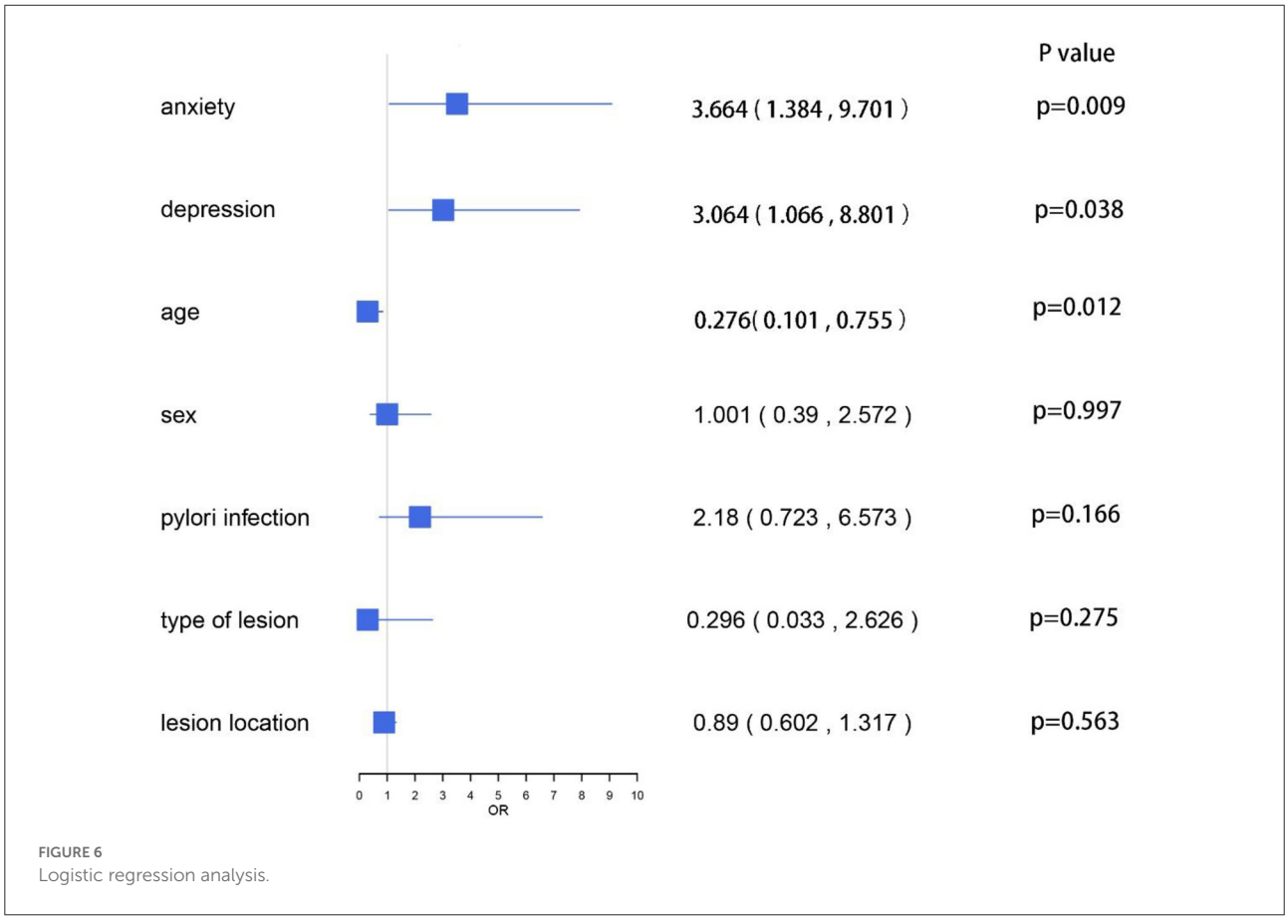

FIGURE 6
Logistic regression analysis.

Conclusion

Our study revealed that patients receiving gastric ESD under the care of relatives during hospitalization had lower HADS-A and HADS-D scores compared with the non-relative group. Besides, the incidence of post-ESD abdominal pain in the relative group was significantly lower compared with the non-relative group. These findings suggested that patients receiving gastric ESD who were accompanied by their families were more conducive to emotional stability, may showing less postoperative clinical manifestations.

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

R-YGao, R-YGan, and J-LH prepared the tables and drafted the manuscript. B-HW and T-TL reviewed the manuscript for its intellectual content. L-SW, D-FL, and JY were responsible for revising the manuscript. All authors have read and approved the final manuscript.

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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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EDITED BY
Steffen Schulz,
Charité Universitätsmedizin Berlin, Germany

REVIEWED BY
Pingyi Xu,
First Affiliated Hospital of Guangzhou Medical University, China
Ivan G. Milanov,
Multiprofile Hospital for Active Treatment in Neurology and Psychiatry St. Naum, Bulgaria
Guigang Li,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
Feng Zhou
362811715@qq.com

†These authors have contributed equally to this work

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Risk of dementia or Parkinson's disease in the presence of Sjögren's syndrome: A systematic review and meta-analysis

Zhen-Zhi Wang[1†], Meng-Si Liu[2†], Zhen Sun[2], Xu-Long Zhang[3], Mei-Ling Zhang[1], Kang Xiong[1] and Feng Zhou[4*]

[1]The First Clinical Medical College of Shaanxi University of Traditional Chinese Medicine, Xianyang, China, [2]Department of Clinical Medicine, Hengyang Medical School, University of South China, Hengyang, China, [3]Shaanxi Province Rehabilitation Hospital, Xi'an, China, [4]The Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang, China

Objective: Evidence from observational studies suggests that Sjögren's syndrome (SS) may contribute to an elevated risk of Parkinson's disease (PD) and dementia. However, few studies have been undertaken to summarize and assess the consistency of the data quantitatively. Therefore, we evaluated the risk of dementia and PD in SS patients through a systematic review and meta-analysis approach.

Methods: Two reviewers independently conducted a systematic search of PubMed, Embase, and Web of Science databases (updated to February 14, 2022) to identify published literature on the association between SS and dementia or PD. The risk estimates of dementia or PD in patients with SS were pooled using fixed or random-effects models.

Results: Of the 631 studies initially searched, 10 were eventually included. Pooled results suggested that the risk of developing dementia significantly increased in patients with SS (HR = 1.24, 95% CI: 1.15–1.33, $P < 0.001$), and such risk in females with SS was similar to that in males. The risk of PD was 1.36 times higher in SS (HR = 1.36, 95% CI: 1.23–1.50, $P < 0.001$). The association between SS and PD risk appeared to occur primarily in female patients (female: HR = 1.28, 95% CI: 1.21–1.35; $P < 0.001$ vs. male: HR = 1.00, 95% CI: 0.87–1.16, $P = 0.962$, respectively). No significant effect of age was observed on the risk of developing PD and dementia in SS patients.

Conclusion: Our study supports that people with SS are at higher risk of PD and dementia than the general population. Further studies are needed to elucidate the underlying mechanisms and to assess whether interventions for SS have the potential to affect dementia and PD development.

KEYWORDS

Sjögren's syndrome, Parkinson's disease, dementia, systematic review, meta-analysis, risk factor

Objective

Sjögren's syndrome (SS) is an autoimmune disorder that plagues 35 million people worldwide. Its main clinical manifestations include dry eyes and dry mouth as well as lymphocytic infiltration of glandular tissues (Sjögren, 1933). SS is characterized by reduced salivary and lacrimal gland function, lymphocytic infiltration, elevated pro-inflammatory cytokines, and circulating autoantibodies. Seventy percent of patients experienced significant fatigue, which greatly disrupted their daily lives (Odani and Chiarini, 2019; Mæland et al., 2021). Among 30–50% of SS patients, extra-glandular symptoms involving the skin, joints, lungs, neurological system, and kidneys, as well as malignant lymphoma were observed (Fox, 2005; Malladi et al., 2012; Ramos-Casals et al., 2015). Recent studies have revealed that the prevalence of neurological manifestations of primary SS (pSS) ranges from 8 to 49% (Margaretten, 2017), such as cognitive dysfunction and dementia (Delalande et al., 2004; Blanc et al., 2013).

Since the beginning of the twenty first century, population aging has become a prominent issue, challenging all countries in the world (Beard et al., 2016). China now ranks first in the world regarding the number of older adults and the rate of aging (Wu et al., 2021). Dementia and PD have emerged as the most common neurodegenerative diseases threatening the health of the age (Jellinger, 2003), with high incidence, serious hazards, and irreversible neuronal damage to the brain (Hindle, 2010). The treatment of these diseases also places a heavy burden on families and society (Alzheimer's Association, 2017; Kwon et al., 2017). This predicament is compounded by the dim prospect for the research and development of medication targeting such diseases.

An association between neuropsychiatric symptoms and autoimmune diseases has been increasingly noted. Several observational studies have explored the association between SS and dementia/PD. Blanc et al. (2013) reported that of 25 patients with SS, 15 suffered from cognitive impairment and 5 developed dementia, revealing the risk of dementia in patients with SS. Several large sample longitudinal cohort studies with long-term follow-up (9–15 years) also confirmed that baseline SS is significantly associated with elevated risks of PD and dementia (Wu et al., 2017; Liliang et al., 2018; Chen et al., 2019; Hsu et al., 2020). Although there is evidence of an association between SS and PD and dementia, no meta-analysis has been conducted to quantitatively summarize and examine data consistency for higher-quality evidence.

Therefore, the present study aimed to quantify the association between SS and dementia/PD. To achieve this end, data were collected to (1) investigate the comprehensive results of the association between SS and dementia, and that between SS and PD; (2) validate the main results by analyzing the results in different subgroups and determining the sources of heterogeneity; (3) test the robustness of the results through sensitivity analysis and assess the potential for publication bias.

Methods

Search strategy

The study was reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-p) statement (Moher et al., 2015). We systematically searched PubMed, Embase, and Web of Science for relevant literature on SS and dementia/PD from inception to February 14, 2022. The following keywords were used: "SS AND PD", "SS AND Alzheimer's disease OR dementia." No restrictions were imposed on the publication type or language of the journal. The detailed search strategy is provided in **Supplementary Table 1**.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they were longitudinal case-control studies or cohort studies, entailed a clear definition of SS, dementia, and PD, or applied standard clinical diagnostic criteria to identify relevant cases. Included studies also should meet the following criteria: assessing the association between SS and dementia as well as SS and PD, or reporting effect estimates and corresponding 95% confidence intervals (CIs). The studies should also include relevant data to calculate hazard ratios (HRs) for the associations between SS and dementia/PD. We excluded reviews, conference abstracts, commentaries, reprinted literature, and studies with duplicated or incomplete data. To avoid omitting any studies, we manually searched the literature cited in the reference lists of included studies.

Data extraction

The final screening results were compared by two authors (WZZ and SZ) based on the same inclusion and exclusion criteria, and any disagreements were resolved by third-party authors. An MS Excel form was created to record essential data from the included studies, including first author, year of publication, study type, country, sample size, the mean age of samples, exposure definition, factors adjusted for the outcome, eligible subgroups, and follow-up periods. All authors approved the final version of the template. Two independent reviewers (WZZ and SZ) extracted data using the pre-determined form, and any discrepancies were addressed through discussion. The corresponding authors of the included literature were also contacted for further information when necessary.

Quality assessment

Two independent reviewers (WZZ and SZ) scored the quality of the included case-control and cohort studies, following the Newcastle-Ottawa Quality Assessment Scale. Studies were rated as high-quality if scored between 7 and 9, medium-quality (5∼6), and low-quality (≤4) (Stang, 2010).

Statistical methods

The HRs were pooled to examine the relationship between SS and PD/dementia risk (Higgins et al., 2003). Heterogeneity was considered acceptable when $I^2 < 50\%$ and $p > 0.05$, and a fixed-effects model was used for analysis. A random-effects model was applied when $I^2 \geq 50\%$ or $p \leq 0.05$. HR, an effective indicator for meta-analysis, was used to calculate pooled effect values, and forest plots were drawn. Further subgroup analyses were conducted based on the available data from the included studies. Sensitivity analysis was performed to evaluate the stability of the results. Publication bias was assessed using Begg's and Egger's tests and graphing funnel plots. All statistical analyses were done using Stata 16.0 software.

Results

Study selection

The screening process is summarized in the flow chart (**Figure 1**). We identified 631 records from PubMed, Embase, Web of Science databases according to a preformulated search strategy. After reviewing titles and abstracts, we excluded 135 studies with duplication and 122 irrelevant studies. The remaining 351 excluded studies were reviews, systematic reviews, animal experiments, and conference abstracts. After further reviewing the full text, 13 studies were excluded due to a lack of control groups or incomplete data. Ultimately, 10 studies were included in this meta-analysis (Wu et al., 2017; Chang et al., 2018; Chen et al., 2018, 2019; Liliang et al., 2018; Lin et al., 2018; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020; Park et al., 2021).

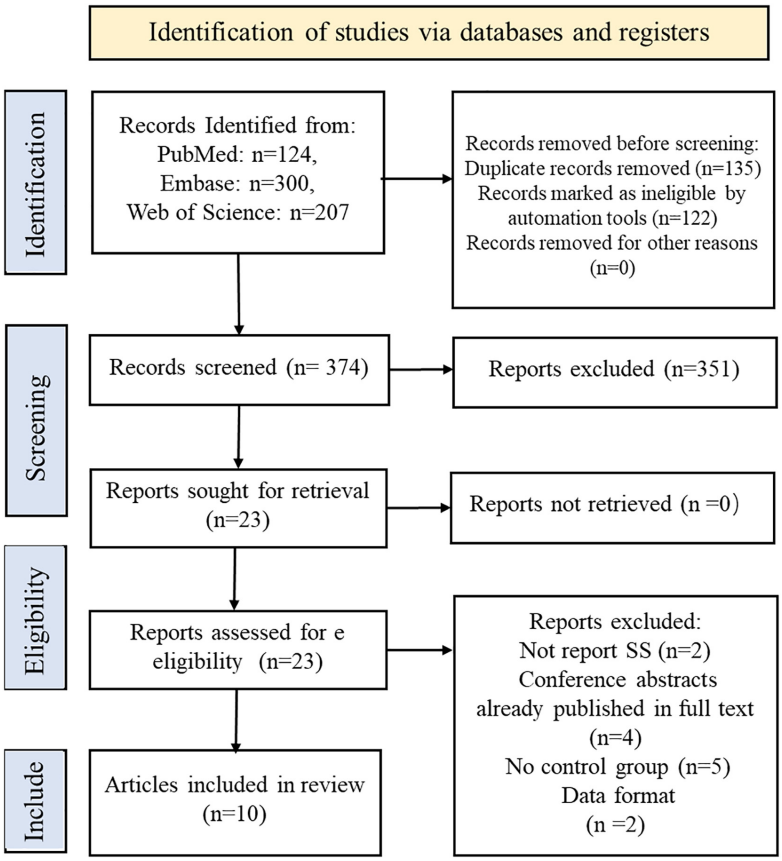

FIGURE 1
Flow diagram of the study selection process.

TABLE 1 The characteristics of included studies.

Study, year	Design	Country	Sources of participants	No. (expose/unexposed)	Occupation	Mean age years (SS/control) (years)	Identification of SS cohort	Control group	Follow up (SS/control) (years)	Diagnosis of dementia/PD	Exposure duration (mean, years)	HR	95%LL	95%UL	Adjustment variables	Subgroup analysis
Park et al. (2021)	case- control, retrospective	Korean	NHIS-NSC database	589 (108/481)	Not reported	Not reported	SS: ICD-10 codes (M35)	Sex and age-matched, randomly selected from the original population	Not reported	prescribed With acetylcholinesterase inhibitors (AChEIs) at least once along with the symptoms outlined in the International Classification of Diseases (ICD)-10 code	Not reported	1.1	0.88	1.38	Age, sex, income, residence, city size, comorbidities	Not reported
Chen et al. (2018)	case-control, retrospective	China	Longitudinal health insurance database	69869 (9918/59951)	Not reported	Not reported/ 73.1 ± 9	SS: ICD-9-CM codes 710.2	Sex and index date with a match ratio 1 : 6, randomly selected from the original population	Not reported	Diagnosis and code (ICD-9-CM codes 290.0–290.4, 294.1, 331.0)	Not reported	1.28	1.11	1.47	Sex, age, and comorbidities	Gender, age
Wu et al. (2017)	case-control, retrospective	China	Longitudinal health insurance database	1,929 (1,036/893)	Not reported	63.7 ± 9.4/ 63.6 ± 9.3	SS: ICD-9-CM codes 710.2	Sex, age, and index date matched, randomly selected from the original population	≥9 years	Diagnosis and code (ICD-9-CM 332)	Not reported	1.38	1.15	1.66	Not reported	Not reported
Chen et al. (2019)	Cohort, retrospective	China	Longitudinal health insurance database	8126 (4063/4063)	Not reported	63.7 ± 9.4/ 63.6 ± 9.3	SS: ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	12	Diagnosis and code (ICD-9-CM)	Not reported	1.21	1.02	1.45	Age, gender, hypertension, hyperlipidemia, Parkinson's disease, and insomnia	Age, gender
Ju et al. (2019)	Cohort, retrospective	China	Taiwan's national health insurance research database	63,200 (12,640/50,560)	Not reported	mean: 54	SS: ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	5.21 ± 3.15/ 5.18±3.16	Diagnosis and code (ICD-9-CM 332)	Not reported	1.23	1.16	1.3	Age, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease, head injury, depression, stroke	Age, sex, follow time
Liliang et al., 2018	Cohort, retrospective	China	Taiwan's national health insurance research database	26,778 (4,463/22,315)	Not reported	Not reported	SS: ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	10	Diagnosis and code (ICD-9-CM codes 331.0)	Not reported	2.69	1.07	6.76	Age, sex, and the geographical region, diabetes, hyperlipidemia, hypertension, coronary artery disease, heart failure, atrial, fibrillation, and stroke	Age

(Continued)

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TABLE 1 (Continued)

Study, year	Design	Country	Sources of partici-pants	No. (expose/ unexposed)	Occu-pation	Mean age years (SS/ control) (years)	Identifi-cation of SS cohort	Control group	Follow up (SS/ control) (years)	Diagnosis of dementia/ PD	Exposure duration (mean, years)	HR	95%LL	95%UL	Adjustment variables	Subgroup analysis
Hou et al. (2019)	Cohort, retrospective	China	Taiwan's national health insurance research database	85,342 (17,072/68,270)	Not reported	54.20/54.02	SS: ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	Not reported	Diagnosis and code (ICD-9-CM: 331.0, 290.0–290.3, 290.4, 294.1, 331.1–331.2, 331.82)	Not reported	1.246	1.123	1.384	Age, gender, comorbidities	Gender, age
Hsu et al. (2020)	Cohort, retrospective	China	Taiwan's national health insurance research database	85,122 (17,028/68,094)	Not reported	Not reported	SS: ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	15	Diagnosis and code (ICD-9-CM 332)	Not reported	1.23	1.07	1.42	Age, gender, comorbidities	Age, gender
Chang et al. (2018)	Cohort, retrospective	China	Taiwan's national health insurance research database	11846 (8422/138424)	Not reported	≥45	SS:ICD-9-CM codes 710.2	Randomly selected from the original population	6.00 ± 5.71/ 6.40 ± 6.21	Diagnosis and code (ICD-9-CM 332)	Not reported	1.56	1.35	1.79	Age, sex, comorbidities	Age
Lin et al. (2018)	Cohort, retrospective	China	Taiwan's national health insurance research database	8,449 (408/8,041)	Not reported	≥45	SS:ICD-9-CM codes 710.2	Sex and age-matched, randomly selected from the original population	5.97 ± 3.05/ 6.37 ± 2.95	Diagnosis and code (ICD-9-CM 332)	Not reported	1.46	1.32	1.63	Age, sex, comorbidities	Age

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TABLE 2 Quality assessment of included studies.

Study (cohort)	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present before study	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow up	Quality score
Chen et al. (2018)	*	*	*	*	**	*	*	*	9
Ju et al. (2019)	*	*	*	*	**	*	*	*	9
Liliang et al. (2018)	*	*	*	*	**	*	*	*	9
Hou et al. (2019)	*	*	*	*	**	*		*	8
Hsu et al. (2020)	*	*	*	*	**	*	*	*	9
Chang et al. (2018)	*	*	*	*	**	*	*	*	9
Lin et al. (2018)	*	*	*	*	**	*	*	*	9

Study (case-control)	Case definition	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability	Ascertainment of exposure	Same method	Non-response rate	Quality score
Park et al. (2021)	*	*	*	*	**	*	*	*	9
Chen et al. (2019)	*	*	*	*	**	*	*	*	9
Wu et al. (2017)	*	*	*	*	**	*	*	*	9

Follow-up long enough: *Median/mean follow-up of more than 5 years or maximum follow-up of more than 10 years was considered enough.
Adequacy of follow up: *A follow-up rate of > 80% and a descriptive analysis of those who were missed was considered adequate.
**Represents a score.

Study characteristics

All included studies were published between 2017 and 2021. Of the 10 included studies, three were case-control studies (Wu et al., 2017; Chen et al., 2018; Park et al., 2021) and seven were cohort studies (Chang et al., 2018; Liliang et al., 2018; Lin et al., 2018; Chen et al., 2019; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020). One was conducted in South Korea (Park et al., 2021), and nine reported the scenarios in China (Wu et al., 2017; Chang et al., 2018; Chen et al., 2018, 2019; Liliang et al., 2018; Lin et al., 2018; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020). Participant sample sizes ranged from 1,929 to 85,342, with an overall mean age from 45 to 63.7 years. Participants diagnosed with Alzheimer's disease, dementia, or PD at baseline were not included in any of the cohort studies or randomized controlled trials. Six of the 10 studies (Wu et al., 2017; Liliang et al., 2018; Chen et al., 2019; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020) were explicitly designed to assess the association between SS and dementia or PD. In comparison, in the remaining four studies (Chang et al., 2018; Chen et al., 2018; Lin et al., 2018; Park et al., 2021), SS was only part of their analysis to assess the relationship between autoimmune disease and dementia/PD. The definitions of dementia and PD varied between studies. Nine Taiwan, China-based studies used the ICD-9 standard, developed by neurologists based on the (UK) Parkinson's Disease (PD) Society Brain Bank Clinical Diagnostic Criteria (Higgins et al., 2003; Stang, 2010; Moher et al., 2015; Wu et al., 2017; Chang et al., 2018; Chen et al., 2018, 2019; Liliang et al., 2018; Lin et al., 2018; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020), and one Korean study followed the ICD-10 classification standard (Park et al., 2021). All eligible studies were assessing dementia, PD, or SS as an outcome event. Seven studies specified the duration of follow-up, ranging from 5.18 to 15 years (Higgins et al., 2003; Stang, 2010; Moher et al., 2015; Wu et al., 2017; Chang et al., 2018; Liliang et al., 2018; Lin et al., 2018; Hou et al., 2019; Ju et al., 2019; Hsu et al., 2020). One study mentioned the follow-up but did not specify the duration (Chen et al., 2019), and the follow-up duration was missed in two studies (Chen et al., 2018; Park et al., 2021). The main characteristics of these studies are summarized in **Table 1**.

The Newcastle-Ottawa Quality Assessment Scale scores for the included studies are shown in **Table 2**. All 10 included studies were considered as high-quality; all of them scored 9, except for the study by Hou et al. (2019), which was rated as 8 because the specific follow-up time was not reported.

Association between Sjögren's syndrome and dementia

We performed meta-analyses and calculated pooled effect estimates for five studies that included 190 704 subjects (Chen et al., 2018, 2019; Liliang et al., 2018; Hou et al., 2019;

Park et al., 2021). Heterogeneity between included studies was subtle [I^2 = 2.0%, p $_{(heterogeneity)}$ = 0.395]. Therefore, a fixed-effects model was used to pool the effect size of each study to determine the association between SS and the risk of dementia (**Figure 2**). The overall pooled results showed that SS was associated with an increased risk of dementia (HR = 1.24, 95% CI: 1.15–1.33, $p < 0.001$).

Our subgroup analyses were conducted by age (<65 and >65) and sex (male and female). Corresponding subgroup analyses of follow-up time and comorbidities on risk were not performed due to the lack of data on the effect (**Table 3**).

In terms of stratified analysis for age, people with SS had a 26% higher relative risk of dementia than those without SS among those over 65 (HR = 1.26; 95% CI: 1.14–1.39; $p = 0.004$), and this risk was similar in patients with SS under 65 years of age (HR = 1.53, 95% CI: 1.19–1.98; $p < 0.001$). Two studies were included in the subgroup analysis by sex (Chen et al., 2018; Hou et al., 2019). Females with SS had a similar risk of developing PD as males. (Females: HR = 1.25; 95% CI: 1.13–1.38; $p < 0.001$ vs. Male: HR = 1.29; 95% CI: 1.08–1.55; $p = 0.005$, respectively).

Evaluation for publication bias and sensitivity analysis

The Begg's and Egger's tests and funnel plot showed no publication bias in the current studies (Begg = 1.000, Egger = 0.446) (**Figure 3**). Furthermore, sensitivity analysis of the pooled results showed that individual studies did not substantially affect the association between SS and dementia (**Figure 4**).

Association between Sjögren's syndrome and Parkinson's disease

A total of five studies involving 163 522 participants (Wu et al., 2017; Chang et al., 2018; Lin et al., 2018; Ju et al., 2019; Hsu et al., 2020) assessed the association between SS and the risk of PD. Tests for heterogeneity showed large heterogeneity between studies (I^2 = 74.5%, p $_{(heterogeneity)}$ = 0.003), so a random-effects model was adopted. Pooled results showed that SS was significantly associated with a subsequent increased risk of PD (HR = 1.36; 95% CI: 1.23–1.50, $p < 0.001$) (**Figure 5**).

We conducted a meta-analysis of subgroups according to age, sex, and duration of follow-up (**Table 4**). In the subgroup analysis based on age, the risk of developing PD was 1.56 and 1.31 times higher in SS patients under and over 65 than in non-SS patients (Chang et al., 2018; Lin et al., 2018; Ju et al., 2019; Hsu et al., 2020), respectively (<65: HR = 1.56; 95% CI: 1.37–1.78 vs. > 65: HR = 1.31; 95% CI: 1.14–1.51, respectively), indicating that age had no significant effect on the increased risk.

In the subgroup analysis by sex, two cohort studies (Ju et al., 2019; Hsu et al., 2020) examined the risk of subsequent PD in male and female SS patients. The pooled HR for PD was 1.28 (95% CI: 1.21–1.35; $p = 0.000$) in female SS patients and 1.00 (95% CI: 0.87–1.16, $p = 0.962$) in male SS patients. These results revealed that the correlation between SS and PD risk seemed to be applicable primarily to female patients.

Only Park et al. (2021) assessed the association between the duration of follow-up on SS and subsequent PD risk. The result showed that the association between SS and PD risk was higher for long-term follow-up (≥9 years) than for follow-up periods of less than 9 years.

Evaluation for publication bias and sensitivity analysis

Begg's and Egger's tests as well as funnel plots were used to assess potential publication bias. No potential publication bias was present (Begg = 0.806 and Egger = 0.242) (**Figure 6**). The robustness of the results was assessed by deleting each study in turn. The exclusion of any individual study did not affect the conclusions (**Figure 7**).

Discussion

Main findings

To our knowledge, this meta-analysis is the first to comprehensively investigate and quantify the association between SS and the risk of dementia/PD. We found a 1.24-fold greater risk of dementia in people with SS compared to the general population; age and gender appear to have no significant effect on this risk. The risk of PD in SS patients was 1.36 times higher in SS individuals. This elevated risk, interestingly, appeared to be prevalent solely in female individuals. Age had no significant effect on the risk of developing PD in SS patients. Based on the fact that over 10,000 patients with both SS and dementia or both SS and PD were involved, the study provided convincing information for the association between SS and PD.

Influence of Sjögren's syndrome on dementia

In recent years, the prevalence of dementia has been rising at an alarming rate in our aging population (Raz et al., 2016). Dementia mainly includes Alzheimer's disease, Lewy body dementia, frontotemporal dementia, vascular dementia, and mixed dementia (Marson et al., 2021). It is estimated that 46.8 million people worldwide were living with dementia in 2015. This number is expected to reach 131.5 million by

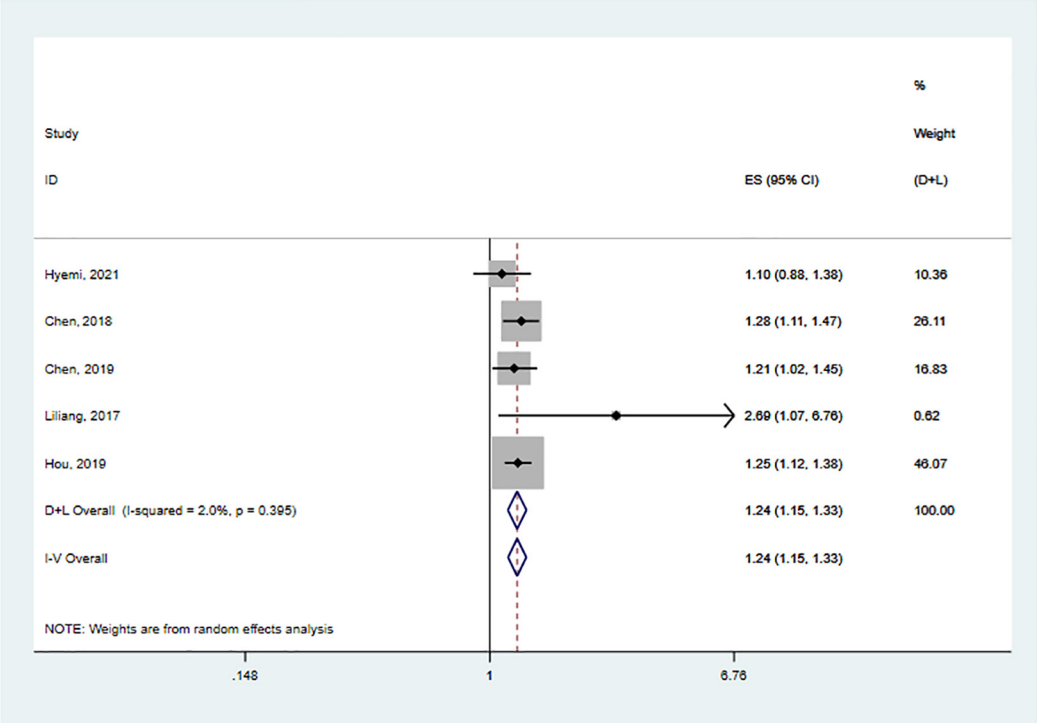

FIGURE 2
Forest plot of the association between SS and risks of dementia.

TABLE 3 Subgroup analysis of the association between SS and risk of dementia.

Subgroup	No. of studies	I^2	P $_{heterogeneity}$	Hazard ratio	95% CI	Pooled model	*P*(overall effect)
Age							
<65	2	0.0	0.518	1.53	1.19–1.98	Fixed-effects model	0.001
>65	3	49.1	0.140	1.26	1.14–1.39	Fixed-effects model	0.000
Gender							
Female	2	0.0	0.889	1.25	1.13–1.38	Fixed-effects model	0.000
Male	2	0.0	0.740	1.29	1.08–1.55	Fixed-effects model	0.005

N, number; HR, hazard ratio.

2050 (Timoszuk et al., 2018). Amyloid-beta (Aβ) peptides and neuroinflammation are the most notable indicators of the disease (Leng and Edison, 2021). Although the molecular mechanisms of tissue damage in these dementias are yet to be fully understood, neuroinflammation and other specific changes in these neurodegenerative diseases, have become the focus of new research (Hensley, 2010; Calsolaro and Edison, 2016). The risk of PD as a comorbidity in patients with SS, one of the most common inflammatory rheumatic diseases with a prevalence between 1:100 and 1:1,000 (Witte, 2019), has received increasing attention (Liliang et al., 2018; Chen et al., 2019; Hou et al., 2019). Since the higher risk of dementia in SS patients may produce significant public health consequences, it is necessary to explore the possibility of SS as an early manifestation of dementia and obtain the potential benefits of early treatment with immunomodulatory or immunosuppressive drugs at an early stage.

The influence of neuroinflammation on dementia remains a controversial topic. The interaction between SS and dementia is becoming more obvious, yet the factors that contribute to progression are unclear. Vasculitis, autoantibodies, immune complex deposition, and cellular inflammation are potential pathways through which SS may elevate the risk of dementia, resulting in nerve damage, cognitive impairment, and initial dementia (Tobón et al., 2012). Previous studies have suggested that inflammation may be a significant event in the pathophysiology of dementia (Newcombe et al., 2018; Webers et al., 2020). Recent studies have found that SS can produce local and systemic inflammation, which in turn leads to a large elevation in IL-1β and TNF-α in vivo (Lisi et al., 2011, 2012)

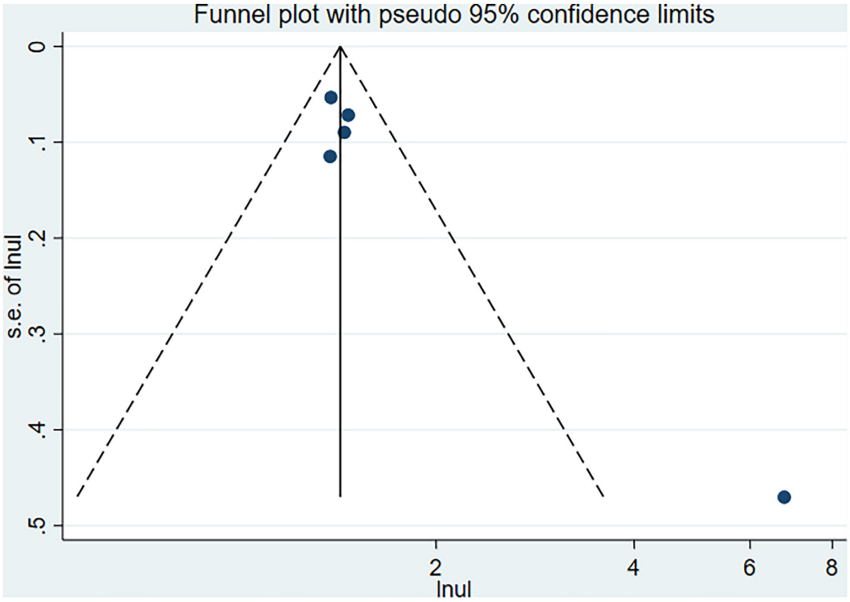

FIGURE 3
The funnel plot for dementia.

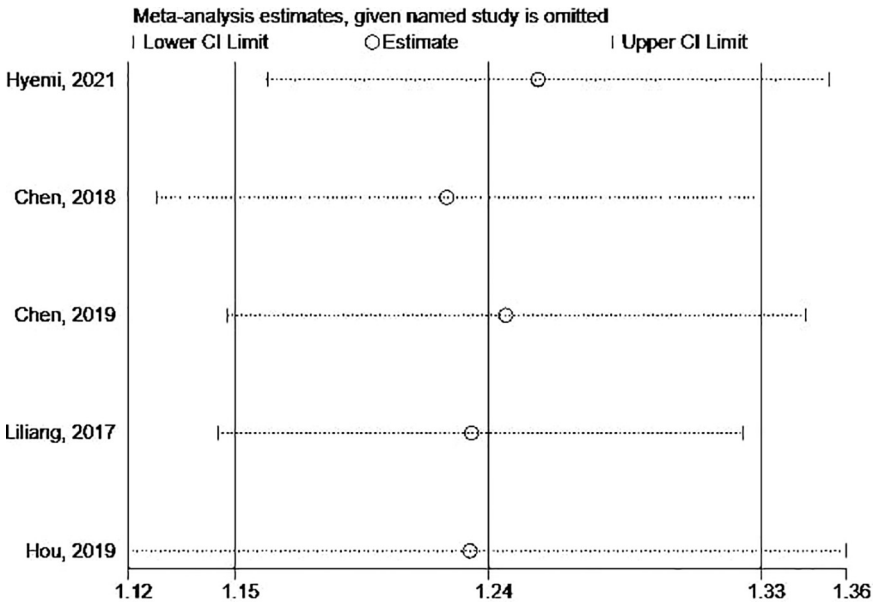

FIGURE 4
The sensitivity analysis of the association between SS and risks of dementia.

and directly or indirectly causes neuronal damage, followed by AD (Ye et al., 2013). Furthermore, Choi et al. (2018) observed that damage to hippocampal neurogenesis in the early stages of AD may increase the vulnerability of hippocampal neurons, resulting in more severe cognitive impairment and neuronal loss in the later stages of AD. Animal experiments by Vom Berg demonstrated that the natural antibody ustekinumab inhibited the pro-inflammatory cytokines IL-12 and IL-23, which are associated with the accumulation of amyloid, and improved cognitive performance in mice (Sue and Griffin, 2013). Although there is no direct evidence on the occurrence of neuroinflammation in the human AD brain, the findings above suggest that neuroinflammation and altered neurogenesis are linked in AD models. However, further studies are needed

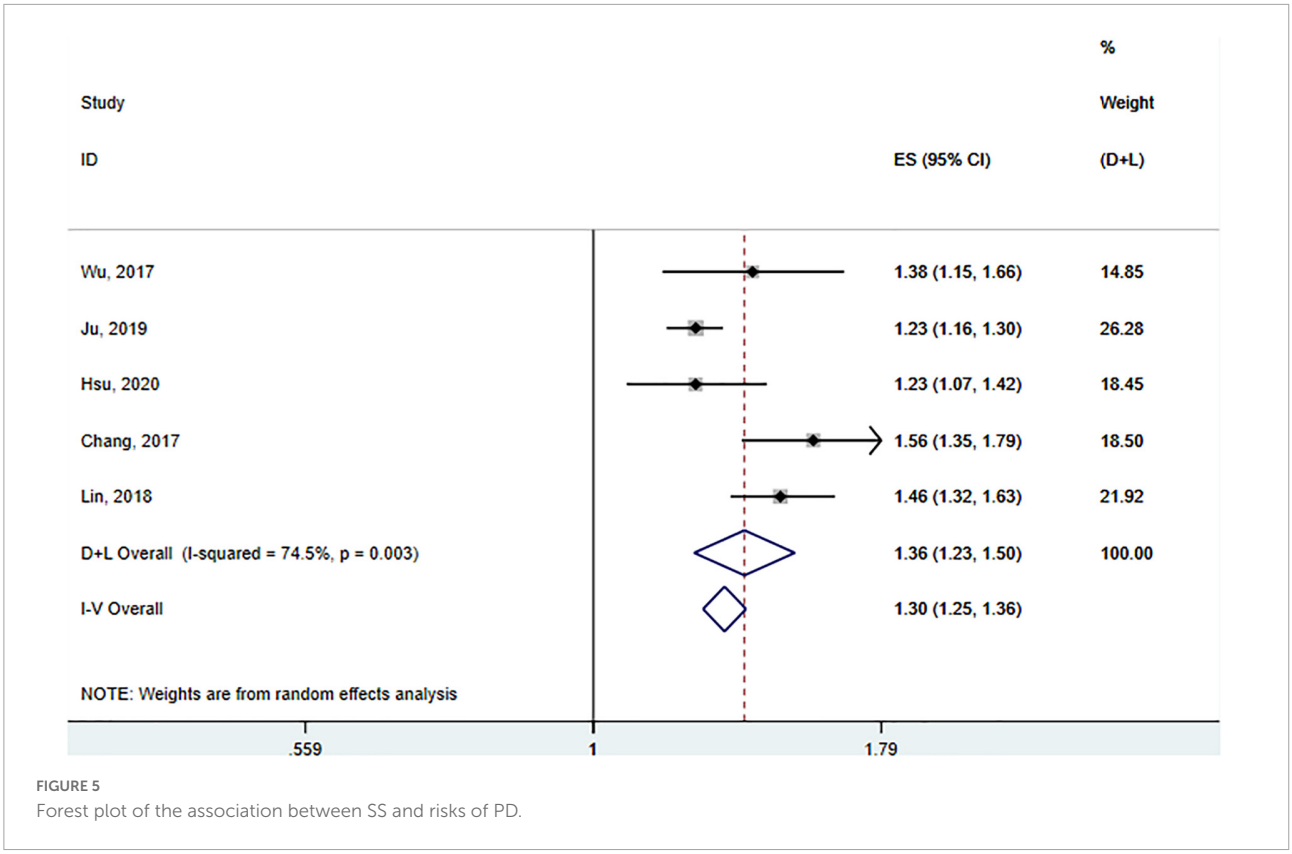

FIGURE 5
Forest plot of the association between SS and risks of PD.

TABLE 4 Subgroup analysis of the association between SS and risk of PD.

Subgroup	No. of studies	I^2	P $_{heterogeneity}$	Hazard ratio	95% CI	Pooled model	*P*
Age							
<65	4	0.0	0.398	1.56	1.37–1.78	Fixed-effects model	0.000
>65	4	65.5	0.034	1.31	1.14–1.51	Random-effects model	0.000
Gender							
Female	2	0.0	1.000	1.28	1.21–1.35	Fixed-effects model	0.000
Male	2	0.0	0.920	1.00	0.87–1.16	Fixed-effects model	0.962
Follow time, years							
<3	1	NA	NA	1.25	1.18–1.32	NA	0.000
4–6	1	NA	NA	1.22	1.14–1.31	NA	0.000
7–9	1	NA	NA	1.26	1.12–1.42	NA	0.000
≥9	1	NA	NA	1.93	1.66–2.23	NA	0.000

N, number; HR, hazard ratio.

to clarify the exact causal relationship between these two phenomena.

Noteworthily, Hou et al. (2019) observed that SS patients with a combination of any other comorbidities (diabetes, hypertension, cardiovascular disease, stroke, and severe mental illnesses) had a higher risk of dementia than non-SS patients without comorbidities. This is consistent with the findings of Chen et al. (2019) who found that SS patients with co-occurring hypertension, PD, and insomnia were more likely to develop dementia. Some studies have confirmed that SS patients are more likely to develop hyperlipidemia, hypertension, and other disorders (Ramos-Casals et al., 2007; Pérez-De-Lis et al., 2010). Many dementias, on the other hand, are associated with diabetes, metabolic syndrome, and cardiovascular disease, suggesting that underlying disease factors may skew the association between SS and increased risk of dementia. This may explain why patients with SS who have comorbidities are more likely to develop dementia. Furthermore, there is no association between substantial cognitive impairment (including dementia) and the use of

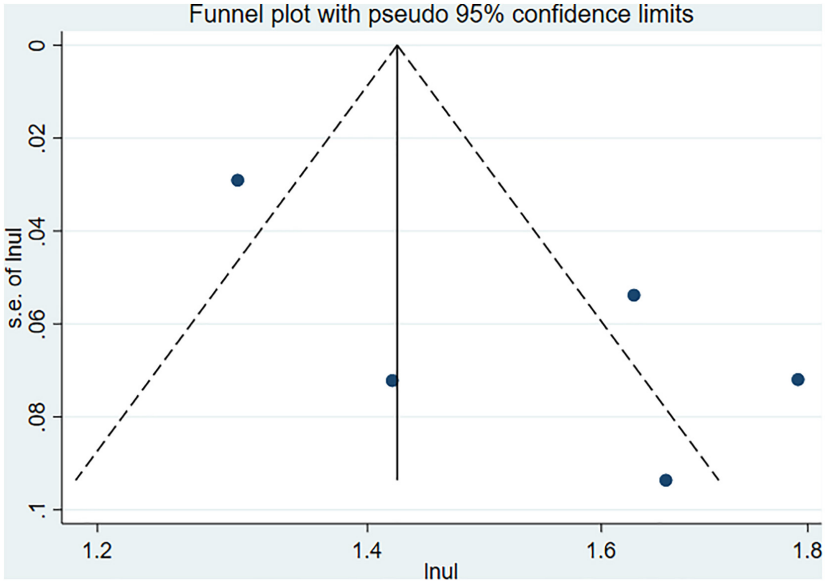

FIGURE 6
The funnel plot for PD.

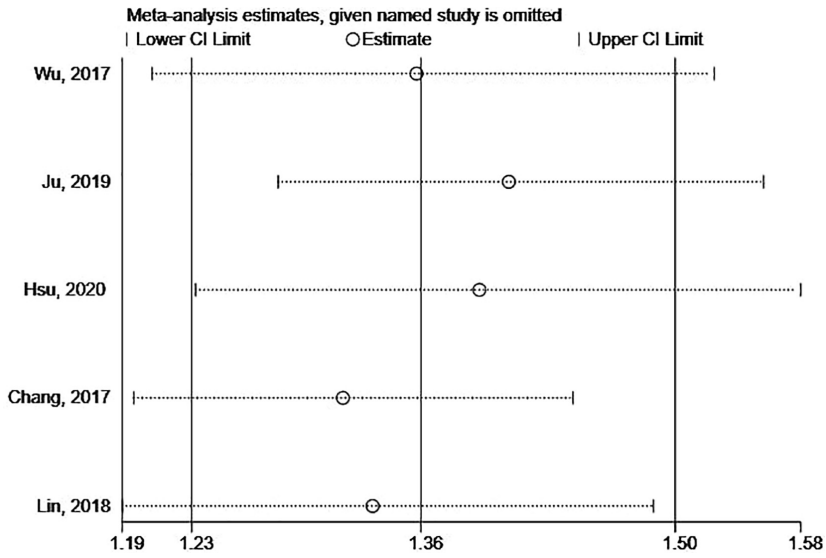

FIGURE 7
The sensitivity analysis of the association between SS and risks of PD.

cardiovascular or hypertensive medications in people with these comorbidities (Hou et al., 2019).

Influence of Sjögren's syndrome on Parkinson's disease

PD is the second most common neurodegenerative disease after Alzheimer's disease, and it is expected to place an increasing medical and economic burden on society as the population ages (de Lau and Breteler, 2006). Typical PD symptoms are resting tremor, rigidity, bradykinesia, postural instability (Aarsland et al., 2017), and pathology characterized by degeneration and death of dopaminergic neurons in the substantia nigra (Obeso et al., 2008). Visser et al. (1993) first reported a case of hemiparkinsonism (partial Parkinson's syndrome) in a patient who presented with both signs and symptoms of the primary SS in 1993. Mochizuki et al. (1997)

discovered a man diagnosed with Parkinson's syndrome who also had SS. His PD was believed to be caused by SS. More recently, Kchaou et al. (2015) concluded that neuroinflammatory processes appear to exist between two completely different diseases, PD and pSS, based on observations of pathophysiological findings in PD patients. A growing number of researchers recognized the risk of PD as a comorbidity in SS patients, and several immune system-mediated mechanisms have been proposed to account for the possible pathogenic mechanism of autoantibodies inducing dopaminergic cell death (Kunas et al., 1995; Monahan et al., 2015). SS and other autoimmune diseases form a spectrum of systemic symptoms ranging from organ-specific to multi-organ involvement. Patients suffer from a significant symptom-related burden, followed by a drop in health-related quality of life and productivity (Meijer et al., 2009). Therefore, health education and risk factor modification are essential for this patient group.

It is crucial to determine the causal relationship between SS and PD. In several of the included studies, all patients with PD were diagnosed after an episode of SS (Wu et al., 2017; Chang et al., 2018; Lin et al., 2018; Ju et al., 2019; Hsu et al., 2020). In the study by Ju et al. (2019), there was a 93% greater risk of PD with SS when the follow-up duration was longer than 9 years compared to subjects without SS. As a result, the available evidence suggests that SS is a risk factor for PD rather than a shared risk factor or a factor with an inverse correlation.

SS is known to be mediated by the interaction of genetic, epigenetic, and environmental factors causing immune dysregulation, which leads to an aggressive autoimmune disease affecting the central nervous system (CNS) and peripheral nervous system (Morgen et al., 2004), often exhibiting a higher female bias (Chatzis et al., 2021). Our study also found that the correlation between SS and PD risk appears to occur primarily in female patients, as opposed to male SS patients, which may be explained by that higher urate levels in men diminish the risk of PD, whereas this is not the case in women (Ascherio et al., 2009; O'Reilly et al., 2010). Autopsy analyses and experimental animal studies of human PD patients have shown that increased pro-inflammatory factors in the brain lead to neuronal degeneration and the development of PD (Wang et al., 2015). Furthermore, both anticardiolipin and anti-β2-glycoprotein-I levels have been reported to be higher in SS patients who develop PD (Mochizuki et al., 1997; Hassin-Baer et al., 2007). Inflammation may thus be a critical factor in the development of PD in patients with SS, yet neuroinflammation has been a controversial topic in the pathogenesis of PD (Figueiredo-Pereira et al., 2015; Renaud et al., 2015). A recent review explored the evidence for autoimmune involvement in PD and proposed targeted inflammatory therapy as a novel neuroprotective approach (Moehle and West, 2015).

Ju et al. (2019) explored the effect of immunosuppression on the risk of PD in patients with autoimmune diseases, including SS, and found that the risk of PD was significantly higher in participants with SS who received hydroxychloroquine, compared to those without SS (HR = 1.46, 95% CI: 1.34–1.59), but the risk of PD in SS participants receiving non-hydroxychloroquine immunosuppressive therapy was relatively low (HR = 0.86; 95% CI: 0.73–1.01). It is, therefore, justifiable to assume that non-hydroxychloroquine immunosuppression plays a crucial role in lowering the risk of PD. The neuroprotective potential of hydroxychloroquine has been debated, and its efficacy in treating systemic lupus erythematosus (Ruiz-Irastorza et al., 2010) and rheumatoid arthritis (Suarez-Almazor et al., 2000) has been widely recognized. Still, its efficacy in the treatment of SS remains unclear. In a study by Fox et al. (1996) on hydroxychloroquine in the treatment of SS, regular use of hydroxychloroquine was found to be effective in treating SS, providing relief from fatigue and arthralgia. However, several studies have indicated that taking hydroxychloroquine for SS had no therapeutic effect for people with pSS when compared to placebo treatment (Kruize et al., 1996). Immunotherapy-related neurological disorders have been progressively documented in recent years (Villoslada et al., 2008; Prior, 2015; General-López, 2018). Future research should concentrate on the association between autoimmune disease and PD, as well as the relation between immunosuppression and PD.

Limitations

There are still some limitations to our meta-analysis. First, we could not distinguish whether SS was primary or secondary to another autoimmune disease in our meta-analysis. Failure to fully elucidate the clinical severity of SS and the subtypes of dementia and PD may lead to inaccurate estimates of their genuine association. Secondly, most of the eligible studies were conducted in Taiwan region (China), which may lead to geographical bias and relatively high overlap of included samples. Therefore, it is unclear whether this association holds for other races and regions in the world. In addition, none of the 10 included studies assessed the effect of monitoring bias on outcomes. Since subjects with SS typically experienced more medical visits than those without SS, they were more likely to be diagnosed with dementia or PD. In this way, the risk of dementia or PD for subjects with SS may be skewed higher in the overall analysis results. Finally, all original studies were designed retrospectively and their data collection did not consider the need for specific scientific research, thus limiting the completeness and homogeneity of the data.

Conclusion

The results of this study reveal that patients with SS are at significantly elevated risk of developing PD and dementia

and that regular neurological screening of SS patients may be warranted. More prospective studies from different regions are necessary to elucidate the underlying mechanisms and to further characterize the impact of SS on development of PD and dementia.

Data availability statement

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

Author contributions

Z-ZW, M-SL, and ZS developed the protocol, participated in the literature search, extracted data, and drafted the manuscript. X-LZ and M-LZ was responsible for the analysis and interpretation of the data. KX contributed to statistical expertise. FZ supervised the study. All authors contributed to the article and approved the submitted version.

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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/fnint.2022.1027044/full#supplementary-material

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EDITED BY
Steffen Schulz,
Charité Universitätsmedizin
Berlin, Germany

REVIEWED BY
Guo Hua Zheng,
Shanghai University of Medicine and
Health Sciences, China
Yong Zhao,
Chongqing Medical University, China
Ting Liu,
Sun Yat-sen University, China

*CORRESPONDENCE
Yao Jie Xie
grace.yj.xie@polyu.edu.hk

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Efficacy and feasibility of a 12-week Tai Chi training for the prophylaxis of episodic migraine in Hong Kong Chinese women: A randomized controlled trial

Yao Jie Xie[1,2]*, Longben Tian[1], Stanley Sai-Chuen Hui[3], Jing Qin[1], Yang Gao[4], Dexing Zhang[5], Tongyu Ma[6], Lorna Kwai Ping Suen[7], Harry Haoxiang Wang[8,9], Zhao-Min Liu[8], Chun Hao[8], Lin Yang[1] and Alice Yuen Loke[1]

[1]School of Nursing, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong, Hong Kong SAR, China, [2]Research Center for Chinese Medicine Innovation, The Hong Kong Polytechnic University, Hong Kong, Hong Kong SAR, China, [3]Department of Sports Science and Physical Education, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China, [4]Department of Sport, Physical Education, and Health, Hong Kong Baptist University, Hong Kong, Hong Kong SAR, China, [5]JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR, China, [6]Department of Health Sciences, Franklin Pierce University, Rindge, NH, United States, [7]School of Nursing, Tung Wah College, Hong Kong, Hong Kong SAR, China, [8]School of Public Health, Sun Yat-sen University, Guangzhou, China, [9]College of Medicine and Veterinary Medicine, The University of Edinburgh, Edinburgh, United Kingdom

Background: Tai Chi has been broadly applied as alternative treatment for many neurological and psychological disorders. Whereas no study using Tai Chi as prophylactic treatment for migraine. The purpose of this study was to preliminarily examine the efficacy and feasibility of a 12-week Tai Chi training on migraine attack prevention in a sample of Chinese women.

Methods: A two-arm randomized controlled trial was designed. Women aged 18 to 65 years and diagnosed with episodic migraine were randomized to either Tai Chi group (TC group) or the waiting list control group. A modified 33-short form Yang-style Tai Chi training with 1 h per day, 5 days per week for 12 weeks was implemented in the TC group, with a 12-week follow up period. The control group received a "delayed" Tai Chi training at the end of the trial. The primary outcome was the differences in attack frequency between 4 weeks before baseline and at the 9–12 weeks after randomization. The intensity and duration of headache were also measured. The feasibility was evaluated by the maintenance of Tai Chi practice and satisfactory level of the participants toward training.

Results: Eighty-two women were randomized, finally 40 in TC group and 33 in control group were involved in the analysis. On average, women in TC group had 3.0 times (95% CI: −4.0 to −2.0, $P < 0.01$) and 3.6 days (95% CI: −4.7 to −2.5, $P < 0.01$) reduction of migraine attack per month. Compared with the control group, the differences were statistically significant (−3.7 attacks/month, 95% CI: −5.4 to −1.9; and −3.0 migraine days/month, 95% CI: −4.5 to −1.5; both $P < 0.001$). The intensity and duration of headache

had 0.6 (95% CI: −1.2 to −0.0, $P < 0.05$) units and 1.2 (IQR: −5.0 to 1.1, $P < 0.05$) hours reduction in TC group, respectively. Most of the participants (69.2%–97.4%) were satisfied with the training. At the end of 24 weeks, on average, the participants maintained 1.5 times of practice per week and 20 min for each practice.

Conclusion: The 12-week Tai Chi training significantly decreased the frequency of migraine attack. It was acceptable and practicable among female migraineurs.

Clinical trial registration: www.ClinicalTrials.gov, identifier: NCT03015753.

KEYWORDS

migraine, prophylaxis, Tai Chi, Chinese, women, randomized controlled trial

Introduction

Migraine is among the most common primary headache disorders worldwide. According to the Global Burden of Disease Study updated in 2019, migraine caused 4.9% of total years lived with disability (YLDs) in both genders, and took the first place in young women (1, 2). The age-standardized disability-adjusted life years (DALYs) of migraine increased from 22nd highest ranking in 1990 to 14th in 2019 among the 369 diseases and injuries (1, 3). Globally, the prevalence of migraine ranged from 9% to 35% across countries (4). Women was two to three times higher than men (5), the age-standardized prevalence was 18.9% for women and 9.8% for men (6). In Hong Kong, the prevalence ranged from 8.4 to 12.5%, which was as high as hypertension (7, 8). Migraine is usually nonfatal but disabling because repeated migraine attacks are pain and personal suffering, which substantially impair quality of life and increase financial cost (9). The disabled productivity during migraine attack also reduced working hours and working effectiveness (10). Furthermore, evidence showed that frequent attack was highly associated with an elevated risk of developing cardiovascular disease (11–13) and progression of white matter lesions (14), with the consequences of increased neurologic deficits, morbidity and mortality. The prevention of migraine attack is thereby of important public health concern.

The pathogenesis of migraine is believed to be highly complex involving neuronal, inflammatory, and vascular mechanisms. Neural events lead to dilation of blood vessels, which in turn aggravates the pain and results in further nerve activation. Cortical spreading depression (CSD) and brainstem generator are the two concepts of migraine genesis (15). Nonpharmacological treatment plays an important role in the prophylaxis of migraine. Compare with pharmacological approach, nonpharmacological prophylaxis is relatively safer, better tolerated, and associated with improved patient satisfaction (16). As one of the most promising nonpharmacological interventions, exercise is recommended for migraine prophylaxis in recent years (17–19). Potential mechanism links to improvement in neuroinflammatory, neurovascular, neurolimbic, and neuroendocrine processes, and/or psychological and behavioral factors (18, 19). However, exercise itself might also be a potential trigger (20). Improper vigorous exercise could initiate attacks through the pathways of hypocretin changes, lactate accumulation, and systolic blood pressure and cardiac output increases (21). Thus, the type, frequency, and intensity of exercise should be carefully determined for migraine prophylaxis. Tai Chi, a traditional Chinese martial art that has been widely practiced in Chinese population and spread worldwide, is a moderate mind–body exercise that integrates physical and spiritual elements to slowly and gently move *qi* (vital energy) throughout the body. By integrating the movements with deep breathing and mental concentration, mind-body communication is enhanced, allowing a practitioner to achieve a state of harmony between mind and body. Its significant physiological and psychosocial benefits on health outcomes have been well documented in the literature (22). However, its effectiveness among migraineurs remains largely unknown.

There was no published study using Tai Chi as prophylactic treatment for migraine. Nonetheless, Tai Chi has been broadly applied in treatment of mental and psychological disorders. It showed significant beneficial effects on reducing the severity of headache, improving energy expenditure, emotional well-being and mental health for general headache (23). Recent systematic review indicated that Tai Chi can relieve stress, improve sleep quality, alleviate fatigue level, and accordingly promote health-related quality of life and wellbeing (24, 25). As stress, sleep disturbances and fatigue are typical migraine triggers (26), Tai Chi may prevent migraine attacks through this indirect way. Thus, we believe that Tai Chi holds therapeutic potential in migraine

prophylaxis. We thereby designed a randomized controlled trial, using Yang-style Tai Chi training as intervention, to preliminarily examine its efficacy in migraine prophylaxis, and test the feasibility of practicing Tai Chi in the study population. We hypothesized that the 12-week Yang style Tai Chi training could significantly decrease the frequency of migraine attacks among Hong Kong Chinese women with episodic migraine.

Methods

Study design and setting

This study was a two-arm individual-level randomized controlled trial (RCT). Participants in the intervention group received a 12-week modified short-form Yang-style Tai Chi training with additional 12-week follow-up, and participants in the waiting list control group just kept their usual exercise and lifestyles for 24 weeks and then took the Tai Chi training. The study was implemented in a University in Hong Kong.

Participants

Eligibility criteria for participants

Hong Kong Chinese women who had a clinical diagnosis of episodic migraine (≤15 migraine days per month) was the study population. The inclusion criteria were: (1) female, aged 18–65 years; (2) have a clinical diagnosis of episodic migraine with or without aura according to the third edition of the International Classification of Headache Disorders (ICHD-III beta version) (27) at least 2 months prior to enrollment; (3) more than two migraine attacks in 1 month; (4) at least one of the following migraine characteristics is met: nausea, vomiting, photophobia, or phonophobia; (5) able to undertake designated level of Tai Chi exercise; (6) live in Hong Kong, can read and speak Cantonese or Putonghua; (7) give written informed consent. The exclusion criteria were those with: (1) severe migraine attacks with disabilities that preclude moderate intensity physical activity; (2) secondary headache and other neurological disease; (3) more than 5 days of non-migrainous headache per month; (4) experience with Tai Chi practice after diagnosis of migraine; (5) regular performance of Tai Chi or other mind-body exercises (yoga, biofeedback, meditation, etc.); (6) undergoing other alternative therapeutic treatments during recruitment period, or received other alternative therapeutic treatments in the past 12 weeks; (7) pregnancy, lactation period, or currently using contraceptives; (8) use of pharmacological prophylactic treatment for migraine in the past 12 weeks; (9) drug use, take antipsychotic or antidepressant drugs, or take analgesics for other chronic pain more than 3 days a month in the past 12 weeks; and (10) epilepsy, or have a psychiatric disease.

Sample size calculation

Since there was no previous intervention study using Tai Chi as migraine prophylaxis, by referring to other complementary treatments, like aerobic exercise (19) and acupuncture (28), we expected 1 attack reduction per month after the Tai Chi intervention. Thus, a sample of 30 in each group was needed to achieve 85% power to detect a difference of 1.0 time (SD: 1.6) reduction in attack, with the significant level of 0.05 for two-sides. By consideration of 10% drop out rate (29), additional five subjects were recruited for each group.

Recruitment

Recruitment was done *via* mass media and internet, including university's internal email system, school's alumni system, WhatsApp, and fliers and posters disseminated in the communities and clinics. Information with details of the RCT and an enquiry phone number and email address was displayed in the posters. During the initial contact, the trained research assistants (RAs) briefed prospective participants about the purpose and logistics of the study, evaluated their initial eligibility by a screening form. Those met the basic criteria were involved in 4 weeks observation subsequently, which required the prospective participants to record the migraine attacks through a migraine diary. The migraine diary is a commonly used tool to record frequency, intensity, duration, and relevant medication of migraine attacks for migraineurs. RAs collected the diaries and consulted the collaborative neurological physician at the University Health Service Center, the latter made the final diagnosis according to the ICHD-III beta version criteria (27). The subjects who met all inclusion and exclusion criteria were invited as eligible participants. Before the study, participants were informed of relevant precautions. If unbearable headache occurred during the trial, they could take acute medication for migraine to relieve the headache (e.g., triptans) as advised by their doctors. They were required to record the name and dosage of medication on the migraine diary. The acute medication was only for symptoms alleviation, it would not influence the prophylaxis effect of Tai Chi on the migraine attacks.

Randomization, blinding, and concealment

A computer random number generator was used to generate the random allocation sequence. Eligible participants were randomly assigned in a 1:1 ratio to one of the two groups: (1) a Tai Chi training group; or (2) a waiting list control group

("control"). Randomization was carried out using a permuted block algorithm with blocks of size 4. To ensure allocation concealment, the RAs assigned a code to each participant and generated several random allocation sequences for each block of size 4. The principal investigator then chose one from each group of generated allocation sequences without knowing the participant identity. Investigators were concealed about the random allocation until the assignments had been made. The RAs who performed the outcome measurements were blinded to the treatment group assignment.

Interventions

Tai Chi training

The 12-week Tai Chi training was prescribed with three 1-h instructor-led sessions and two 1-h self-practice sessions per week. Qualified Tai Chi instructors were recruited from the Gentle and Tranquil Tai Chi Chuan Association, to teach the participants a modified 33-short form Yang-style Tai Chi Chuan, which is the most popular and widely practiced form of Tai Chi in the world. This form is adapted from original 32-short form Yang-style Tai Chi Chuan by including the last form "closing". It is typically done with slow, steady movements, which is a practical entry point for many beginners. The recruited Tai Chi instructors attended a training session before the commencement of the intervention, to ensure that they agreed on the exact procedure of the Tai Chi intervention protocol and would adhere to the protocol throughout the study.

Each 1-hour training session consisted of 10 min brief warm-up stretching movements followed by 45-min standard Tai Chi routine activities, and 5 min of cool-down stretching. Every instructor-led training session had 15–18 participants, which were performed at an open space with relatively less pedestrians in the University. Also, handouts about the Tai Chi movements and lesson schedule were distributed to the participants to facilitate their learning and practice. Two parallel Tai Chi classes were arranged for the participants. Class A was scheduled on Monday, Wednesday, and Friday; class B was set on Tuesday, Thursday, and Saturday. Both classes followed the same intervention protocol (Supplementary material). Participants could choose one of the two classes according to their available date. To ensure the fidelity of the intervention, the Tai Chi instructors were required to follow the intervention protocol to deliver the Tai Chi training. The RAs monitored all the instructor-led Tai Chi sessions on spots. With the permission of the Tai Chi instructors, the RAs videoed their movements and sent the videos to the participants right after each instructor-led session, to facilitate participants recalling and practicing the Tai Chi forms. Participants were asked to record the date, time, duration, and Tai Chi forms of their self-practices as well as daily physical activities in an exercise log. They were also encouraged to video the self-practices and share the videos in a WhatsApp group that involved all the participants from the intervention group. RAs reviewed exercise logs and WhatsApp group at least twice a week to check whether the participants followed the intervention protocol. If not, RAs would contact them and discussed with them the barriers and challenges toward the Tai Chi training, and encouraged them to follow the intervention protocol.

Waiting list control

Participants randomly assigned to the control group were asked to maintain their usual exercise and lifestyles for 24 weeks. At the trial end, they were offered Tai Chi training similar as Tai Chi group. The arrangement of waitlist intervention was intended to provide the participants opportunity for Tai Chi training, and to reduce dropout rate. A delayed Tai Chi training for them might encourage them to stay in the study. Both Tai Chi group and control group participants received a HK$100 supermarket coupon at baseline, those in control group received another HK$100 supermarket coupon at 12 weeks, as an additional incentive to encourage them to keep participation until the end of the study.

Outcome measures

Primary outcome

The primary outcome was the changes in frequency of migraine attack. It was calculated as: (1) the difference in the number of attacks per month between 4 weeks before randomization and weeks 9–12/21–24 after randomization; and (2) the difference of migraine days per month between 4 weeks before randomization and weeks 9–12/21–24 after the randomization. We considered the end of the 12th week as the primary time point. The monthly frequency of migraine attack was defined as the number of attacks per month. The monthly migraine days were defined as the total days that the participant suffered the migraine attacks per month. Participants firstly self-recorded each migraine attacks by migraine diary 4 weeks before the baseline, and then self-recorded from once the intervention commenced until the end of the trial.

Secondary outcomes

Intensity and duration of headache

The migraine diary was used to record these variables. Intensity of headache was measured by a Visual Analog Scale (30) integrated into the migraine diary. Duration of headache attack was defined as the time of onset of headache to the time of headache disappeared, which was recorded to the nearest 0.1 hour. Participants were asked to record this information soon after experiencing the headache attack. The changes of intensity and duration from the baseline to 12 and 24 weeks were then calculated.

The proportion of responders

This was defined as the proportion of patients with at least a 50% reduction of the number of attacks per month (28). The 50% reduction of attacks at 12 and 24 weeks in each group were calculated respectively.

Feasibility of the Tai Chi training

Feasibility was defined as how successful the Tai Chi intervention is implemented. It was evaluated by the duration of recruitment, retention rate in Tai Chi training, and maintenance of the Tai Chi self-practice. The RAs also monitored and recorded the adverse effects from the participants. We defined an instructor-led session attendance rate of $< 10\%$ as invalid attendance. The participants were encouraged to follow the Tai Chi protocol to practice for a certain amount of time during each self-practice session, which was not < 20 min (31). The maitemnance of Tai Chi self-practice was determined in two aspects: (1) what percentage of the participants in the intervention group performed Tai Chi exercise for at least 4 weeks in the 12-week follow up period; and (2) how many weeks in the 12-week follow up period the participants in the intervention group practiced Tai Chi at least once per week (32).

Covariates

At baseline, a structured interview was conducted to collect information on the socio-demographic characteristics, medical history, physical activity, dietary intake, lifestyle factors (drinking and smoking), reproductive information, and family history of migraine. Anthropometric measurements, including weight, height, waist and hip circumference, and percent body fat, were taken, with participants wearing light clothing and following standard protocols. Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm using a calibrated scale with a height bar. Waist and hip circumference were measured using a tape measure to the nearest 0.1 cm. Body fat percentage was measured by bioelectrical impedance analysis (Tanita, BC 581, Japan). Body mass index [BMI, weight (kg)/height (m^2)] and waist-to-hip ratio (waist circumference/hip circumference) were calculated. Furthermore, the typical migraine triggers including fatigue, stress level, and sleep quality were assessed by the numeric rating scale-fatigue, the 14-item Perceived Stress Scale, and the Pittsburgh Sleep Quality Index, respectively (33). All above measurements at baseline were conducted again at the 12th and the 24th week.

Statistical analysis

Missing values were handled by multiple imputations. Mean and standard deviation (SD) or median and interquartile range were used to describe continuous variables where appropriate. Categorical variables were presented as numbers and percentage (%). Independent t-test, Mann-Whitney U-test, Pearson chi-square test or Fisher's exact test, were conducted to compare the differences between groups for normal distributed, skewed, and categorical data, respectively. The 12-week and 24-week changes for each outcome variable in each group were calculated firstly. Then the paired t-test, Wilcoxon signed-rank test, and McNemar test were used for within group comparison for normal distributed, skewed, and categorical data, respectively. To finally test intervention effects between groups, differences in changes were compared across the two arms using repeated analyses of covariance (ANCOVA), with adjustment of baseline characteristics; the time $\times$ group interaction effects across baseline, 12-week and 24-week were examined subsequently. Both per-protocol analysis and Intention to Treat (ITT) analysis were adopted according to the CONSORT guidelines (34). Statistic software SPSS 23.0 (SPSS Institute) was used for analysis. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

From 2016 to 2017, 189 women who indicated initial interests in participating were enrolled. After screening of eligibility, 80 women were excluded according to the inclusion and exclusion criteria. The remaining 109 subjects were made appointment for baseline measurement. While 26 of them canceled due to the time conflict, and one woman did not attend because of health problem. A total of 82 participants completed the baselines measurement. They were randomly allocated to Tai Chi group ($n = 42$) and control group ($n = 40$). After the allocation, two participants in the Tai Chi group and seven participants in the control group withdrew immediately. The former two participants withdrew due to time conflict. Those seven participants in the control group withdrew because they had high expectations to be selected to the Tai Chi group. As result, a total of 40 participants started the Tai Chi training in the intervention group, and 33 participants remained in the control group, who were considered as valid participants.

After 12 weeks intervention, 39 participants in the Tai Chi group and 30 participants in the control group completed the 2nd round data collection. During the 12 weeks follow up period, all participants in the Tai Chi group remained in the study and completed the 3rd round data collection, while seven participants in the control group dropped out due to personal reasons. The five participants who attended < 10 Tai Chi sessions were not considered as valid attendance and were excluded from the per protocol analysis. The whole study flow was shown in Figure 1, indicating the exact number of participants in each period, from the enrollment to the data analysis. The retention rates at the 12th and 24th week were both 98% (39/40) for the Tai Chi group, and 82% (27/33) and

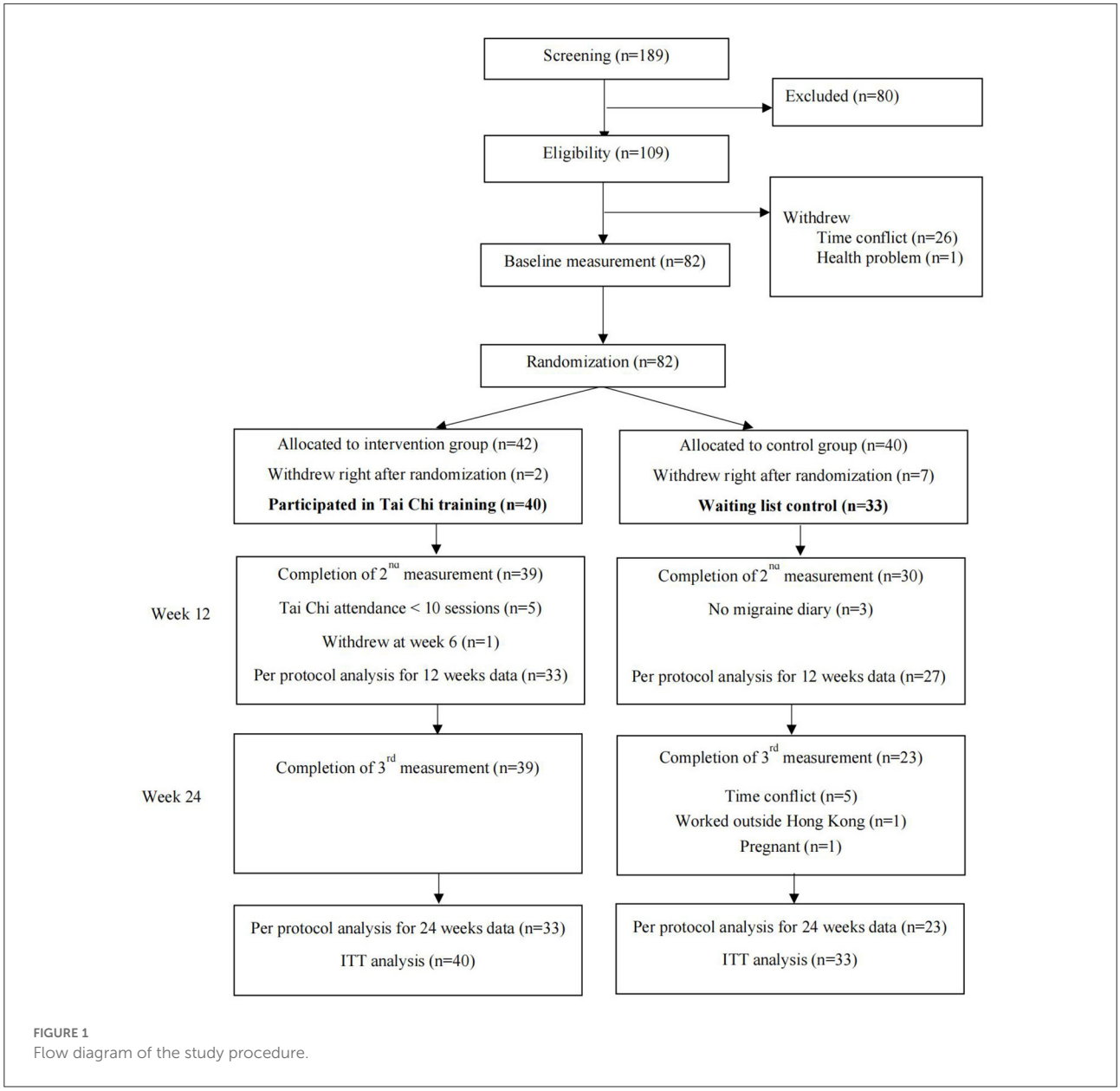

FIGURE 1
Flow diagram of the study procedure.

70% (23/33) for the control group, respectively. No significant differences were observed in the baseline characteristics between participants who completed the entire study and those who were lost to follow-up (all $P > 0.05$).

Basic characteristics of the participants

The basic characteristics of the 73 participants were shown in Table 1. The average age was 50.9 ± 10.2 years and 47.1 ± 11.8 years in the Tai Chi group and the control group, respectively. More than half of the participants were employed (58.9%), with a monthly family income between HK$ 20,000 and HK$ 80,000 (64.4%). Most of the participants (95.9%) had secondary or above education level, and the majority of the participants were married (63.0%). The mean BMI and body fat percentage was 22.7 ± 3.5 kg/m^2 and 32.1 ± 5.4% for the intervention group, and 23.6 ± 3.8 kg/m^2 and 33.1 ± 4.3% for the control group. Although participants in the control group had higher values of BMI, weight, body fat percentage, and waist circumference when compared with the Tai Chi group, all these anthropometrical values showed no statistically significant difference between two groups (all $P > 0.05$). Also, no difference was observed in terms of fatigue, stress level, and sleep quality (33). The only difference was observed in the drinking, which participants in the control group had

higher proportion of drinking than those in the Tai Chi group ($P < 0.05$).

Migraine features at baseline

At baseline, the average frequency of migraine attack was 6.3 times/month both in the Tai Chi group and control group. Participants experienced 7.4 ± 3.6 and 8.4 ± 6.5 migraine days per month in Tai Chi and control groups, respectively. The intensity of headache was moderate (4.4 in Tai Chi group and 4.5 in control group, 10 as the most severe status). The median attack duration was 6.7 (Interquartile range, IQR: 3.9–11.9) hours in Tai Chi group and 10.3 (IQR: 3.7–22.7) hours in control group. All these migraine features were not significantly different between two groups (all $P > 0.05$).

Reduction of frequency, intensity, and duration of migraine attack after Tai Chi training

Table 2 shows the changes in outcomes from the baseline to the 12 and 24 weeks with the comparisons within and between groups. Table 3 shows the between-group differences by the time × group interaction effects with adjustment of baseline characteristics. According to the ITT analysis, at 12 weeks, we observed a significant decrease of 3.0 (95% CI: −4.0 to −2.0) migraine attacks and 3.6 (95% CI: −4.7 to −2.5) migraine days within 1 month in the Tai Chi group (all $P < 0.01$), whereas the control group did not show any significant changes ($P > 0.05$). Compared with baseline, the significant decrease in frequency of migraine attack was also observed at 24 weeks, with reduction of 2.6 attacks and 3.4 days of migraine (all $P < 0.01$) within one month. A slight alleviation of headache intensity was found in the Tai Chi group (−0.6, $P < 0.05$), and the duration of headache was shortened of 1.2 h and 1.8 h at 12 and 24 weeks, respectively. However, compared with the control group, the intensity and duration had no statistically significant difference (all $P > 0.05$). Regarding the proportion of responders, 52.5% participants in the Tai Chi group had 50% reduction of attacks at 12 weeks, this proportion slightly increased to 55% at 24 weeks. In control group, the proportion of 50% reduction of attacks was only 12.1% at 12 weeks and 27.3% at 24 weeks (all $P < 0.05$).

Compared with control, at 12 weeks, the between-group differences of attacks/month and migraine days/month was−3.7 (95% CI: −5.4 to −1.9) attacks and −3.0 (95% CI: −4.5 to −1.5) days, respectively (both $P < 0.001$). A slightly greater reduction was observed at 24 weeks (Table 3). No significant between-group difference was observed in terms of intensity and duration of headache (all $P > 0.05$) (Table 3). Similar findings were observed by the per protocol analysis (Tables 2, 3).

TABLE 1 Basic characteristics of the participants [a].

	Intervention ($n = 40$)	Control ($n = 33$)	p[b]
Age, year(s)	50.9 (10.2)	47.1 (11.8)	0.151
Height, cm	156.2 (6.6)	157.0 (5.4)	0.558
Weight, kg	55.5 (10.0)	58.2 (9.5)	0.247
BMI, kg/m^2	22.7 (3.5)	23.6 (3.8)	0.276
Overweight/obesity [#, †]	19 (47.5)	16 (48.5)	0.933
Waist circumference, cm	77.5 (9.3)	81.1 (10.8)	0.134
Central obesity [#, †]	16 (40.0)	15 (45.5)	0.639
Hip circumference, cm	94.5 (6.5)	96.3 (8.3)	0.305
Waist-hip ratio	0.8 (0.1)	0.8 (0.1)	0.169
Body fat, %	32.1 (5.4)	33.1 (4.3)	0.383
Hypertension [#]	2 (5.0)	6 (18.2)	0.13
High Cholesterol [#]	8 (20.0)	3 (9.1)	0.325
Physical activity category (by IPAQ)[‡]		0.313	
Low	6 (15.0)	2 (6.1)	
Moderate	29 (72.5)	26 (78.8)	
High	3 (7.5)	5 (15.2)	
Drinking [#]	21 (52.5)	25 (75.8)	0.041
Nutritional supplement intake [#]	10 (25.0)	12 (36.4)	0.292
Medication taken for migraine [#]	8 (20.0)	8 (24.2)	0.663
Pain relief medication taken [#]	25 (62.5)	25 (75.8)	0.225
Menopause [#]	23 (57.5)	13 (39.4)	0.164
Family history of migraine [#]	11 (27.5)	14 (42.4)	0.181
Marital status			0.249
Single	14 (35.0)	6 (18.2)	
Married/cohabitating	22 (55.0)	24 (72.7)	
Divorced/separated/widowed	4 (10.0)	3 (9.1)	
Education			0.716
Primary or below	2 (5.0)	1 (3.0)	
Secondary or matriculation	21 (52.5)	15 (45.5)	
Tertiary or above	17 (42.5)	17 (51.5)	
Occupation			0.221
Employed	21 (52.5)	22 (66.7)	
Not employed / Retired	19 (47.5)	11 (33.3)	
Monthly family income[‡]			0.538
<$20,000	13 (32.5)	6 (18.2)	
$20,000-$39,999	15 (37.5)	15 (45.5)	
$40,000-$79,999	9 (22.5)	8 (24.2)	
≥$80,000	2 (5.0)	3 (9.1)	

[a]Values reported as mean (SD), n (%) or median (interquartile range) for each group where appropriate. [b]p-values generated from Pearson chi-square test, Fisher's exact test, independent t-test or Mann-Whitney U-test where appropriate. [#]Variables were showed the number and percentage that counted "Yes" for each group. [†]Overweight/obesity was defined as BMI≥23.0 kg/m^2, central obesity was defined as waist circumference≥ 80.0 cm. [‡]There were missing data in variables "Physical activity category" (n = 2) and "Monthly family income" (n = 2).

TABLE 2 Changes of migraine features from baseline to 12-week and 24-week.

Migraine features[a]	ITT		p[b]	Per protocol[c]		p[b]
	Intervention ($n = 40$)	Control ($n = 33$)		Intervention	Control	
Frequency, times of attack/month						
Baseline	6.3 (3.3)	6.3 (5.9)	0.998			
12-week	3.3 (2.7)	7.0 (7.1)	0.008	3.2 (2.9)	5.8 (5.2)	0.016
24-week	3.7 (4.0)	5.7 (6.3)	0.107	3.6 (4.2)	4.7 (3.6)	0.311
Mean change from baseline to 12-week	−3.0 (−4.0 to −2.0)**	0.7 (−0.9 to 2.2)	<0.001	−3.1 (−4.2 to −2.0)**	0.7 (−1.0 to 2.4)	<0.001
Mean change from baseline to 24-week	−2.6 (−3.8 to −1.4)**	−0.6 (−1.8 to 0.5)	0.017	−2.6 (−3.9 to −1.3)**	−0.6 (−2.1 to 1.0)	0.040
50% reduction of attacks at 12-week	21 (52.5)	4 (12.1)	<0.001	19 (57.6)	4 (13.3)	0.001
50% reduction of attacks at 24-week	22 (55.0)	9 (27.3)	0.017	19 (57.6)	7 (30.4)	0.045
Number of days with migraine						
Baseline	7.4 (3.6)	8.4 (6.5)	0.398			
12-week	3.8 (3.3)	7.9 (7.0)	0.004	3.6 (3.5)	6.8 (5.2)	0.005
24-week	4.0 (4.2)	6.5 (6.2)	0.04	3.9 (4.5)	5.5 (3.5)	0.162
Mean change from baseline to 12-week	−3.6 (−4.7 to −2.5)**	−0.5 (−1.6 to 0.5)	0.001	−3.8 (−4.9 to −2.6)**	−0.6 (−17 to 0.6)	<0.001
Mean change from baseline to 24-week	−3.4 (−4.6 to −2.2)**	−1.9 (−3.3 to −0.5)*	0.136	−3.4 (−4.6 to −2.2)**	−2.2 (−4.0 to −0.4)*	0.195
Headache intensity, VAS score (0-10)						
Baseline	4.5 (1.6)	4.4 (1.8)	0.812			
12-week	3.9 (1.7)	4.5 (2.2)	0.209	3.8 (1.8)	4.5 (2.3)	0.192
24-week	3.9 (2.1)	4.4 (2.2)	0.369	3.7 (2.0)	4.1 (1.9)	0.566
Mean change from baseline to 12-week	−0.6 (−1.2 to −0.0)*	0.1 (−0.6 to 0.7)	0.072	−0.6 (−1.3 to 0.1)	0.1 (−0.6 to 0.8)	0.154
Mean change from baseline to 24-week	−0.6 (−1.2 to −0.0)*	−0.1 (−0.8 to 0.6)	0.138	−0.7 (−1.3 to −0.1)*	−0.4 (−1.0 to 0.2)	0.496
Headache attack duration, hr (s)						
Baseline	6.7 (3.9 to 11.9)	10.3 (3.7 to 22.7)	0.335			
12-week	5.0 (2.0 to 7.8)	8.0 (3.5 to 14.3)	0.079	4.8 (1.7 to 7.6)	8.8 (3.6 to 15.1)	0.040
24-week	4.9 (2.0 to 9.4)	8.0 (3.6 to 18.9)	0.125	4.6 (2.2 to 9.5)	8.0 (3.8 to 17.4)	0.214
Change from baseline to 12-week	−1.2 (−5.0 to 1.1)*	0.0 (−3.8 to 2.3)	0.668	−1.4 (−6.0 to 1.0)*	0.3 (−4.1 to 2.9)	0.743
Change from baseline to 24-week	−1.8 (−4.5 to 1.4)*	0.0 (−4.0 to 2.8)	0.889	−1.7 (−5.4 to 1.2)	−0.5 (−4.4 to 2.5)	0.648

[a]Values were presented as mean (SD), median (Interquartile range) and n (%) for 12-week and 24-week measurement; mean (95% CI), median (Interquartile range) and % for change from baseline respectively. [b]p-values generated from Pearson chi-square test, Fisher's exact test, independent t-test and Mann-Whitney U-test where appropriate; univariate ANCOVA was used to compare the mean change difference between groups; variables with significant different between groups at baseline were adjusted as covariates. [c]Per protocol at 12-week: intervention (n = 33), control (n = 27); at 24-week: intervention (n = 33), control (n = 23). *$p < 0.05$ generated from within group comparison by paired t-test, Wilcoxon signed-rank test and McNemar test where appropriate. **$p < 0.01$ generated from within group comparison by paired t-test and McNemar test where appropriate.

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TABLE 3 Between-group differences of migraine features at 12-week and 24-week.

Migraine feature[a]	Between group difference at 12-week		Between group difference at 24-week		
	Intervention vs. Control	p^b	Intervention vs. Control	p^b	p^c
Frequency					
ITT	−3.7 (−5.4 to −1.9)	<0.001	−2.0 (−3.7 to −0.3)	0.017	0.001
Per protocol[d]	−3.8 (−5.8 to −1.9)	<0.001	−2.0 (−4.0 to −0.1)	0.040	0.002
Number of days with migraine					
ITT	−3.0 (−4.5to −1.5)	0.001	−1.5 (−3.4 to 0.3)	0.136	0.003
Per protocol	−3.2 (−4.7 to −1.6)	<0.001	−1.2 (−3.2 to 0.8)	0.195	0.001
Intensity					
ITT	−0.7 (−1.5 to 0.2)	0.072	−0.5 (−1.5 to 0.4)	0.139	0.169
Per protocol	−0.7 (−1.6 to 0.3)	0.154	−0.3 (−1.2 to 0.6)	0.496	0.637
Duration					
ITT	−0.3 (−5.7 to 5.1)	0.668	−1.5 (−7.2 to 4.2)	0.894	0.747
Per protocol	−1.1 (−7.0 to 4.7)	0.743	−0.9 (−8.1 to 6.3)	0.648	0.759

[a]Values were presented as mean (95% CI) for mean change between groups. [b] p-values were calculated for the time × group interaction effects from baseline to 12-week or from baseline to 24-week between groups by repeated ANCOVA; variables with significantly different between groups at baseline were adjusted as covariates. [c]p-values were calculated for the time × group interaction effects across baseline, 12-week and 24-week between groups by repeated ANCOVA; variables with significantly different between groups at baseline were adjusted as covariates. [d]Per protocol at 12-week: intervention (n = 33), control (n = 27); at 24-week: intervention (n = 33), control (n = 23).

TABLE 4 Satisfactory level of Tai Chi training ($n = 39$).

	Unsatisfied (%)	Neutral (%)	Satisfied (%)	Very satisfied (%)	Mean (SD)
Frequency	5.1	25.6	51.3	17.9	3.8 (0.8)
Length	0.0	20.5	64.1	15.4	4.0 (0.6)
Time	2.6	20.5	66.7	10.3	3.9 (0.6)
Venue	5.1	17.9	59.0	17.9	3.9 (0.8)
Content	0.0	12.8	66.7	20.5	4.1 (0.6)
Complexity	0.0	23.1	66.7	10.3	3.9 (0.6)
Teaching skill	0.0	2.6	41.0	56.4	4.5 (0.6)
Teaching preparation	0.0	2.6	43.6	53.8	4.5 (0.6)
Overall satisfaction	0.0	5.1	38.5	56.4	4.5 (0.6)

Satisfactory level, maintenance, and adverse effects of the Tai Chi training

Table 4 shows the participants' satisfactory level in terms of Tai Chi training frequency, length, time, venue, content, complexity, as well as Tai Chi instructors' teaching skill, teaching preparation, and the overall satisfaction level. The great majority of them were satisfied with the training programme. The percentage of those who selected "Satisfied" and "Very satisfied" ranged from 69.2% (for training frequency) to 97.4% (for teaching skill and teaching preparation; Figure 2). The most unsatisfied aspects were the frequency of the training and the venue of practice. Some participants indicated that 5 times training per week was too many, and an indoor practice room was better for practice because it was more private, quieter and cooler.

Regarding maintenance of the Tai Chi practice, Figure 3 shows the times of Tai Chi practice per week and the length of practice for 24 weeks. At the end of the 24 weeks, on average, the participants kept 1.5 times of practice per week and 20 min for each practice. As times went by, the frequency and duration of practice slightly decreased. But all participants in the intervention group kept the Tai Chi practice in the 12-week follow up period, and they practiced at least one time per week during that period. For the adverse effects, some participants reported joint pain (33.8%), muscle pain (33.3%), slight sprain (10.3%), and dizziness (5.1%). But all of them indicated tolerable for these symptoms, no serious case was founded.

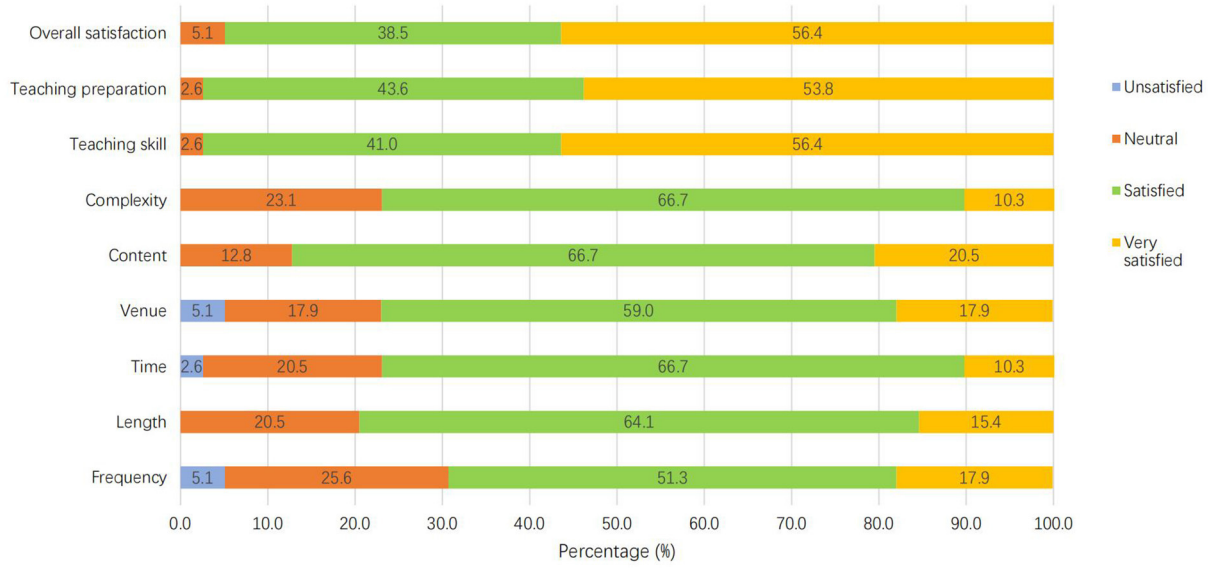

FIGURE 2
Satisfactory level of the Tai Chi training.

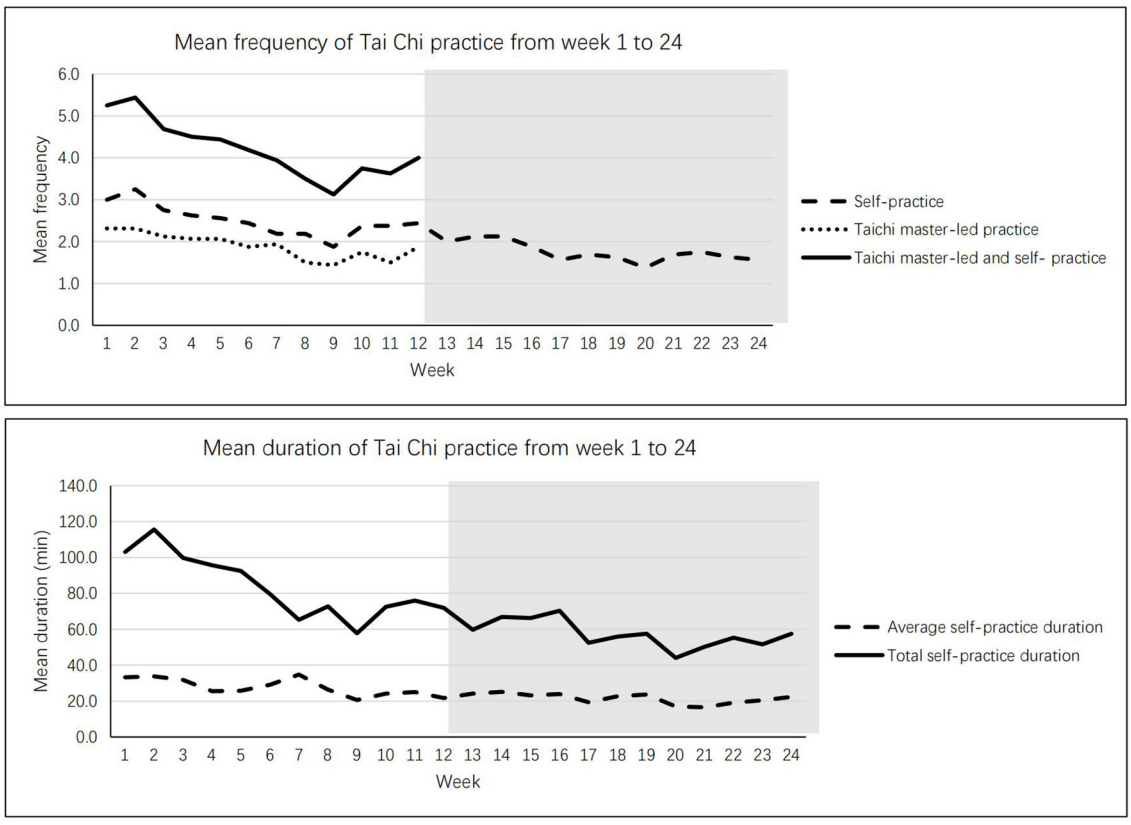

FIGURE 3
Maintenance of Tai Chi practice from week 1 to week 24.

Discussion

To our knowledge, this is the first experimental study using Tai Chi as prophylactic treatment for migraine attack in women. The findings from this study demonstrated that the 12-week Tai Chi training had significant effects on reducing the frequency of migraine attack and the number of migraine days. It could also slightly alleviate headache intensity and shorten the duration of headache after intervention. Most of the participants in the study were satisfied with the Tai Chi training course. Compared with the full form of Tai Chi practice, this short form Yang-style Tai Chi reduced the complexity and time required; hence participants could learn to practice within a relatively short period of time and kept a relatively good maintenance during the whole trial (35). Also, all the adverse effect reported were mild without affecting Tai Chi training, which suggested that Tai Chi was an acceptable and safe mind-body exercise for migraine patients.

Our study findings are in line with the effectiveness of nonpharmacological treatments like exercise (36, 37), acupuncture (28, 38), and other behavioral interventions (39) on the prophylaxis of episodic migraine. As a typical traditional Chinese medicine treatment, acupuncture showed a standardized mean difference (SMD) of 0.56 (95% CI: −0.65 to −0.48) reduction of headache frequency compared with no acupuncture (40). For those behavioral headache interventions with an aerobic exercise component, the headache frequency was reduced by 0.76 SMD (95% CI: 0.32–1.2) among six studies (41). A study conducted in 91 Swedes with episodic migraine showed that participants who conducted 40-minute aerobic exercise with three times per week for 3 months could averagely reduce 0.93 (95% CI: 0.31–1.54) attacks per month, it was comparable to the topiramate and relaxation training in the same treatment duration (37). Multiple levels of evidence support a role of aerobic exercise in migraine prevention and treatment: exertion reduces pain intensity, frequency, duration of attacks, and medication use; moreover, lower cardiovascular fitness levels increase the lifetime risk of developing migraine (42). Tai Chi training in our study showed stronger effect than those previous studies. On average, 3.6 migraine days per month reduction after the 12-week training was observed. We certainly would not ignore the placebo effect due to the waiting list control design, but we still believe that such large effect size indicates that Tai Chi has the potential to be "at least non-inferior" comparing conventional treatments for migraine prophylaxis. We consider it as reasonable inference because Tai Chi has shown its significant health benefits on many mental and neurological disorders (22, 24, 43). Of course, this clinical efficacy should be further carefully examined by comparing with regular pharmacological prophylaxis with enough observation periods in future studies.

We did not find significant differences regarding intensity and duration of headache between groups in the study. While in the Tai Chi group, the significant headache alleviation was observed within group when compared the data before and after the intervention. A recent review suggested that, mind–body interventions, including Tai Chi, had a positive effect on migraine and tension headaches (44). A cross-sectional study in German showed that frequent headache, severe impact of headache on daily life, and depressive symptoms were associated with more frequent analgesic use in both men and women, for women, physical inactivity was associated with higher frequency of analgesic use adjusted for sociodemographic and headache-related variables (45). Another systematic review and meta-analysis of 1,012 participants from 15 studies that assessed 6–20 weeks Tai Chi training for chronic pain, including headache, demonstrated that Tai Chi was associated with a significant reduction in headache (SMD: −1.85, −2.73 to −0.97). Tai Chi has a therapeutic value in the treatment of tension-type headache because of the mind-body interaction and relaxation effects (23, 46). It is our opinion that if the between-group differences are too small to discover in a sample of this size in our study, except the relative insufficient study power for testing headache alleviation, other factors than effect might be just as important to consider, such as participants' beliefs about Tai Chi, individual's bodily function, and the duration of the intervention, etc.

What biological and psychological mechanisms underlie the efficacy of Tai Chi as a prophylaxis treatment for migraine? Currently it is far from definitive. Some experts have deduced the mechanisms of aerobic exercise for the reducing of migraine burden and summarized the models of change processes (19). In general, the biological (neuroinflammatory, neurovascular, neurolimbic, neuroendocrine) and psychological (social-cognitive, social support, locus of control, mood state, tress, depression, anxiety) pathways operating independently, synergistically, or perhaps antagonistically, in the link between aerobic exercise and migraine improvement (17, 19, 36, 37, 47). Tai Chi is also an aerobic exercise, we believe that the mechanism of Tai Chi on the migraine prophylaxis would at least partially similar as other aerobic exercises. Studies showed that Tai Chi could improve white matter network (48), enhance cerebrovascular blood flow and reactivity (49), boost immunity (50), and avoid migraine trigger factors (25) such as stress, fatigue, and sleep quality. Moreover, Tai Chi involves movement of the whole body in fluidity and harmony, which requires concentration and mindfulness meditation. This may modulate multiple aspects of health, including mood, pain, and functions of the immune and peripheral autonomic nervous systems (51–53). Furthermore, low VO_2 max is significantly associated with migraine (54), and the benefits of Tai Chi in improving VO_2 max have been identified in literature (55), as well as in our previous study (56, 57). More studies

with mechanism exploration in Tai Chi-migraine relationship are suggested.

There were some limitations in our study. Firstly, to consider the difficulty of administration and operation, double-blind study design was not used. Given that Tai Chi is behavior-based treatments, participants in the intervention groups might have higher expectations of the treatment results. Also, a waiting list control group was adopted. Thereby the placebo effects could not be ignored. Although the effect might be a little bit overestimated, we suggest that the evidence got from our study is valuable and could be considered as fundamental for future relevant studies, and an active control group is recommended. Secondly, measurements used in this study for migraine features (frequency, intensity, and duration) were subjective, which may have recall bias. But the migraine diary was a widely used tool with acceptable reliability and validity. It is unlikely to cause a significant impact on the results of outcomes. Thirdly, migraine types were not measured in our study, e.g., migraine with aura and migraine without aura. Since this is a pilot trial, we suggest that the relevant small sample size in each group might lead to the subgroup effect undetectable for migraine with aura cases. Fourthly, the 12 weeks of intervention might not be sufficient to observe long-term effectiveness of Tai Chi training on certain health outcomes, thus, extended intervention duration is suggested for future studies. Fifthly, the real dropout rate was a little bit higher than the designed dropout rate, the study power could be lowered a little bit. Whereas, we believed that the evidence obtained by both ITT and per protocol analyses in this pilot trial still has significant reference for future studies. Finally, compared with other studies adopting nonpharmacological prophylaxis, the participants in our study were relatively older (58, 59); and the sample size was relatively small. Although the study has acceptable power, we cannot exclude the notion that the differences of effectiveness on headache alleviation between groups exist. More studies with a larger sample size and a longer intervention period are needed to further evaluate the clinical efficacy of the Tai Chi training on the reduction of migraine burden. Despite these limitations, we believe that Tai Chi would be an easily adopted mind-body exercise with significant psychosocial and biophysiological benefits on the prevention of migraine attack.

Conclusion

In conclusion, our study indicated that Tai Chi was an effective mind-body exercise in preventing migraine attack. Tai Chi can be well self-administered after a training period; it has the potential to empower migraineurs for their self-management of migraine. Evidence from our study provides a perspective that Tai Chi could be incorporated in integrative medicine that prompts physicians, healthcare providers, and healthcare policy makers to consider its efficacy in the whole management process. Future studies can be implemented to further examine any Tai Chi-migraine relief dose response exists, and whether Tai Chi can be synergistic with other behavioral or pharmacologic treatments. Furthermore, more advanced Tai Chi modality with mechanism-based exploration including neurovascular and neuroimaging examination, inflammatory factors and others would be adopted in migraine prevention with promising results.

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 human participants were reviewed and approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (reference no.: HSEARS20160329002). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YJX conceived, designed the study, provided administrative, technical, or material support to the study, collected, analyzed the data, and drafted the manuscript. YJX, LT, SH, JQ, YG, DZ, TM, LS, HW, Z-ML, CH, LY, and AL made critical revisions of the manuscript. All authors read and approved the manuscript.

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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.2022.1000594/full#supplementary-material

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EDITED BY
Arch Mainous,
University of Florida, United States

REVIEWED BY
Fatemeh Darsareh,
Hormozgan University of Medical Sciences, Iran
Eron Grant Manusov,
The University of Texas Rio Grande Valley, United States

*CORRESPONDENCE
Inga Mühlenpfordt
✉ i.muehlenpfordt@gmx.de

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Touching body, soul, and spirit? Understanding external applications from integrative medicine: A mixed methods systematic review

Inga Mühlenpfordt[1]*, Sarah B. Blakeslee[1], Janina Everding[1], Holger Cramer[2,3], Georg Seifert[1,4] and Wiebke Stritter[1]

[1]Department of Pediatrics, Division of Oncology and Hematology, Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany, [2]Institute of General Practice and Interprofessional Care, University Hospital Tübingen, Tübingen, Germany, [3]Bosch Health Campus, Stuttgart, Germany, [4]Department of Pediatrics, Faculty of Medicine, University of São Paulo, São Paulo, Brazil

Introduction: External applications from anthroposophic medicine (EAAM) are touch-based applications such as rhythmical massages, embrocations, and compresses that serve as components of complementary treatment concepts for various diseases. The aim of this review is to gain an understanding of typical indications and outcomes and to systematically assess the effectiveness and safety of EAAM.

Materials and methods: Medline/PubMed, CINAHL, the Cochrane Library, Embase, and PsycINFO were searched through May 2021 and supplemented by searches in specialized databases and personal requests to experts in the field. Studies and case reports on EAAM in patients, as well as healthy individuals, were included in the qualitative synthesis. Outcome parameters depending on each study were grouped as effect themes and assigned to study clusters using Thematic Analysis for a thematic overview of effect patterns.

Results: Four RCTs, 7 cohort studies, 1 mixed-methods, 1 retrospective, 4 qualitative studies, 3 case series, and 25 case reports on EAAM were identified. The analysis indicated various effects of EAAM on physiological as well as psychological health indicators and patterns of effect development. Study quality was found to be high for only 2 studies, and moderate for 1 study, and all remaining 45 studies showed a moderate or high risk of bias or were not ratable with used rating tools.

Conclusion: The included studies present a wide range of potential indications for EAAM, while showing methodological drawbacks. To determine whether EAAM can be considered an effective treatment option, clinical studies

exploring the effect of different EAAM modalities on defined patient groups are recommended for the future.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=214030], identifier [CRD42020214030].

KEYWORDS

external application, integrative medicine, anthroposophic medicine, touch, mixed methods systematic review

Introduction

Supporting individual patient needs at times goes beyond the limits of conventional medicine. Integrating methods from traditional, complementary, and integrative medicine into treatments may extend therapeutic options and add valuable knowledge on health promotion (1, 2). While biomedical clinical treatments often place great value on the established diagnosis and its specific treatment, integrative treatments offer holistic treatment with a focus on individual health and well-being (3, 4). External applications and massage techniques involving interpersonal attention, touch, and natural substances play a central role in complementary medical systems and are used in various medical conditions (5–9).

Effect mechanisms of external applications

In general, external applications unfold their effects through several different mechanisms: the effect of physical treatment, the touch of the therapist, a calming environment, and the substance on the skin (10). These factors, as well as warmth and olfaction, have been found to be beneficial for social interaction, emotional state, and relaxation (11). While little is known about the effects of external applications, some of the crucial facets of external applications have been subject to research.

Temperature and added substances

The effect of applications with altered temperatures on the organism can be explained by the principle of hormesis, a physiological regulatory reaction to activation by external stimuli or moderate stressors, such as heat or cold (12, 13). These reactions might also result from substances with heating and cooling capacities due to their chemical composition. An example of hormesis on a cellular level was described as the heat shock response, where heat is understood to trigger the organism to activate self-regulatory processes and therefore modulate longevity (14). Natural substances such as essential oils added to external applications are assumed to unfold their aromatherapeutic effects through scent and olfactory receptors on the skin (15). Certain odors may alter endogenous opioid pathways that reduce pain and anxiety and have antibacterial, antifungal, anti-inflammatory, immunomodulatory, and antioxidant effects (16). Positive effects on physiological and psychological parameters have been found with aromatherapy (17, 18), while the effects of aromatherapy on other health indicators have been found to be inconclusive (19). While research on the impact of individual substances on the body is scarce, research within the field of aromatherapy points to challenges in the differentiation of the principle of action of essential oils (20). However, lavender essential oil is presumed to have relaxing and sedative as well as analgesic, anticonvulsive, and neuroprotective capacities (21, 22). Ginger and mustard were found to have warming properties in external hydrotherapeutic treatments (23, 24).

Interpersonal touch and massage

Through the complex system of nerve fibers on the skin, the sense of touch is of great importance for haptic and tactile perception and social interaction (25). At the hormonal level, touch can inhibit the release of cortisol, while it can promote the release of dopamine, serotonin, and oxytocin. Oxytocin, in particular, is associated with modulating pain, increasing wound healing, and reducing stress (11, 26–28). Touching the skin with a certain pace and pressure stimulates pressure receptors. This has shown positive affective valence by stimulating especially C-tactile afferents in the skin, leading to increased vagal activity that may mediate the positive effects of touch (29, 30). Psychological effects of touch are shown in improved emotion regulation and attentiveness as well as decreased stress, depression, and anxiety levels (30, 31). The effects of massage therapy have been the subject of many studies, proposing stress relief and effects on symptoms through physiologic and psychological mechanisms, such as improvement in hypothalamus–pituitary–adrenocortical (HPA) axis function, reduction in heart rate, and increase in blood flow as underlying mechanisms (32), resulting in beneficial effects on various health conditions (9).

External applications in anthroposophic medicine

Anthroposophic medicine (AM) is an integrative medical system developed in Europe around 1900 by Rudolf Steiner and

M. D. Ita Wegman. AM is based on the views of the spiritualist movement of Anthroposophy and is intended to be applied in combination with recognized science-based medical methods (33). Aiming at a holistic promotion of health, AM facilitates a multimodal spectrum of methods that are mostly based on experience (34). Medical views in AM are based on the concept of *Four Levels of Formative Forces* in humans consisting of the physical body and its vital processes (*Body*), psychological processes (*Soul*), and the superordinate consciousness (*Spirit*) (33). According to AM, the human organism also consists of interconnected *Threefold Functional Subsystems*: One for sensory perception and consciousness (*Nerve-Sense System*), one for cardiovascular and respiratory function (*Rhythmic System*), and one for muscular activity and volition (*Motor-Metabolic-Limb System*) (34, 35). In AM, etiologies and pathogenesis of diseases are seen as abnormal interactions between these different levels and subsystems and are defined as defective processes of maturation or defective impulses leading the organism to disbalance (34–36). The AM methods spectrum includes the use of medications made from natural products, art and movement therapies, counseling, meditation practice, hydrotherapy, and different massage and nursing techniques in the form of external applications from anthroposophic medicine (EAAM). With the intention to synergize the effects of different therapeutic modalities, AM treatment concepts are often multimodal, individually tailored, and take into account the physical, emotional, mental, spiritual, and social situation of a person (34) and are supposed to address vital processes (37). The therapeutic goals of AM recognize and stimulate self-efficacy by enabling flexible autonomic self-regulation as well as psycho-emotional and spiritual self-regulation (34), a concept raised in a similar manner in *Salutogenesis* where it is described as heterostasis in the body (38, 39).

External applications from anthroposophic medicine are intended to stimulate autonomic self-regulation and salutogenic processes by physically influencing the distribution of warmth in the organism, and therefore, integrating the functions of *Body, Soul, and Spirit* according to AM (40, 41). Applications such as massage including rhythmical massage (RM), rhythmical embrocation (RE), Pressel stream massage (PM), and compress or wrap applications are used. They are performed by trained nurses, physiotherapists, or caregivers. Applications combine interpersonal attention, touch, pressure, and rhythmic movements with temperature with aroma by using tempered water, etheric or fatty oils, essences, tinctures, and ointments on the skin (34). The applications are performed as part of integrative treatment concepts or as single interventions (42, 43). The massages are usually applied 1–2 times a week in units of 30–60 min and cycles of 8–12 treatments, and the duration of the compresses depends on the applied substance (42, 43). All EAAMs are generally followed by a therapeutic resting period of 30 min (42). **Table 1** shows an overview of the different types of EAAM.

State of research on external applications from anthroposophic medicine

While literature reviews are available for multimodal application and other treatment modalities of AM (47–51), a systematic review on EAAM has not yet been published and is necessary for establishing the safety and evaluating the effectiveness of the method.

TABLE 1 Types of external applications from anthroposophic medicine.

Application type	Origin	Practice description	Intention
Rhythmical massage	Developed as an independent massage technique in anthroposophic medicine (AM), extending basic movements of classical massage.	Extends basic movements of classical massage by rhythmic, expanding and contracting, circular and lemniscate movements, and movements progressing from the depths to the periphery of the body.	Intended to influence the tissue, as well as the body, soul and spirit through the *Rhythmical System* according to AM (44).
Rhythmical embrocation	Differentiation of specific elements of rhythmical massage.	Using only stroking, embrocation is mainly done in the form of rhythmically performed circles or spirals, perceived more locally on the skin rather than in the deeper tissue.	Intended to influence the body, soul, and spirit through the *Rhythmical System* according to AM (45).
Pressel stream massage	Advanced form of rhythmical massage.	Alternately treating the lower and upper body and/or the left and right side of the body during a treatment sequence. Calves, thighs and the lower back are usually massaged in one session followed by the treatment of the upper back, arms and neck in the next.	Sequences are described to set a stimulating energy flow in motion (46).
Compresses		Application in different body regions using natural substances on the skin. Typical forms are warm wet compresses using *Achillea millefolium* (yarrow) infusion (applied for 30 min), etheric or fatty oils (applied for 30 min and longer), sinapi (mustard) flour (applied for 5, increasing to 12 min), and *Zingiber officinale* (ginger) powder (applied for up to 20 min).	Intended to support self-regulation (42).

Aims of the review

Given the research gap regarding EAAM, the overall aim of this mixed methods systematic review is to clarify existing applications and indications and to assess the effects and safety of EAAM. This aim has three specific outcomes: the analysis will describe typical indications for EAAM, typical outcomes will be summarized, and the effectiveness and safety will be systematically assessed.

Materials and methods

The review was planned following the principles of a mixed methods systematic review (52) and registered in the *International Prospective Register of Systematic Reviews* (PROSPERO) (Registration ID: CRD42020214030). The study selection and assessment were conducted in accordance with *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (53) and following the recommendations of the *Cochrane Collaboration* (54). Data analysis and synthesis were conducted qualitatively.

Eligibility criteria

For the description of eligibility criteria, refer to **Table 2**. Only isolated EAAM interventions were included; multimodal treatments, for instance as part of a wider AM regimen, were excluded. Hydrotherapy interventions were excluded since they do not necessarily involve interpersonal touch. Interventions that used EAAM-like applications but not specified as applications of AM were excluded as well.

Search strategy

The literature search was built around search terms for "anthroposophic medicine" and "External Applications." The following electronic databases were searched from their inception through 31 May 2021: Medline/PubMed, CINAHL, the Cochrane Library, Embase, and PsycINFO. The Anthromedics Merkurstab archive[1], CAMbase[2], CAM-Quest[3], ResearchGate[4], and the System for Information on Grey Literature in Europe[5] for inclusion of gray literature. The search strategy was adapted for each database as necessary and conducted in English and/or German, depending on the database. Additionally, 104 international experts and professional institutions of AM were asked to contribute articles of relevance by direct contact *via* e-mail from 15 April 2019 and submissions were accepted until 31 May 2021. The complete search strategy for each database is shown in **Table 3**. Finally, reference lists of identified original articles were searched manually.

TABLE 2 Eligibility criteria.

Criteria	Inclusion
Study types	Quantitative studies, e.g., randomized controlled trials (RCTs); quasi-experimental studies; qualitative studies; case studies and reports.
Publication	Peer-reviewed publications, gray literature records, extensive abstracts.
Language	English or German.
Participants	No restrictions on the types of participants, symptoms, and indications.
Interventions	Interventions involving direct interpersonal touch, including rhythmical massage, rhythmical embrocation, Pressel stream massage, compresses and wraps. Studies could test external applications from anthroposophic medicine (EAAM) either as an adjuvant to other modalities/therapies or as a single therapeutic approach. Only studies examining the effects of EAAM in isolation from other treatment modalities were included.
Outcome measures	Any health indicators, such as somatic and psychological parameters.

Qualitative analysis of studies

Using a *Thematic Analysis* approach to identify, analyze, and report patterns (themes) within the data, an inductive text analysis of the included records was carried out with MAXQDA2020 (Release 20.4.1) (55). First, the result sections of the included studies were coded according to the described effects on outcomes. Then, key themes regarding the treatment effects were generated based on these codes and summarized in a brief description of the subthemes separately for massage and compress studies. Subsequently, significant effects ($p \leq 0.05$) of massages and compresses on participants were summarized for each of the generated themes.

Quality assessment of the individual studies

Since studies of different methodologies were eligible for inclusion the assessment of study quality was undertaken in 3 steps. First, we sorted the studies by the level of evidence. For the detailed quality assessment, the recommended tool for risk of bias assessment of controlled trials in systematic

1 https://www.anthromedics.org
2 https://www.cambase.de
3 https://www.cam-quest.org
4 https://www.researchgate.net
5 https://www.opengrey.eu/

TABLE 3 Search strategy.

Source type	Source	Terms/Strategy
Electronic data bases	Medline/PubMed	anthroposoph*[All Fields] AND (extern*[Title/Abstract] OR rhythmic*[Title/Abstract] OR massage[Title/Abstract] OR embrocation[Title/Abstract] OR wash*[Title/Abstract] OR compress[Title/Abstract] OR pack[Title/Abstract] OR poultice[Title/Abstract] OR wrap[Title/Abstract] OR essence[Title/Abstract] OR liniment[Title/Abstract] OR ointment[Title/Abstract] OR oil[Title/Abstract] OR tincture[Title/Abstract])
	CINAHL	*FULLTEXT*: anthroposoph* AND *ABSTRACT*: (extern* OR rhythmic* OR massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR essence OR liniment OR ointment OR oil OR tincture)
	Cochrane Library	anthroposoph* AND (extern* OR rhythmic* OR massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR essence OR liniment OR ointment OR oil OR tincture)
	Embase	anthroposoph* AND (extern* OR rhythmic* OR massage OR embrocation OR wash* OR poultice OR wrap OR pack OR compress OR essence OR liniment OR ointment OR oil OR tincture)
	PsycINFO	*FULLTEXT*: anthroposoph* AND *ABSTRACT*: (extern* OR rhythmic* OR massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR essence OR liniment OR ointment OR oil OR tincture)
Alternative electronic data bases	Anthromedics Merkurstab data base	*MERKURSTAB HAUPTARTIKEL: TITEL:* extern* OR rhythm* OR massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR essence OR liniment OR ointment OR oil OR tinctur* OR äußer* OR äusser* OR aeußer* OR aeusser* OR Einreibung OR Wasch* OR Wickel OR Auflage OR Salbe OR Öl OR Oel
	CAMbase	anthroposoph* AND (extern* OR rhythm* OR massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR essence OR liniment OR ointment OR oil OR tinctur* OR äußer* OR äusser* OR aeußer* OR aeusser* OR Einreibung OR Wasch* OR Wickel OR Auflage OR Salbe OR Öl OR Oel)
	CAM-Quest	CATEGORY: "Anthroposophische Medizin": rhythmic; massage; embrocation; compress; pack; poultice; wrap; wash; Rhythmische; Massage; Einreibung; Wickel; Auflage; Waschung
	Open gray	anthroposophy; anthroposophic; Anthroposophie
	ResearchGate	*PUBLICATIONS: ALL TYPES:* anthroposoph* AND (massage OR embrocation OR wash* OR compress OR pack OR poultice OR wrap OR Einreibung OR Wickel OR Auflage OR Wasch*)
Personal inquiry	Experts and institutions	E-mail inquiry to a total of 104 international experts and institutions of anthroposophic medicine and nursing

reviews *Cochrane Risk of Bias Tool* (RoB) (56) was used and supplemented by the *Quality Assessment Tool for quantitative studies* (QA-Tool) by the Effective Public Health Practice Project (57). This quality assessment provided insight into the available study types and appropriate classification of studies according to their methodology.

All assessments were conducted by IM. Half of the QA-Tool assessments as well as half of the RoB assessments were also performed by JE independently. The remaining assessments were reviewed by JE. Conflicts of rating were discussed until a consensus was reached.

Level of evidence assessment

We first performed a Level of Evidence (LoE) assessment for all included studies, using an adapted version of the *Evidence-based Nursing Care Guidelines Scheme* (58), p. 7; as a heuristic framework assigning LoE by 7 levels.

Study quality assessment

For the quality assessment of the quantitative studies, we used the QA-Tool. The tool assesses study quality according to a strong, moderate, or weak rating quality along with the following domains: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analyses (57). Studies with no weak component rating were rated as having overall strong quality, studies with one weak component rating were rated as having moderate quality, and studies with two or more weak ratings were rated as having weak quality.

Risk of bias assessment

The RoB tool assesses the risk of bias in the domains of selection bias, performance bias, attrition bias, reporting bias, and detection bias using 8 criteria (56). Each criterion in the quantitative studies was rated as low risk, unclear risk, or high risk of bias. To provide comparability with the QA-tool, we supplemented the RoB-rating with an assessment of the overall risk of bias. Studies that met at least six of the criteria were rated as having an overall low risk of bias, studies that met four to five criteria were rated as having a moderate risk of bias, and studies that met zero to three criteria were rated as having a high risk of bias.

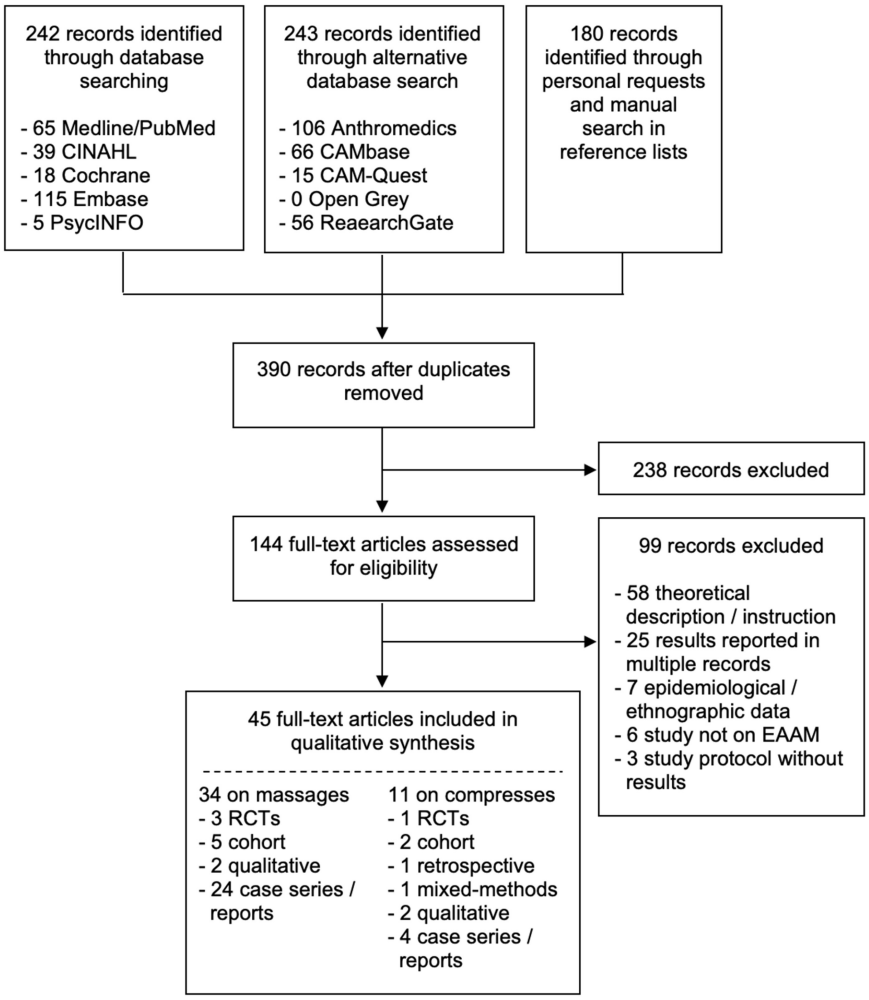

FIGURE 1
Flowchart of the results of the literature search.

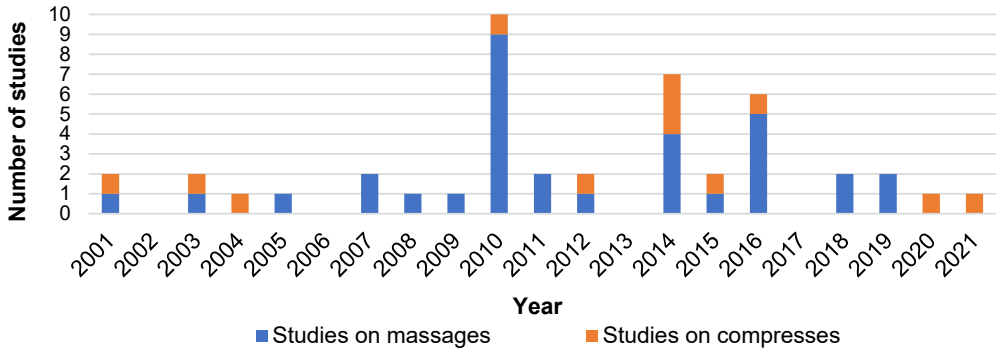

FIGURE 2
The number of studies on EAAM in a given year reported in absolute terms. Studies exploring a mixed intervention of massages and other application types were counted as massage studies.

Results

Literature search

The literature search revealed a total of 665 records, resulting in 390 non-duplicate records of which 238 were excluded because they did not report on EAAM studies in English or German. Out of 144 full-texts assessed for eligibility, 99 articles were excluded because they were theoretical descriptions or instructions of EAAM (58 records), were double publications on the same study (25 records), reported epidemiological or ethnographic data (7 records), were not studied on EAAM (6 records), or were study protocols without results (3 records).

Finally, 45 studies were included, out of these 34 studies were on massage interventions and 11 were on compresses interventions. On massages, there were 3 RCTs, 5 cohort studies, 2 qualitative studies, and 24 case reports or series. On compresses, there were 1 RCT, 1 mixed methods study, 2 cohort studies, 1 retrospective study, 2 qualitative studies, and 4 case reports or series. The flowchart of the results of the literature search is depicted in **Figure 1**.

Publication characteristics

Of the 45 studies, 18 were published in peer-reviewed journals (59–76), and 27 studies were records of gray literature (77–103). Fifteen studies were only available in the form of an abstract (77, 80, 82, 85, 87, 88, 90–95, 97, 101, 102).

The first included study was published in 2001, in fact as the second edition of a study originally published in 1992 (98). The number of studies published each year reached a peak between the years 2010 and 2016 (**Figure 2**).

Study characteristics

Characteristics of the study methodologies, samples, interventions, outcome assessments, and results are shown in **Tables 4–9**. The studies in the result tables are sorted by their assigned LoE and grouped in tables per studies on massages and studies on compresses.

Setting and participant characteristics

Of the 45 included studies, 21 studies originated from Germany (59, 60, 63–65, 69–73, 78, 79, 81, 83, 84, 86, 89, 96, 98, 99, 103), 15 studies originated from Switzerland (66–68, 80, 82, 85, 87, 88, 90, 93, 95, 101, 102), 5 studies originated from New Zealand (61, 62, 74–76), 2 studies originated from the United Kingdom (91, 92), 1 study originated from Brazil (94), and 1 study originated from the United States (100).

Participants were recruited during inpatient treatment in integrative AM clinics in 10 studies (63, 68, 76, 86, 89, 91, 92, 96, 98, 99), during outpatient treatment in integrative AM clinics in 3 studies (64, 66, 67), during inpatient treatment in conventional or unspecified clinics in 7 studies (61, 62, 72, 74, 75, 94, 100), in private practices in 2 studies (78, 81), mainly in primary care practice in 1 study (65), through physician referral or advertisement in 2 studies (59, 73), and through advertisement at a university hospital in 3 studies (69–71). In 17 studies, the recruitment of participants was not specified. All EAAMs to patients were applied complementary to their respective usual treatment regimen if there was one.

In total, 45 studies reported results on 815 participants. Seventy of them participated in different study parts and are, therefore, part of multiple publications. The reported age of the participants ranged from 6 to 83 years, with some studies reporting mean age, some median age, some age ranges, and some not reporting the age of the participants at all. Of the participants in all studies, 74% were female participants and 20% were male participants. In 6% (3 studies), the authors did not report the gender of the participants (60, 74, 94).

Seven studies included patients with various symptoms among the participants (61, 66–68, 83, 94, 98). One study included patients with various chronic diseases, e.g., musculoskeletal or mental diseases (65), and one study included patients with chronic pain (64). Four studies included patients with cancer, e.g., with nausea and fatigue (72, 86, 96, 99). Three studies were on patients with gynecological issues, e.g., with dysmenorrhea or amenorrhea (59, 73, 81). Five studies included patients with neurological disorders, such as hypersensitivity to sensory stimuli after brain injury (91), migraines (103), Morbus Parkinson (88), pain and spasticity after artery stroke (92), and sensory neuropathy (80). Seven studies included patients with orthopedic diseases, of these, 3 studies were on patients with chronic osteoarthritis (62, 74, 76), 2 on patients with spinal disorders (79, 102), 1 on a patient after surgery on humerus fracture (97), and 1 on a pediatric patient with spastic tetraparesis (87). Three studies included patients with pulmonary diseases, such as pneumonia (89), asthma bronchiale (77), and sleep apnea (82). Eight studies included patients with psychiatric or psychological symptoms, out of these, there were 2 studies on patients with burnout syndrome (90, 101); the other was on a geriatric patient with sleep disturbance (84) and on patients with depression and concurrent abdominal complaints (85), exam anxiety (95), psychological trauma (75); 1 included a pediatric patient with restlessness (78) and 1 included a pediatric patient on the autism spectrum (93). One study included patients with acute fever (100) and 1 study included a patient with prolonged postoperative ileus (gastroenterological) (63). Three studies were on healthy adults (69–71), and 1 study performed a qualitative analysis of interviews with nursing experts (60).

TABLE 4 Summary of quantitative studies on massages.

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters	Level of evidence, quality, risk of bias
Kanitz et al. (70)	RCT, 3 groups, single-blinded	$N = 101$, healthy adults, 25.2 ± 4.7 years	TSST followed by 1× treatment in individualized body regions, 3 groups: (1) RA: RM with aroma oil with peat and lavender extracts, (2) RM with jojoba oil, (3) SM with jojoba oil (control)	(A) Well-being: MDBF, Bf-S, assessment BT, AT (B) Somatic complaints: B-L, VAS; assessment BT, AT (C) Salivary cortisol; assessment at 5 points (D) Open questions; assessment AT	BG and AT vs. BT (A) ns (B) ns (C) ns (D) Description of application as relaxing after treatment in the groups: (1) 100% (2) 82% (3) 42%	LoE: II QA: Strong RoB: Moderate risk
Seifert et al. (69)	RCT, 3 groups, single-blinded	$N = 44$, female healthy adults, 26.2 ± 4.71 years [Selection of the sample of Kanitz et al. (70)]	TSST followed by 1× treatment in individualized body regions, 3 groups: (1) RA: RM with aroma oil with peat and lavender extracts, (2) RM with jojoba oil, (3) SM with jojoba oil (control)	Autonomic regulation: HRV parameters of ECG; 24-h assessment of 12 parameters: BT (T1), after massage (T2), after 12 h (T3), after 24 h (T4)	BG: Most of the HRV parameters: (1) vs. (2): $p < 0.01$ (1) vs. (3): $p < 0.01$ (2) vs. (3): $p < 0.01$ BG after 24 h: Most of the HRV parameters: (1) and (2) vs. (3): $p < 0.01$	LoE: II QA: Strong RoB: Moderate risk
Vagedes et al. (73)	RCT, 3 groups, not blinded	$N = 60$, female with dysmenorrhea, 29.7 ± 8.0 years	Treatment over 3 months, 3 groups: (1) RM, substance/region unspecified, 12×, weekly (2) HRV-Biofeedback: Daily, training/booster sessions every 4 weeks (3) Waiting control, TAU	(A) Pain intensity during menstruation: NRS (B) QoL: SF-12 (C) HRV: 24-h ECG (D) Use of analgesics; assessment BT and AT	(A) BG: (1) vs. (3): $p < 0.01$, $d = -0.80$, (1) vs. (2): ns, (2) vs. (3): ns (B) BG: ns, AT vs. BT in (1): $d = 0.60$, (C) BG: ns, AT vs. BT in (1): ns (D) (1) Reduction from 70% BT to 60% AT	LoE: II QA: Weak RoB: Moderate risk
Hamre et al. (65)	Cohort study, 1 group, not blinded	$N = 85$, chronic diseases (musculoskeletal, mental etc.), 35.7 ± 19.3 years	RM, substance/region unspecified, 12× (median) within 84 days (median)	(A) Disease score (B) Symptom score (C) QoL: SF-36 scales (D) Therapy ratings: Overall, satisfaction, effectiveness (0–10) (E) AE; assessment BT and after 3, 6, 12, 18, 24, and 48 months	12 months after start vs. BT: (A) $p < 0.001$, $d = 1.45$ (B) $p < 0.001$, $d = 1.14$ (C) Physical Health: $p < 0.001$, $d = 0.57$, Mental Health: $p = 0.001$, $d = 0.63$ (D) Overall rating: 7.50 ± 2.34, satisfaction: 8.18 ± 2.08, Effectiveness: Positive rating in 83% patients, 77% physicians; continued good ratings of satisfaction/effectiveness in follow-ups (E) In 4 cases: Cardiac palpitations, arterial hypotension, pain and vertigo, symptom aggravation	LoE: IV QA: Weak RoB: High risk
Wälchli et al. (67)	Cohort study, 1 group, not blinded	$N = 59$, any indication, 49.4 ± 12.5 years	RM with individualized oils/ointments, in individualized body regions, 9× (average), 1–2× per week within 3 months	(A) Disease score (B) Symptom score (C) QoL: SF-36 (D) Goal attainment: GAS (E) AE; assessment BT, AT, 6 months after first session	AT vs. BT/after 6 months vs. BT: (A) $p < 0.001/ < 0.001$ (B) $p < 0.001/ < 0.001$ (C) Physical Health: $p = 0.005/ = 0.008$, Mental Health: $p < 0.001/p < 0.001$ (D) $p < 0.001/p < 0.001$ (E) None	LoE: IV QA: Weak RoB: High risk

(Continued)

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TABLE 4 (Continued)

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters	Level of evidence, quality, risk of bias
Wälchli et al. (66)	Cohort study, 1 group, not blinded	$N = 13$, any indication, 54.8 ± 3.8 years, IRI: $n = 9$, ECG: $n = 11$ [Selection of the sample of Wälchli et al. (67)]	RM with individualized oils/ointments, in individualized body regions, 10× (average), 1–2 × per week within 3 months	(A) Surface temperature: IRI of dorsal region; assessment in waiting periods BT and AT (B) Autonomic regulation: HRV parameters of ECG; assessment of 6 parameters in waiting periods BT and AT, and after therapeutic rest	AT vs. BT: (A) $p < 0.001$ (B) $p = 0.0105/0.0001/0.0001/0.0353/0.3909/0.0001$ (different HRV parameters), further regulation of HRV during the therapeutic rest	LoE: IV QA: Weak RoB: High risk
Ostermann et al. (64)	Cohort study, 1 group, not blinded	$N = 100$, chronic pain, 47.3 ± 13.9 years	RE with aroma oil with peat and lavender extracts, in individualized body regions, 3× within 24 days	(A) Mental state: Bf-S mood scale (B) Sensory pain: MPQ (C) Affective pain: MPQ (D) Pain intensity: VAS before-after RE (E) Associated medication (F) AE; assessment BT, after each treatment, AT	AT vs. BT: (A) $p < 0.001$, $d = 0.81$ (B) $p < 0.001$, $d = 0.55$ (C) $p < 0.001$, $d = 0.85$ (D) $p < 0.001$, consistent reduction after each treatment (E) No change reported (F) None	LoE: IV QA: Weak RoB: High risk
Vieira et al. (94) (gray, abstract)	Cohort study, 1 group, not blinded	$N = 27$, unspecified geriatric patients	Threefold External Therapy: Body sliding/organ rubbing/foot baths/compresses, substances unspecified, individualized treatment, 12 weekly sessions	(A) Cognitive function: MMSE (B) Incidental memory: FT (C) Immediate memory: FT (D) Evocation: FT (E) Visual perception: FT (F) Nomination: FT (G) Depression: DSM-IV (H) QoL: WHOQOL-bref; assessment BT and AT	AT vs. BT: (A) $p = 0.008$ (B) $p = 0.003$ (C) $p = 0.006$ (D) $p = 0.001$ (E) ns (F) ns (G) $p = 0.002$ (H) Physical: $p = 0.05$, psychological: $p = 0.007$, social: $p = 0.048$, environment: $p = 0.02$	LoE: IV QA: Weak RoB: High risk

Abstract, only abstract of study available; AE, adverse effects; AM, anthroposophic medicine; AT, after treatment; B-L, 24-item list of somatic complaints; Bf-S, Zerssens Adjective Mood Scale for assessment of mental state; BG, between groups; BT, before treatment; *d*, Cohen's *d* (reported when available); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders edition IV; ECG, electrocardiogram; GAS, Goal Attainment Scale; FT, figures test. HRV-BF, Heart Rate Variability biofeedback; IRI, infrared imaging; LoE, level of evidence based on the evidence-based nursing care guidelines scheme [Ackley et al. (58), p. 7]—rating on level I to VII (see text); MDBF, multidimensional questionnaire on mental state; MMSE, mini-mental state exam; MPQ, McGill Pain Questionnaire; ns, not significant; NRS, Numeric Rating Scale; *p*, *p*-value (reported when available); PPS, Pain Perception Scale; QA, quality assessment according to the Effective Public Health Practice Project scheme (57)—rating 8 criteria and global rating as strong, moderate, or weak (see text); RA, rhythmical massage with aroma oil; RE, rhythmical embrocation; RM, rhythmical massage; RoB, risk of bias assessment according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (56)—rating on 7 domains and global rating as low, moderate, or high risk of bias (see text); QoL, quality of life; SF-36, Health-Related Quality-of-Life questionnaire short form; SF-12, health survey short form of SF-36; SM, Sham massage; TAU, treatment as usual; TSST, Trier Social Stress Test; VAS, Visual Analog Scale; WHOQOL-bref, World Health Organization Quality of Life questionnaire short form.

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TABLE 5 Summary of quantitative studies on compresses.

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters	Level of evidence, quality, risk of bias
Ghadjar et al. (72)	RCT pilot, 2 groups, not blinded	*N* = 24, cancer, during palliative RT, 58.5 (median), 34–83 years	2 groups (1) Yarrow liver compress, 10.5×, daily (average) (2) Waiting control, TAU	(A) Fatigue: MFI-20 Subscale (B) Psychological distress: Distress thermometer (C) QoL: QLQ-C30 (D) Symptoms: VAS; assessment BT, after 1 week, AT	BG: (A) General Fatigue scale: ns ($p = 0.13$), but clinically relevant difference of 2 points, Reduced Motivation scale: $p = 0.035$ (B) ns (C) ns (D) Fatigue: $p = 0.015$, tension: $p = 0.044$, lack of drive: $p = 0.028$	LoE: IV QA: Weak RoB: High risk
Stritter et al. (71)	Qualitative part of a mixed methods study: Case cross-over, 1 group, single-blinded (qualitative results: see Table 7)	*N* = 30, healthy adults, 27 ± 4.44 years	4 different chest compresses over 4 weeks in 1 group: (1) Dry (2) Hot water (3) Hot with ginger powder (4) Hot with mustard flour	(A) Somatic complaints: B-L (B) Calmness: MDBF (C) Mood: MDBF (D) Experience: RS (E) AE; assessment BT, after each application	AT vs. BT per each treatment: (A) All compresses: ns (B) All compresses: $p < 0.05$ (C) (1) $p = 0.03$, (2) $p = 0.01$, (3) $p < 0.001$, (4) ns (D) (1) ns, (2) ns, (3) Relaxation: $p < 0.001$, emotional balance: $p = 0.03$, deep breathing: $p = 0.03$, slow breathing: $p < 0.001$, warm hands: $p = 0.03$, warm feet: $p = 0.00$, (4) ns (E) None	LoE: IV QA: Moderate RoB: High risk
Klich-Heartt (100) (gray)	Cohort study, 1 group, not blinded	*N* = 10, fever, 20–74 years	Calf compress with lemon aroma oil, 1×	(A) Temperature: Clinical thermometer (B) Subjective perception of headaches: RS (C) Pulse, respiratory rate, blood pressure; assessment BT, 30 min. AT, and (A) also 60 min. AT	AT vs. BT: (A) $p = 0.027$, BT vs. 60 min. AT: $p = 0.006$ (B) $p = 0.01$ (C) ns	LoE: IV QA: Weak RoB: High risk
Therkleson (62)	Cohort study, 2 treatment groups, not blinded	*N* = 20, chronic osteoarthritis, 64 (mean) years	Ginger compresses, 2 treatment groups, both 1-week daily ginger patch/compress applied to the midlumbar region: (1) Manually prepared ginger compress (2) Ginger patch; additional 24 weeks of self-treatment at home with the patch as required	(A) Health assessment: Arthritis MHAQ/HAQ-II (B) Health satisfaction: RS (C) Use of analgesics; assessment for 21-days: daily/1 week BT, 12 h AT, 1 week AT, 4-weekly for 24 weeks	BG: ns, both groups reported together in percentages of patients, (A) Improvement in mean scores 1 week AT vs. BT: Pain: 48%, fatigue: 49%, GEO: 40%, functional status: 31%; improvement in all scores for all participants in all domains over following 24 weeks of self-treatment (B) BT: 80% dissatisfied, 7 days AT: 70% satisfied, 24 weeks AT: 82% satisfied (C) BT: 70%, 4 weeks AT: 15%	LoE: IV QA: Weak RoB: High risk

(Continued)

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TABLE 5 (Continued)

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters	Level of evidence, quality, risk of bias
Simoes-Wüst et al. (68)	Retrospective descriptive study, 1 group, not blinded	*N* = 221, any indication, 49,6 ± 19,2 years	Various compress types, patients treated with at least one compress during their hospital stay	State of health: 13 items; one-time assessment	Improvement in state of health attributed to the compresses: 70%, considerable recovery: 85%, considerable success of compresses: 76%	LoE: VI QA: Weak RoB: High risk

AT, after treatment; B-L, list of somatic complaints; BT, before treatment; distress thermometer, German version of the distress thermometer of the National Comprehensive Cancer Network; GEO, global effect of osteoarthritis; HAQ-II, Health Assessment Questionnaire II; LoE, level of evidence based on the evidence-based nursing care guidelines scheme [Ackley et al. (58), p. 7]—rating on Level I to VII (see text); MDBF, Questionnaire on mental state; MFI-20, multidimensional fatigue inventory; MHAQ, Modified Health Assessment Questionnaire; ns, not significant; *p*, *p*-value (reported when available); QA, quality assessment according to the Effective Public Health Practice Project scheme (57)—rating 8 criteria and global rating as strong, moderate, or weak (see text); QLQ-C30, quality of life questionnaire of the European Organization for Research and Treatment of Cancer; QoL, quality of life; RoB, risk of bias assessment according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (56)—rating on 7 domains and global rating as low, moderate, or high risk of bias (see text); RS, Subjective Rating Scale; RT, radiation therapy; TAU, treatment as usual; VAS, Visual Analog Scale.

Intervention characteristics

Of the 45 studies, 34 were on massage interventions and 11 on compress interventions. **Table 10** describes the distribution of studies per application type and substance.

Of the 34 massage studies, 23 studies were on RM, of which 2 studies were on RM with aroma oil with peat and lavender extracts (69, 70), and 21 studies were on RM with unspecified or various substances (59, 65–67, 73, 77–79, 82, 87, 88, 90–93, 96, 97, 99, 101–103). Six studies were on RE of which 2 were on RE with aroma oil with peat and lavender extracts (64, 84) and 4 were on RE with unspecified substances (60, 80, 85, 95). Two studies were on PM with unspecified substances (81, 83). Three studies were on massages mixed with compresses and/or footbaths: 1 using various aroma oils and ointments (63), 1 using aroma oil and ointment with peat, lavender, and oxalis extracts (75), and 1 using unspecified substances (94).

Of the 11 studies on compresses, 5 studies were on ginger powder compresses (61, 62, 74, 76, 98), 2 on yarrow infusion compresses (72, 86), 1 on a mustard flour compress (89), 1 on lemon aroma oil compresses (100), and 2 on differing compresses, 1 comparing ginger and mustard with neutral dry and wet compresses (71), and 1 describing effects of various compresses (68).

Of the 4 RCTs, 2 compared RM with aroma oil with peat and lavender extracts to RM with neutral oil and sham massage with neutral oil (69, 70), 1 compared RM with heart rate variability biofeedback and treatment as usual (73), and 1 compared yarrow liver compress therapy to treatment as usual (72). One study compared 4 compresses (mustard, ginger, hot water, and hot dry) with different substances within one treatment group (71), and 1 study used different forms of application for ginger compresses (manual application vs. patch) (62). The other studies did not use comparisons or control groups.

Outcome measures

The 13 included quantitative studies focused on both the subjective assessment of physical outcomes such as symptom manifestation and therapy effectiveness and objectively measured physical and psychological outcomes.

Physical measures

Physiological outcomes were assessed using subjective instruments by the 24-Item List of Somatic Complaints (B-L) (70, 71), by measuring the manifestation of disease and symptoms by Visual Analog Scales (70, 72), disease scores and symptom scores (65, 67), and a questionnaire for the state of health assessment (68). Health assessment in patients with osteoarthritis was conducted by Modified Health Assessment Questionnaires for arthritis (MHAQ, HAQ-II) (62), and fatigue in a patient with cancer was assessed using the multidimensional fatigue inventory (MFI-20) (72). Pain intensity was assessed by

TABLE 6 Summary of qualitative studies on massages.

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Berger et al. (59)	Qualitative study, selection of the sample of Vagedes et al. (73)	$N = 13$, female, dysmenorrhea, 16–46 years [those treated with RM, other results see Vagedes et al. (73)]	RM, substance/region unspecified, 12×, weekly over 3 months	Semi-structured interviews, drawings ($n = 6$), questionnaire 1 year after intervention ($n = 7$)	Perception of RM as soft and overall beneficial, feeling different to conventional massage, influence on the whole body; improved pain management, calming, relaxing, increased self-awareness, cause for a process of transformation; reactions depend on the emotional state and readiness to resonate with the therapeutic process
Bertram et al. (60)	Qualitative study, phenomenology	$N = 13$ nursing experts on RE	RE (theoretical)	Semi-structured interviews	Psychosomatic reactions to RE rely on changes in physical parameters and changes in vegetative, mental and spiritual dimensions; Key patterns of patient reaction process: Being uncaged à re-identifying à being empowered

Gray, study from gray literature; RE, rhythmical embrocation; RM, rhythmical massage.

a numeric rating scale in patients with dysmenorrhea (73), and sensory and affective pain in patients with chronic pain were assessed by the McGill Pain Questionnaire (MPQ), while pain intensity was assessed with a Visual Analog Scale (64). The intensity of headaches during fever was assessed using a rating scale for subjective assessment by the patients (100). The use of analgesics and other medication was assessed in 3 studies (62, 64, 73). Overall therapy effectiveness was assessed in 3 studies using rating scales (62, 65) and the Goal Attainment Scale (67).

Objective measures of physiological parameters assessed autonomic regulation using heart rate variability data from electrocardiogram assessments in 3 studies (66, 69, 73). Body surface temperature was assessed by infrared imaging of the dorsal region in 1 study (66). Body temperature by a clinical thermometer and also pulse, respiratory rate, and blood pressure were assessed in patients with fever (100). One study assessed salivary cortisol (70).

Psychological assessments

The mental state was assessed in 3 studies by the Multidimensional Questionnaire on Mental State (MDBF) (70, 71) and Zerssens Adjective Mood Scale (Bf-S) (64, 70). One study used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to assess symptoms of depression (94) and 1 study used the German version of the distress thermometer of the National Comprehensive Cancer Network to assess psychological distress (72). As outcome assessments for the cognitive state, the Mini-mental State Exam (MMSE) and Figures Tests (FT) were used (94). Rating scales were used to assess the experience of relaxation and warmth (71) and additional open questions were used to assess the remarks of participants (70).

Physical–psychological assessment

Quality of life (QoL) was assessed by Health-Related Quality-of-Life questionnaire short forms SF-36 (65, 67) and SF-12 (73), World Health Organization Quality of Life questionnaire short form (WHOQOL-bref) (94), and the Quality of life questionnaire of the European Organization for Research and Treatment of Cancer (QLQ-C30) (72).

Assessment of long-term effects

All quantitative studies assessed short-term effects, while 3 studies also assessed long-term effects (62, 65, 67).

Outcome assessment in qualitative studies and case reports

The qualitative studies included interviews (59–61, 71, 74). The case reports mainly used observations and interviews for outcome assessment, while some case studies additionally used questionnaires for outcome assessment, such as the Health-Related Quality-of-Life questionnaire short form (SF-36) (82, 95, 99), the Arthritis Health Assessment Questionnaire (HAQ) and a Visual Analog Scale for pain assessment (76), and diaries (76, 80, 88, 99) for progress documentation. One case series exclusively used patient self-reports in 2 cases (96).

TABLE 7 Summary of qualitative studies on compresses.

Reference	Type of study	Participants: *N*, diagnosis, age	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Stritter et al. (71)	Qualitative part of a mixed methods study: Case cross-over, 1 group, single-blinded (Quantitative results: see Table 5)	*N* = 15, healthy adults, 27 ± 4.44 years	4 different chest compresses over 4 weeks in 1 group: (1) Dry (2) Hot water (3) Hot with ginger powder (4) Hot with mustard flour	Interviews after each application, follow-up interview	Different onset of relaxation after all 4 applications and resting periods, different qualities of warmth through the ingredients ginger and mustard; (3) Ginger: Most warming and relaxing, instant relaxation, spread of warmth into the whole body, feeling alert and well rested afterward; (4) Mustard: Initial tension, perception of heat mostly in compress area, burning, sudden and strong onset of relaxation in resting period after application
Therkleson and Sherwood (61)	Qualitative study, phenomenology	*N* = 7, various indications, 21–54 years	Ginger kidney-compress, 1×	Semi-structured interview	4 key themes: - Warmth in the body, increasing in intensity and radiating outward - Stimulation of internal activity within the body - Changes in thought-life, sensory perception, and body tension - Centeredness within oneself and greater sense of personal boundary in relation to the world
Therkleson (74)	Qualitative study, phenomenology	*N* = 10, osteoarthritis, >45 years	Ginger kidney-compress on 7 consecutive days	Daily diaries, drawings, personal/phone follow-up interviews	Unique qualities of heat, stimulation, anti-inflammation, and analgesia; 7 key themes: - Meditative-like stillness, relaxation of thoughts - Constant penetrating warmth in the body - Positive change in outlook - Increased energy and interest in the world - Deeply relaxed state with a gradual shift in pain and increased interest in others - Increased suppleness within the body - More comfortable, flexible joint mobility

Assessment of adverse effects and safety

While most studies assessed positive effects on the patients, there were 4 quantitative studies (62, 64, 65, 67) and the mixed-methods study (71) which additionally assessed adverse effects. Three case series and reports reported adverse effects (81, 93, 98).

Outcomes

Effect themes

The *Thematic Analysis* of the 45 studies resulted in 4 themes describing different areas of effects (1) physical effects, (2) psychological effects, (3) effect development over time, and (4) adverse effects. The 4 themes contained 7 subthemes. An overview of the themes and subthemes is shown in Table 11, where study clusters are marked when a theme was extracted from a study cluster at least once. Each of the developed themes could be extracted from the outcomes of the massage and compress studies with different characteristics and in some studies with significant effects, as described below.

Physical effects of massages

In the studies on massage interventions, physiological effects were presented in the form of various reactions of the body and symptom relief. Reactions of the body showed in form of

TABLE 8 Summary of case reports on massages.

Reference	Type of study	Participant: Age/gender, diagnosis	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Gierse (97) (gray, abstract)	Prospective case study	78/female, after surgical treatment of a humerus fracture	RM, substance/region/number unspecified	Observation, interviews, schematic progress documentation	Warming sensation, deepened breath, improvement of pain, hypoesthesia and mobility, improvement of mental state
Göbels and Allmer (99) (gray)	Prospective case study	39/female, mammary carcinoma, after bilateral mastectomy	RM, substance/region unspecified, 7× over 4 weeks	Observation, interviews, schematic progress documentation, guided diary for self-observation, SF-36; assessment each time	Positive effects on warmth regulation, body experience, emotional well-being, improved emotional well-being
Klocker (101) (gray, abstract)	Prospective case study	Unspecified/male, burnout syndrome	RM, different regions, substance/number unspecified, in 2 cycles	Observation, interviews, schematic progress documentation	Muscle relaxation, warming sensation, harmonizing and deepening the breath, improved self-observation/self-awareness and self-reflection, improved drive
Kögler (102) (gray, abstract)	Prospective case study	47/female, lumbar syndrome	RM, substance unspecified, different regions, 14× in 2 cycles	Observation, interviews, schematic progress documentation	Reduction of pain intensity and frequency of pain attacks, muscle relaxation, warming sensation, harmonizing and deepening the breath, improved decisiveness
Radünz (82) (gray, abstract)	Prospective case study	41/male, obstructive sleep apnea	RM, substance/region unspecified, 10×	Observation, interviews, schematic progress documentation, SF-36; assessment each time	Reduced vertigo, increased appetite, improved sleep, strengthening feeling, less fatigue and improved concentration, anxiety and panic states become increasingly weaker, increase in libido, improved self-awareness
Schober (87) (gray, abstract)	Prospective case study	17/male, spastic tetraparesis	RE, substance/region unspecified, 14× in 7 weeks	Observation, interviews, schematic progress documentation	Warming sensation in the whole body, improved mobility, loosening feeling, improved gross and fine motor skills, vitalizing feeling
Schwarz (88) (gray, abstract)	Prospective case study	64/male, Morbus Parkinson	RM, substance unspecified, different regions, 11× in 11 weeks	Observation, interviews, schematic progress documentation, medical findings of the general practitioner, diary	Increased flexibility in facial expression, deepened breathing, improved balance and upright posture, improved sense of smell, improved sleep and mood
Schwinger (90) (gray, abstract)	Prospective case study	61/female, burnout syndrome	RM, substance/region unspecified, 21× weekly in 3 cycles over 6 months	Observation, interviews, schematic progress documentation, SF-36, assessment each time	Improved self-awareness, mood, well-being, and sleep, vitalizing and relaxing effect
Seedheeyan et al. (91) (gray, abstract)	Prospective case study	50/female, hypoxic brain injury, hypersensitivity to sensory stimuli, pain	RM, substance/region/number unspecified	Pain assessment tools: Body map to indicate location, Wong-Baker Faces Pain Rating Scale, response to qualitative pain description words	Reduced levels of hypersensitivity, anxiety and confusion, improved self-awareness: perception of and ability to describe pain
Uhlenhoff (93) (gray, abstract)	Prospective case study	11/male, on the autism spectrum	RM, substance/region unspecified, 14× biweekly in 7 weeks	Observation, interviews, schematic progress documentation, SF-36	Warming sensation, deepened breath, increased tolerance for touch; AE: discomfort caused by high sensitivity to touch
Amman Albertin (77) (gray, abstract)	Retrospective case report	68/female, asthma bronchiale, hypertension, bilateral osteoarthritis	RM, substance/region/number unspecified	Use of clinical and personal records of the patient	Improvements in asthma symptoms, withdrawal of pharmaceutical therapy, decrease in blood pressure

(Continued)

TABLE 8 (Continued)

Reference	Type of study	Participant: Age/gender, diagnosis	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Börner (78) (gray)	Retrospective case report	6/male, restlessness, sleeping problems, social anxiety, and conflicts	RM, substance/region unspecified, weekly for 6 months	Observation, interviews with parents, schematic progress documentation	Relaxation, improved sleep, improved social interaction
Maier-Schnorr (103) (gray)	Retrospective case report	38/female, migraines, vomiting, nausea, restless, mood swings,	RM of the lower back, hips, abdomen, arms, substance/number unspecified	Observation, interviews	Reduction of vomiting, improvement in restlessness, mood swings, increased attention on avoiding personal overexertion
Meyer (79)(gray)	Retrospective case report	male, pelvic obliquity, scoliosis, muscle tension in the lumbar spine region	RM of the lower back, substance unspecified, biweekly for 3 months, occasional follow-up in following months	Observation, interviews	Improved perception of and strength in the back, ability to lift heavy loads and to work physically without triggering pain or cramps, feeling of well-being and possibility to become active
Vajnai et al. (92) (gray, abstract)	Retrospective case series	59/male, mid-cerebral artery stroke, pain, and spasticity after surgery	RM, substance/region/number unspecified	Observation, interviews	Improved pain management and spasticity management
Weidtke (96) (gray)	Retrospective case series	41/female, operated mammary carcinoma	RM, 3× per week, substance/region/timeframe unspecified	Self-report	Warming sensation, relief of congestion after 1 or 2 days, relieving sensation, relaxing/flowing/healing feeling, feeling of comfort during the after-rest
		68/female, metastasized mammary carcinoma	RM, substance/region/number unspecified	Self-report	Deepened breath, deep relaxation, vitalizing, harmonizing, strengthening, releasing and re-identifying feeling
		50/female, sigmoid carcinoma	RM with various oils (melissa, aurum, lavendula, sloe), region unspecified, 3×	Observation, interviews, schematic progress documentation	Increased comfort in the body, strengthening feeling
Praxl (80) (gray, abstract)	Prospective case study	Not specified/female, hereditary motor sensory neuropathy	RE, substance/region unspecified, 10× in 7 weeks	Observation, interviews, schematic progress documentation, diary	Warming sensation in the legs, improved sensibility in the legs and walk, improvement in sleep and mood, deep relaxation during RE
Reisinger (85) (gray, abstract)	Prospective case study	55/female, depression, multiple abdominal complaints	RE, substance/region unspecified, 7× in 7 weeks	Observation, interviews, schematic progress documentation	Improvement of bloating and abdominal complaints, warming sensation in the whole body, improved wellbeing
Roggatz (84) (gray)	Prospective case study	79/female, sleep disturbance	RE with aroma oil with peat and lavender extracts, on the feet and calves, in the evening for 4–6 weeks	Observation, interviews	RE feel beneficial, pleasant heaviness in the body, light feeling in the feet, relaxation of the body: slower breathing, calmer pulse, relaxed muscles, enhanced warming of the skin after each time; first not calming, but calming down and falling asleep the after rest; after multiple treatments: regularly fast asleep after the RE, less waking in the night, discontinuation of sedative, more relaxed and better sleep

(Continued)

TABLE 8 (Continued)

Reference	Type of study	Participant: Age/gender, diagnosis	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Voit (95) (gray, abstract)	Prospective case study	23/female, exam anxiety	RE, substance/region unspecified, 7× in 7 weeks	Observation, interviews, schematic progress documentation, SF-36, assessment each time	Warming sensation, regulating effect on anxiety and well-being, relaxing and releasing, improved self-awareness and confidence
Pressel (81) (gray)	Retrospective case series	21/female, neck tension, sleep disturbances, amenorrhea	PM in classic regimen, substance unspecified, 6×	Observation, interviews	Improvement of neck tension, return of menorrhea and stable cycle, improved sleep
		34/female, sleep disturbances, depression	PM calf and back massages, substance unspecified, 40×		AE: Headaches, hemorrhage on the calf with accompanying swelling and sensitivity throughout the leg, tiredness, improved sleep
		53/female, chronic fatigue, sleep disturbance	PM calf and back massages, substance unspecified, 10×		Initiation of menstrual bleeding, release of headache, feeling of release and inner alignment, increased well-being
		56/female, recurrent cystitis and appendicitis	PM calf massage, substance unspecified, 1×		Following day after massage: severe pain in the lower abdomen and discharge of blood coagulum, no further bleeding in the following 4 years; AE: Feeling of depression in the evening after massage
Robert (83) (gray)	Retrospective case report	65/female, chronic pain syndrome, chronic depression	PM in classic regimen, substance/number unspecified, weekly sessions	Observation, interviews	Improvement of mobility, sensation of self-healing powers and revitalization, feeling of well-being and new drive
Therkleson and Stronach (75)	Prospective case study	82/female, psychological trauma/characteristics diagnosed as Broken Heart Syndrome	RM with aroma oil with peat and lavender extracts, region unspecified; lavender footbath; oxalis ointment compress to the abdomen, 4× weekly sessions	Observation, schematic progress documentation	Warming sensation, increased attention, improved sleep, relaxation, more able to cope with life's issues, feeling grounded and more integrated
Deckers et al. (63)	Retrospective case report	61/male, episode of prolonged postoperative ileus, pain	RM with melissa oil to the abdomen; abdominal compress with thuja and argentum ointment, 1×	Observation, schematic progress documentation	Gradual improvement of symptoms over the next 10 days; no prokinetic medications were needed to manage the episode, decrease in pain

Abstract, only abstract of study available; AE, adverse effect; gray, study from gray literature; RM, rhythmical massage; SF-36, Health-Related Quality-of-Life questionnaire short form; PM, Pressel stream massage.

improvement of general condition and vitalization (59, 63, 65, 67, 82, 83, 90, 96, 99, 102), a warming sensation in the whole body (75, 80, 81, 84, 85, 87, 95, 96, 101), deepened breathing (84, 87, 88, 93, 95, 96, 102), an increase in body temperature and blood circulation (66, 87, 93, 97, 101, 102), a decrease in blood pressure (77), a stimulation of heart rate variability (HRV) (66, 69), an improvement of skin texture (81) and an increase in libido (82). Symptom relief after massage interventions was shown in the form of general symptom relief and general rating of applications as effective (65, 67), a reduction in local pain and muscle relaxation (63, 64, 73, 81, 83, 97, 99, 101, 102), an improvement of mobility (83, 87, 88, 96, 97), improvements of digestion and bloating (63, 81, 85), reductions in headaches (81, 95), improvements in asthma symptoms (77), an improvement of sensitivity in the legs (80), an improvement of vertigo (82), a regulation of the menstrual cycle (81), improvements in cognitive function (94), and the possibility for discontinuation of analgesia and sedatives (63, 77).

Significant effects of massages on physical outcomes

The quantitative studies on massage interventions revealed significant effects for some of the stated physiological outcomes: RM treatment for 3 months compared to treatment as usual (TAU) led to a significant reduction in pain intensity in patients with dysmenorrhea between groups ($p < 0.01$) (73). RM led

TABLE 9 Summary of case reports on compresses.

Reference	Type of study	Participant: Age/gender, diagnosis	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Glaser et al. (98) (gray)	Retrospective case series	49/female, recurrent influenza, herpes corneae	Ginger kidney compress, unspecified number	Observation, interviews	Warming sensation, feeling overwhelmed by inner images with following positive processing and feeling of dissolution
		55/female, food intolerance, diarrhea	Ginger kidney compress, 31× in 2 cycles	Observation, interviews	Warming sensation, feeling of release, improved sleep quality, relaxation, feeling of inner support; AE: Tiredness after first treatment, reduction of ginger powder
		50/male, asthma bronchiale	Ginger kidney compress, 9×	Observation, interviews	Warming sensation, relaxation; AE: emerging of problematic thoughts during one treatment
		33/female, asthma bronchiale	Ginger thorax compress, 7×; ginger kidney compresses, number unspecified	Observation, interviews	First AE: Feeling tightness, coughing, after break: warming sensation, improvement of expectoration
		70/female, spastic bronchitis	Ginger thorax compress, number unspecified	Observation, interviews	Warming sensation
		55/female, depression, restlessness	Ginger kidney compress, 7×	Observation, interviews	Warming sensation, relaxation, increased duration of sleep
		48/female, back and joint pain, adipositas	Ginger kidney compress, 10×	Observation, interviews	Warming sensation, relaxation; AE: No pain release
		47/male, back pain, subfebrile temperature, leukocytosis	Ginger kidney compress, 8–10×	Observation, interviews	Warming sensation, but no pain release, relaxation
		68/female, pancreatic carcinoma, abdomen/back pain	Ginger kidney compress, 17×	Observation, interviews	Warming sensation, pain release (only before noon)
		79/female, abdomen carcinoma, skin metastases, ascites	Ginger kidney compress, 12×	Observation, interviews	Warming effect, calming effect on respiration, increased appetite, decreased ascites
		33/male, colon carcinoma, liver metastases etc.	Ginger kidney compresses over 3 weeks, number unspecified	Observation, interviews	First AE: Feeling tightness and restlessness, then warming sensation and relaxation
		48/female, pneumonia	Ginger thorax compress, 1×	Observation, interviews	Increasing warming effect, energized feeling
		83/female, pneumonia after cardiac arrest	Ginger kidney compress, 9×, treatment discontinued	Observation, interviews	First improvement: respiration, expectoration, sleep; later decrease in effect
		56/female, primary chronic polyarthritis, joint pain	Ginger kidney compress, 4×, treatment discontinued	Observation, interviews	First warming sensation, later AE: Weakening, discomfort of the skin in form of burning, itching, and redness
		28/female, melanoma, sleep disturbance	Ginger kidney compress, 2×, treatment discontinued	Observation, interviews	AE: Sensation of wetness and cold, restlessness
		27/female, eating disorder, underweight, sleep disturbance	Ginger kidney compress, 5×, treatment discontinued	Observation, interviews	AE: Subjective sensation of cooling, no feeling of release, continued sleep disturbance

(Continued)

TABLE 9 (Continued)

Reference	Type of study	Participant: Age/gender, diagnosis	Intervention: Modality, substance, body region, number/time span	Main outcome assessment	Main results: Improvements of outcome parameters
Therkleson (76)	Prospective case study	>65/male, osteoarthritis, pain	Ginger kidney compress, 7× in 7 consecutive days; patch self-treatment at home for a further 24 weeks	Arthritis HAQ, pain VAS, diary; assessment daily, 8 days BT until 6 days AT, and after 24 weeks	Diary: Warming sensation, increase in flexibility and mobility, decrease in pain; improvement of global effect, fatigue, and mobility, continued improvements in global effect, fatigue, and mobility over the 24-week of self-treatment
Schier and Bruchner (86) (gray)	Prospective case study	40/male, seminoma, in the third chemotherapy cycle	Yarrow liver compress during chemotherapy, 5× daily	Observation, interviews, schematic progress documentation, self-reports	Symptom relief compared to the first two cycles of chemotherapy: No symptoms of nausea, loss of appetite or tension during the application days, enhanced appetite, warming sensation, feeling of relaxation
Deckers (89) (gray)	Retrospective case report	20/male, pneumonia, pain	Mustard compress on the chest followed by lavender oil, 1×	Observation, interviews, schematic progress documentation	Hyperemia of the skin followed by pain reduction, deepened breathing, expectoration

AE, adverse effects; AT, after treatment; BT, before treatment; gray, study from gray literature; HAQ, Health Assessment Questionnaire; VAS, Visual Analog Scale.

to a significant pre-post reduction in disease manifestation (short-term: $p < 0.001$/long-term: $p < 0.001$) and symptom scores (short-term and long-term: $p < 0.001$) in patients with various indications (67) and to a significant reduction in disease manifestation ($p < 0.001$) and symptom scores ($p < 0.001$) in patients with chronic disease (65). After RM, the patients' rating of therapy goal attainment was also significantly higher (short-term and long-term: $p < 0.001$) in the various indications sample (67). RE had significant positive effects on sensory ($p < 0.001$, $d = 0.55$) and affective ($p < 0.001$, $d = 0.85$) pain, and pain intensity ($p < 0.001$), in patients with chronic pain (64). An intervention using embrocations together with compresses and footbaths led to a significant increase in cognitive function ($p = 0.008$) and incidental ($p = 0.003$) and immediate ($p = 0.006$) memory as well as an increase in evocation capacity ($p = 0.001$) in elderly patients (94). Significant positive effects in autonomic regulation (assessed by HRV) between treatment with RM with aroma oil over a treatment with RM with neutral oil ($p < 0.01$ in most HRV parameters) and over a treatment with sham massage ($p < 0.01$ in most HRV parameters) were evident in healthy adults (69). RM also had significant positive effects on autonomic regulation (HRV) ($p < 0.001$ in most HRV parameters) and surface temperature (IRI) ($p < 0.001$) in patients with various indications (66).

TABLE 10 The number of studies per application type and substance.

External application/Number of studies *Of which with Substance/Number of studies*
Massages: 34
Rhythmical massage: 23
Oil with lavender and peat: 2
Unspecified/various substances: 21
Rhythmical embrocation: 6
Oil with lavender and peat: 2
Unspecified/various substances: 4
Pressel stream massage: 2
Unspecified/various substances: 2
Massage with other applications: 3
Unspecified/various substances: 3
Compresses: 11
Ginger powder: 5
Yarrow infusion: 5
Mustard flour: 1
Lemon aroma oil: 1
Ginger/mustard/wet/dry: 1
Unspecified/various substances: 1

Physical effects of compresses

Effects on physical parameters in the studies on compress interventions were extracted as reactions of the body such as an improvement of general condition and vitalization (61, 62, 74, 98), warming sensations in the whole body (61, 71, 74, 76, 98) that were described as a different quality of warmth in ginger and mustard (71), deepened breathing (71, 98), an increase in appetite (86, 98), and increases in body temperature and blood circulation (61, 76, 89, 98, 100). Compresses led to symptom relief in the form of general symptom relief and rating of treatments as effective (68), improvements in fatigue symptoms (62, 72), improvements in mobility (62, 74, 76, 89), reduction in local pain and muscle relaxation (62, 74, 76, 89, 98),

TABLE 11 Effect themes and subthemes.

	Studies on massages				Studies on compresses				
	Rhythmical massage (23 studies)	Rhythmical embrocation (6 studies)	Pressel stream massage	Massage/compress/footbath (3 studies)	Ginger (5 studies)	Yarrow (2 studies)	Mustard (1 study)	Lemon (1 study)	Mixed/different compresses (2 studies)
1 Physiological effects									
1.1 Reactions of the body									
1.1.1 Decrease in blood pressure	×								
1.1.2 Deepened breathing	×	×			×				×
1.1.3 Improvement of skin texture			×						
1.1.4 Increase of appetite					×	×			
1.1.5 Increase of body temperature/blood circulation	×				×		×		
1.1.6 Increase of libido	×								
1.1.7 Stimulation of HRV	×								
1.1.8 Strengthening/vitalizing/overall improvement	×			×	×	×			
1.1.9 Warming sensation	×	×	×	×	×	×			×
1.1.9.1 Different quality of warmth in ginger/mustard									×
1.2 Symptom relief									
1.2.1 General symptom relief/rating as effective	×								×
1.2.2 Expectoration					×				
1.2.3 Discontinuation of medication (pain, sedatives etc.)	×			×	×				
1.2.4 Improvement of ascites					×				
1.2.5 Improvement of asthma symptoms	×								
1.2.6 Improvement of digestion/bloating		×	×	×					
1.2.7 Improvement of fatigue					×	×			
1.2.8 Improvement of fever								×	
1.2.9 Improvement of cognitive functions				×					
1.2.10 Improvement of mobility	×		×		×		×		
1.2.11 Improvement of sensitivity in the legs		×							
1.2.12 Improvement of vertigo	×								
1.2.13 Reduction of headaches		×	×					×	
1.2.14 Reduction of pain and muscle relaxation (local)	×	×	×	×	×		×		
1.2.15 Regulation of menstruation			×						

(Continued)

TABLE 11 (Continued)

	Studies on massages				Studies on compresses				
	Rhythmical massage (23 studies)	Rhythmical embrocation (6 studies)	Pressel stream massage	Massage/compress/footbath (3 studies)	Ginger (5 studies)	Yarrow (2 studies)	Mustard (1 study)	Lemon (1 study)	Mixed/different compresses (2 studies)
2 Psychological effects									
2.1 Activating effects									
2.1.1 Feeling of release, liberating	×	×	×		×				
2.1.2 Improvement of confidence		×							
2.1.3 Improvement of mood/feeling light	×	×	×	×		×			×
2.1.4 Improvement of quality of life/health satisfaction	×			×	×				
2.1.5 Psychological activation						×			
2.2 Relaxing effects									
2.2.1 Feeling of relaxation	×	×		×	×	×			×
2.2.1.1 Relaxation only in the after rest		×							
2.2.2 Improvement of sleep	×	×	×	×	×				
2.2.3 Pleasant and restful feeling	×	×				×			×
2.3 Improvement of competencies									
2.3.1 Feeling in balance/stable/Sense of coherence	×	×	×	×	×				×
2.3.2 Improved regulation of anxiety	×	×							
2.3.3 Improvement in symptom management (pain etc.)	×				×	×			
2.3.4 Improvement of competencies in daily life	×	×	×		×				
2.3.5 Improvement of self-awareness	×	×		×	×				
2.3.6 Improvement of social skills	×				×				
3 Development of effects over time									
3.1 Being uncaged à re-identifying à being empowered		×							
3.2 Long-term effect	×	×							×
3.3 Improvement of effect after multiple applications	×	×	×	×	×				
3.4 Decrease in effect after multiple applications					×				
4 Adverse effects									
4.1 Physiological adverse effects									
4.1.1 No symptom relief/no effect		×			×				×
4.1.2 Symptom aggravation	×								

(Continued)

TABLE 11 (Continued)

	Studies on massages				Studies on compresses				
	Rhythmical massage (23 studies)	Rhythmical embrocation (6 studies)	Pressel stream massage	Massage/compress/footbath (3 studies)	Ginger (5 studies)	Yarrow (2 studies)	Mustard (1 study)	Lemon (1 study)	Mixed/different compresses (2 studies)
4.1.3 Exhaustion/tiredness			×		×				
4.1.4 Flattening of breath		×							
4.1.5 Irritation of the skin					×				
4.1.6 Occurrence of cardiac palpitations	×								
4.1.7 Occurrence of coughing					×				
4.1.8 Occurrence of hypotension	×								
4.1.9 Occurrence of pain: Abdomen			×						
4.1.10 Occurrence of pain: Headache, dental pain			×						
4.1.12 Occurrence of vertigo	×								
4.1.13 Sensation of cold and wetness					×				
4.2 Psychological adverse effects									
4.2.1 Emotional agitation/feeling depressed/restless	×		×		×				
4.2.2 Overwhelmed by touch	×								

a reduction in headaches (100), a stimulation of expectoration (98), and improvements of fever (100) and ascites (98).

Significant effects of compresses on physical outcomes

Significant effects of compress interventions on physical outcomes were significantly reduced fever (measured temperature) (after treatment: $p = 0.027$, after 60 min: $p = 0.006$) and headaches ($p = 0.01$) after lemon compresses (100). After ginger compresses, significant effects on healthy adults were deepened breathing ($p = 0.03$), slowed breathing ($p < 0.001$), and the sensation of warmer hands ($p = 0.03$) and warmer feet ($p < 0.001$) (71).

Psychological effects of massages

The effects of massages on psychological outcomes were presented as activating effects such as an improved mood and feeling light (64, 67, 70, 80–82, 87, 94–97, 99, 102), a feeling of release and liberation (60, 81, 87, 95, 96), improvements in QoL and health satisfaction (73, 82, 94, 99, 101), and improved confidence (95). The relaxing effects of massages were improvements in sleep (75, 78, 80–82, 84, 88, 90, 99), a pleasant restful feeling (59, 65, 78, 84, 85, 90, 99), and a feeling of relaxation (59, 70, 75, 80, 84, 87, 88, 90, 95, 96, 99). Some participants described the effects of improved competencies through massages, like strengthening through an increased perception of balance and meaning (60, 75, 80, 81, 83, 85, 95, 96, 99), an improved self-awareness (59, 70, 75, 79, 84, 87, 88, 90, 95, 96, 99, 103), an improvement of competency in daily life (59, 60, 79, 81, 82, 87, 88, 93, 95, 102, 103), an improved ability to regulate anxiety (82, 91, 95, 102), improved capacities for symptom management (79, 91, 92, 97), and improved social skills (78, 82, 90).

Significant effects of massages on psychological outcomes

Rhythmical massage had significant positive effects on QoL in patients with chronic diseases (physical and mental:

$p < 0.001$) (65), dysmenorrhea (no p-value reported, $d = 0.60$) (73) and in patients with various indications (physical short-term: $p = 0.005$/physical long-term: $p = 0.005$, mental short-term: $p < 0.001$/mental long-term: $p < 0.001$) (67). RM significantly improved mood ($p < 0.001$, $d = 0.81$) in patients with chronic pain (64). An intervention using embrocations along with compresses and footbaths led to a significant increase in QoL (Physical: $p = 0.05$, psychological: $p = 0.007$, social: $p = 0.048$, environment: $p = 0.02$), and a significant decrease in depression ($p = 0.002$) in elderly patients (94).

Psychological effects of compresses

The effects of compresses on psychological outcomes were extracted in the form of activating, relaxing effects, and effects of competencies as well: After compresses, patients described improvement in mood and feeling light (71, 86), feelings of release and liberation (98), improvements in QoL and health satisfaction (62), and a feeling of psychological activation (72). Feelings of overall relaxation (71, 72, 74, 98), pleasant and restful feelings (68, 86), and an improvement of sleep (98) were described after compressing as well. Furthermore, strengthening through an increased perception of balance and meaning (71, 76), improvements in symptom management (76, 86), daily life competencies (61, 74), self-awareness (61), and social skills (74) also showed after compress interventions.

Significant effects of compresses on psychological outcomes

Daily yarrow liver compresses for 7–14 days led to a significant reduction in fatigue ($p = 0.015$), tension ($p = 0.044$), lack of drive ($p = 0.028$), and an improvement of the scale on reduced motivation in fatigue ($p = 0.035$) compared to TAU in patients with cancer during radiation therapy (72). After ginger compresses, healthy adults were significantly more relaxed ($p < 0.001$) and emotionally balanced ($p = 0.03$) (71). Their mood was significantly improved after dry compresses and compresses using hot water and ginger (all compresses: $p < 0.05$), and calmness was significantly improved after dry, hot water, ginger, and mustard compresses (all compresses: $p < 0.05$) (71).

Development of effects in massage

In the massage studies, development of effects over time was described in manifesting an increase of effects after multiple applications in various studies (63, 82–84, 96, 99) as well as long-term effects (65–67, 85, 88, 103), and a pattern of effect consisting of a feeling of liberation, followed by a feeling of re-identification and a feeling of empowerment (60).

Significant long-time effects of massages

One study on patients with various indications reported significant long-term effects in a pre-post reduction in disease manifestation ($p < 0.001$), symptom scores ($p < 0.001$), therapy goal attainment ($p < 0.001$), and QoL (physical: $p = 0.005$, mental: $p < 0.001$) (67).

Development of effects in compresses

The studies on compresses depicted a development of effects over time as well, shown in an increase of effects after multiple applications (62, 76) as well as a decrease of effect over time in some cases (98) and long-term effects (68). No significant long-term effects of compresses were reported.

Adverse effects of massages

Adverse physical effects in massage studies were symptom aggravation, arterial hypotension, cardiac palpitations, vertigo after treatment (65), exhaustion and tiredness after the treatment (81), flattening of breath (85), pain in the abdomen (81), headaches, and dental pain (65, 81, 103). The adverse psychological effect after massages was emotional agitation and a depressed and restless feeling (59, 81), and being overwhelmed by the interpersonal touch (93).

Adverse effects of compresses

In the compress studies, adverse effects were only reported in a case series on ginger compressions in the form of exhaustion after the treatment, irritation of the skin, cough, an unpleasant sensation of cold and wetness, emotional agitation, and feelings of restlessness (98).

Study quality

Since the study methodologies, the outcome measurements and the samples were heterogeneous and the studies were generally of low quality, the data did not allow for meta-analysis of the results. Study quality according to LoE, QA-Tool, and RoB is presented in **Table 12**.

Level of evidence

The assignment of the individual studies to the heuristic of LoE resulted in a distribution of the studies between the levels according to their methodology (**Figure 3**). Level II was assigned 3 studies on massages (69, 70, 73) and 1 study on compresses (72). Level IV was assigned 5 studies on massages (64–67, 94) and 3 studies on compresses (62, 71, 100). Level VI was assigned 2 studies on massages (59, 60) and 3 studies on compresses (61, 68, 74). Level VII was assigned 23 studies on massages (75, 77–85, 87, 88, 90–93, 95–97, 99, 101–103) and 5 studies on compresses (63, 76, 86, 89, 98). Mixed methods studies were counted as quantitative studies (Level IV). Studies exploring a mixed intervention of massages and other application types were counted as massage studies.

Study quality assessment

Out of the 13 quantitative studies, 2 had strong quality (69, 70), 1 had moderate quality (71), and 10 had weak quality

TABLE 12 Summary of the assessment of study quality and risk of bias in the quantitative studies.

			Quality assessment			Risk of bias assessment												
	Reference	Level of evidence	Selection bias: Representation of population	Study design: Design, randomization	Confounders: Detection and controlling of confounders	Blinding of outcome assessors and participants	Data collection methods: Tools shown to be valid + representative	Withdrawals and dropouts: Reporting of dropouts, completing	Quality: Global rating	Random sequence generation: Selection bias	Allocation concealment: Selection bias	Blinding of participants and personnel: Performance bias	Blinding of objective outcome assessment: Detection bias	Blinding of subjective outcome assessment: Detection bias	Incomplete outcome data: Attrition bias	Selective reporting: Reporting bias	Other bias	Risk of bias: Global rating
Massages	Kanitz et al. (70)	II	strong	strong	strong	mod.q.	strong	strong	strong	low	low	high	high	high	low	low	low	mod.r.
	Seifert et al. (69)	II	mod.q.	strong	strong	mod.q.	strong	mod.q.	strong	low	low	high	high	n.a.	low	low	high	mod.r.
	Vagedes et al. (73)	II	weak	strong	mod.q.	weak	strong	strong	weak	low	low	high	high	high	high	low	low	mod.r.
	Hamre et al. (65)	IV	strong	mod.q.	weak	weak	strong	mod.q.	weak	high	high	high	uncl.	high	low	low	uncl.	high
	Wälchli et al. (67)	IV	mod.q.	mod.q.	weak	weak	strong	mod.q.	weak	high	high	high	uncl.	high	low	low	uncl.	high
	Wälchli et al. (66)	IV	mod.q.	mod.q.	weak	weak	mod.q.	mod.q.	weak	high	high	high	high	n.a.	low	uncl.	high	high
	Ostermann et al. (64)	IV	mod.q.	mod.q.	weak	weak	strong	strong	weak	high	high	high	n.a.	high	low	low	uncl.	high
	Vieira et al. (94)	IV	mod.q.	mod.q.	weak	weak	weak	strong	weak	high	high	high	n.a.	high	low	low	high	high
Compresses	Ghadjar et al. (72)	II	mod.q.	strong	strong	weak	strong	weak	weak	low	uncl.	high	n.a.	high	high	low	high	high
	Stritter et al. (71)	IV	weak	mod.q.	mod.q.	mod.q.	strong	strong	mod.q.	high	high	high	n.a.	high	low	low	high	high
	Klich-Heartt (100)	IV	weak	weak	weak	weak	mod.q.	weak	weak	high	high	high	high	high	low	low	high	high
	Therkleson (62)	IV	weak	mod.q.	weak	weak	strong	strong	weak	high	high	high	n.a.	high	low	high	high	high
	Simoes-Wüst et al. (68)	VI	weak	weak	weak	weak	weak	weak	weak	high	high	high	n.a.	high	low	low	high	high

Strong, strong quality; mod.q., moderate quality; weak, weak quality; low, low risk of bias; mod.r., moderate risk of bias; high, high risk of bias; uncl., unclear risk of bias; n.a., not applicable.

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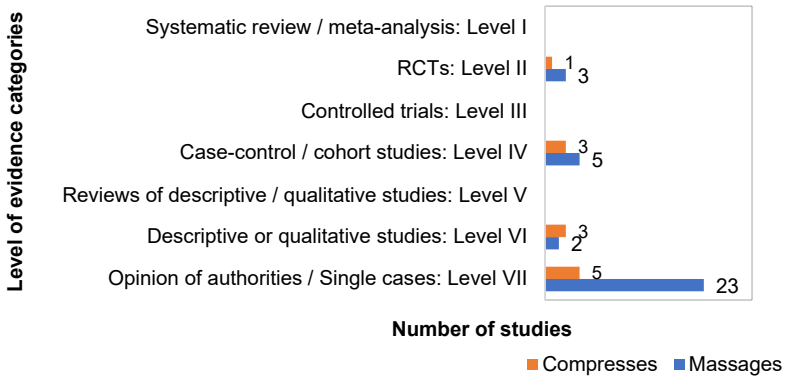

FIGURE 3
Studies on EAAM per level of evidence category reported in absolute terms.

(62, 64–68, 72, 73, 94, 100) (**Table 12**). Two studies showed strong quality in representation of the population (selection bias), while 6 studies had moderate and 5 had weak quality in this domain. The study design was of strong quality in 4 studies (RCTs), moderate in 7 studies, weak in 2 studies, with 3 strong, 2 moderate, and 8 weak in the detection and controlling of confounders. Blinding of outcome assessors and participants was moderate in 3 studies and weak in 10 studies. Data collection methods were strong in 9 studies, moderate in 2 studies, and weak in 2 studies. Reporting of withdrawals and dropouts was strong in 6 studies, moderate in 4 studies, and weak in 3 studies.

Risk of bias assessment

Out of the 13 quantitative studies, 3 had a moderate risk of bias (69, 70, 73) and 10 had a high risk of bias (62, 64–68, 71, 72, 94, 100) (**Table 12**). The risk of selection bias was high in most studies as only 4 studies reported random sequence generation and only 3 studies reported adequate allocation concealment. While no study reported blinding of participants or personnel to the intervention, the study comparing different compresses reported blinding of participants to the used substances (71). No study reported adequate blinding of outcome assessors. Attrition bias was low in most studies as well as reporting bias. Other bias was caused mainly by small sample sizes and was only low in two studies.

Discussion

This mixed methods systematic review of 45 studies on EAAM included 34 studies on massage interventions and 11 studies on compress interventions. In both groups, various substances were applied. The methodologies of the included studies ranged from RCTs to cohort, retrospective, mixed methods and qualitative studies, and case series and reports. While a broad range of possible indications for applications could be identified by the *Thematic Analyses* of all included studies, limited statistically significant evidence for improvements was found in the outcomes. The safety of the different EAAMs needs further detailed evaluation.

External and internal validity

Overall, the results of this review are applicable mainly to European patients interested in integrative medical treatments and might be most applicable to the female gender. Further studies on EAAM applied to different participants are needed to ensure the external validity of the results. The employed methodology and the results of the quality and risk of bias assessments limit the interpretability of the results. More studies of high quality with low risk of bias need to be conducted and compared before conclusions can be drawn about the impact of EAAM.

Touching body, soul, and spirit: Intersections with other theories on health

The results on the effects of EAAM in this review suggest various health promoting effects, and therefore, match the findings on the health promoting capacities of the application of warmth and substances (14, 16–18, 21–24) as well as on touch and massage (9, 30, 31). The importance given to rhythmical stroking in massages matches the findings on the impact of a certain pace and pressure to stimulate especially C-tactile afferents in the skin to reach a positive effect and affective value (29).

While scientific medical and psychological research investigates if and how treatments affect individuals, Anthroposophy and AM already present views on effect mechanisms (104, 105). Suiting interpretations of the effect

mechanisms of EAAM could also be detected in some of the included studies of this review, postulating a stimulation of self-regulation by the integration of the *Four Levels of Formative Forces* and/or through the regulation of the *Threefold Functional Subsystems* of the organism (80, 83–89, 95, 96, 99–101). In addition, the emergent effect themes could be interpreted as the influence of EAAM on the *Formative Forces* of the body (*Material Body* and vital *Etheric Body*), soul, and spirit according to AM (34): Physiological effects could be translated as affecting the body (*Material Body* and vital *Etheric Body*), psychological effects as affecting the soul, and the effects on psychological competencies could be translated as affecting the spirit.

However, as underlined by the findings of this review, the explanations of EAAM effect mechanisms according to AM do not translate directly into evidence according to conventional scientific research standards. To bridge this gap between the findings of this review and conventional scientific research, a digression into other scientific theories on health can provide alternative models to explain the effects of EAAM.

Benefits of interpersonal attention

External applications from anthroposophic medicine use interpersonal attention and touch. While the health-promoting capacities of touch have been described repeatedly (30, 106), two theories from psychological research specifically emphasize the importance of social contact to promote health. The *Social Baseline Theory* states that through social regulation of emotion, interaction with other people helps individuals to conserve somatic and neural resources, inhibit the release of stress hormones, reduce the risk of developing physical and mental illnesses, and promote health and longevity (107). The *Tend and Befriend Model* defines interpersonal tending as a natural reaction to stress and therefore as a baseline condition for health (108). These findings support the assumption that EAAM, as applications involving interpersonal contact and attention, may support health. In addition, findings suggest advantages for the practitioners when giving touch as well (109).

Impact of intentions and expectations

External applications from anthroposophic medicine are performed in a defined recurrent way, similar to rituals, and are often based on beliefs in their specific effect mechanisms according to AM. An approach to explain the efficacy of including a certain meaning in medical treatments is the *Meaning Model,* proposing that positive responses to applications may result from patients feeling listened to and attended to by caregivers, receiving an explanation for their disease that is consistent with their own worldview, receiving care and compassion, and experiencing an increased sense of mastery or control over their health (110). The setting of EAAM may, therefore, promote placebo effects (111) that can be used to ensure maximum benefit for patients (112, 113).

Holistic, positive, and dynamic approach to health

External applications from anthroposophic medicine are presumed to have health-promoting effects, to affect health holistically and dynamically. Holistic and positive support models underscore this, such as approaches of positive psychology and positive health [Seligman (114)] and person-centered medicine (115) as well as the *Health Wellness Model*, which promotes the integration of body, mind, and spirit to promote health (116). The consideration of spiritual factors for health promotion is mentioned in the literature as well, proposing that health care that addresses spiritual needs may contribute to recovery (117). The salutogenic definition of health defines a strong *Sense of Coherence* where one perceives the world as comprehensible, manageable, and meaningful as an indicator of health (38). Dynamic well-being conditioned by biopsychosocial potential (118) and health-defining heterostasis in the body (38, 39) are other concepts similar to the concept of flexible regeneration in organisms such as the EAAM underlying intention to stimulate self-regulation of the organism through treatments in order to enable healing (40, 41).

Strengths and limitations of this review

This is the first review of EAAM. We used the design of a mixed methods systematic review to cover the heterogeneous empirical literature on the different types of EAAM, sample characteristics, methodologies, and outcome parameters (52). The broad scope of the review and the extensive literature search process enables a comprehensive overview of the areas of use and effectiveness of EAAM. Studies in English and German were included, covering most of the available literature on the topic. The quality of the included studies and the applicability of the results were assessed. In order to sort the heterogeneous result data of the included studies, we decided to use the approach of a *Thematic Analysis*. While using this method to summarize results is not common in review papers, it was quite helpful to inductively get an overview of the effect patterns in the included studies.

However, the heterogeneity of the included studies limits their generalizability. Only a small number of quantitative studies could be identified, which limits the expressiveness of the review. Many of the studies were only accessible in the form of gray literature and/or abstracts. As assessed by the LoE classification, the validity of the included studies had to be described as low in many of the studies. Study quality was assessed as low and the risk of bias as high in most studies. The safety of EAAM could only be assessed qualitatively on the basis of a few of the included studies reporting it.

We used a combination of the 3 tools LoE assessment, QA-Tool, and RoB to sort and adequately evaluate the quality and validity of the heterogeneous studies. Quality assessment

of the included studies was conducted by two members of the research group (IM, JE). However, the QA-Tool and the RoB are repetitive in some domains and would have benefited from better tailored tools for the evaluation.

Implications for research and clinical practice

The implementation of complementary EAAM in clinical practice can be an opportunity to consider the patient's needs for caregiving as well as spiritual needs in some patients in a manner of person-centered medicine.

Since the interpretability of the evidence found in this review is limited by the methodological quality of the included studies, we endorse studies of high quality on the different EAAM for different patient groups. These studies should ensure rigorous methodology and reports (119). In order to gain a deeper understanding of the interpretations of the effect mechanisms of EAAM according to Anthroposophy, a phenomenological analysis (120) based on the result and discussion sections of the included studies and/or theoretical manuscripts on EAAM might be of merit.

Users should adhere to the procedure specifications of the different EAAMs, and caution is advised with regard to the mentioned adverse effects. EAAM is not indicated in patients with adverse attitudes toward touch or in patients with sensitive skin or tissue damage. As illness was described in sections by Steiner and Wegman as depending on personal faculties (37), the underlying views of AM might be perceived as discriminating against people with diseases. When applying EAAM, users should, therefore, be cautious about their intentions with the applications. Furthermore, it is strongly advised to use EAAM complementarily to evidence-based treatments to promote well-being as intended (33, 121).

Conclusion

The mixed methods systematic review illustrates the potential benefits of the different EAAM modalities as complementary treatments. The data reveal a broad spectrum of effect themes, suggesting that EAAM is suitable to address physical and psychological health indicators by improving the general condition and inducing symptom relief as well as psychologically activating and relaxing effects. Limitations in study quality, varying application modalities, different outcome assessments, and different sample characteristics complicate a substantiated comparison of the outcomes. We recommend further clinical studies exploring the effects and safety of distinguished EAAM modalities on defined patient groups to determine to what extent EAAM can be considered an effective and safe treatment option.

Data availability statement

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

Author contributions

IM contributed to the conceptualization, methodological planning, data analysis, writing, and revision of the manuscript. SB contributed to the revision and editing. JE contributed to the data analysis. HC and GS contributed to the supervision, revision, and editing. WS contributed to the conceptualization, supervision, revision, and editing. All authors contributed to the article and approved the submitted version.

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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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EDITED BY
Kathryn Toy Knecht,
Loma Linda University, United States

REVIEWED BY
Janet Schloss,
Southern Cross University, Australia
Claudia Löffler,
University Hospital Würzburg, Germany

*CORRESPONDENCE
Michael Jeitler
✉ Michael.jeitler@charite.de

†These authors have contributed equally to this work

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Self-care and lifestyle interventions of complementary and integrative medicine during the COVID-19 pandemic—A cross-sectional study

Michael Jeitler[1,2]*, Avital Erehman[1], Daniela A. Koppold[1,2], Miriam Ortiz[1], Lea Jerzynski[1], Barbara Stöckigt[1], Gabriele Rotter[1], Sarah Blakeslee[3], Benno Brinkhaus[1], Andreas Michalsen[1,2], Georg Seifert[3,4], Holger Cramer[5,6,7,8], Farid I. Kandil[1,3†] and Christian S. Kessler[1,2†]

[1]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Social Medicine, Epidemiology and Health Economics, Berlin, Germany, [2]Department of Internal and Integrative Medicine, Immanuel Krankenhaus Berlin, Berlin, Germany, [3]Department of Paediatric Oncology/Haematology, Otto-Heubner Centre for Paediatric and Adolescent Medicine (OHC), Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [4]Departamento de Pediatria, Faculdade de Medicina, Instituto de Tratamento do Câncer Infatil (ITACI), Universidade de São Paulo, São Paulo, Brazil, [5]Department of Internal and Integrative Medicine, Evang. Kliniken Essen-Mitte, Faculty of Medicine, University of Duisburg-Essen, Essen, Germany, [6]Institute for General Practice and Interprofessional Care, University Hospital Tuebingen, Tübingen, Germany, [7]Bosch Health Campus, Stuttgart, Germany, [8]National Centre for Naturopathic Medicine, Southern Cross University, Lismore, NSW, Australia

Background: Complementary and Integrative Medicine (CIM), including self-care healthy life-style promotion strategies, is widely used in Germany. Aim of this study was to assess the use of self-care and lifestyle interventions as well as mental/emotional state experienced during the COVID-19 pandemic.

Methods: An exploratory cross-sectional online study was conducted with adults in Germany through an online survey. Custom-developed questions in respiratory disease-status (including COVID-19), CIM-based self-care/lifestyle interventions and dietary patterns, and mental/emotional state as well as parameters for wellbeing (World Health Organization Well-Being Index, WHO-5) and self-efficacy (General Self-Efficacy Short Scale, GSE-3) were assessed. Data was analyzed using frequency and parametric measures.

Results: The online survey was performed from January to March 2021 and included 1,138 participants (81.5% female; mean age: 49.2 ± 13.7 years; 54.9% holding a university degree) living in Germany, of which 62 had had a positive SARS-CoV-2 test, 4 an influenza infection and 375 participants other respiratory infections. The following individual health promotion strategies were reported: spending time in nature (90%; n = 1,024), physical activity (69.3%; n = 789), naturopathic remedies (63.1%; n = 718), plant-based diet (56.3%; n = 640), and Mind-Body interventions (54.7%; n = 623).

No differences in strategies between individuals with respiratory diseases or the sample overall were found. Well-being had a mean value of 15.2 ± 5 (WHO-5) and self-efficacy 4.1 ± 0.6 (GSE-3). Nearly 8% reported a low mental/emotional state regarding the COVID-19 pandemic.

Conclusion: Self-care and lifestyle interventions during the COVID-19 pandemic were reported by participants who were predominantly female, middle-aged, and well-educated. Most participants showed an overall balanced mental/emotional state. Further studies should include a representative control group from the general population.

Clinical trial registration: clinicaltrials.gov, identifier NCT04653727.

KEYWORDS

self-care, lifestyle medicine, prevention, COVID-19 pandemic, complementary medicine, integrative medicine, infectious respiratory diseases

1. Introduction

With the ongoing coronavirus disease 2019 (COVID-19) pandemic, humanity still faces a global health threat: by the end of August 2022, more than 600 million infections and 6 million deaths worldwide are expected to be related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The COVID-19 pandemic, as well as previous viral epidemics or world-wide pandemics, will most likely continue to threaten health systems, societies, and economies worldwide (2, 3).

Evidence-based Complementary and Integrative Medicine (CIM) interventions, such as Mind-Body Medicine (MBM), herbal therapies, and nutritional medicine, are increasingly used in Germany, Europe and worldwide and have the potential to provide personally-tailored complementary medical strategies as part of an optimized overall health care management (4–6). CIM offers a variety of preventive and therapeutic options for strengthening physical and mental resilience that may be useful during the COVID-19 pandemic and beyond (7).

The multifold relationships between the immune system and a variety of health-increasing lifestyle factors such as exercise, stress reduction, healthy diet, spending time outdoors, maintaining a positive attitude, and preserving wellbeing have been demonstrated in various studies (8–15). Thus, CIM interventions have the potential to be used to improve immune functions and enhance quality of life and wellbeing in the COVID-19 pandemic, which caused stress, anxiety, fear, and depression in many individuals and societies around the world (16).

Global recommendations on how to stay healthy during the COVID-19 pandemic from authorities and health professionals, refer to a healthy lifestyle in addition to appropriate hygiene and social measures. Sufficient sleep, healthy diet including ample consumption of fresh fruit and vegetables, stress reduction, and staying active are examples of such measures recommended by the World Health Organization, yet are insufficiently studied (17).

Cross-sectional surveys have been conducted at different time points during the pandemic. Physical activity, nature stays and MBM-interventions such as yoga, meditation, and relaxation techniques were the most frequently used health-promoting interventions (18–20). However, the extent of the use of such self-care interventions among CIM users in Germany during the pandemic remains largely unclear.

The aim of this cross-sectional study was to investigate the extent of CIM self-care and lifestyle interventions use and their associations with infectious respiratory diseases including COVID-19 and assess the mental/emotional state during the first and second wave of the COVID-19 pandemic in Germany.

2. Materials and methods

2.1. Study design and setting

This explorative cross-sectional study was conducted between January 6th, 2021 and March 5th, 2021. People were asked to participate *via* an anonymous online survey in German, English, Spanish, or Portuguese language. The study was conducted by the Charité Outpatient Department for Complementary and Integrative Medicine at Immanuel Hospital Berlin and the Institute of Social Medicine, Epidemiology and Health Economics of the Charité – Universitätsmedizin Berlin. The study was approved by the Charité – Universitätsmedizin Berlin Ethics Committee (EA1/187/20) and registered at ClinicalTrials.gov (NCT04653727).

2.2. Participants and recruitment

Participation required internet access. Participants were recruited primarily through social media (e.g., Twitter, Facebook, websites, and online newsletters) and *via* the following non-profit associations "Kneipp-Bund e.V." (Kneipp association), "Natur und Medizin e.V." (Nature and Medicine), "Gesundheit aktiv e.V." (active health), "ProVeg Deutschland e.V." (ProVeg Germany), and printed flyers in the Charité Outpatient Department for Complementary and Integrative Medicine at Immanuel Hospital Berlin. The questionnaire was aimed at adults who considered themselves to have an affinity for CIM and/or lifestyle interventions. Prior to participation, each participant was asked to provide informed consent by checking a box on the digital platform, and the participant's age was verified.

2.3. Outcome measurement and data collection

The questionnaire was implemented using Limesurvey (LimeSurvey GmbH, Hamburg, Germany, version 4) on a Charité server. Depending on the question content, answers enabled either single or multiple responses. The estimated time to complete the questionnaire was around 30 min.

Sociodemographic data including age, gender, household size, school education, employment status, and monthly net income was collected. Participants were asked whether COVID-19, influenza, and other respiratory infections had occurred since March 2020, and if so, asked to give additional detail on symptom severity and hospitalization. Moreover, risk factors for a severe course of COVID-19 were asked. Using a custom questionnaire, a selection of general health-related lifestyle factors and duration of their use since March 2020 were queried, including dietary habits, sports activity and CIM interventions such as time spent in nature, individual use of hydrotherapy/Kneipp applications, anthroposophical medicine, intermittent and/or periodic and therapeutic fasting, botanical/herbal remedies, and Mind-Body interventions. Also, illness-related lifestyle behavior was asked about including alcohol consumption, tobacco consumption, and sedentary behavior. Additional interventions could be entered in an open-ended free text field after choosing "other." Validated questionnaires assessed the current self-efficacy with a 3-item questionnaire General Self-Efficacy Short Scale (GSE-3), the German-language scale is called Allgemeine Selbstwirksamkeit Kurzskala (ASKU), and well-being within the last 2 weeks with the 5-item World Health Organization Well-Being Index (WHO-5) (21, 22). To measure the mental/emotional state since March 2020, eight custom-developed questions with numerical rating scales (NRS; 0–10 points; 0 = minimum to 10 = maximum) were used. These eight items included distress, anxiety, depression, exhaustion caused by COVID-19 pandemic, fear of being infected with SARS-CoV-2, fear of financial/economic consequences, fear of negative societal consequences with referred examples of loneliness, or increase in social inequality, and sleep quality. The values of the eight items related to the mental/emotional state were added to a total sum score ranging from 0 to 80 points. Participants that had a calculated 0–26 points were defined as having a "positive mental/emotional state" whereas those with a calculated 54–80 points were defined as having a "negative mental/emotional state." In subgroup analysis participants with a calculated positive mental and emotional state were compared to those with a negative mental/emotional state to investigate how mental/emotional state is related to specific CIM interventions. Further subgroup analyses compared gender (male and female) and age categories (18–30 years, 31–50 years, 51–65 years, and ≥66 years old).

As an incentive for survey participation, participants had the option in the anonymized survey to provide their email address in order to enter a lottery to win one of 20 books about CIM that were drawn and distributed the end of the study in March 2021.

2.4. Statistical analysis

Descriptive statistical analysis was carried out with both International Business Machines Corporation (IBM) SPSS Statistics (version 26) and Python (version 3.7). Given the explorative nature of the study, no sample size calculation was performed. We initially aimed to include 3,000 participants.

Data were analyzed with descriptive statistics first for the whole group for absolute and relative frequencies (numbers and percent), for observed numbers, and for mean and standard deviation ("M" and "SD"). Subsequent subgroup-analysis was conducted for a number of predefined factors, including gender (female vs. male participants); age group (18–30, 31–50, 51–65, and ≥66 years of age); experienced infection with COVID-19, influenza or any other respiratory infection during March 2020 (with yes-no options for each factor); and lastly, given the calculated positive vs. negative mental/emotional state in our custom-written questionnaire (see above). Due to the exploratory nature of the study, statistical hypothesis tests were not conducted.

3. Results

3.1. Sociodemographic data

This exploratory cross-sectional online-study was launched on January 6th, 2021 and was accessible online for 2 months.

A total of 1,563 people consented and participated in the survey. This survey was conducted as an international survey in four different languages (German, English, Spanish, and Portuguese). A total of 1,287 participants completed the survey. To keep the study population as homogeneous as possible, we decided to report only the $n = 1{,}138$ (96%) data sets of survey-participants who lived in Germany since March 2020 in this publication. Of these, 1,134 participants completed the questionnaire in German language, three in English, and one in Spanish. Apart from these, 57 complete data sets from Brazil, 30 complete data sets from Austria, 22 complete data sets from Switzerland, 7 complete data sets from Spain, and 3 data sets each from Portugal and United Kingdom and 31 data sets from other countries, which are not reported in detail in the following, were obtained. $N = 277$ started the survey without completing it, or even beginning to answer the first question, and were thus excluded from the analysis. Recruitment was discontinued due to a sharp decrease in responses on March 5th, 2021.

All in all, the 1,138 datasets from the German were included in the final descriptive analysis in this paper.

Participants were mainly female (81.5%; $n = 927$), middle-aged (49.2 ± 13.7 years), had a high level of average income and education (Table 1). There are four age groups described in this publication, which were distributed as follows: 11.6%; $n = 132$ were 18–30 years old, 35.4%; $n = 403$ were 31–50 years old, 43.2%; $n = 492$ were 51–65 years old and 9.8%; $n = 111$ were ≥66 years old. More than half of the participants (54.9%; $n = 625$) had a university degree. Most participants worked full-time (more than 35 h/week) (36.9%; $n = 420$), while 26.7% ($n = 304$) worked part-time (15–34 h/week). Retirement was reported by 11.7% ($n = 133$) of participants. Nearly half of the participants were married (44.5%; $n = 529$) and an additional 23.1% ($n = 263$) were in a relationship (Table 1).

3.2. Chronic diseases, alcohol/cigarette use and sick leave

The mean Body mass index (BMI) was 23.9 ± 6.3 kg/m^2, 7% ($n = 83$) were obese (BMI ≥ 30 kg/m^2) and 3% ($n = 36$) were underweight (<18.5 kg/m^2) (Supplementary Table 1). Nine percent of participants ($n = 116$) listed a diagnosis of chronic cardiovascular disease (most frequently high blood pressure with $n = 82$; 7.2% of participants) and 10.3% ($n = 132$) a chronic respiratory disease (most frequently bronchial asthma with $n = 70$; 6.2% participants), see Supplementary Table 1. Consumption of alcohol had a mean of 6.4 ± 7.7 units per week for 33% ($n = 379$) of the participants. Men consumed twice as many units of alcohol (10.9 ± 12.1) as women (5.3 ± 5.8) and those who had negative mental/emotional state consumed more alcohol (average 8.7 ± 6.5 units) than those with positive mental/emotional state (average 6.9 ± 6.1 units; one alcoholic unit meant 0.25 L beer, 0.1 L wine, 0.1 L sparkling wine, or 0.04 L spirits). Cigarette use averaged 7.8 ± 6.4 cigarettes, with men using slightly more (9.1 ± 7.7) than women (7.4 ± 6 cigarettes per week).

Nearly a quarter, 22.8% ($n = 259$), had taken sick leave since March 2020 (8.9 ± 39.5 days), and those who had a negative mental/emotional state (19.9 ± 58.8 days) and who tested positive for SARS-CoV-2 (15.3 ± 39.2 days) having had longer sick leaves.

3.3. Affectedness by COVID-19

Positive testing for SARS-CoV-2 was reported by 5.4% ($n = 62$) (Supplementary Table 2). Only a single participant (0.9%; $n = 1$) had tested positive for SARS-CoV-2 in the age group ≥66 years (of all $n = 111$ in this age group). One percent, $n = 11$, of those who had tested positive the SARS-CoV-2 reported being symptom-free again and 4.5%; $n = 51$ continued to have symptoms of COVID-19. Mainly mild or moderate symptoms were described with a symptom duration of 19.1 ± 23.3 days. The symptom with the highest described impact was "exhaustion" with 6.7 ± 2.7 (on a NRS; 0–10 points; 0 = minimum to 10 = maximum). None of those who described symptoms reported needing hospitalization or in intensive care treatment. Twenty-nine participants (46.8% of those tested positive for SARS-CoV-2) reported persisting Post-COVID symptoms with a moderate symptom severity (3.9 ± 3.9) (NRS 0–10).

Since March 2020, those who reported a COVID-19 diagnosis regularly used various CIM self-care and lifestyle interventions, such as spending time outdoors (91.9%; $n = 57$), exercise (74.2%; $n = 46$), MBM interventions (51.6%; $n = 32$), fasting (46.8%; $n = 29$), anthroposophical medical applications (3.2%; $n = 2$), hydrotherapy or water treatments (16.1%; $n = 10$), nasal rinses (11.3%; $n = 7$), naturopathic remedies (see below) (53.2%; $n = 33$), digital health services (30.6%; $n = 19$), and aromatherapy ($n = 6$; 9.7%). More than half of all participants who had tested corona-positive had used naturopathic remedies as well as dietary supplements, particularly vitamin D (33.9%; $n = 21$), vitamin B complex or vitamin B12 (27.4%; $n = 17$) and magnesium (9.7%; $n = 6$).

Views about restrictions during the pandemic split the sample into approximate thirds: 38.4% of all participants ($n = 437$) felt that the restrictions during the pandemic were just right, while 34.7% ($n = 395$) thought they were excessive and 26.9% ($n = 306$) thought they should be tougher. Vaccinations on the other hand skewed toward resistance to being vaccinated: 32.5% of all participants ($n = 370$) planned to get vaccinated (25%; $n = 285$ might/40.2%; $n = 458$ would not). In terms of adhering general hygiene regulations (distance, mask, etc.) starting March 2020,

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TABLE 1 Sociodemographic data.

				Gender			
		All		Female		Male	
		N	%	*N*	%	*N*	%
Age	(Mean ± SD)	49.16 ± 13.7		49.07 ± 13.33		49.74 ± 15.3	
Gender	Male	207	18.2	0	0	207	100
	Female	927	81.5	927	100	0	0
	Diverse	4	0.4	0	0	0	0
Family status	In relationship	263	23.1	214	23.1	48	23.2
	Married	529	46.5	423	45.6	106	51.2
	Single	198	17.4	155	16.7	41	19.8
	Divorced	93	8.2	86	9.3	6	2.9
	Widowed	24	2.1	22	2.4	2	1
	Not specified	31	2.7	27	2.9	4	1.9
Adults in household	(Mean ± SD)	2.47 ± 7.97[1]		2.32 ± 7.75[1]		3.12 ± 8.92[1]	
Children in household	(Mean ± SD)	0.58 ± 2.33		0.51 ± 1.71		0.94 ± 4.07[1]	
Monthly net income	<1,000 €	176	15.5	154	16.6	21	10.1
	1,001–1,500 €	135	11.9	118	12.7	16	7.7
	1,501–2,000 €	198	17.4	170	18.3	28	13.5
	2,001–3,000 €	206	18.1	153	16.5	53	25.6
	3,001–4,000 €	116	10.2	83	9	33	15.9
	>4,000 €	84	7.4	56	6	27	13
	Not specified	223	19.6	193	20.8	29	14
Monthly net income for entire household	<1,500 € $	86	7.6	72	7.8	12	5.8
	1,501–2,000 €	106	9.3	93	10	13	6.3
	2,001–3,000 €	164	14.4	130	14	34	16.4
	3,001–4,500 €	224	19.7	174	18.8	50	24.2
	4,501–6,000 €	142	12.5	110	11.9	32	15.5
	>6,001 €	122	10.7	97	10.5	24	11.6
	Not specified	294	25.8	251	27.1	42	20.3
Highest educational qualification	University degree	625	54.9	507	54.7	117	56.5
	Completed training in an apprenticeable trade	176	15.5	145	15.6	29	14
	Higher education entrance qualification (A-level)	202	17.8	163	17.6	39	18.8
	Intermediate school leaving certificate or secondary school leaving certificate	93	8.2	79	8.5	14	6.8
	Secondary school diploma	16	1.4	10	1.1	6	2.9
	Elementary School Certificate	2	0.2	2	0.2	0	0
	No school-leaving qualification yet (pupil)	24	2.1	21	2.3	2	1

(Continued)

TABLE 1 (Continued)

		All		Gender			
				Female		Male	
		N	%	*N*	%	*N*	%
Current employment	Full time (min 35 h/week)	420	36.9	318	34.3	101	48.8
	Part-time (15–34 h/week)	304	26.7	264	28.5	40	19.3
	By the hour (under 14 h/week)	72	6.3	65	7	7	3.4
	Training/study	53	4.7	44	4.7	9	4.3
	Maternity/parental leave	21	1.8	20	2.2	1	0.5
	Long-term sick leave (>4 weeks)	16	1.4	14	1.5	1	0.5
	Retired	133	11.7	104	11.2	29	14
	Unemployed with social benefits	26	2.3	22	2.4	4	1.9
	Working with social benefits	9	0.8	8	0.9	1	0.5
	Not specified	84	7.4	68	7.3	14	6.8

Tables report *n* and % (if not specified). [1] $n = 5$ live in "extended" families between 5 and 40 children.

participants who had been COVID-19 positive were similarly compliant (8.18 ± 2.25) to the sample overall (8.09 ± 2.29) (NRS 0–10).

3.4. Effect of influenza and other infectious respiratory diseases

A total of 33% of participants ($n = 375$) had had other infectious respiratory diseases since March 2020 (**Supplementary Table 3**). These respondents had predominantly experienced moderate symptoms for an average duration of 12.5 ± 19.2 days. Only 0.4% of participants ($n = 4$) had been infected with influenza. All of them reported experiencing severe symptoms (8.0 ± 1.8 on a 0–10 NRS), with none being hospitalized or treated in intensive care. Those who reported being affected by influenza did not show major differences from the overall sample in terms of CIM self-care and lifestyle interventions. A total of 17.3% of all participants ($n = 197$) had received the seasonal flu vaccine.

A slightly larger proportion of the participants suffering from other respiratory diseases (8.5%; $n = 32$) were in a negative mental/emotional state compared to the overall sample (7.6%; $n = 87$). In comparison to the overall sample, participants who reported having been infected with other respiratory diseases, were shown to have slightly higher average levels of psychological stress parameters (NRS 0–10) during the pandemic like feeling stressed about the SARS-CoV-2 pandemic (4.9 ± 2.7 vs. 4.4 ± 2.7), anxious (3.2 ± 2.6 vs. 2.7 ± 2.5), depressed (3.5 ± 2.8 vs. 3 ± 2.8), exhausted (4.3 ± 2.8 vs. 4 ± 2.8), fear of being infected by SARS-CoV-2 (2.8 ± 2.5 vs. 2.4 ± 2.4), and had a lower sleep quality (4.2 ± 2.7 vs. 3.8 ± 2.7).

3.5. Use of self-care/lifestyle and CIM interventions during the COVID-19 pandemic

Starting in March 2020, respondents described various self-care and lifestyle interventions, with a preference for spending time outdoors (90%; $n = 1,024$), practicing physical activity (69.3%; $n = 789$), using naturopathic remedies (63.1%; $n = 718$), and undertaking MBM activities (54.7%; $n = 623$) (see **Supplementary Table 4** and **Figure 1**). Other interventions such as intermittent fasting (32.3%; $n = 368$), digital health services (27.5%; $n = 313$), Kneipp/hydrotherapy (17%; $n = 193$), aromatherapy (13.4%; $n = 153$), and anthroposophical medicine (11.6%; $n = 132$) were also used. Yoga and meditation were the most frequently practiced MBM interventions (38.3%; $n = 436$ and 34.6%; $n = 394$, respectively). For other listed interventions reported see **Supplementary Table 4**.

Complementary and Integrative Medicine methods were used more frequently by women than by men, e.g., naturopathic remedies (+16.2%), MBM interventions (+13.7%), digital health applications (+12.9%), and aromatherapy (+11.6%). Differences were also found in the age categories. Thus, participants from the older age category (≥66 years old) reported using anthroposophical medicine applications (+13.8%) and hydrotherapy or water treatments (+15.4%) more frequently and less frequently used physical activity (−18.8%) and digital health applications (−20.3%) than younger participants (18–30 years old). Moreover, participants in a positive mental/emotional state used MBM techniques (+13%) more often than those in a negative emotional state, which was accompanied by differences in practice duration of MBM. Respondents in a positive mental/emotional state demonstrated a longer practice duration of yoga

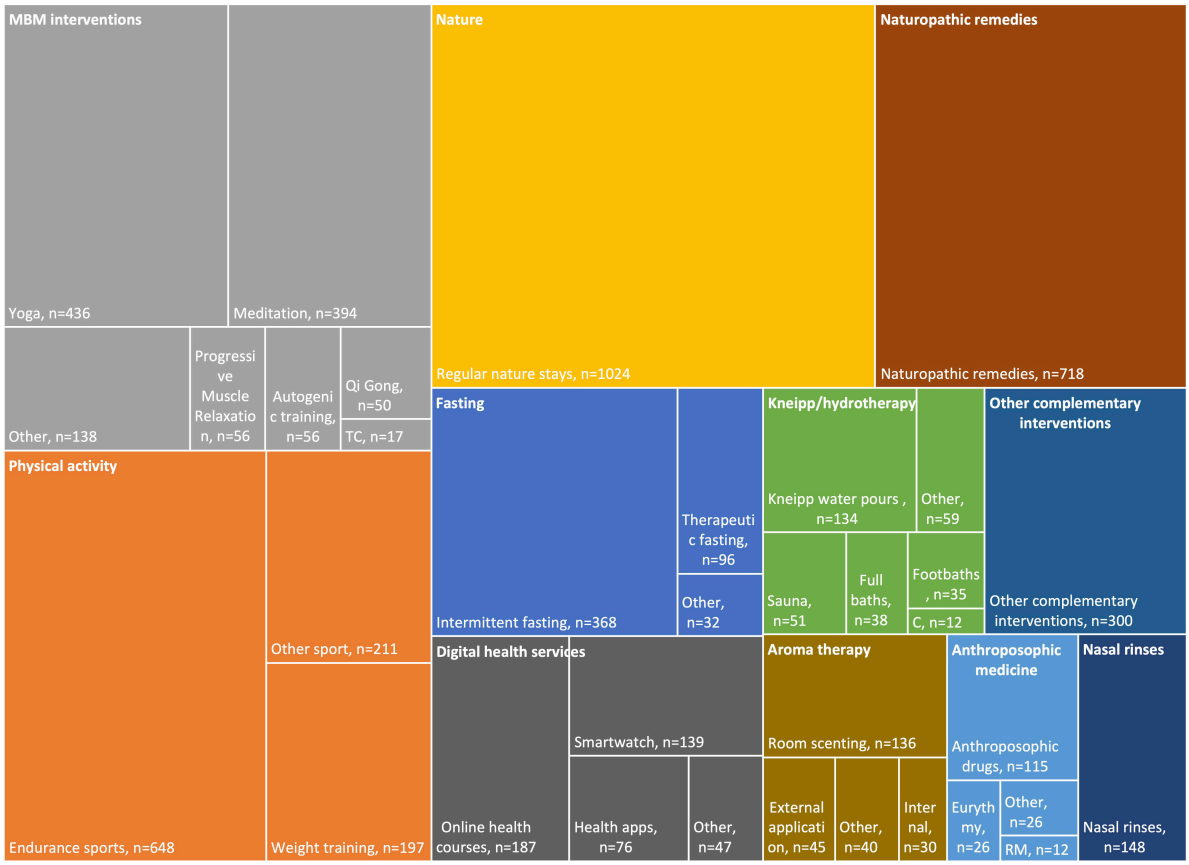

FIGURE 1
Treemap on Complementary and Integrative Medicine (CIM) self-care interventions during the COVID-19 pandemic, sorted by main topic (upper left corner). *C*, Compresses; MBM, Mind-Body Medicine; RM, Rhythmical Massage; TC, Tai Chi.

(144 ± 142.2 vs. 104.8 ± 115.2 min/week), meditation (148.2 ± 171.6 vs. 88.6 ± 62 min/week), Tai Chi (52.8 ± 44.3 vs. 33.3 ± 23.1 min/week), and progressive muscle relaxation (44.3 ± 39.2 vs. 40 ± 35.8 min/week), compared to respondents in a negative emotional state who had a longer practice of Qi Gong (74.8 ± 69.3 vs. 130 ± 180.7 min/week) and autogenic training (50.3 ± 44.9 vs. 61 ± 40.7 min/week).

For participants in a positive emotional state, longer durations were found for spending more time outdoors (420.8 ± 420.8 vs. 355.7 ± 395.1 min/week), training physical strength (117.4 ± 147.3 vs. 86.6 ± 72.7 min/week), sat less (6.74 ± 3.9 vs. 7.1 ± 3 h/day), or practicing other sports (240.3 ± 248.7 vs. 112.7 ± 85 min/week). At the same time, this group used more anthroposophical medicine applications (78.8 ± 167.7 vs. 44.4 ± 43.1 min/week), nasal rinses (4.7 ± 3.3 vs. 3.8 ± 2.3 use/week), underwent more therapeutic fasting days (14.5 ± 17.8 vs. 11.8 ± 9.7 days/year), and conducted hydrotherapy or water treatments for shorter time periods (51.3 ± 74.8 vs. 65.9 ± 57.2 min/week), digital health applications (956.5 ± 4,004 vs. 1,048.8 ± 2,318.7 min/week) and aromatherapy (330.1 ± 769.2 vs. 655 ± 1,132.4 min/week).

In terms of use of CIM self-help and lifestyle interventions, there were no major differences in COVID-19 participants compared to the overall sample. A slightly larger proportion of the COVID-19 participants reported a negative emotional state (8.1%; $n = 5$) compared to the overall sample (7.6%; $n = 87$).

Regarding naturopathic remedies (including herbal remedies or supplements, anthroposophical or homeopathic drugs) $n = 718$ (63.1%) took at least 1 remedy, $n = 537$ (47.2%) took 3–5 remedies, and $n = 185$ (16.3%) took 6 or more remedies.

3.6. Diet during the COVID-19 pandemic

More than half of participants followed a plant-based diet and stated to be vegetarians or vegans (56.3%; $n = 640$)–the majority of these followed a vegan diet (32.1%; $n = 365$), which excluding all animal products, or a lacto-ovo-vegetarian diet (15.6%; $n = 177$), excluding animal products except eggs and dairy (**Supplementary Table 5**). One-third of the overall sample

followed an omnivorous diet (32.7%; $n = 372$), including both plant and animal food.

Regarding gender differences, male subjects were slightly more likely to follow an omnivorous diet than women (+4.9%). Other diets, such as those based on Traditional Chinese Medicine or Ayurvedic principles, played a subordinate role (**Supplementary Table 5**).

Concerning the differences in the different age groups, a higher proportion of participants younger than 30 years was found to follow a vegan diet (18–30 years: 55.3%; $n = 73$) compared to older ones (31–50 years: 33%, $n = 133$; 51–65 years: 28.5%, $n = 140$; ≥66 years: 17.1%, $n = 19$). Accordingly, the older ones were more likely to follow an omnivorous diet (31–50 years: 29%, $n = 117$; 51–65 years: 37.2%, $n = 183$; ≥66 years: 45%, $n = 50$) compared to younger ones (18–30 years: 16.7%; $n = 22$).

Interestingly, participants in a positive emotional state tended to follow a vegan diet (+11.1%) more often (32.9%; $n = 190$) than participants in a negative emotional state (21.8%; $n = 19$). Moreover, participants in a positive emotional state reported a higher proportion of organically grown products in their diet (69.7 ± 23.8%) compared to participants in a negative emotional state (57.8 ± 26.7%) and an overall healthier diet with an emphasis on plant-based and less processed foods.

No major differences in dietary patterns were found between subjects with the respiratory diseases mentioned above and the overall sample.

3.7. Self-efficacy (General Self-Efficacy Short Scale, GSE-3)

The overall sample achieved a mean scale value of 4.1 ± 0.6 in the assessment of general self-efficacy, with the maximum achievable mean scale value being five (**Supplementary Table 6**). There were no major differences regarding gender and different age groups. In addition, participants in a negative emotional state showed lower levels of general self-efficacy (3.8 ± 0.8) than participants in a positive emotional state (4.3 ± 0.5). No major differences in general self-efficacy scores were found between subjects with the respiratory diseases mentioned above and the overall sample.

3.8. Well-being (World Health Organization Well-Being Index, WHO-5)

The overall sample achieved a mean scale value of 15.2 ± 5 in the assessment of wellbeing, with the maximum achievable mean scale value being 25 (**Supplementary Table 6**). The following differences were found in the level of wellbeing: males showed higher levels of wellbeing (16.3 ± 4.5) than females (15 ± 5.1). Subjects younger than 30 achieved a lower wellbeing index (18–30 years: 14.1 ± 4.5) than older respondents (31–50 years: 14.7 ± 5; 51–65 years: 15.6 ± 5; ≥66 years: 16.8 ± 5.1). Furthermore, subjects in a positive mental/emotional state showed a higher wellbeing index (17.4 ± 4) compared to subjects in a negative emotional state (9.5 ± 5).

Participants who reported COVID-19, influenza, and other respiratory diseases achieved a lower wellbeing index (COVID-19: 14.6 ± 4.7; influenza: 12.3 ± 6.3; other respiratory diseases: 14 ± 5.2) compared to the overall sample.

3.9. Mental/emotional state

Only low scores were reported on average for mental/emotional state during the COVID-19 pandemic (**Supplementary Table 6**). Of the eight questions (NRS 0–10) regarding mental/emotional state the item "negative societal consequences (e.g., loneliness, increase in social inequality, political decisions) from the SARS-CoV-2 pandemic" was rated the worst (5.1 ± 3.1) and the item "anxiety since the SARS-CoV-2 pandemic began in Europe (approximately March 2020)" was rated the lowest (2.7 ± 2.5), for the other questions see **Supplementary Table 6**.

4. Discussion

Respondents of this cross-sectional online study regarding self-care and lifestyle interventions during COVID-19 pandemic were predominantly female, middle-aged, and had higher levels of education. Of the participants who had tested positive for SARS-CoV-2 or had had symptoms of COVID-19, none required hospitalization. Use of self-care CIM interventions was high in this population during the pandemic. Respondents used a wide range of CIM self-care methods in addition to the commonly recommended healthy lifestyle interventions. Spending time outdoors, physical activity, naturopathic remedies, healthy dietary patterns, and MBM interventions were favored as individual health promotion strategies. No differences in the use of CIM interventions, dietary patterns, or lifestyle interventions were observed between participants who reported respiratory diseases, including COVID-19, and the overall sample. Only 87 participants had a low mental/emotional state regarding the COVID-19 pandemic.

The sociodemographic characteristics of the study population (predominantly female, higher education, and middle age) are consistent with other studies that examined the characteristics of CIM interventions in the general population (23–25). Our study population appears to be healthier and more health-conscious than the general population in Germany that have higher rates of smoking (20%) and greater rate of obesity

(16%) (26, 27). Moreover, our study population had a lower rate of chronic cardiovascular diseases (9%) and chronic respiratory diseases (10%).

Preliminary evidence showed that a healthy diet could reduce the burden of infectious diseases (28–30). In a recent survey among 592.571 UK and US participants, a diet characterized by healthy plant foods was associated with a lower risk (hazard ratio [HR] 0.91; 95% confidence interval [CI] 0.88–0.94) and severe COVID-19 (HR 0.59; 95% CI 0.47–0.74) (29). For immune system functioning and cytokine release, phytochemicals—e.g., from plant-based food—rich of trace elements (zinc, copper, selenium, and iron), vitamins (A, B6, B12, C, D, and E, and folate), docosahexaenoic/eicosapentaenoic acid play key roles in immune system function (30, 31). In our study, participants in a positive mental/emotional state tended to follow a plant-based diet more often. Moreover, they reported a higher proportion of plant-based and organically grown products than participants in a negative mental/emotional state. However, no differences in dietary behavior were observed between participants who reported respiratory diseases, including COVID-19, and the overall sample.

At the time the study was conducted, vaccines against SARS-CoV-2 were rarely available. Individuals regularly using CIM often have rather critical opinions regarding vaccines in general (32, 33). This was also reflected in our study population with 40% of all participants not planning to get COVID-19 vaccinated. However, in spring 2021, first vaccines were launched and few long-term data regarding potential adverse effects of vaccines were available. Presumably, these attitudes might have changed. However, in a recent (December 2021), representative survey commissioned by the German Association of Pharmaceutical Manufacturers (Bundesverband der Arzneimittel-Hersteller, BAH) showed no correlation between vaccination rate and homeopathy use (34). The study sample showed a high level of adherence to COVID-19 regulations on average comparable to the general German population: In September 2020, 88% of the German general population reported wearing a face mask, 89%, adhered hygiene regulations, and 67% reduced social contact (35).

Overall, half of our study participants were found to be in a positive mental/emotional state and only few (8%) participants were in a negative mental/emotional state. Participants with a positive mental/emotional state used CIM interventions on average more and longer than participants with a negative mental/emotional state. In a recent study the use of self-care strategies to prevent COVID-19 and the consultation with health care providers were positively associated with concern about being infected with COVID-19 (18). However, these aspects were not covered in our survey.

The COVID-19 pandemic is associated with higher levels of psychological distress and mental health problems, and particularly the presence of chronic diseases was associated with anxiety and stress (36–40). Compared with the overall study sample, participants infected with other respiratory diseases were on average in a lower mental/emotional state and reported higher levels of psychological stress parameters related to the SARS-CoV-2 pandemic.

The study population showed similar levels of general self-efficacy as a sample representative of the resident population in Germany over the age of 18 (4 ± 0.7) (41). Participants in a negative mental/emotional state showed lower levels of general self-efficacy than participants in a positive mental/emotional state. There is a relationship between low self-efficacy and low mental/emotional state and depression (42). Further research is needed, particularly on how CIM interventions may positively influence self-efficacy.

The level of the WHO-5 is slightly below the level of wellbeing in a sample representative of the resident population in Germany aged 41–60 years (17.5 ± 4.9) (43). Younger participants had lower wellbeing than older participants. Other studies also found an age gradient in which younger participants had worse mental wellbeing than older participants (44). The values for the age groups are below the level of wellbeing in a sample representative of the resident population in Germany at the age of $\leq$40 years (18.4 ± 4.8) and similar to those of the $\geq$61-year-olds (16.7 ± 5.1) (43). One may speculate that the consequences of the pandemic restricted the public life of the younger population and thus reduced general wellbeing (45).

In other studies, lower stress was associated with mindfulness (39, 40), which was not directly surveyed in our survey. However, our study population practiced yoga and meditation–presumably also the other queried MBM techniques–at a higher rate than in the general population on a whole (46, 47). This may have effects for mental/emotional state that should be explored further. Moreover, regular times spent outdoors by 90% of our participants could have important effects on the general positive mental/emotional state found here (48). In addition, it is interesting to note that participants reporting COVID-19, influenza, and other respiratory diseases achieved only a slightly lower wellbeing index than the overall sample.

Several studies investigated lifestyle changes during the COVID-19 pandemic, e.g., exercise, nutrition, and sleep patterns (19). In an online survey among the general population living in Spain during the COVID-19 home-isolation, a substantial proportion of participants reported meaningful lifestyle changes during the COVID-19 pandemic (19). Most participants reported substantial changes on time spent outdoor (94%) and physical activity (70%). Moreover, about one third of participants reported significant changes on stress management, social support, and restorative sleep (19). In another survey with a total of 338 adults, 68.8% indicated that they participated in mind-body activities during the early months of the COVID-19 pandemic (20). Physical activity was the most frequently (61.5%, $n = 227$) used practice, followed by meditation

(n = 221), breathing techniques (n = 229), and relaxation techniques (n = 213). In this study, commonly cited reasons for using mindfulness practices were to promote health, reduce stress, and relax.

The strengths of our study lies in its relatively large sample-size, including respondents from all over Germany, so that more general assumptions can be made about tendencies in the German population using CIM strategies for health promotion. Also, we included validated instruments and different non-profit organizations in the spread of our survey, so that different types of CIM users could be reached.

Several limitations of our study need mention. First, a cross-sectional survey is unable to confirm a direct causal relationship between healthy self-care/lifestyle CIM interventions and COVID-19 risk nor can specific mechanisms be identified. Second, our study population is not a representative or random sample of the general German population; our study population is more a profile of the typical CIM user (majority female, well-educated, practicing a healthy lifestyle). Third, our results may have a bias because of the long data collection period, which, included both the first and second wave of the COVID-19 pandemic in Germany. Also, we did not assess lifestyle changes, and depended on reliable values and data entry. The prevalence of COVID-19 was variable during the long recruitment period and could have affected internal validity. First evidence suggests that lifestyle/dietary changes may be altered in both negative and positive ways during lockdowns (49, 50). Fourth, the self-reported nature of the survey is prone to measurement error and bias. Fifth, a survey of CIM use prior to the pandemic would have been of interest for comparison of CIM use during the pandemic. Finally, data on further comorbidities (e.g., diabetes) were not collected in this study, which may limit the results. Linkage with general practice data on comorbidities would strengthen future research (51, 52).

5. Conclusion

Complementary and Integrative Medicine self-care strategies and practices, including general lifestyle interventions, as spending time outdoors, healthy eating, physical activity, naturopathic remedies, and MBM exercises were practiced most frequently during the COVID-19 pandemic by this study responders. Study participants with a positive mental/emotional state used CIM interventions including lifestyle interventions more frequently and for a longer time on average than participants with a negative mental/emotional state. Further research, preferably studies including a control group using a representative sample should further clarify the impacts of the use of CIM self-care strategies on health and on the mental/emotional state. Also, follow-up studies are needed to determine whether the use of lifestyle interventions change over the course of the pandemic and how different lifestyle factors may influence susceptibility to and progression of COVID-19 as well as manifestation of Long- and Post-COVID symptomatology.

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 human participants were reviewed and approved by Ethics Committee Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MJ, GS, HC, and CK: methodology, project administration, and conceptualization. MJ and AE: data curation and writing—original draft. FK: formal analysis. MJ: visualization, investigation, and software. MJ, BB, AM, GS, HC, and CK: supervision. DK, MO, LJ, BS, GR, SB, BB, AM, GS, HC, FK, and CK: writing—review and editing. All authors contributed to the article and approved the submitted version.

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/fmed.2022.1033181/full#supplementary-material

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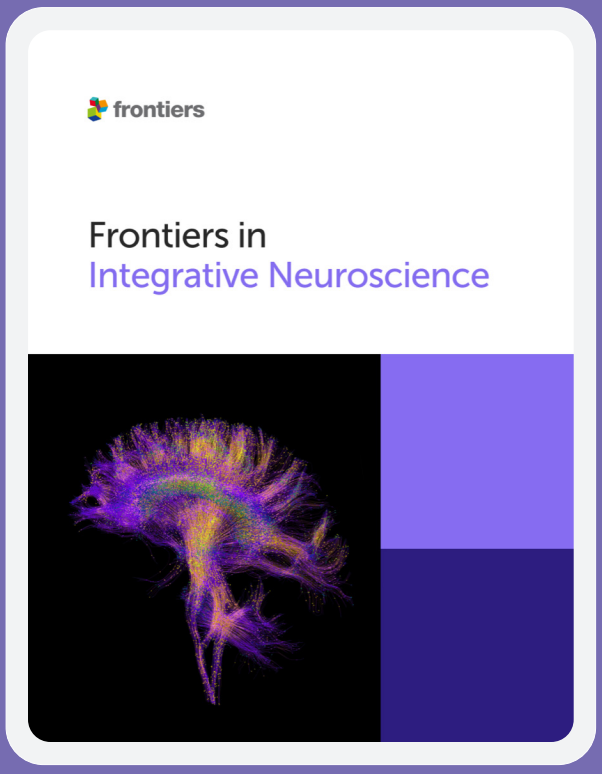

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