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Insights into the effectiveness of exercise/lifestyle recommendations in primary care

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Insights into the effectiveness of exercise/lifestyle recommendations in primary care

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Editorial: Insights into the effectiveness of exercise/lifestyle recommendations in primary care

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Editorial on the Research Topic
Insights into the effectiveness of exercise/lifestyle recommendations in primary care

Exercise and lifestyle modifications have established themselves as the pillars of primary care, proving to be potent weapons in the war against non-communicable diseases. With the World Health Organization (WHO) naming physical inactivity as a leading risk factor for global mortality (1), it is clear and critical that we need to move to efficacious, sustainable, and feasible incorporation of exercise prescriptions into primary care practice (2).

There is extensive research highlighting the wide-ranging benefits of physical activity, spanning from mitigating the risks of cardiovascular diseases, diabetes, and stroke, as well as mental health conditions (3) including Alzheimer's disease (4). Furthermore, it has been shown to enhance the quality of life during cancer treatments (5). Despite this wealth of evidence supporting the significant health benefits associated with exercise, it remains concerning that approximately 27.5 % of adults globally (6) and 81% of adolescents (7) do not meet the recommendations for aerobic exercise, as outlined in the 2010 Global Recommendations on Physical Activity for Health report (8). This issue could possibly be attributed to the absence of consensus and consistent scientific interpretations concerning the factors and mechanisms that give rise to variations in individual responses to exercise training (9), specifically when we consider the variations in clinical conditions, symptoms, and diseases (9–11) and aging (12). This lack of clarity extends to the factors moderating exercise response (9), all of which are pivotal in striving to optimize the clinical impact of exercise prescription (11). Acquiring a deeper understanding of these factors is vital as it would facilitate the clinical adoption of precise and individualized exercise prescriptions (13).

Considering this, primary care professionals across the world are progressively incorporating exercise-based lifestyle modifications, (14) particularly physical activity, into their daily routines (15). The trend involves prescribing gym memberships, using technology and apps, and initiatives centered around promoting exercise's positive influence on population health (16). Nevertheless, the successful implementation, adoption, and completion of tailored exercise prescription plans face several impediments (9, 14). Thus, the primary focus of the investigation should center on evaluating the effectiveness of exercise and lifestyle prescriptions in enhancing patient outcomes within the realm of primary care (2, 10). While synthesis methodology reviews (4, 5, 15) have pointed to a positive impact on patient health outcomes, there is a distinct need for more comprehensive and intricate

studies to elucidate the specifics of this impact (16). Further research efforts should be directed toward pinpointing the elements that characterize successful interventions (10) and discerning which factors contribute most significantly to fostering positive outcomes (5, 16).

Addressing the evaluation of physical activity within the context of primary care practice presents a noteworthy challenge (2). The implementation of standardized, culturally sensitive, and objective tools for assessing levels of physical activity is essential (1, 17). Such tools ensure a precise representation of patients' lifestyle habits, thus paving the way for the development of more personalized and efficacious exercise prescriptions (17). The complexities within this realm of scientific exploration are further heightened when considering the management of neurological diseases through exercise prescriptions (4, 10, 14). Existing research demonstrates promising outcomes, particularly in conditions such as Alzheimer's (4), Parkinson's disease, and multiple sclerosis (18). However, there is a clear need for an in-depth exploration of various prescription modalities to both maximize benefits and mitigate potential risks associated with managing neurological diseases through exercise interventions (14).

In addition, adherence rates continue to fall below satisfactory levels, underscoring the imperative need for the development of strategies aimed at bolstering acceptance and participation (15). Central to this endeavor is the need to effectively understand the hurdles faced by patients, especially from underrepresented backgrounds (19), in adhering to exercise plans, coupled with the creation of systems that cultivate motivation, sustained engagement, and perseverance (20). Establishing effective communication between patients and physicians stands as a pivotal factor in the implementation of an exercise plan (17). The refinement of this interaction requires concentrated efforts, encompassing clear, consistent messaging and an approach that places the patient at the center, as this approach has demonstrated the most notable success (2). Moreover, it is crucial to acknowledge the presence of confounding factors that can influence patients' adherence to exercise plans (9). Crafting inclusive and adaptable strategies is imperative to accommodate these variables effectively (19).

Furthermore, illustrating instances of successful integration of exercise recommendations within real-world settings can serve as practical models for future endeavors (16). Collaborations between clinical and community settings, involving allied health professionals such as exercise physiologists, yield valuable insights and facilitate the multidisciplinary approach necessary for the advancement of patient outcomes (17, 21). While the integration of exercise and lifestyle recommendations into primary care presents its share of challenges (13, 15), it possesses the potential to revolutionize the landscape of primary health care (11). The journey to optimize this facet of healthcare delivery is already underway (2, 8, 10), and with sustained research efforts, collaborative initiatives, and unwavering dedication, there exists a profound opportunity to enact a substantial positive impact on global health (1). The advantages of exercise and lifestyle recommendations within primary care are extensive, spanning a range of diseases and conditions (2, 16, 17). This editorial highlights 11 recent research papers that contribute to the expanding landscape of this crucial subject (Zhang et al.; Hu et al.; Liu Y. et al.; Cheng et al.; Mainous et al.; Lin et al.; Wattanapisit et al.; Liu Z. et al.; Feng et al.; Felemovicius et al.; Heyn et al.).

Zhang et al. in their paper "*Exercise for Neuropathic Pain: A Systematic Review and Expert Consensus*" emphasize that a proper exercise program can serve as an effective alternative treatment or complementary therapy for most patients with neuropathic pain (NP). This consensus provides actionable recommendations for clinicians and policymakers alike in formulating exercise prescriptions to treat NP.

A population-based study by Hu et al. evaluated all-cause mortality and cardiovascular mortality in the Guangzhou Heart Study (GZHS), an ongoing prospective population-based cohort study in South China. Specifically, they investigated the effect of the Healthy Lifestyle Index and lifestyle patterns on the risk of mortality in a large Chinese population. Their study results suggest that accumulative dimensions of a healthy lifestyle can lower the risk of death, and adherence to the healthy lifestyle pattern was associated with non-smoking and low-level alcohol consumption which reduces the risk of all-cause mortality. These findings highlight the need to consider multi-dimensional lifestyle approaches when developing health promotion strategies.

The clinical trial "*Efficacy of electro-acupuncture in postpartum women with diastasis recti abdominis: A randomized controlled clinical trial*" by Liu Y. et al. evaluated the long-term efficacy and safety of electro-acupuncture (EA) in treating diastasis rectus abdominis (DRA) during postpartum. The study results showed that AE treatment improved multiple health parameters and symptoms related to Diastasis Recti Abdominis (DRA), displaying lasting effects up to 26 weeks postpartum.

Furthermore, Cheng et al. investigated the effectiveness and response of a multidisciplinary Workplace health promotion (WHP). They used a retrospective cohort sample of healthcare workers participating in a multidisciplinary WHP program in five healthcare facilities. The 20-week intervention included exercise classes, nutrition consultation, and behavioral education followed by anthropometrics, body composition, and physical fitness (PF) measures. Their study results demonstrated that a multidisciplinary WHP could enhance anthropometric and physical fitness profiles among healthcare workers.

Mainous et al. evaluated the relationship between depression-high depressive symptomatology and adherence to lifestyle interventions among patients with prediabetes. They analyzed the 2017-20 20 National Health and Nutrition Examination Survey (NHANES), a nationally representative population of U.S. adults. Their findings showed that depression-high depressive symptomatology decreases the likelihood of adherence to exercise-based lifestyle recommendations among patients with a confirmed diagnosis of prediabetes underscoring the interplay between mental health and lifestyle changes.

A randomized trial by Lin et al. conducted a randomized controlled trial with 66 full-term infants with eczema randomly assigned to an eczema control (EC) group and an eczema with MPIM (EM) group as compared to a healthy control (HC) group. The mothers in the EC group received the instruction of routine care, while the mothers in the EM group applied massage on the infants plus receiving the same instruction of the routine care. HC

group received no specific intervention. Compared with the EC group, the EM group showed significantly lower scores on eczema outcomes supporting the reduction of infantile eczema, along with relieving maternal anxiety and depression.

An intriguing opinion paper by Wattanapisit et al. highlights the importance of training, integrating, and applying knowledge and skills pertaining to PA promotion in clinical settings with the goal of covering several aspects of sport and exercise science. They remind us that PCPs are usually not specialists in these subject areas, and it is essential to supplement and provide knowledge for proper clinical practices. They include the collective perspective of experts in the field.

Liu Z. et al. conducted a systematic review and meta-analysis to evaluate the effects of a traditional Chinese Qigong therapy called Baduanjin which is characterized by symmetrical body posture and actions, breathing control, meditative state, and concentration. They reviewed randomized controlled trials evaluating Baduanjin therapy's effects on neck pain and functional movement in older individuals. Although the results of the synthesis methods support Baduanjin therapy as a safe and positive treatment for neck pain in older individuals, they called for caution as more studies are needed to validate and support its benefit.

Feng et al. through a population-based study in Taiwan, investigated whether physical activity (PA) is associated with a reduced risk of hemorrhagic stroke (HS). Their study supports the beneficial effect of PA on reducing HS risk. However, high-PA did not appear to have a greater protective effect than low-PA in diabetes and hypertension outcomes. Thus, their conclusions support that even <90 min of PA per week might be beneficial in reducing HS risk. They also note that recommendations based on low PA levels are more likely achievable and sustainable across the general population. Additionally, personalized recommendations, based on pre-existing comorbidities, may help optimize the beneficial effects of PA on HS prevention.

The SOOTHER Trail by Felemovicius et al. evaluated a novel composite topical Lidocaine agent treatment for Pruritus ani, or rectal or anal itch, which is a common perianal disorder that affects approximately five percent of the population of the developed world. The SOOTHER Trial showed efficacy in providing rapid and effective relief of pruritus ani in an ambulatory population.

Finally, a study by a research team (Heyn et al.) from the University of Colorado School of Medicine and Colorado Children's Hospital underscores the importance of lifelong monitoring of children with disabilities to identify and modify disease-induced risk factors through lifestyle interventions. Their study, "*The association between isometric strength and cognitive function in adults with cerebral palsy*," supports using simple tests like hand grip strength to evaluate early signs of frailty and neurocognitive decline in adults with Cerebral Palsy.

In summary, when considering the results of the studies from this Research Topic collectively (Zhang et al.; Hu et al.; Liu Y. et al.; Cheng et al.; Mainous et al.; Lin et al.; Wattanapisit et al.; Liu Z. et al.; Feng et al.; Felemovicius et al.; Heyn et al.), it becomes evident that they underscore the pivotal significance of exercise and lifestyle modifications within primary care. Through their findings, they shed light on the multifaceted roles of these interventions across various health contexts. As we continue to navigate the intricacies involved in implementing efficacious exercise prescriptions and clinical physical activity recommendations in primary care settings, these studies serve as valuable resources that enrich our comprehension and improve our ability to promote healthier lifestyles effectively for diverse patients within the realm of primary care.

Author contributions

PH: Writing—original draft, Writing—review and editing.

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We extend our sincere appreciation to the authors whose valuable contributions have enriched this editorial. Their dedication to advancing the field within primary care has not only expanded our understanding of exercise and lifestyle recommendations but also inspired future work. The insights presented in their research papers have significantly contributed to illuminating the critical importance of exercise and lifestyle modifications in promoting healthier lives within primary care settings.

Conflict of interest

The author declares 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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OPINION
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What Elements of Sport and Exercise Science Should Primary Care Physicians Learn? An Interdisciplinary Discussion

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INTRODUCTION

Primary care physicians (PCPs) contribute to a wide range of healthcare services from health promotion and prevention to treatment and supportive care. A higher PCP-to-population ratio is associated with positive outcomes including longer life expectancy of the population and reduction in cardiovascular, cancer, and respiratory mortality (1). Promoting an active lifestyle is one of the roles of PCPs. Specifically, promoting physical activity (PA) in healthcare settings is an important strategy to reduce the prevalence of insufficient PA and counter excessive sedentary behavior (SB) according to the World Health Organization (WHO) Global Action Plan on Physical Activity 2018–2030 (2). The expected endpoints of promoting PA include a reduction in the risk of premature mortality and several chronic medical conditions such as diabetes mellitus, hypertension, ischemic heart disease, stroke, breast cancer, and colon cancer (3).

The promotion of PA in primary care is an effective intervention for motivating sedentary people to become physically active (4). Several PA and exercise promotion campaigns have been implemented in clinical settings such as Exercise is Medicine (EIM), which emphasizes the assessment of PA of a patient as the fifth vital sign and recommends PA counseling/prescription during clinical consultations (5).

PA promotion is a standard practice in primary care settings. However, the implementation of PA counseling is hindered by several factors such as limited resources (e.g., heavy clinical workload and time constraints); patients' limitations (e.g., physical condition and communication difficulties); and physicians' lack of knowledge and skills and attitude toward PA promotion (6, 7). The last of these is considered as a modifiable factor that can be improved. However, there is little training in PA promotion during undergraduate medical education (8–10) and postgraduate primary care training (11). The continuing professional development training, consisting of face-to-face training, online materials, or workshops, has the potential to fulfill a lack of formal training (12).

The knowledge and skills pertaining to PA promotion in clinical settings cover several aspects of sport and exercise science (13). As PCPs are not specialists in these subject areas, it is important to identify the essential elements for the practices

of PCPs. In this article, we present the collective opinion of experts in the field of primary care medicine (AW and CJN), sport and exercise science (MPNN, PH, SH, and CP), and PA (AA) regarding this point.

DISCUSSIONS ON SPORT AND EXERCISE SCIENCE

Defining Physical Activity, Exercise, and Sport

PA is a relatively new concept in many countries and is recognized by the general public as specific activity domains—i.e., sports or exercise. Thus, the term "physical activity" needs to be clarified and distinguished from "exercise" and "sport" to facilitate the promotion of this concept by PCPs.

PA is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (14). PA incorporates movement activities in daily life. Exercise is planned, structured, repetitive, and is undertaken with the purpose of improving and maintaining physical fitness (14). Exercise is a subset of but not synonymous with PA. However, the two terms are often used interchangeably. Sport is a subset of exercise that consists of a set of rules and defined goal (e.g., competition) (15). Thus, exercise and sport are important domains of PA (**Figure 1**). For example, running is a PA and can be considered as an exercise. If the running session is a competition, it is defined as sport. Current perceptions and characteristics of sports are variable and dynamic. Some types of sport are not considered as PA or exercise. For example, most eSports require players to control their characters in the virtual world while sitting in front of a monitor during competitions (16). PA is categorized according to its objectives as occupational, transport, domestic, and recreational (including exercise and sport) activities (15), which are collectively known as "PA domains".

Clarifying the exact meaning of PA is critical for promoting active lifestyles. Given the broad definition of PA, it can be (wrongly) argued that sitting in front of a computer monitor and clicking a mouse with a few fingers—which requires skeletal muscle contraction and uses energy—is PA. However, PA is defined based on the level of energy expenditure. A person engages in both movement and non-movement activities within a 24-h day–night cycle including sleep, SB, and PA. The amount of energy consumed during sleep is approximately 1 metabolic equivalent (1 MET = oxygen uptake of 3.5 ml/kg/min) (17). SB is any waking behavior in a sitting, reclining, or lying posture that expends $<$1.5 MET of energy (17). PA is characterized by an energy expenditure of $\geq$1.5 METs while in any posture (17).

Current evidence supports that the benefits of PA are a dose-response basis (18–20). In other words, a higher dose of PA is more beneficial than a lower dose, however, an optimal dose is needed to identify. A very low dose of PA may minimally affect the health benefits while an extremely high dose of PA may cause harm and injuries. The dose of PA depends on two factors—namely, intensity and duration. The intensity of PA can be classified into three levels: light (1.5–2.9 METs), moderate (3–5.9 METs), and vigorous ($\geq$6 METs). Although moderate-to vigorous-intensity PA is considered an effective intensity to improve health, light-intensity PA is also advantageous for health benefits. According to the dose-response basis, it cannot be concluded whether PA, exercise, or sport is the most effective activity. For example, brisk walking at 4 METs (moderate-intensity aerobic PA) for 150 min/week is equal to 600 MET-min/week (about the weekly recommended PA). This dose of running (8 METs for 75 min/week = 600 MET-min/week) may have similar health benefits whether the running session is PA, exercise, or sport. Thus, in this instance, the name given to the activity has no bearing on the benefit that it provides. The challenge for PCPs is designing an appropriate program or intervention for an individual to achieve the recommended levels of PA.

Integrating Sport and Exercise Science Into Primary Care Medicine

The 2020 WHO guidelines on PA and SB provide recommendations for children and adolescents (aged 5–17 years), adults (aged 18–64 years), older adults (aged $\geq$65 years), pregnant and postpartum women, and people living with chronic conditions and disabilities (21). The recommendations

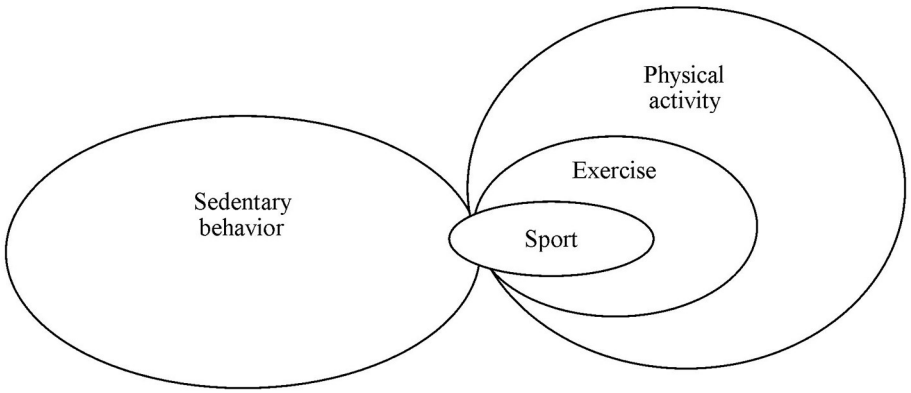

FIGURE 1 | Relationships among sedentary behavior, physical activity, exercise, and sport.

are simple and can be adopted by both healthy individuals and those with health issues. However, translating public health PA guidelines into clinical practice is challenging. Understanding the concepts of sport and exercise can potentially fill the gaps in the knowledge and skill of PCPs.

Identifying the essential elements of sport and exercise sciences is one of the main objectives of this interdisciplinary discussion. The term "sport" may be omitted from the practices of PCPs because PA or exercise promotion is more relevant to most of the population in primary care. The key competence required in this context is PA counseling or prescription.

Pre-exercise screening and the Frequency, Intensity, Time, and Type (FITT) principle (22) are required knowledge for PCPs to perform PA counseling or prescription. Pre-exercise screening is used to assess an individual's readiness and safety for PA or exercise, while the FITT principle can be adopted as a framework to translate scientific and medical concepts to practice and design a tailored PA program.

Promoting Safe Physical Activities

PA is generally safe for most people; however, the risks and harms increase with the intensity and dose. PA may increase risks of injuries from minor musculoskeletal injuries to sudden cardiac arrest. One study shows that a PA-related injury over 30 days during walking, gardening, weightlifting, outdoor bicycling, and performing aerobics is 0.9 to 2.4% (23). The incidence of sudden cardiac arrest related to exercise is still low (0.6 to 2.1 per 100,000 person-years) compared with out-of-hospital cardiac arrest (65.4 to 108.9 per 100,000 person-years) (22). There are several challenges faced by PCPs when providing care and PA/exercise prescriptions to patients; the two main ones are discussed in detail below.

Firstly, readiness and safety are critical issues for patients engaging in PA. Health screening may be required to ensure readiness and thereby reduce the risks of adverse events. A variety of approaches for this purpose can be adopted in clinical practice (22). For example, self-screening tools such as Physical Activity Readiness for Everyone (PAR-Q+) and the electronic Physical Activity Readiness Medical Examination (ePARmed-X+) are freely available online for public access (https://eparmedx.com/). For patients who require medical advice, PCPs can perform an evaluation based on patients' current PA levels, history of illness as well as signs and symptoms prior to their engagement in PA according to the American College of Sports Medicine's health screening process (24). High-risk patients should be given careful consideration and may need to be referred to medical specialists prior to initiation of PA.

Secondly, the depth of disease-specific knowledge required by PCPs to promote PA is a major concern. Sport and exercise scientists are content experts with detailed knowledge of exercise physiology, biomechanics, and anatomy and possess tools to evaluate patients with chronic conditions. It can be an exhausting task for PCPs to study all of these sub-disciplines of sport and exercise science along with disease-specific exercise guidelines (e.g., for cancer survivors or patients with heart disease or musculoskeletal disorders). Therefore, PCPs only need to understand the basic concepts of PA or exercise and the contraindications and precautions for PA for specific medical conditions. A scheme for referrals to sport and exercise specialists is strongly suggested for patients who require special care.

The FITT Principle as a Framework to Promote Physical Activity

PA recommendations include specific details for each group within the population. For example, the recommendation for healthy adults (18–64 years) is 150–300 min/week of moderate-intensity or 75–150 min/week of vigorous-intensity aerobic PA (21). Additionally, adults should undertake muscle-strengthening activities at moderate or greater intensity $\geq$2 days/week (21). The time spent engaging in SB should be limited and replaced with PA at any intensity, including light activities (21).

Notably, PA recommendations for adults include details on the frequency, intensity (i.e., light to vigorous), time (i.e., 150–300 min/week), and type (aerobic). PCPs can rely on the FITT principle based on WHO PA recommendations when providing PA counseling. The recommended 150–300 min/week of moderate-intensity PA can be designed in different ways. The 150 min/week target can be achieved with five 30-min sessions per week of brisk walking. Alternatively, the target can be achieved by combining 120 min of recreational swimming and 30 min of gardening with heavy tools.

Vague advice such as "move more and sit less", "go exercise", or "increase your PA", are superficial and may be ineffective in changing people's behaviors. The FITT principle can provide a supportive framework that can aid PCPs in PA counseling or in writing a PA/exercise prescription. Otherwise, general advice regarding SB—e.g., "limit sitting time" or "reduce time spent on SB"—may be suitable. The informative content of PA counseling provided by PCPs can help individuals to achieve the recommended PA goals.

CONCLUSION

This interdisciplinary discussion highlights the important role of PCPs in promoting PA and reducing SB in the primary care setting. The basic concepts of sport and exercise sciences, as well as WHO PA recommendations, constitute essential knowledge for PCPs that should be integrated into their professional practices. Pre-PA/exercise screening may be required, particularly for high-risk patients. Safety issues must also be taken into account when providing PA/exercise counseling or prescriptions. The FITT principle is suggested as a framework to perform the PA/exercise counseling and prescription. Integration of sport and exercise science into the primary care practice requires an understanding and incorporation of underlying concepts, as well as coordination between PCPs and sport/exercise scientists.

AUTHOR CONTRIBUTIONS

AW and MPNN conceived the manuscript. PH, MPNN, SH, AA, CP, and CJN contributed comments. AW wrote the first draft of the manuscript. AW and AA edited the manuscript. All authors participated in the discussions, read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

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ORIGINAL RESEARCH
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Is There Limited Utility for Lifestyle Recommendations for Diabetes Prevention Among Overweight or Obese Depressed Patients?

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Background: Lifestyle interventions like diet and exercise are commonly recommended for diabetes prevention, but it is unclear if depression modifies the likelihood of adherence. We evaluated the relationship between high depressive symptomatology and adherence to lifestyle interventions among patients with pre-diabetes.

Methods: We conducted an analysis of the nationally representative National Health and Nutrition Examination Survey (NHANES) 2017–2018. Adults, aged ≥18 years old who were overweight or obese (BMI ≥25) and had diagnosed or undiagnosed pre-diabetes (HbA1c 5.7–6.4) were included. Depressive symptomatology was classified by the Patient Health Questionniare-9 (PHQ-9). We used self-reported adherence to physician suggested lifestyle changes of diet and exercise.

Results: In this nationally representative survey of overweight or obese adults with pre-diabetes, 14.8% also have high depressive symptomatology. In unadjusted analyses, an interaction was observed with high depressive symptomatology acting as an effect modifier for adherence to exercise oriented interventions among patients with diagnosed pre-diabetes ($p = 0.027$). In logistic regressions, adjusting for age, sex, race, outpatient medical care in the past 12 months, and obesity, among patients with diagnosed pre-diabetes, depressed patients were less likely to attempt to exercise more (OR = 0.31; 95% CI: 0.10, 0.94) and no association between high depressive symptomatology and attempting to lose weight was observed (OR = 0.45; 95% CI: 0.14, 1.42).

Conclusions: The findings of this nationally representative study of US adults, high depressive symptomatology decreases the likelihood of adherence to exercise based lifestyle recommendations among patients with diagnosed pre-diabetes.

Keywords: diabetes risk, depression, NHANES, prevention, exercise

INTRODUCTION

Diabetes is a chronic, progressive disease that has reached epidemic proportions in the USA (1). The American Diabetes Association and United States Preventive Services Task Force recommend screening, early detection, and treatment for pre-diabetes as a necessary strategy to prevent diabetes and its severe complications (2–5). Diabetes prevention focuses on the use of lifestyle interventions and/or prescription metformin among the general population.

Individuals with depression are a vulnerable and important population in relation to diabetes and diabetes prevention. Diabetes and depression are common comorbid conditions and having both diabetes and depression is related to worse health outcomes than just having one of the conditions (6–8). Individuals with depression and pre-diabetes are at a greater risk of developing diabetes than those with only one of these risk factors (9–12).

Although lifestyle interventions are recommended and evidence-based for diabetes prevention, adherence to an intense lifestyle program may be difficult for depressed patients. Little research has focused on the adherence of lifestyle interventions for diabetes prevention among patients with pre-diabetes and depression (13). One of the few studies to investigate this question examined utilization of weight loss as strategy by patients but included people at normal weight, a population unlikely to try and increase exercise and try and lose weight. This is an important gap in our knowledge base because depressed patients are a particularly vulnerable group, and the standard approach for diabetes prevention, advice for lifestyle change, may not be an optimal strategy for depressed patients.

The purpose of this study was to investigate the adherence to physician reported diabetes prevention lifestyle interventions, increased exercise and weight loss, among overweight or obese adult patients with pre-diabetes and depression.

RESEARCH DESIGN AND METHODS

We analyzed the 2017–2018 National Health and Nutrition Examination Survey (NHANES). The NHANES is a large, nationally representative survey that samples the non-institutionalized population of the United States using a stratified multistage probability sample design. To account for nationally representative population estimates, the National Center for Health Statistics applies a multilevel weighting system. The survey included a standardized medical examination including blood analysis for examining biomarkers and a number of health-related interviews. The application of weights and variables accounting for the complex survey design allows the study to provide nationally representative population estimates for the United States. Our study focused on adults $\geq$18 years of age who were overweight or obese as defined by body mass index (BMI) of $\geq$25. BMI was obtained from body weight divided by height squared (kg/m^2). Weight and height were measured by a trained examiner in the mobile examination center, and these were used to calculate BMI.

Exclusions

We excluded patients who reported that they had undergone bariatric surgery since that would confound our assessment of lifestyle recommendations for weight loss. This was assessed by the individual's response to the question "Have you ever had weight loss surgery?" Individuals who indicated they received medication for ADHD were also excluded because this may affect their motivation for exercise.

Identification of Previously Diagnosed Diabetes

Individuals were considered to have diabetes if they reported ever being told by a health care provider that they had diabetes, excluding gestational diabetes. We also removed individuals with an A1C $\geq$6.5% to account for undiagnosed diabetes.

Identification of Pre-diabetes

Individuals participating in the NHANES undergo a physical examination that includes laboratory analysis of blood. We defined diagnosed pre-diabetes as any respondents who reported being told that they had pre-diabetes or borderline diabetes. The specific wording was, "Have you ever been told by a doctor or other health professional ever been told by a doctor or other health professional that you have any of the following: pre-diabetes, impaired fasting glucose, impaired glucose tolerance, borderline diabetes or that your blood sugar is higher than normal but not high enough to be called diabetes or sugar diabetes?" We defined undiagnosed pre-diabetes among individuals without previously diagnosed or undiagnosed diabetes or diagnosed pre-diabetes using the A1C range of 5.7–6.4% (39–46 mmol/mol), as specified by the ADA (2).

We excluded individuals with previously diagnosed diabetes or pre-diabetes from the computation of undiagnosed pre-diabetes because the glycemic status of those individuals may simply have represented diabetes control. This recoded variable was binary.

Depressive Symptomatology

Depressive symptomatology was assessed using the Patient Health Questionniare-9 (PHQ-9) (14). The reliability and validity of the PHQ-9 has been assessed both in the general population and in clinical samples (15). For the purposes of this analysis, individuals with a PHQ-9 score of 10 or greater were classified as having high depressive symptomatology.

The focus for this variable was on the self-report of symptoms for depression. There were some individuals who reported taking medication for depression. It was felt that with diagnosed depression whose depression was under control should not be classed as depression in relation to the likelihood of adherence with lifestyle change recommendations.

Physician Recommended Lifestyle Modifications and Adherence

Patients who responded "Yes" to the interview question, "During the past 12 months have you ever been told by a doctor or health professional to control your weight or lose weight?"

were classified as having received a recommendation from their physician to lose weight. Patients who further indicated that they were currently attempting to lose or control their weight were categorized as attempting to complete a recommended weight-loss lifestyle modification. The same criteria were used to establish attempting to complete a recommendation to exercise more based on their responses to the interview question, "During the past 12 months have you ever been told by a doctor or health professional to increase your physical activity or exercise?" and further indicated that they were currently trying to increase their physical activity or exercise habits.

Demographics and Covariates

Age, sex and race/ethnicity was derived from the NHANES interview. Race/ethnicity was categorized into four groups: (1) Non-Hispanic White, (2) Non-Hispanic Black, (3) Hispanics and (4) Other. We also included whether individuals had seen a physician or other healthcare provider at least once in the past 12 months. We also assessed among who had been seen in an outpatient setting whether individuals had seen a mental health provider in the past 12 months.

Statistical Analysis

All analyses were conducted using the survey package in R. v4.0.3. Weighting and design variables applied to all analyses to account for the stratified multistage probability sample design. Incorporation of the weighting and design variables allows us to calculate population estimates for the non-institutionalized US population. Unadjusted odds ratio from logistic regression models were used to determine the associations between pre-diabetes and follow-through on lifestyle modifications. Interaction terms between high depressive symptomatology and lifestyle modifications were used to test for the presence of effect modification from depressive symptoms. For analyses on weight-loss, individuals who had never received a recommendation to lose weight were excluded. Similarly for exercise, individuals who had never received a recommendation to exercise more were excluded from analyses. Additional logistic regression analyses exploring the adjusted relationship between attempting lifestyle modifications and high depressive symptomatology among patients with diagnosed pre-diabetes were also performed, adjusting for age, obesity, sex, outpatient health care in the past 12 months, and race/ethnicity.

RESULTS

The characteristics of the sample are shown in **Table 1**. The prevalence of individuals with pre-diabetes who also have high depressive symptomatology is not uncommon at 14.8%. This accounts for 6,736,053 adults in the US.

Table 2 shows the unadjusted odds ratios between lifestyle modifications and pre-diabetes stratified by depression. Individuals diagnosed with pre-diabetes had lower odds of attempting physician-recommended weight-loss and exercise-oriented lifestyle modifications than individuals without diagnosed pre-diabetes among patients with depression. However, no statistically significant associations between attempting lifestyle modifications and diagnosed pre-diabetes were observed among patients with low depressive symptomatology. A statistically significant interaction term between depressive symptomatology and exercise suggests that depressive symptomatology on may be an effect modifier for attempting recommended changes in physical activity among patients with diagnosed pre-diabetes, though the same effect was not seen for weight loss recommendations. There were no statistically significant interactions between depressive symptomatology and lifestyle modifications for patients with undiagnosed pre-diabetes.

Additional adjusted analyses were used to confirm the associations between diagnosed pre-diabetes and attempting to complete a lifestyle intervention. Among patients with diagnosed pre-diabetes, depressed patients were less likely to attempt to exercise more (OR = 0.31; 95% CI: 0.10, 0.94) and no association between high depressive symptomatology and attempting to lose weight was observed (OR = 0.45; 95% CI: 0.14, 1.42).

DISCUSSION

The findings of this study indicate that many patients with pre-diabetes also have high depressive symptomatology. Depressed, overweight patients with diagnosed pre-diabetes are less likely to follow physician recommendations for exercise in a lifestyle modification. However, the same is not true of overweight patients with low depressive symptomatology, whose attempts to follow physician-recommended lifestyle modification to treat diagnosed pre-diabetes is not hindered by depressive symptoms. Lack of motivation and cognitive impairments are the main symptoms preventing depressed patients from attempting lifestyle modification. A core symptom of depression is anhedonia, defined as a "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" (16). Anhedonia leads to reductions in physical and cognitive effort, both components in goal-directed, motivated behavior (17). Motivation is interdependent with cognitive control, which is also deficient in depressed patients and leads to impairments in attention, interpretation, and memory. Taken together, deficits in motivation and cognition make it challenging for patients with depression to accomplish tasks and goals.

Depression affects a patient's ability to attempt exercise compared to the ability to lose weight, which is not surprising. The daily fatigue, psychomotor retardation (being slowed down), and feelings of worthlessness often experienced by depressed patients make it difficult to exercise, while the loss of appetite and unintentional weight loss typical of depression may have made it appear that intentional weight loss was easier (16).

The results of this study are consistent with some past research which showed that adherence to an intense lifestyle intervention is lower for patients with depression (18). Previous research has shown the effectiveness of pharmacotherapy (i.e., metformin) for diabetes prevention (19). Although the National Diabetes Prevention Program (National DPP) showed that both an intense lifestyle intervention and metformin were effective strategies for diabetes prevention, the lifestyle intervention had greater

TABLE 1 | Descriptive statistics of overweight or obese adults who have never been diagnosed with diabetes.

	Overall	Undiagnosed pre-diabetes	Diagnosed pre-diabetes	No pre-diabetes
Unweighted sample size	3,453	761	448	2,244
Weighted sample size	141,851,135	28,790,161	18,992,903	94,068,071
Age				
18–39	38.8%	23.5%	23.8%	47.0%
40–70	50.6%	60.4%	60.9%	45.4%
71+	10.6%	16.1%	15.3%	7.5%
Gender (female)	48.0%	46.5%	50.7%	47.6%
Race/ethnicity				
Non-hispanic white	59.7%	55.6%	58.9%	61.3%
Non-hispanic black	12.1%	17.5%	9.7%	10.7%
Hispanic	18.7%	16.2%	22.7%	18.7%
BMI ≥30–34.9	30.1%	30.4%	29.2%	30.1%
BMI ≥35–39.9	14.3%	16.3%	18.5%	12.5%
BMI ≥40	10.9%	12.8%	13.5%	8.9%
High depressive symptomatology	7.2%	5.2%	6.7%	7.9%
Outpatient visit (past 12 mos.)	81.4%	83.0%	91.6%	79.6%
Mental health (past 12 mos.)	10.1%	6.8%	13.7%	10.7%
Told to lose weight	30.4%	29.5%	54.9%	24.3%
Trying to lose weight	24.6%	23.0%	43.6%	20.0%
Told to exercise more	40.5%	40.2%	67.4%	33.9%
Trying to exercise more	29.0%	25.9%	48.4%	25.3%

TABLE 2 | Unadjusted odds ratios and 95% confidence intervals for the associations between pre-diabetes and trying to complete lifestyle changes after a doctor's recommendation stratified by depressive symptomatology.

	High depressive symptomatology	Low depressive symptomatology	$P^{\ddagger}$	High depressive symptomatology	Low depressive symptomatology	$P^{\ddagger}$
	Undiagnosed pre-diabetes vs. diagnosed/no pre-diabetes			Diagnosed pre-diabetes vs. undiagnosed/no pre-diabetes		
Trying to lose weight	1.24 (0.42, 3.65)	0.75 (0.40, 1.39)	0.462	0.28 (0.10, 0.76)	0.97 (0.46, 2.05)	0.102
Trying to exercise more	2.00 (0.55, 7.30)	0.60 (0.38, 0.95)	0.162	0.24 (0.08, 0.75)	1.16 (0.68, 1.98)	0.027

‡*P-values represent the significance of an interaction between major depression and trying to complete a lifestyle recommendation.*

benefits. However, the DPP did not consider depression or depressive symptomatology, and it may be that the effectiveness of an intense lifestyle intervention in actual practice may have significantly lower adherence than metformin among patients who are depressed. This research suggests that an alternative to a lifestyle intervention may be warranted. Future research should focus on this considering the millions of patients with pre-diabetes and depression.

There are several limitations to this study which need to be noted. First, the information collected in the NHANES on physician recommendation for lifestyle change and reports of attempts for lifestyle change are based on self-reports. Thus, the lifestyle interventions may vary and may not be as intense as the National DPP. However, the current results suggest that individuals with high depressive symptomatology are still less likely to do exercise programs regardless of the range of intensity suggested by the physicians. Moreover, the NHANES is a survey and is not a chart audit and so aspects of the respondent's medical history, if not collected in the survey with specific questions, will not be available for analysis. Second, the patients reported their depressive symptomatology. This is not a diagnosis via a clinical interview. It should be noted that as was expected, the effect was found based on whether individuals exhibit the depressive symptomatology that may impact on adherence to lifestyle changes. Third, although the results are nationally representative based on population weighting and the adjusted analyses control for race/ethnicity, a subpopulation only analysis could yield different results.

In conclusion, this study indicates that millions of people with pre-diabetes have significant depressive symptomatology, and this may affect the effectiveness of prescribing an intense lifestyle intervention for diabetes prevention. The next step is to determine in a more controlled fashion whether lifestyle interventions or pharmacotherapy are equally effective for diabetes prevention among patients with depression.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

AM led the analysis plan, wrote the first draft, and is the guarantor of the paper. BR conducted the analysis. All authors contributed to the initial idea, final writing, and editing of the manuscript.

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Exercise for Neuropathic Pain: A Systematic Review and Expert Consensus

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Background: Neuropathic pain (NP), a severe and disruptive symptom following many diseases, normally restricts patients' physical functions and leads to anxiety and depression. As an economical and effective therapy, exercise may be helpful in NP management. However, few guidelines and reviews focused on exercise therapy for NP associated with specific diseases. The study aimed to summarize the effectiveness and efficacy of exercise for various diseases with NP supported by evidence, describe expert recommendations for NP from different causes, and inform policymakers of the guidelines.

Design: A systematic review and expert consensus.

Methods: A systematic search was conducted in PubMed. We included systematic review and meta-analysis, randomized controlled trials (RCTs), which assessed patients with NP. Studies involved exercise intervention and outcome included pain intensity at least. Physiotherapy Evidence Database and the Assessment of Multiple Systematic reviews tool were used to grade the quality assessment of the included RCTs and systematic reviews, respectively. The final grades of recommendation were based on strength of evidence and a consensus discussion of results of Delphi rounds by the Delphi consensus panel including 21 experts from the Chinese Association of Rehabilitation Medicine.

Results: Eight systematic reviews and 21 RCTs fulfilled all of the inclusion criteria and were included, which were used to create the 10 evidence-based consensus statements. The 10 expert recommendations regarding exercise for NP symptoms were relevant to the following 10 different diseases: spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, cervical radiculopathy, sciatica, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, HIV/AIDS, and surgery, respectively. The exercise recommended in the expert consensus involved but was not limited to muscle stretching, strengthening/resistance exercise, aerobic exercise, motor control/stabilization training and mind-body exercise (Tai Chi and yoga).

Conclusions: Based on the available evidence, exercise is helpful to alleviate NP intensity. Therefore, these expert consensuses recommend that proper exercise programs can be considered as an effective alternative treatment or complementary therapy for most patients with NP. The expert consensus provided medical staff and policymakers with applicable recommendations for the formulation of exercise prescription for NP. This consensus statement will require regular updates after five–ten years.

Keywords: exercise, training, neuropathic pain, chronic pain, expert consensus

INTRODUCTION

Neuropathic pain (NP) is defined as pain driven by a lesion or disease of the somatosensory nervous system (1, 2). Meanwhile, central or peripheral nerve lesions can lead to sensory loss in the corresponding body regions to the damaged central nervous part or in the innervation territory of injured peripheral nerve. Indeed, one of the most important features of NP is a complex combination of sensory loss and pain. It is well-known that NP is not only an exclusive symptom for patients with direct nervous injuries but also indirect nervous peripheral neuropathy. For instance, the incidence of NP is around 50% in patients with spinal cord injury and ∼21% in patients suffering from diabetic neuropathy (3). Compared with males (5.7%), the female population is more likely to suffer from chronic NP (8%) (1). Additionally, the related more affected body regions are low back, neck, and extremities (4). The symptoms of NP, such as spontaneous pain, evoked pain, aftersensation, hyperalgesia, and referred pain, could seriously disturb patients' motor function and emotions and result in a low quality of life, anxiety, and depression. The current management of NP aim to control or ameliorate symptoms due to the difficulty of treating damaged nerve directly. However, traditional pharmacological treatment is not effective enough and may lead to cardiac conduction block, sedation, anticholinergic effects or opioid-related adverse effects (5, 6). Thus, non-pharmacological approaches, such as exercise, have gained the attention of physicians.

Exercise, a feasible and economical way, has been widely accepted as an effective treatment for musculoskeletal disorders. As a treatment, exercise refers to the physical activities aiming to correct impairment and improve physical and cognitive function, which can positively contribute to health (7). Normally, therapeutic exercise could be divided into various types, such as muscle stretching, strengthening/resistance exercise, aerobic exercise, motor control/stabilization training and mind-body exercise (8). Considering the benefits of exercise, such as blood glucose and blood lipid reduction, exercise-induced hypoalgesia and emotional improvement, it might be an effective way to prevent and treat NP (9, 10). The effectiveness of exercise training as a complementary therapy or interventional treatment for patients with NP has been previously reported and exercise program seems to be beneficial to the recovery of damaged peripheral nerve, the alleviation of pain symptoms, and the improvement of physical status (11). However, the distinct content of exercise, different intensities of training, and various frequencies of physical activities can produce different effects and influence on patients with NP. Similarly, NP from different causes have diverse characteristics and are likely to respond to exercise treatment differently. A proper exercise plan for the management of NP in patients has been a challenge for physicians and physiotherapists.

Several clinical guidelines, systematic reviews, and meta-analyses regarding to clinical therapies for some specific diseases with NP symptoms have been published (12–17). However, these guidelines and reviews more focus on pharmacological treatment; non-invasive treatments, such electrical and magnetic stimulation; and other non-pharmacological approaches, but not exercise. Although exercise has been reported as a safe and useful method to improve functions and relieve pain in patients with NP, few guidelines or expert consensus review exercise program as a treatment for different types of NP in detail. Therefore, the Chinese Association of Rehabilitation Medicine needs to establish an exercise program consensus for diseases with NP that could be applicable to physiotherapists.

The Chinese Association of Rehabilitation Medicine invited experts in physiotherapy, sports science, orthopedics, and sports

medicine to develop evidence-based recommendations and expert consensus. This expert consensus aimed to: (1) summarize the effectiveness and efficacy of exercise for various diseases with NP supported by evidence; (2) describe evidence-based exercise recommendations for NP from different causes, including central and peripheral nerve damage; and (3) inform policy makers of the guidelines.

METHODS

Data Sources

A systematic search was conducted in PubMed. We searched all sources from their inception up to January 25, 2021. The search used the following keywords: neuropathic pain, neuralgia, neurodynia, and exercise. The details of the search strategy for the PubMed database are provided in the **Supplementary Material**.

Inclusion Criteria

Types of Studies

Systematic reviews, meta-analyses, and randomized controlled trials (RCTs) in peer-reviewed journals were included. We excluded retrospective studies, case–control studies, meeting abstracts, conference presentations, book reviews, news items, and corrections. Studies, including Systematic reviews, meta-analyses, and RCTs, with higher levels of evidence were prioritized but lower-quality studies were also evaluated. The language was limited to English.

Types of Participants

We included studies that assessed patients suffering from NP caused by spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, cervical radiculopathy, sciatica, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, HIV/AIDS, and surgery (2).

Types of Interventions

We only considered studies that involved exercise, such as muscle stretching, strengthening/resistance exercise, aerobic exercise, motor control/stabilization training and mind-body exercise (Tai Chi, yoga, and Pilates). Furthermore, the intervention groups should be able to show the effect of exercise through at least one group. For example, at least one intervention group received exercise only; or one intervention group received exercise combined with usual therapy while another intervention group received usual therapy.

Types of Outcome Measures

Outcome measures must include but are not limited to pain intensity. Other outcomes, such as muscle strength, motor functions, and balance, were also considered.

Study Selection

Two reviewers independently screened the titles, abstracts, and full contents of the proper studies according to the same inclusion criteria. We excluded studies that did not fulfill the inclusion criteria. Any disagreements were resolved by a discussion and a third reviewer was consulted if a disagreement persisted.

TABLE 1 | Oxford center for evidence based medicine, level of evidence.

Level	Intervention
I	Evidence obtained from systematic reviews, high-quality diagnostic studies, prospective studies, or randomized controlled trials
II	Evidence obtained from systematic reviews, lesser-quality diagnostic studies, prospective studies, or randomized controlled trials, such as weaker diagnostic criteria and reference standards, improper randomization, no blinding, <80% follow-up
III	Retrospective studies or case-control studies
IV	Case series
V	Expert opinion

Levels of Evidence

Individual clinical research studies were evaluated in accordance with the criteria adapted from the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence (CEBM) (available at http://www.cebm.net/index.aspx?o=5653). Two reviewers independently assessed the levels of evidence for each clinical study using an appraisal tool. The abbreviated version of the levels of evidence id shown in **Table 1** (18). Additionally, the level of evidence for the recommendation for each disease was determined by the lowest level of evidence from related researched studies.

Grades of Recommendation

According to the established clinical guidelines by the American Physical Therapy Association (18–20), the recommendation was graded based on strength of evidence. The authors considered the benefits, side effects of physical therapies, and the strengths and limitations of the evidence body to develop the recommendations. The grades of recommendation are shown in **Table 2**.

Quality of Evidence

According to Collins et al. (21) and Shea et al. (22), Physiotherapy Evidence Database (PEDro) score (total score/10) and the Assessment of Multiple Systematic Reviews (AMSTAR) score (total score/11) were used to grade the quality of the included RCTs and the methodological quality of the included systematic reviews and meta-analyses, respectively. Two reviewers independently assessed the quality of the included studies through PEDro and AMSTAR. The included studies were graded as low, moderate, or high quality based on the consensus statements (21, 23). Studies with PEDro and AMSTAR scores of $\leq$3, 4–6, and $\geq$7 were considered to have low, moderate, and high quality, respectively.

Consensus Process

X-Q.W. and G-E.F. formulated the population, intervention, comparator, and outcome (PICO) research topics and drafted the recommendation statements. During the first round, the 21 experts from the Chinese Association of Rehabilitation Medicine reviewed and commented on the text online using a 5-point scale: 1. strongly agree; 2. agree; 3. no opinion; 4. disagree; 5. strongly disagree (24). A score of 1–2 was determined as "Agreement." In the second round, the recommendation

TABLE 2 | Grades of recommendation.

Grades of recommendation		Strength of evidence
A	Strong evidence	A preponderance of level I and/or level II studies support the recommendation. This must include at least 1 level I study
B	Moderate evidence	A single high-quality randomized controlled trial or a preponderance of level II studies support the recommendation
C	Weak evidence	A single level II study or a preponderance of level III and IV studies, including statements of consensus by content experts, support the recommendation
D	Conflicting evidence	Higher-quality studies conducted on this topic disagree with respect to their conclusions. The recommendation is based on these conflicting studies
E	Theoretical/foundational evidence	A preponderance of evidence from animal or cadaver studies, from conceptual models/principles, or from basic science/bench research support this conclusion
F	Expert opinion	Best practice based on the clinical experience of the guideline's development team

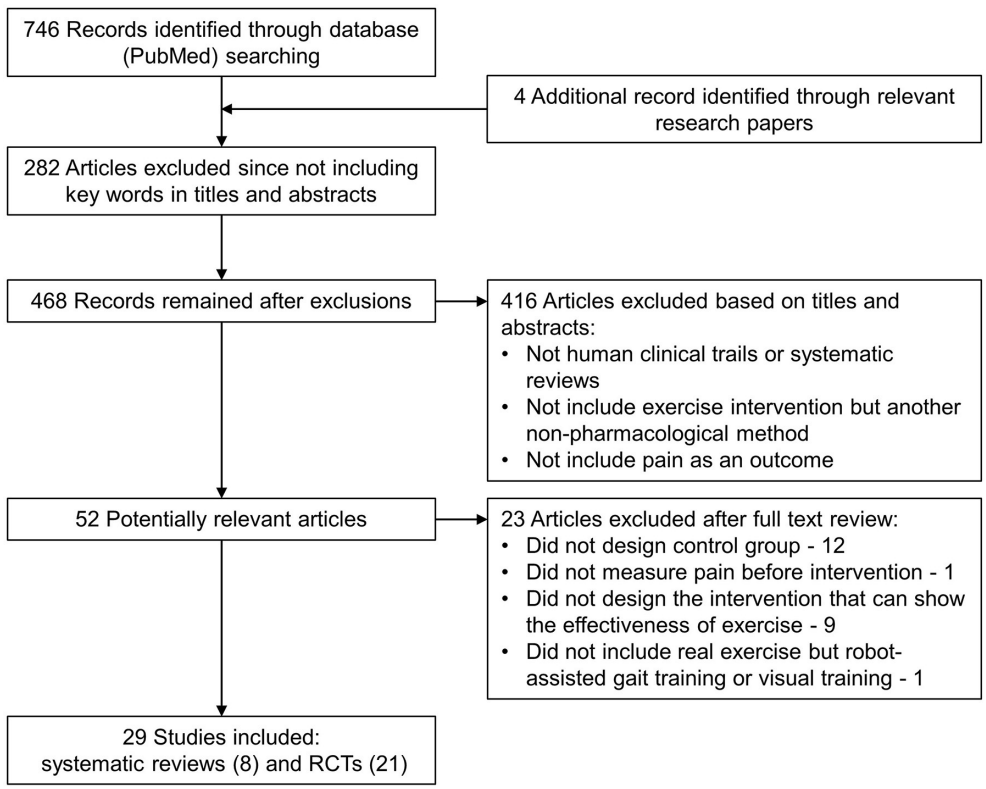

FIGURE 1 | Study flow diagram.

statements that were regarded as "Disagreement" were discussed further. If 75% agreement could be not gained after discussion, the recommendation statements were further rated in a third round (25). Finally, the grades of recommendation were assigned based on the strength of evidence and a consensus discussion of the results of the Delphi rounds.

RESULTS

Eight systematic reviews and 21 RCTs met the inclusion criteria after the evaluation of the titles, abstracts, and full contents of the relevant studies (**Figure 1**). The characteristics and quality of evidence of the included studies are shown in **Table 3** (characteristics of RCTs), **Table 4** (characteristics of systematic reviews), **Table 5** (quality of evidence of RCTs), and **Table 6** (quality of evidence of systematic reviews), respectively. Based on PEDro scores, 10 RCTs (47.62%) have high quality, and 11 RCTs (52.38%) have moderate quality. According to AMSTAR scores, six systematic reviews (75%) have high quality, and two systematic reviews (25%) have moderate quality. The summary of the consensus recommendations for exercise as NP treatment is presented in **Table 7**.

Consensus Recommendations for Pain Associated With Spinal Cord Injury

Chronic pain is a common and serious symptom in patients with spinal cord injury with a high prevalence at around 73% in Denmark (26). About 30% of patients considered the pain as a

TABLE 3 | Characteristics of included RCT studies.

References	Participants		Intervention protocol		Outcome assessment	Outcome measures	Results of pain	Safety
	Population Sample size Study design	Age (years)	Intervention group 1	Intervention group 2 or control group				
Labruyère and van Hedel (29)	Patients with incomplete spinal cord injury $n = 9$ 2 groups	• 59 ± 11 • Group 1 ($n = 5$) • Group 2 ($n = 4$)	• Robot-assisted gait training (45 min per session; 16 sessions within 4 weeks) • Strength training (45 min per session; 16 sessions within the following 4 weeks)	• The same interventions in reversed order	• After the interventions • At follow-up 6 months	• Pain (VAS) • 10-m Walk Test • Balance	Robot-assisted gait training and strength training reduced pain intensity.	No adverse events
Costantino et al. (31)	Patients with chronic post-stroke $n = 32$ 2 groups	• Group 1 ($n = 17$): 62.59 ± 15.39 • Group 2 ($n = 15$): 60.47 ± 16.06	• Local muscle vibration during voluntary isometric contraction • 12 sessions; 3 times per week over 4 weeks	• Voluntary isometric contraction (12 sessions; 3 times per week over 4 weeks)	• After the 4-week interventions	• Pain (VNRS) • Grip strength	Voluntary isometric contraction reduced pain intensity.	NA
Jeon et al. (32)	Patients with post-stroke hemiparesis $n = 12$ 2 groups	• Group 1 ($n = 6$): 58.0 ± 13.6 • Group 2 ($n = 6$): 50.5 ± 8.9	• Monkey Chair and Band exercise (joint motion, strengthening training, and relaxation) • 30 mins per session; 3 times per week;12 weeks	• No intervention	• At 4 weeks • At 8 weeks • At 12 weeks	• Pain (VAS) • ROM • MMAS	Joint motion and strengthening training reduced pain intensity.	NA
Wei et al. (33)	Patients with hemiplegic shoulder pain $n = 40$ 2 groups	• Group 1 ($n = 20$): 63.85 ± 11.07 • Group 2 ($n = 20$): 65.55 ± 13.30	• Acupuncture combined with neuromuscular joint facilitation (NJF) • Once a day; 6 times a week for 3 weeks	• Acupuncture alone • Once a day; 6 times a week for 3 weeks	• After 3-week intervention	• Pain (VAS) • Fugl-Meyer assessment • Passive ROM	NJF training reduced pain intensity.	NA
Horsley et al. (34)	Patients after stroke $n = 50$ 2 groups	• Group 1 ($n = 25$): 65.9 ± 12.7 • Group 2 ($n = 25$): 68.5 ± 13.0	• Active, intensive, repetitive upper limb training using the SMART Arm device (1 h a day; 5 days a week for 5 weeks) • Upper limb therapy (5 days a week for the same 5 weeks)	• Usual upper limb therapy (5 days a week for 5 weeks)	• After 5-week interventions • At 7-week follow-up	• Pain (VAS)	No significant effects of upper limb training by SMART Arm device on pain intensity.	NA
Pilutti et al. (38)	Patients with Multiple Sclerosis $n = 8/11$ 2 groups	• Group 1 ($n = 4$): 57.3 ± 6.0 • Group 2 ($n = 4$): 48.5 ± 7.7	• Functional electrical stimulation (FES) cycling exercise • Same cadence (50 rpm); 3 weekly sessions for 24 weeks	• Passive leg cycling • 3 weekly sessions for 24 weeks	• After 24-week intervention	• Pain (McGill Pain Questionnaire) • Cognitive processing speed • Symptoms of fatigue	The FES cycling exercise reduced pain intensity.	Six mild adverse events

(Continued)

TABLE 3 | Continued

References	Participants		Intervention protocol		Outcome assessment	Outcome measures	Results of pain	Safety
	Population Sample size Study design	**Age (years)**	**Intervention group 1**	**Intervention group 2 or control group**				
Grubić Kezele et al. (39)	Patients with Multiple Sclerosis $n = 19$ 2 groups	• Group 1 ($n = 10$): 53.9 ± 10.7 • Group 2 ($n = 9$): 48.2 ± 9.3	• Combined upper limb and breathing exercise (60 mins per session; 2 sessions a week for 4 weeks) • Independent home exercise (20 mins per session; 3 sessions per week for the same 4 weeks) • On-going physical therapy	• On-going physical therapy without exercise	• After 4-week intervention	• Pain (Short-form 36) • Fatigue • Quality of life	The combined upper limb, breathing and home exercise reduced pain intensity.	NA
Hasanpour-Dehkordi et al. (40)	Patients with Multiple Sclerosis $n = 60$ 2 groups	• 30.0 • Group 1 ($n = 30$) • Group 2 ($n = 30$)	• Yoga exercises • 60–70 mins 3 sessions a week for 12 weeks	• No exercise	• After 12-week intervention	• Pain (Bayer numerical scale) • Fatigue severity	Yoga exercise reduced pain symptoms.	NA
Young et al. (41)	Patients with Multiple Sclerosis $n = 81$ 3 groups	• Group 1 ($n = 27$): 49.67 ± 9.40 • Group 2 ($n = 26$): 48.35 ± 9.95 • Group 3 ($n = 28$): 47.29 ± 10.33	Group 1: movement-to-music • Strength, cardiorespiratory endurance, and balance • 60 mins per session; 3 sessions per week for 12 weeks Group 2: adapted yoga • 60 mins per session; 3 sessions per week for 12 weeks	• Waitlist control (biweekly newsletters *via* mail)	• After 12-week intervention	• Pain (PROMIS) • Timed Up and Go • 6-min walk test	No significant effect of movement-to-music or adapted yoga on pain intensity.	One muscle strain in movement-to-music group
Pérez de la Cruz (43)	Patients with Parkinson's disease $n = 30$ 2 groups	• Group 1 ($n = 15$): 66.80 ± 5.867 • Group 2 ($n = 15$): 67.53 ± 9.89	• Aquatic Tai Chi • 45 mins per time; 2 times per 10 weeks	• Therapy on dry land (strength training and aerobic exercises) • 45 mins per time; 2 times per 10 weeks	• After 10-week intervention • At 1-month follow-up	• Pain (VAS) • Balance • Test get up and go • Five times test	Both aquatic Tai Chi and strength training and aerobic exercises reduced pain intensity.	NA
Diab and Moustafa (44)	Patients with unilateral lower cervical spondylotic radiculopathy $n = 96$ 2 groups	• Group 1 ($n = 48$): 46.3 ± 2.05 • Group 2 ($n = 48$): 45.9 ± 2.1	• Posture corrective exercise program (strengthening and stretching exercise; 4 times per week for 10 weeks) • Ultrasound and infrared radiation (20 mins per time; 3 times per week for 10 weeks)	• Ultrasound and infrared radiation • 20 mins per time; 3 times per week for 10 weeks	• After 10-week intervention • At 6-month follow-up	• Pain (VAS) • Somatosensory evoked potentials • Craniovertebral angle	Strengthening and stretching exercise significantly reduced pain intensity.	NA

(Continued)

TABLE 3 | Continued

References	Participants		Intervention protocol		Outcome assessment	Outcome measures	Results of pain	Safety
	Population Sample size Study design	**Age (years)**	**Intervention group 1**	**Intervention group 2 or control group**				
Halvorsen et al. (45)	Patients with cervical radiculopathy $n = 50/75$ 2 groups	• Group 1 ($n = 27$): 47 ± 10.9 • Group 2 ($n = 23$): 49 ± 9.4	• Neck-specific training with a cognitive behavioral approach • Prescribed physical activity • 3 times a week for 14 weeks	• Prescribed self-mediated physical activity	• After 14-week intervention • At 12-month follow-up	• Pain (VAS) • Neck endurance test	Neck-specific training and physical activity reduced neck pain intensity.	No adverse events
Fritz et al. (46)	Patients with neck pain and signs of radiculopathy $n = 86$ 3 groups	• Group 1 ($n = 31$): 48.1 ± 10.0 • Group 2 ($n = 27$): 47.6 ± 10.9 • Group 3 ($n = 28$): 44.9 ± 11.3	Group 1: exercise with mechanical traction • Exercise (scapula and cervical strengthening) • Mechanical cervical traction during treatment • 30–45 mins per session; 10 sessions over a 4-week treatment Group 2: exercise with over-door traction • Exercise (scapula and cervical strengthening) • Traction using a Chattanooga Overdoor Traction Device during treatment • 30–45 mins per session; 10 sessions over a 4-week treatment	Group 3: exercise • Scapular and cervical strengthening • 30–45 mins per session; 10 sessions over a 4-week treatment	• After 4-week intervention • At 6-month follow-up • At 12-month follow-up	• Pain (pain catastrophizing scale) • Neck disability	Scapula and cervical strengthening with or without traction reduced pain intensity.	5.6% severe adverse events
Albert and Manniche (48)	Patients with radicular pain below the knee $n = 181$ 2 groups	• Group 1 ($n = 95$): 46 (38–52) • Group 2 ($n = 96$): 44 (37–51)	• Symptom-guided exercises (stabilizing and dynamic exercises) • Information • Advice to stay active • 4–8 times for 8 weeks	• Sham exercises (not back related) • Information • Advice to stay active • 4–8 times for 8 weeks	• At 8-week intervention • At 1-year follow-up	• Pain (VAS) • Global improvement • Functional status	Symptom-guided exercise reduced leg pain.	NA
Cox et al. (50)	Patients with type 2 diabetes $n = 32$ 3 groups	• Group 1 ($n = 10$): 57.8 ± 6.9 • Group 2 ($n = 10$): 58.7 ± 9.2 • Group 3 ($n = 12$): 59.5 ± 11.1	Group 1: supervised combined aerobic and resistance moderate-intensity continuous training (C-MICT) • 52.5 mins per time; 4 times per week for 8 weeks Group 2: supervised combined high-intensity interval training (C-HIIT) • 26 mins per time; 3 times per week for 8 weeks	• Group 3: usual care • 8 weeks	• After 8-week intervention	• Pain (VAS) • Neuropathy symptom	C-HIIT and C-MICT exercise groups showed reduction in pain intensity but not neuropathic symptoms.	Nineteen mild adverse events in C-HIIT group; 17 in C-MICT group.

(Continued)

TABLE 3 | Continued

References	Participants		Intervention protocol		Outcome assessment	Outcome measures	Results of pain	Safety
	Population Sample size Study design	Age (years)	Intervention group 1	Intervention group 2 or control group				
Win et al. (51)	Patients with diabetic peripheral neuropathy $n = 75/104$ 2 groups	• Group 1 ($n = 32$): 55.38 ± 9.54 • Group 2 ($n = 43$): 55.72 ± 10.55	• Simple hand, finger, and foot exercises • Three times a week for 8 weeks	• Usual care • Diabetic foot care education	• After 8-week intervention • At 16-week follow-up	• Pain (VAS) • Activities of daily living	Simple hand, finger, and foot exercises reduced pain intensity.	No adverse event
Hwang et al. (54)	Female patients before radiotherapy after various operations $n = 37/40$ 2 groups	• Group 1 ($n = 17$): 46.3 ± 7.5 • Group 2 ($n = 20$): 46.3 ± 9.5	• Supervised moderate-intensity exercise (stretching, aerobic and strengthening exercise) • 50 mins per time; 3 times per week for 5 weeks	• Self-shoulder stretching education and advice to normal activities	• After 5-week intervention	• Pain (VAS) • QOL • Shoulder range of motion	Supervised moderate-intensity exercise reduced pain intensity.	No significant adverse events
Dhawan et al. (55)	Patients with neck pain and signs of radiculopathy $n = 45$ 2 groups	• Group 1 ($n = 22$): 50.5 ± 7.9 • Group 2 ($n = 23$): 52.5 ± 6.6	• Home-based muscle strengthening • Balancing exercise • 30 mins daily for 10 weeks	• Usual care	• After 10-week intervention	• Pain (Leeds Assessment of Neuropathic Symptoms and Signs) • QOL	Muscle strengthening and balancing exercise significantly reduced neuropathic pain.	No adverse effects
Maharaj and Yakasai (57)	Patients with HIV-induced distal symmetrical polyneuropathy $n = 136$ 3 groups	• Group 1 ($n = 45$): 38.29 ± 8.06 • Group 2 ($n = 44$): 35.98 ± 8.53 • Group 3 ($n = 47$): 36.13 ± 8.10	Group 1: Aerobic exercise • 30 mins per time; 3 times per week for 12 weeks Group 2: progressive resisted exercise • 30 mins per time; 3 times per week for 12 weeks	Group 3: control group • Attended HIV talks, video presentations, and counseling	• After 6-week intervention • After 12-week intervention	• Pain (VNRS)	Aerobic exercise and progressive resisted exercise significantly reduced pain intensity.	No adverse effects
Tumusiime et al. (58)	Patients with HIV-associated peripheral neuropathy $n = 120$ 2 groups	• Group 1 ($n = 60$): 41.2 ± 7.8 • Group 2 ($n = 60$): 40.4 ± 7.7	• Physiotherapy-led aerobic exercises (stretching, strengthening and balance exercises) • Routine Health Care • 60 mins per each session; 3 times a week for 12 weeks	• Routine Health Care	• After 12-week intervention • At 12-week follow-up	• Pain (VNRS)	Physiotherapist-led aerobic exercises reduced neuropathic pain.	NA
Ammitzbøll et al. (62)	Female patients after breast cancer surgery $n = 158$ 2 groups	• Group 1 ($n = 82$): 53 ± 10 • Group 2 ($n = 76$): 53 ± 10	• Supervised and self-administered, progressive resistance training intervention initiated 3 weeks after surgery • The first 20-week physiotherapist-led exercise (weekly once) • The following 30-week self-administered exercise	• Usual care (information concerning post-operative care and mobility exercises)	• After 20-week intervention • After 12-month intervention	• Pain (VNRS)	Supervised and self-administered, progressive resistance training reduced pain intensity.	NA

Age were showed as mean ± SD or median (25–75% Interquartile Range). Simple size was shown as "the number of finial analysis"/"the number of included patients."
VAS, visual analog scale; VNRS, verbal numerical rating scale; ROM, range of motion; MMAS, modified motor assessment scale; PROMIS, patient-reported outcomes measurement information system; NA, not available.

TABLE 4 | Characteristics of included systematic reviews.

References	Participants	Study and sample size	Intervention	Control	Results of pain
Boldt et al. (27) and Harvey et al. (15)	Patients with spinal cord injury	3 RCT, $n = 149$	Exercise (stretching and strengthening exercises)	Control (no treatment or 1-h educational video control)	Exercise decreased pain intensity.
Gómara-Toldrà (28)	Patients with spinal cord injury	5 trials, $n = 81$	Exercise (treadmill training, strengthening, and stretching exercises)	NA	Exercise decreased pain intensity.
Demaneuf et al. (36)	Patients with multiple sclerosis	10 RCT, $n = 389$	Exercise (aerobic, resistance, and the combination exercises)	Passive control groups (waiting list or normal treatment)	Exercise decreased pain intensity.
Fernandez et al. (47)	Patients With Sciatica	5 RCT, $n = 604$	Exercise (Stabilization exercises, hydrotherapy and isometric exercises.)	Advice to stay active	Exercise decreased pain intensity.
Tough et al. (53)	Patients with cancer	1 trial, $n = 81$	Exergaming (Breakout 3D, Card Island and other exergaming)	NA	Exercise decreased pain intensity.
McNeely et al. (60) and De Groef et al. (61)	Female patients following breast cancer surgery	1 trial, $n = 30$	Exercise (exercise for arm/shoulder, posture correction, coordination, and strengthening exercises)	Leaflet with advice and exercises for arm and shoulder	Exercise decreased pain intensity.

RCT, randomized controlled trial; NA, not available.

severe health problem that influences their physical and mental functions and daily lives. Three systematic reviews reported that exercise is effective in relieving pain in patients with spinal cord injury (15, 27, 28). Two systematic reviews (15, 27), which involved the same three RCTs ($n = 149$ patients with spinal cord injury) illustrated that both short–term and long–term stretching and strengthening exercises can decrease chronic shoulder pain through the 36-Item Short Form Survey for pain experience [weight mean difference (WMD) $= -1.9$, 95% CI $= -3.4$ to -0.4, $P = 0.01$] and pain visual analog scale (WMD $= -2.8$, 95% CI $= -3.77$ to -1.83, $P < 0.00001$) compared with no treatment or 1-h educational video control (Level of evidence I). Furthermore, a randomized cross-over study by Labruyère and van Hedel (29) ($n = 9$) found that strength training ($-6.8\% \pm 2.5\%$) and robot-assisted gait training ($-4.5\% \pm 2.2\%$) can relieve pain experience during single training intervention and after 16 sessions in patients with incomplete spinal cord injury. Meanwhile, the immediate pain relief was slight whereas integral effect was substantial, and the difference in pain is in favor of strength training compared with robot-assisted gait training ($P < 0.01$). Additionally, strength training could improve the 10-meter walk test and balance function (Level of evidence II).

Expert Recommendation

We recommend using exercise programs, such as stretching and strengthening exercises, as treatment for NP in patients with spinal cord injury (Level of evidence II, A).

Consensus Recommendations for Post-stroke Pain

Up to 50% of patients with stroke report pain after stroke (30). Post-stroke chronic pain makes motor function, cognition, quality of life, and depression worse. However, post-stroke pain is commonly underestimated by patients and physicians who more focus on hemiplegia and deficient motor functions. One RCT by Costantino et al. (31) including 32 patients with stroke found that the subjects who underwent voluntary isometric muscle contraction in upper extremities with and without vibrations for 4 weeks reported decreased pain (Level of evidence II). According to another RCT (32) on 12 post-stroke patients, the participants who did joint motion and strengthening training *via* a specific exercise tool experienced less pain than the participants without intervention at 4, 8, and 12 weeks (Level of evidence II). Similarly, a RCT ($n = 40$) pointed out that 3-week neuromuscular joint facilitation combined with acupuncture can reduce post-stroke pain more than 3-week pure acupuncture therapy (33) (Level of evidence II). By contrast, another RCT involving 50 patients with stroke observed that a 1-h active, high-intensity, and repetitive training of the upper extremities had no clinically important effects on pain intensity compared with usual upper limb therapy (34) (Level of evidence II). The different findings might be caused by the specific training device, called SMART Arm, or severe physical condition of participants, which is no more than 90° of the affected shoulder flexion.

Expert Recommendation

We recommend using strengthening exercise and neuromuscular joint facilitation as a treatment for patients with post-stroke pain (Level of evidence II, C).

Consensus Recommendations for Pain Associated With Multiple Sclerosis

Multiple sclerosis is characterized by demyelination and axonal loss in the central nervous system accompanied by NP. According to previous studies, 29–86% of patients with multiple sclerosis suffer from NP, leading to depression and low-quality of life (35). One systematic review and two RCTs reported the effectiveness of exercise training in relieving pain in patients

TABLE 5 | Physiotherapy evidence database scores of included RCT studies.

References	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	Total (0–10 Scale)	Quality
Labruyère and van Hedel (29)	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	6	Moderate
Costantino et al. (31)	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6	Moderate
Jeon et al. (32)	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5	Moderate
Wei et al. (33)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4	Moderate
Horsley et al. (34)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8	High
Pilutti et al. (38)	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5	Moderate
Grubić Kezele et al. (39)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7	High
Hasanpour-Dehkordi et al. (40)	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5	Moderate
Young et al. (41)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7	High
Pérez de la Cruz (43)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7	High
Diab and Moustafa (44)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7	High
Halvorsen et al. (45)	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5	Moderate
Fritz et al. (46)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8	High
Albert and Manniche (48)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7	High
Cox et al. (50)	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6	Moderate
Win et al. (51)	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4	Moderate
Hwang et al. (54)	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5	Moderate
Dhawan et al. (55)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7	High
Maharaj and Yakasai (57)	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6	Moderate
Tumusiime et al. (58)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8	High
Ammitzbøll et al. (62)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7	High

High quality: total score ≥7; moderate quality: total score 4–6; low quality: total score ≤3.

TABLE 6 | Quality ratings of included systematic reviews evaluated using AMSTAR.

References	Priori design	Duplicate study selection and data extraction	Comprehensive literature search	Search for gray literature	List of studies included and excluded provided	Characteristics of included studies provided	Scientific quality assessed	Scientific quality used to formulate conclusions	Methods to combine study findings appropriate	Publication bias assessed	Conflict of interest	Total (0–11 Scale)	Quality
Harvey et al. (15)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	CA	Yes	8	High
Boldt et al. (27)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Gómara-Toldrà et al. (28)	Yes	Yes	Yes	CA	No	Yes	Yes	Yes	No	No	No	6	Moderate
Demaneuf et al. (36)	Yes	Yes	Yes	CA	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Fernandez et al. (47)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	NA	No	7	High
Tough (53)	Yes	Yes	Yes	CA	No	Yes	Yes	Yes	No	Yes	Yes	8	High
McNeely (60)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CA	Yes	10	High
De Groef et al. (61)	Yes	Yes	Yes	CA	No	Yes	Yes	Yes	No	No	No	6	Moderate

High quality: total score ≥ 7; moderate quality: total score 4–6; low quality: total score ≤3.
CA, cannot answer; NA, not applicable.

with multiple sclerosis. The systematic review and meta-analysis of 10 RCTs involving 389 patients by Demaneuf et al. (36) demonstrated that exercise interventions, including single aerobic exercise, aquatic aerobic exercise, resistance training, and the combination of these interventions, have more positive effects on the pain intensity by patients with multiple sclerosis than passive control groups [standardized mean difference (SMD) = −0.46, 95% CI = −0.92 to 0.00, between-study heterogeneity (I^2) = 77.0%; Level of evidence I]. A RCT (37, 38) showed that 24-week cycling exercise with functional electrical stimulation could help alleviate pain in comparison with passive leg cycling exercise (SMD = −0.67; Level of evidence II). Similarly, another RCT illustrated that 4-week upper extremity, breathing and independent home exercises has a trend toward less pain than physical therapy without exercise (39) (Level of evidence II).

Furthermore, a RCT (n = 60) reported that the exercise group with 12-week yoga intervention showed an improvement in pain intensity and physiological indices compared with the group without exercise (40) (Level of evidence II). However, one three-arm RCT (n = 81) reported by Young et al. (41) argued that the pain conditions among 12-week movement to music, adapted yoga with a series of stationary poses, and waitlist control have no substantial differences (Level of evidence II). The conflicting results could be explained by different study design, such as participants, control groups and movement positions during yoga.

Expert Recommendation

We recommend using aerobic, aquatic aerobic, and resistance training as pain treatment for patients with multiple sclerosis (Level of evidence II, B).

Consensus Recommendations for Pain Associated With Parkinson's Disease

In addition to dystonia, pain is another serious symptom that impacts the motor function, depression condition, and daily lives of patients with Parkinson's disease (42). A single-blinded RCT (n = 30) found that 10-week aquatic Tai Chi training and usual exercise that focuses on gait, balance, and muscle strength can decrease pain intensity in people with Parkinson's disease (43) (Level of evidence II). Moreover, aquatic Tai Chi is more superior than usual exercise in pain reduction and gait and balance condition improvement.

Expert Recommendation

We recommend using aquatic Tai Chi, muscle strengthening training, and balance exercise as treatment for pain in patients with Parkinson's disease (Level of evidence II, C).

Consensus Recommendations for Painful Radiculopathy

Cervical Radiculopathy

Cervical radiculopathy is a subgroup of neck pain characterized by pain radiating along the affected arms. The sort and intensity of symptoms, such as NP and muscle weakness, depend on the extent of cervical spinal nerve root compression. Three RCTs suggestion the use of an exercise program as a treatment for

TABLE 7 | Recommendation summary of exercise for neuropathic pain management.

Neuropathic pain	Recommendations	Level of evidence	Grades of recommendation	Consensus
Spinal cord injury	Yes	II	A	100% Yes (21 voters)
Post-stroke pain	Yes	II	C	95% Yes (21 voters)
Multiple sclerosis	Yes	II	B	95% Yes (21 voters)
Parkinson's disease	Yes	II	C	100% Yes (21 voters)
Cervical radiculopathy	Yes	II	B	100% Yes (21 voters)
Sciatica	Yes	I	A	100% Yes (21 voters)
Diabetic neuropathy	Yes	II	B	95% Yes (21 voters)
Chemotherapy-induced peripheral neuropathy	Yes	II	B	95% Yes (21 voters)
Neuropathy due to HIV/AIDS	Yes	II	B	100% Yes (21 voters)
After surgery for breast cancer	Yes	I	A	86% Yes (21 voters)

subjects with cervical radiculopathy. According to Diab and Moustafa (44), one RCT ($n = 96$) reported that a 10-week physical exercise comprised of neck muscle strengthening and stretching combined with ultrasound and infrared radiation are more effective on pain relief than the combination of ultrasound and infrared radiation in the short term and 6-month follow-up (Level of evidence II). Another RCT, which involved 75 patients with cervical radiculopathy, suggested that 14 weeks of neck-specific training targeting sensory and motor function and 14-week physical activities can reduce NP intensity and increase the endurance of neck flexors in the long term (45) (Level of evidence II). Furthermore, a RCT ($n = 86$) reported by Fritz et al. (46) suggested that although exercise that aimed to strengthen the scapula and cervical muscles are helpful to alleviate neck and arm pain, the combination of exercise and mechanical traction has a greater advantage in pain relief and function improvement than single exercise at 4-week, 6-month, and 12-month time points (Level of evidence II).

Expert Recommendation

We recommend using exercise training that targets neck muscle strength and stretch as treatment or complementary therapy for NP associated with cervical radiculopathy (Level of evidence II, B).

Sciatica

Sciatica is a defined as a subgroup of low back pain with a specific symptom, that is, radicular leg pain radiating along the distribution of the sciatic nerve (14). Although the prevalence of sciatica is much lower than low back pain, the affected region and prognosis are normally more severe; therefore, sciatica contributes a high degree of hopelessness and depression. A systematic review and meta-analysis (5 RCTs, $n = 604$) pointed out that an exercise program comprised of static and dynamic stabilizing exercises, hydrotherapy, and isometric exercises that target the trunk and lower extremity muscles is beneficial to leg pain reduction (WMD = 11.43, 95% CI = 0.71–22.16) but not disability (WMD = 1.45, 95% CI = −2.86–5.76) in the short term compared with advice to stay active among patients suffering from sciatica (47) (Level of evidence I). According to a single-blinded RCT that involved 181 patients with severe sciatica by Albert and Manniche (48), symptom-guided exercises, such as postural instructions, stabilizing exercises for deep muscles, and dynamic exercises for surface muscles in the trunk region, had a trend to a larger reduction of leg pain than the sham exercise group that performed low-intensity and no back-related training (Level of evidence I).

Expert Recommendation

We recommend using motor control, aquatic stabilizing movements, and isometric exercises that target the trunk and lower extremity muscles as an adjunct treatment for pain in patients with sciatica (Level of evidence I, A).

Consensus Recommendations for Painful Polyneuropathy

Diabetic Neuropathy

Diabetic peripheral neuropathy marked by pain and sensory and mobility loss, is a common and often disabling complication of diabetes mellitus (49). Diabetic neuropathy has been considered a serious problem because its treatments are likely ineffective. Two clinical trials investigated the effectiveness of exercise training on pain in diabetic neuropathy. One three-arm RCT divided 32 inactive patients with type 2 diabetes into three treatment groups: usual care, the combination of aerobic exercise and continuous moderate-intensity resistance training, and the combination of aerobic exercise and high-intensity interval training (50). The findings suggested that 8-week moderate-intensity and high-intensity exercise interventions are more beneficial in decreasing pain intensity but not neuropathic symptoms compared with single usual care lasting for 8 weeks (Level of evidence II). Particularly, the combination of aerobic exercise and high-intensity interval training significantly alleviated pain intensity. Based on another RCT ($n = 104$) comparing an 8-week simple hand, finger, and foot exercise with health education and control group with health education by Win et al. (51), both groups appeared decreased pain and the exercise intervention could relieve more pain than the control group in the short term and at 16-month follow-up (Level of evidence II).

Expert Recommendation

We recommend using general exercise focusing on distal extremities, or the combination of aerobic and

moderate-intensity or high-intensity exercises, as a treatment for pain in patients with diabetes (Level of evidence II, B).

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy, a common side effect of cancer treatment with a prevalence of 30–80%, is a small-fiber sensory neuropathy in the hands or feet (17). The typical symptoms are shooting pain, stabbing pain, or burning pain, which progressively becomes worse with chemotherapy (52). A systematic review by Tough et al. (53) mentioned that one pre–post clinical trial found a slight reduction in pain intensity and improvement of balance, motor functions, and depression status with higher adherence rates and enjoyment after 8 weeks of progressive exergaming program, which is a combination of exercise and games (Level of evidence II). Similarly, in a RCT study ($n = 40$), Hwang et al. (54) found that a 30-min exercise program that includes stretching and aerobic training could reduce pain and improve motor functions in patients after radiotherapy more than self-stretching training after 5 weeks of intervention (Level of evidence II). According to one RCT involving 45 patients with cancer reported by Dhawan et al. (55), a 10-week muscle strength and balance training has more positive effects on decreasing the NP intensity ($P < 0.0001$) and increasing quality of life ($P = 0.0002$) in patients with cancer who suffer from chemotherapy-induced peripheral neuropathy compared with usual care (Level of evidence II).

Expert Recommendation

We recommend muscle strengthening and balance training as treatment and exergaming as adjunct therapy for chemotherapy-induced NP (Level of evidence II, B).

Neuropathy Due to HIV/AIDS

Up to 90% of patients with HIV/AIDS complain about pain due to various reasons, including viral infection of the peripheral or central nervous system and side effects of anti-retroviral therapy (56). A three-arm RCT compared 12-week aerobic exercise (cycling), progressive resistance exercise focused on muscles in the lower extremities, and no exercise control among 136 patients with HIV (57). The findings suggested that aerobic and progressive resistance exercise are helpful and safe in the treatment of NP compared with no exercise at 6- and 12-week points (Level of evidence II). Moreover, one high-quality RCT, which involved 120 patients with HIV who underwent anti-retroviral treatment, supported that supervised aerobic exercise, including isometric, balance, and breath training, could alleviate NP more than non-exercise control after 12 weeks of intervention and at the 12 weeks of follow-up (58) (Level of evidence II).

Expert Recommendation

We recommend aerobic and progressive resistance training as an adjunct treatment for NP in people with HIV/AIDS (Level of evidence II, B).

Consensus Recommendations for NP Following Surgery

Chronic postsurgical pain is multifactorial and affects up to 50% of patients who underwent operation. Surgeries operated in the thorax, breast, and hernia regions and those that easily produce nerve injury have a high risk of postsurgical NP (59). According to a systematic review by McNeely et al. (60), exercise intervention is more effective in improving pain intensity than usual care despite no significant difference and has no adverse effects for post-operation patients with breast cancer after 3 weeks of intervention or in the 6-month follow-up (Level of evidence I). Additionally, one systematic review reported that posture correction and strengthening exercises are more beneficial to alleviate the post-operation pain and improve the motor functions in patients undergoing breast cancer surgery compared with education only or no intervention (61) (Level of evidence I). One RCT that consists of 158 female patients with breast cancer who underwent axillary lymph node dissection showed that a 12-month self-administered progressive resistance exercise program focusing on the whole body could alleviate NP more than usual care (62) (Level of evidence I).

Expert Recommendation

We recommend using muscle strengthening and posture correction as treatment for NP after operation for breast cancer (Level of evidence I, A).

DISCUSSION

The study aimed to review the effectiveness and efficacy of exercise on diseases with neuropathic pain through evidence, thereby producing evidence-based exercise recommendations for NP and informing medical staff and policymaker about the formulation of exercise prescription. A total of eight systematic reviews and 21 RCTs were included, which involved various exercise, such as strengthening, stretching, aquatic aerobic, balance trainings. Finally, 10 recommendations for NP caused by different disorders, including spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, cervical radiculopathy, sciatica, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, HIV/AIDS, and surgery, were described. Various exercise programs may have some benefits in improving pain and functions and proper exercise can be used as an effective alternative treatment or complementary therapy for different disorders with NP.

This paper was the first expert consensus to report exercise recommendations for different diseases with NP, including spinal cord injury, stroke, multiple sclerosis, Parkinson's disease, cervical radiculopathy, sciatica, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, surgery, and HIV/AIDS. We searched studies published before January 2021. Then, the grades of recommendations were based on the strength of evidence and a consensus discussion of the results of the Delphi rounds. In addition, we used PEDro and AMSTAR to assess the quality of the included RCTs and systematic reviews. Finally, all studies that met the inclusion criteria and were

deemed to have levels of evidence of I and II were included in this expert consensus.

Some limitations have to be considered in this study. First, the recommendations were made through qualitative analysis in this consensus whereas more specific and rigorous clinical recommendations that include the types, intensity, and frequency of exercise should be decided by quantitative analysis. Second, different from most guidelines that used Grading of Recommendations, Assessment, Development and Evaluations to make clinical practice recommendations (63, 64), we assessed the levels of evidence through Oxford CEBM and evaluated the grades of recommendation according to the methods established by the American Physical Therapy Association. Moreover, most of the RCTs (47.62%) and systematic reviews (75%) have high quality based on PEDro and AMSTAR scores, respectively. Nevertheless, some outcomes of the meta-analyses had considerable heterogeneity, thereby providing relatively inferior evidences. Furthermore, because studies on the various exercise for NP are limited, we did not summarize the recommendations according to different types of exercise, such as aerobic exercise or progressive resistance training, or provide detailed information about intensity, time, or frequency of exercise prescription. Finally, we did not adequately describe the effect of exercise on other aspects among patients with difference diseases since the NP intensity was the focus in the study.

CONCLUSION

Exercise can be considered as a feasible, and effective alternative treatment or complementary therapy for most patients with NP caused by different diseases. An updated consensus statement will be required if adequate new studies will be available in the future. This consensus statement will require regular updates after 5–10 years to guarantee that treatments and recommendations continue to be supported by the latest evidence. More high-quality randomized controlled trails are required to provide more superior evidence in the future. Exercise with various types, intensities, and frequencies; patient preference; and facility conditions should be considered as well in further studies.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

G-EF and X-QW: conceptualization and supervision. Y-HZ, Y-CX, GP, LH, Y-ZK, Y-LW, J-BG, SB, T-SL, L-JA, C-HW, Y-LB, LF, CM, L-RL, HL, YZ, Z-JZ, C-LL, G-EF, and X-QW: methodology and visualization. Y-CX, CP, LH, Y-ZK, Y-LW, J-BG, SB, T-SL, L-JA, C-HW, Y-LB, LF, CM, L-RL, HL, YZ, Z-JZ, C-LL, G-EF, and X-QW: validation. Y-HZ and H-YH: writing—original draft preparation. Y-HZ and X-QW: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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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.2021.756940/full#supplementary-material

Supplementary Material 1 | The details of the search strategy for the PubMed database.

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Physical Activity and the Risk of Hemorrhagic Stroke: A Population-Based Longitudinal Follow-Up Study in Taiwan

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Background: Data on the relationship between physical activity (PA) and hemorrhagic stroke (HS) are limited in Asian populations. This population-based longitudinal follow-up study therefore investigates whether PA is associated with a reduced risk of HS in Taiwan.

Methods: A total of 58,857 subjects who had participated in the Keelung Community-based Integrated Screening Program between 2005 and 2012 were enrolled. Information about their PA, obtained using questionnaires, was used to categorize them into three groups according to their average weekly time engaged in it: (1) no PA, (2) low PA (<90 min weekly), and (3) high PA (90 min per week or more). Cox proportional hazard regression was used to evaluate the effect of PA on HS. Stratified analysis by sex and comorbidities (diabetes mellitus, hypertension, and hyperlipidemia) were conducted to evaluate their impact on the relationship between PA and HS.

Results: Compared to the no-PA group, the adjusted hazard ratio of HS for the low-PA group was 0.74 (95% CI, 0.57–0.96, $p = 0.0219$), and for the high-PA group, 0.72 (95% CI, 0.58–0.90, $p = 0.004$). The stratified analyses showed that, for the non-comorbidity strata, the beneficial effect of PA on reducing HS risk became stronger as PA increased. However, in the diabetes and hypertension strata, high PA did not appear to have any greater protective effect than low PA.

Conclusions: Our findings suggested that even <90 min of PA per week might be beneficial to reduce HS risk. Such a low level of PA is likely to be more achievable and easier to maintain for the general population. Additionally, personalized recommendations based on pre-existing comorbidities may help optimize the beneficial effects of PA on HS prevention.

Keywords: physical activity, hemorrhagic stroke, risk factor, cohort study, comorbidities

INTRODUCTION

Stroke is a leading cause of death and disability worldwide. Up to 80% of strokes can be prevented through the management of risk factors such as hypertension, diabetes mellitus (DM) (1), smoking, and physical inactivity (2). Physical activity (PA) is considered one of the most important modifiable risk factors for strokes (3), and in recent years, there has been an increased interest in the effects of PA on stroke prevention. PA may improve vascular function and reduce the risk of stroke by preventing the development of risk factors such as DM and hypertension (4, 5). However, while previous studies have demonstrated that PA may prevent strokes, their evidence base mostly comprises ischemic strokes (6), and data linking PA and hemorrhagic stroke (HS) are relatively limited (7). Moreover, most of the prior studies regarding the relationship between PA and HS were conducted in Western countries, and parallel evidence drawn from Asian populations is even more sparse (4). As well as their different genetic backgrounds, such populations have different lifestyles from their Western counterparts, and their incidence of HS is higher (1). One study from Japan showed that moderate levels of PA were associated with a reduction of approximately 30% in the risk of HS (4). However, a Korean study reported that PA had no significant protective effect against HS (8). Given the limited and inconsistent findings on the relationship between PA and HS in Asian populations, we conducted the present population-based, longitudinal follow-up study to investigate whether PA is associated with a reduced risk of HS and the optimal level of PA for HS prevention in Taiwan. The primary outcome of this study was a new diagnosis of HS retrieved from Taiwan's healthcare database.

MATERIALS AND METHODS

Data Source

This study used data from the Keelung Community-based Integrated Screening program (KCIS), which was conducted by health-service centers in Keelung City, Taiwan (9). The implementation of KCIS started in 1999, and it was originally designed for national neoplastic disease screening. Subjects were invited to participate in it by public-health nurses, and data on their demographic characteristics and lifestyle habits (smoking, drinking, PA, diet, etc.) were collected using structured questionnaires.

The present study used KCIS data from 2005–2012, and linked them to Taiwan's national health insurance research database (NHIRD) and mortality registry for the same 8-year period plus the three following years, i.e., 2013–2015. The NHIRD and mortality-registry data were from the Health and Welfare Data Science Center database at National Taiwan University's Health Data Research Center. Taiwan's national health insurance program is single-payer, compulsory social insurance, and NHIRD is a large-scale healthcare database covering more than 98% of Taiwan's population. Therefore, by linking these databases, a large-scale representative sample of screening data and healthcare records can be collected for analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

The present study was approved by the National Taiwan University Hospital Research Ethics Committee. Before analyzing the data, all personal ID numbers in the database were encrypted as alphanumeric codes to protect personal information. The health data used in this study could only be accessed in a privacy-protected room within the Health Data Research Center. Because the data were in de-identified form and analyzed anonymously in a privacy-protected environment, the requirement for informed consent was waived.

Study Subjects and Covariates

We carried out a longitudinal follow-up study to investigate the impact of PA on HS risk. The questionnaire asked each subject *Are you currently in the habit of engaging in PA?* (Answer options: 0. Never 1. Yes); and those who answered yes were also asked *How many times do you engage in PA in a week?* and *How many minutes is your PA each time?* Based on the answers to these two follow-up questions, each subject's weekly PA time was obtained by multiplying his/her self-reported number of weekly PA sessions by the minutes each one lasted.

Based on the weekly PA time we calculated, the subjects were categorized into three groups: (1) a no-PA (NPA) group, comprising subjects who answered "Never" to our initial PA question; (2) a low PA (LPA) group, consisting of subjects whose weekly PA times were <90 min; and (3) a high PA (HPA) group, which included subjects whose weekly PA times were 90 min or more. We chose 90 min as the cut-off point between LPA and HPA because a prior population-based study in Taiwan showed that 90 min a week of PA reduced mortality from all causes (10). The recruitment process for the three groups is shown in **Figure 1**.

We defined the date of initial screening, i.e., questionnaire completion, as the index date. Subjects aged 20 or above at their index dates, provided that those index dates fell within 2005–12, were included ($N = 61{,}466$). We excluded subjects who had ever been diagnosed with a stroke [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), code 430-438] prior to their respective index dates. After excluding 1,811 subjects who had a history of stroke, 59,655 subjects were left.

As the risk of HS may be affected by demographic factors, lifestyle, and comorbidities (8, 11, 12), these covariates were included in our analysis. The baseline demographic and lifestyle factors collected upon initial screening included sex, age, body mass index, smoking, drinking, and education level. Healthcare records in the NHIRD dating from prior to each patient's the index visit were used to gather information on his/her comorbidities, including DM (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9- CM code 272), coronary heart disease (ICD-9-CM codes 410-414, 429.2), atrial fibrillation (ICD-9-CM code 427.31), cancer (ICD-9-CM code 140-208), chronic obstructive pulmonary

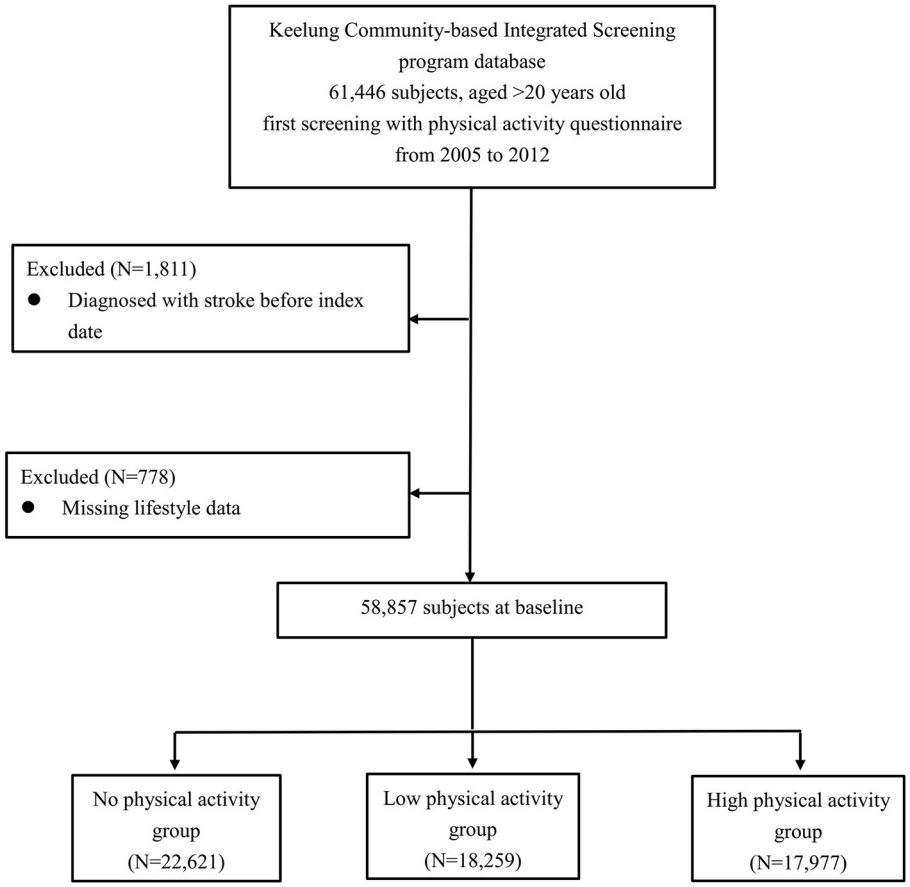

FIGURE 1 | Flow chart illustrating the enrollment process of the study population.

disease (ICD-9-CM codes 491, 492, 496), osteoarthritis (ICD-9-CM code 715), and chronic kidney disease (ICD-9-CM code 585). To maximize the case ascertainment of such diagnoses, we defined a comorbidity as present if there was at least one discharge record or two outpatient visits with the relevant diagnosis code(s). This case definition has been adopted in previous studies that relied on administrative data (13). Due to missing lifestyle data, a further 778 subjects were excluded, leaving a final sample of 58,857 subjects, who were then divided into the NPA, LPA, and HPA groups as described above.

Outcome

The primary outcome of this study was a new diagnosis of HS. All outpatient and inpatient healthcare records for each subject were retrieved from the NHIRD. The subjects were tracked from their respective index dates to the earliest of (1) their first occurrence of HS, (2) their death, or (3) the end of 2015. A diagnosis of HS was determined by at least one inpatient discharge or two outpatient visits with a principal diagnostic code of HS (ICD-9-CM codes 430–432). Death dates and causes of death were obtained from the mortality registry.

Statistical Analysis

We examined the differences in demographic, lifestyle, and comorbidity variables across the three PA groups using chi-square tests and analysis of variance. The incidence rate was calculated as the number of HS events in the group divided by the total follow-up time of the group (per 1,000 person-years). We used the Cox proportional hazard regression analysis to estimate the effects of different PA levels on HS. Since the association between PA and HS may vary with sex and comorbidities, we conducted stratified analysis by sex and comorbidities to evaluate their impact on the association between PA and HS risks (14). An alpha level of 0.05 was considered statistically significant. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Table 1 lists the distribution of baseline demographic factors, lifestyle factors, and comorbidities in the NPA, LPA, and HPA groups. In the LPA group, the median PA time was 45 min per week [interquartile range (IQR) = 30], and in the HPA group it was 210 minutes per week (IQR = 270). There were significant differences in the distribution of baseline characteristics across these three groups ($p < 0.0001$).

TABLE 1 | Baseline characteristics of the no physical activity (NPA), low physical activity group (LPA), and high physical activity (HPA) groups.

Variable	NPA (*N* = 22,621)	LPA (*N* = 18,259)	HPA (*N* = 17,977)	*p*-value*
Sex (women)	14,791 (65.4)	10,790 (59.1)	9,413 (52.4)	<0.0001
Age (years)	44.0 ± 14.4	42.3 ± 13.4	52.8 ± 15.6	<0.0001
Body mass index (kg/m^2)	24.0 ± 4.2	23.9 ± 3.9	24.5 ± 3.7	<0.0001
Smoking status				<0.0001
Non-smoker	15,754 (69.6)	13,368 (73.2)	13,377 (74.4)	
Ex smoker	1,150 (5.1)	1,284 (7.0)	1,446 (8.1)	
Current smoker	5,717 (25.3)	3,607 (19.8)	3,154 (17.5)	
Drinking				0.0001
Non-drinker	17,480 (77.3)	13,751 (75.3)	13,775 (76.6)	
Ex drinker	746 (3.3)	682 (3.7)	622 (3.5)	
Current drinker	4,395 (19.4)	3,826 (21.0)	3,580 (19.9)	
Education				<0.0001
Less than high school	5,442 (24.1)	2,369 (13.0)	5,676 (31.6)	
High school	10,730 (47.4)	8,185 (44.8)	7,298 (40.6)	
College diploma	6,449 (28.5)	7,705 (42.2)	5,003 (27.8)	
Diabetes mellitus	1,176 (5.2)	766 (4.2)	1,626 (9.0)	<0.0001
Hypertension	2,842 (12.6)	1,914 (10.5)	3,992 (22.2)	<0.0001
Hyperlipidemia	1,627 (7.2)	1,251 (6.9)	2,274 (12.7)	<0.0001
Coronary heart disease	874 (3.9)	514 (2.8)	1,336 (7.4)	<0.0001
Atrial fibrillation	55 (0.2)	42 (0.2)	81 (0.5)	<0.0001
Cancer	262 (1.2)	196 (1.1)	410 (2.3)	<0.0001
COPD	482 (2.1)	292 (1.6)	696 (3.9)	<0.0001
Osteoarthritis	1,282 (5.7)	820 (4.5)	1,819 (10.1)	<0.0001
Chronic Kidney Disease	80 (0.4)	46 (0.3)	95 (0.5)	<0.0001

Data are presented as N (%) or mean ± standard deviation.
COPD, Chronic obstructive pulmonary disease.
**Chi-square tests and analysis of variance.*

The average age of the HPA group (52.8 years) was higher than the NPA (44.0 years) and LPA (42.3 years) groups. Moreover, the prevalence of pre-existing comorbidities, such as diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, cancer, chronic obstructive pulmonary disease, and osteoarthritis, were higher in the HPA group than in the NPA and LPA groups.

The three groups' respective numbers of HS events and adjusted hazard ratios (HR) are shown in **Table 2**. The NPA group collectively experienced 171 HS events (0.98 per 1,000 person-years), the LPA group, 85 (0.60 per 1,000 person-years), and the HPA group, 168 (1.19 per 1,000 person-years). As compared with its NPA counterpart, the LPA group's adjusted HR for the risk of HS was 0.74 (95% CI, 0.57–0.96, $p = 0.0219$), and the HPA group's, 0.72 (95% CI, 0.58–0.90, $p = 0.004$).

Figure 2 presents our analysis stratified by sex and comorbidities. With regard to the former, in the women stratum, LPA and HPA had a protective effect against HS (LPA: adjusted HR = 0.62, 95% CI, 0.43–0.89; HPA: adjusted HR = 0.73, 95% CI, 0.55–0.96). In the men stratum, only HPA had a (slight) protective effect on HS (LPA: adjusted HR = 0.88, 95% CI, 0.63–1.23; HPA: adjusted HR = 0.75, 95% CI, 0.57–1.00).

TABLE 2 | Number of hemorrhagic stroke events and adjusted hazard ratios for the no physical activity (NPA), low physical activity (LPA), and high physical activity group (HPA) groups.

Variable	NPA (*N* = 22,621)	LPA (*N* = 18,259)	HPA (*N* = 17,977)
Hemorrhagic stroke events, *N*			
Yes	171	85	168
No	22,450	18,174	17,809
Risk per 1,000 person-year (95% CI)	0.98 (0.84–1.14)	0.60 (0.48–0.75)	1.19 (1.02–1.39)
Adjusted† Hazard ratio (95% CI)	1.00	0.74 (0.57–0.96)*	0.72 (0.58–0.90)*

CI, confidence interval.
**Cox proportional hazard regression analysis, significant at $P < 0.05$.*
†Adjusted for sex, age, body mass index, smoking status, drinking, education, diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, cancer, chronic obstructive pulmonary disease, and chronic kidney disease.

In our analysis stratified by DM (**Figure 2**), both LPA and HPA had protective effects against HS for the non-DM stratum (LPA: adjusted HR = 0.75, 95% CI, 0.57–0.98; HPA: adjusted HR = 0.67, 95% CI, 0.53–0.84). In the DM stratum, LPA seemed to be associated with a lower risk of HS although lacking statistical significance (adjusted HR = 0.58, 95% CI, 0.25–1.31). The effect of HPA on HS risk was close to null (adjusted HR = 1.07, 95% CI, 0.73–1.57).

In our analysis stratified by hypertension (**Figure 2**), for the non-hypertension stratum, LPA had a slight protective effect against HS (adjusted HR = 0.75, 95% CI, 0.56–1.00), whereas HPA had a significant protective effect (adjusted HR = 0.58, 95% CI, 0.44–0.75). However, for the hypertension stratum, only the LPA group tended to have a lower risk of HS (adjusted HR = 0.68, 95% CI, 0.41–1.11), and HPA was not associated with a reduced risk of HS (adjusted HR = 1.03, 95% CI, 0.78–1.37).

For the non-hyperlipidemia stratum in our analysis stratified by hyperlipidemia, the LPA group had a slightly lower risk of HS but lacking statistical significance (adjusted HR = 0.82, 95% CI, 0.63–1.07), and being a member of the HPA group was associated with a lower risk of HS (adjusted HR = 0.73, 95% CI, 0.58–0.93). In the hyperlipidemia stratum, on the other hand, both the LPA and HPA groups had a significantly reduced risk of HS (LPA: adjusted HR = 0.27, 95% CI, 0.11–0.67; HPA: adjusted HR = 0.62, 95% CI, 0.41–0.94).

In sum, for the non-DM, non-hypertension, and non-hyperlipidemia strata, the protective effect of PA against HS became stronger as PA time increased. However, in the DM and hypertension strata, HPA was not associated with a lower risk of HS than LPA was.

DISCUSSION

Although PA has been associated with a reduced risk of stroke (6, 15), the published evidence regarding the association between PA and HS in Asian populations has been limited and inconsistent

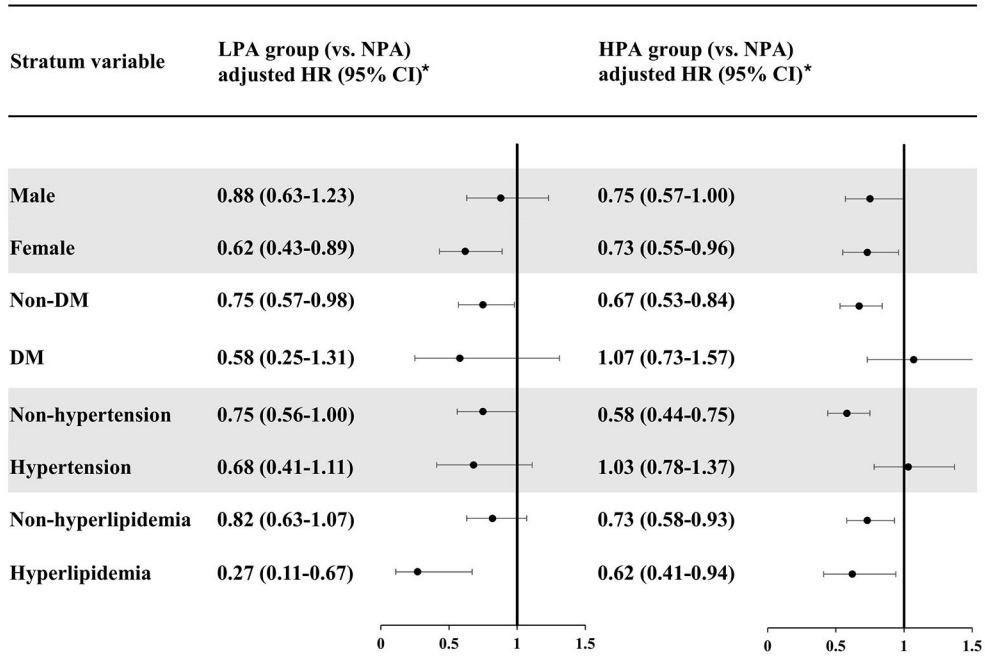

FIGURE 2 | Risk analyses of hemorrhagic stroke, stratified by sex, hypertension, diabetes mellitus, and hyperlipidemia. *Each cox regression model was adjusted for the baseline characteristics in **Table 1** except the stratum variable itself. NPA, no physical activity; LPA, low physical activity; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

(4, 8). Moreover, little is known about whether there is a dose-response relationship between PA and HS risk. The present study has shown that LPA and HPA were both associated a reduced risk of HS, as compared with NPA; and, as can be seen in **Table 2**, this risk reduction appeared to be of a similar magnitude for both LPA and HPA (adjusted HRs, 0.74 and 0.72, respectively). This latter finding that an increase in PA volume does not necessarily lead to a proportional reduction in HS risk seems to be compatible with previous researchers' suggestion that there is a non-linear dose-response relationship between PA and HS risk (4).

For primary prevention of cardiovascular diseases, the World Health Organization recommends ≥150 min per week of moderate intensity or 75 min per week of vigorous-intensity of aerobic PA, or an equivalent mixture of the two (16). The American Heart Association/American Stroke Association guidelines for primary prevention of stroke recommend that healthy adults perform at least moderate-to-vigorous intensity of aerobic PA at least 40 min a day, three to 4 days a week, i.e., 120–160 min per week (17). Our findings, however, imply that <90 min of PA a week might be sufficient to prevent HS, an amount considerably lower than the above-mentioned recommendations, and probably a more achievable goal for most adults. People should therefore be encouraged to take up any level of PA, however low, as a means of gaining the health benefits discussed above.

To our knowledge, only a handful of studies have been published on the relationship between PA and HS risk in Asian populations. One study from Japan reported that moderate levels of PA seemed to be optimal for HS prevention, reducing the risk by ∼30% (4). Similarly, in the present study, we found that <90 min a week of PA reduced HS risk by roughly 25% (**Table 2**). Although detailed information regarding types and intensities of PA was not included in the KCIS data, previous surveys have shown that about half of Taiwan's residents engage in strolling and brisk walking (18, 19). Lower PA times may be perceived as easier goals both to set and to achieve, given that lack of time has been found to be an important barrier to individuals engaging in PA (20).

Likewise, few previous studies have assessed the impact of sex and pre-existing cardiovascular risk factors on the relationship between PA and HS risk. Our stratified analysis by sex (**Figure 2**) suggests that PA is associated with a lower risk of HS in Taiwanese women, and that the protective effect of PA is stronger for these women than for their male counterparts.

In our analyses that were stratified by DM and by hypertension, PA seemed to have a greater protective effect against HS in the non-DM, non-hypertension strata. In addition, the HPA group experienced greater protective effects than the LPA group in those two strata. However, HPA was no better than LPA when it came to reducing HS risk in the DM and hypertension strata; i.e., there might be no advantage of HPA over LPA in individuals with these two conditions. But the cause of this apparent lack of benefit of more PA is unclear. It has previously been suggested that microangiopathy caused by DM or hypertension can lead to cerebral microbleeds (21), which may increase vulnerability to HS. Moreover, some adverse cardiovascular effects after excessive PA have been sporadically reported (22). Therefore, we hypothesize that DM-

or hypertension-related microangiopathy might counteract the potential benefit of HPA in reducing HS risk.

Our analysis stratified by hyperlipidemia, in contrast, showed that both LPA and HPA were associated with more HS risk reduction in the hyperlipidemia stratum than in the non-hyperlipidemia one (**Figure 2**). Previously, low cholesterol levels have been found to be associated with increased risk of HS (23). Therefore, the protective effect of PA on HS may be counteracted by the potential detrimental impact of low lipid levels on HS risk, and this could explain why the protective effect of PA on HS in the non-hyperlipidemia stratum in our study was less than that in the hyperlipidemia stratum.

According to our analyses stratified by comorbidities (DM, hypertension, hyperlipidemia), the HPA group had a higher magnitude of HS risk reduction than the LPA group in the non-comorbidity strata. Such findings imply that more PA per week should probably be recommended for relatively healthy persons without pre-existing cardiovascular risk factors as a means of HS prevention. In the comorbidity strata, however, the LPA group tended to experience a higher magnitude of HS risk reduction than the HPA group. Therefore, <90 min of PA per week might be a more appropriate approach to HS prevention for persons with pre-existing comorbidities such as hyperlipidemia. Accordingly, personalized recommendations based on the presence or absence of DM, hypertension, and hyperlipidemia may be helpful in optimizing the beneficial impact of PA on HS risk.

Most previous studies conducted in the western countries have reported that participation in PA decreases with age (24, 25). On the contrary, our study showed that the average age of the HPA group was higher than the NPA and LPA groups. Such finding is compatible with other studies conducted in Asia (26–28), and may be explained by increased exercise participation after retirement (29). In addition, because young or middle-aged people typically need to work long hours and take care of family, they may not have much time to engage in regular PA. Another interesting finding is the higher prevalence of pre-existing comorbidities in the HPA group. This finding may also be explained by the higher age in the HPA group, as the prevalence of comorbidities usually increases with age. Moreover, health-seeking behaviors after a disease diagnosis may also increase motivation to engage in PA (26).

The key strength of the present study is its use of a representative, population-based sample with longitudinal follow-up. This enabled us to examine the long-term relationship between PA and the subsequent risk of HS. In addition, we included a variety of comorbid medical conditions in the adjustment for regression analysis. Nonetheless, several limitations should be acknowledged. First, this study used self-reported PA, and detailed information on exercise types and intensities was not available in the original KCIS questionnaires. Therefore, misclassification errors may be present. Second, diagnoses of HS and comorbidities in this study were determined using ICD codes from the NHIRD. This may raise concerns about diagnostic accuracy. However, as well as seeking maximize case ascertainment as described above, we should point out that the Bureau of NHI has formed various audit committees that randomly sample claim data and review the sampled patients' healthcare records so as to optimize diagnostic accuracy and quality of care (30). Third, residents in Taiwan are of Chinese ethnicity, so it is uncertain whether our findings can be generalized to other ethnic groups.

CONCLUSIONS

Asian populations suffer HS more frequently than other populations. The present study has shown that even <90 min a week of PA might help to reduce HS risk in one such population. For most people, this level of PA is likely to be more achievable than the longer times recommended by the WHO and other organizations. Additionally, individualized recommendations regarding PA based on pre-existing comorbidities may help optimize the beneficial effects of PA on HS prevention. A modest amount of PA may be more favorable to lowering HS risk in patients with cardiovascular comorbidities (e.g., hyperlipidemia) than a greater amount. Conversely, more intense and/or lengthy PA may be more conducive to reducing HS risk in people without such comorbidities. However, future studies are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets are managed by the Health and Welfare Data Science Center at National Taiwan University's Health Data Research Center. Requests to access these datasets should be directed to ntuhdrc@ntu.edu.tw.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Taiwan University Hospital Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-HF, L-SC, K-CY, and S-LP designed the research, wrote the manuscript, and conducted the research. S-HF, K-CY, and S-LP analyzed data. All authors have read and approved the final manuscript.

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Effectiveness and response differences of a multidisciplinary workplace health promotion program for healthcare workers

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Background: Workplace health promotion (WHP) in the healthcare industry is an important yet challenging issue to address, given the high workload, heterogeneity of work activities, and long work hours of healthcare workers (HCWs). This study aimed to investigate the effectiveness and response differences of a multidisciplinary WHP program conducted in HCWs.

Methods: This retrospective cohort study included HCWs participating in a multidisciplinary WHP program in five healthcare facilities. The 20-week intervention included multiple easy-to-access 90-min exercise classes, one 15-min nutrition consultation, and behavioral education. Pre- and post-interventional anthropometrics, body composition, and physical fitness (PF) were compared with paired sample *t*-tests. Response differences across sex, age, weight status, and shiftwork status were analyzed with a generalized estimating equation.

Results: A total of 302 HCWs were analyzed. The intervention effectively improved all anthropometric (body mass index, waist circumference, waist-hip ratio, and waist-to-height ratio), body composition (body fat percentage, muscle weight, visceral fat area), and PF (grip strength, high jump, sit-up, sit-and-reach, step test) parameters in all participants (all $p < 0.05$). Subgroup analyses revealed shift workers had a more significant mean reduction in body mass index than non-shift workers (adjusted $p = 0.045$). However, there was no significant response difference across sex, age, and weight subgroups.

Conclusion: This study suggested that a multidisciplinary WHP program can improve anthropometric and PF profiles regardless of sex, age, and weight status for HCWs, and shifter workers might benefit more from the intervention.

KEYWORDS

anthropometrics, exercise intervention, hospital employee, multidiscipline, physical fitness, shiftwork, workplace health promotion

Introduction

While focusing on preserving people's health as their work duties, healthcare workers (HCWs) themselves are also in need of health promotion (1, 2). The literature has indicated that unfavorable working conditions, such as night shifts, long work hours, psychosocial job strain, and job insecurity, can lead to negative health outcomes, including obesity (3), metabolic syndrome (4), muscular-skeletal discomforts (5), mental disorders (6, 7), and certain cancers (8–13). It is not uncommon that HCWs have to work under stressful conditions with long hours and irregular shifts, which may have negative impacts on their health (14, 15). HCWs have been reported to have higher levels of sickness absence, work dissatisfaction, distress and burnout than workers in other industries (16).

The importance of workplace health promotion (WHP) is well recognized (17). Previous studies have suggested that WHP can lead to lower disease prevalence, reduced medical costs, and higher productivity (18–22). However, the high workload, heterogeneity of work activities, and long work hours can make hospitals a difficult setting to address WHP (23). Moberg et al. found significant associations between physical activity, physical capacity (defined with maximal oxygen uptake (VO_{2max}) and handgrip strength), and levels of musculoskeletal pain among HCWs (24). The same association was not observed in construction workers, suggesting that HCWs might be a population more likely to benefit from exercise-based WHPs (24).

Moreover, effectiveness of and predictors for the responses to WHP are not yet well understood (25–27). A systematic review conducted in 2012 showed positive effects of WHP on physical activity, diet, and body mass index (BMI) but insufficient evidence on absenteeism and mental health (28). According to a randomized clinical trial conducted by Reif et al., a significantly higher proportion of employees reported having a primary care physician and showed improvements in a set health belief in the treatment group of a 24-month WHP; however, no significant differences were observed in biometrics, medical diagnoses, or medical use (29). After an 18-month WHP in a clustered randomized trial, Song and Baicker found some positive self-reported health behaviors among the employees exposed but no significant improvement in health measures, healthcare spending and utilization, or employment outcomes (29). Another randomized controlled trial conducted by Patti and colleagues demonstrated that, subjects participating in different exercise programs differed in their improvements of physical performance (30). Mixed evidence indicates that WHP interventions can be somewhat effective (31), but it is still inconclusive and needs more research to confirm the benefit.

The global pandemic of COVID-19 has caused an unprecedented impact on healthcare systems worldwide, and research interests in the safety and health of HCWs have been growing ever since (32, 33); however, most focused on the infection of COVID-19 (34), vaccination against COVID-19 (35, 36), or mental health issues (37, 38). The latest review on HCWs health promotion was conducted by Brand et al., which included only 11 studies with system approaches (16). Data on effectiveness and response differences of WHP among HCWs remain insufficient. Validating WHP programs designed for use in hospitals and exploring the factors that influence intervention outcomes would benefit future design and implementation. This study examined the effectiveness of a multidisciplinary 20-week WHP program in northern Taiwan and analyzed response differences by sex, age, weight, and shiftwork statuses.

Materials and methods

Study design

This study was a retrospective case series to assess the effectiveness and response differences of a multi-site and multidisciplinary WHP program regarding anthropometrics, body composition (BC), and physical fitness (PF) of hospital employees. The original study was approved by the Institutional Review Board of the Chang Gung Memorial Foundation (No. 102-4004B). Informed consent was obtained from each subject. This study followed the guidelines of the World Medical Association Declaration of Helsinki (39) and the template for intervention description and replication (TIDieR) (40).

Participants

Participants were recruited to the WHP program *via* posters, emails, and e-bulletin systems between February 23rd to March 22nd, 2015, from three hospitals and two nursing centers of Chang Gung Medical Foundation in northern Taiwan. The participants had to primarily meet the following criteria: (1) employees of the aforementioned five healthcare facilities of Chang Gung Medical Foundation, (2) aged between 18 and 64 years, and (3) voluntary participation in the program. Participants with the following condition were excluded: self-reported history of stroke, coronary artery disease, or other major vascular diseases.

Basic information, anthropometrics, BC, and PF were assessed before and after the single-arm intervention program. Participants who did not complete the intervention or had no available pre- and post-interventional data of BC and PF were not eligible for statistical analysis. Unless the above conditions, all cases that met the inclusion criteria would be included.

Intervention – multidisciplinary program

The program was conducted by a multidisciplinary team, including family physicians, rehabilitation physicians, sport science experts, PF trainers, clinical dietitians, and research assistants. A diagrammatic overview of the intervention is presented in **Figure 1**.

The intervention was workplace-based, 20 weeks long, and multi-faceted, comprising three parts:

Exercise classes

Up to 24 group exercise classes per week (including 5 in the morning and 19 in the evening) were held during the intervention period. Styles of the classes included aerobic dance, kickboxing, cycling, and Yogalates. Each class had a limit on the number of participants, depending on the characteristic of the exercise style and the size of the venue. The sizes of venues ranged from 73 to 165 square meters. The limit number of classes ranged from 15 to 40 participants. Each participant was requested and allowed to register for one class per week in a first-come, first-served manner. A class would be closed for registration once the limit number of participants was reached.

All sessions were held either in or nearby the study hospitals and instructed by certified trainers. Every exercise class was 80 min, including stretching and warming up for the first 20 min, main exercise for 50 min, and cool down for the last 10 min. The intensities of classes varied. All courses were gender-neutral. Best efforts were made to ensure the accessibility of the exercise program by offering multiple choices of time, location, style, and intensities of the classes so that participants could easily find ones fitted into their schedule and preference.

In aerobic dance classes, the PF trainer leads the participants to dance to lively music. In kickboxing classes, participants boxed under a PF trainer's instruction, and the speed of boxing was emphasized to increase instantaneous velocity. Participants in cycling classes rode on spinning bikes under the guidance of the trainer. Yogalates was performed with participants doing yoga with a yogic instructor. The sustaining posture in yoga focused on the participants' muscle endurance and respiration.

Nutrition consultation

A 15-min one-on-one nutrition consultation session by professional clinical dietitians was provided to participants with overweight or obesity, excessive body fat percentage (BF%), or metabolic syndrome. Overweight was defined as BMI $>$ 24 according to the Ministry of Health and Welfare in Taiwan (41). Excessive body fat percentage was defined as BF% $>$ 20% in males and BF% $>$ 30% in females, according to the Sports Administration, Ministry of Education in Taiwan (42, 43). Metabolic syndrome was defined as the presence of three or more of the following five risk factors: (1) Abdominal obesity: (waist circumference: male $\geq$ 90 cm, female $\geq$ 80 cm). (2) Hypertension: systolic blood pressure (SBP) $\geq$ 130 mmHg/diastolic blood pressure (DBP) $\geq$ 85 mmHg. (3) Hyperglycemia: fasting blood glucose $\geq$ 100 mg/dl. (4) High-density lipoprotein cholesterol: male $<$ 40 mg/dl, female $<$ 50 mg/dl. (5) High triglyceride $\geq$ 150 mg/dl. The criteria were determined by the Ministry of Health and Welfare in Taiwan (41).

Nutrition consultation sessions were arranged in the fourth and fifth weeks of the intervention. The anthropometrics and BC of the individuals were provided to dietitians before the consultation by the assistants. During a consultation, the dietitian would ask the participant what he or she typically ate for breakfast, lunch, dinner, and late-night supper. After a dietitian learned about the participant's nutritional status and daily lifestyle routine, the dietitian would make personalized suggestions according to each participant's weight status, BC and personal concerns. For instance, instructions for participants with overweight or obesity would be focused on a healthy diet with a negative caloric balance. Participants with an unbalanced diet would learn about macronutrients. Individuals with low MW or high VFA would be given suggestions on the ratio of macronutrients and types of exercise.

Behavioral education

Multiple campaign activities were done to promote the WHP based on essential principles of the theory of planned behavior, namely behavioral beliefs, normative beliefs, and control beliefs (self-efficacy) (44). To increase *behavioral beliefs*, educational materials on exercise, PF, and weight management were delivered through emails, website bulletin boards, and posters in the workplace (**Supplementary Figures 1–4**). The educational materials were all designed by the multidisciplinary

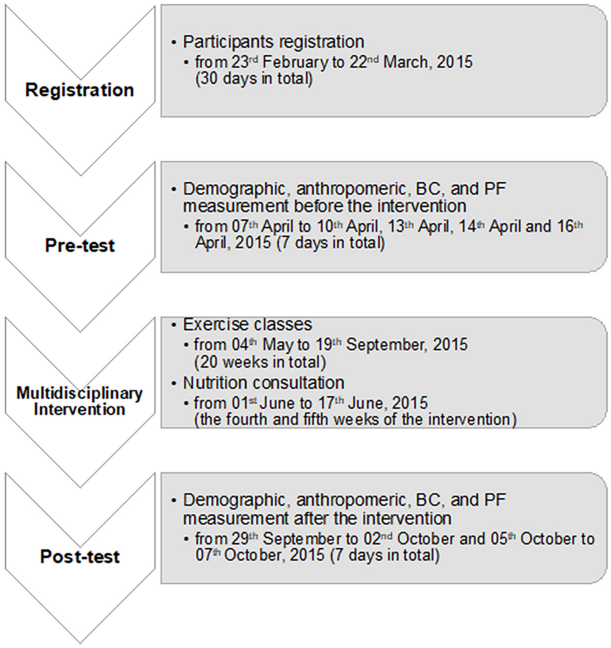

FIGURE 1
Flow chart of the multidisciplinary. BC, body composition; PF, physical fitness.

team. Messages encouraging HCWs to exercise were sent intensively by assistants and PF trainers during the intervention to enhance *normative beliefs*. For example, PF trainers were requested to publicize the benefits of exercise during the classes to increase their exposure to information on healthy behaviors. Moreover, by having a big ceremony to celebrate the success of the program and publicly reward participants with high attendance rates and considerable physical improvements, the intervention was also able to increase the *self-efficacy* of participants in terms of performance attainment (mastery experience), vicarious experience, and verbal persuasion.

Measurements

General characteristics

Participants' general characteristics were assessed by completing registration sheets at participants' entry into the study. The following characteristics were assessed: age, sex, medical history, profession (nurse, medical technician, administration staff, and others), and shift status [day-shift only or night-shift only (i.e., non-shift workers); irregular shift work (shift workers)].

Anthropometrics

Body height, body weight, waist circumference (WC), and hip circumference (HC) were measured and used to calculate body mass index (BMI), waist-hip ratio (WHR), and waist-to-height ratio (WHtR).

Body composition

BC was measured using bioelectrical impedance analysis, which is based on differences in the conductivity of various components of the human body. We used the IOI-353 BC analyzer (Jawon Medical, Yuseong, South Korea) for the analysis, measuring segmental multi-frequency impedance values at 1, 5, 50, 250, 550, and 1,000 kHz with a tetra-polar 8-point tactile electrode system (45). Variables assessed included body fat percentage (BF%), muscle weight (MW), and visceral fat area (VFA).

Physical fitness

PF was tested as follows. The assessments of PF were implemented in accordance with the protocols developed and published by the Sports Department, Ministry of Education in Taiwan (46). All the assessments were completed by board-certificated exercise trainers.

Explosive muscle strength of the upper limbs was assessed with handgrip strength. Participants put their hands by the body side in a standing position. Then they were asked to grasp the handgrip by the dominant hand and gripped it instantaneously with their biggest strength. Two measurements were done to get the best record (47).

Explosive muscle strength of the lower limbs was assessed with vertical jumping. Vertical jumping was measured by

participants jumping from the floor with both feet and touching the ruler with a hand as tall as they could. Two measurements were required to get the tallest value (48).

Muscular endurance was assessed with 1-min sit-up. Participants did 1-min sit-up with their upper body lying on the ground and knees had a 90-degree angle. Their feet were flat on the floor and PF trainers would lightly press on the feet to help stabilize. As a preparation position, participants had their forearms crossed to touch the contralateral shoulder and elbows upon the chest. Participants were asked to contract abdominal muscles to get up and touch the knees with elbows. After they returned to the preparation position, it was considered a count. PF trainers recorded the number of completions in 1 min (46, 49).

Flexibility was assessed with sit-and-reach technique. Participants sit on the ground with knees straight and toes faced upward. Their two heels were 30 cm apart and aligned with the 25 cm on the measured ruler. Participants leaned forward their upper body and stretched their hands to touch the ruler. After the folded two middle fingers touched the ruler, participants were asked to hold for 2 s to record. The measurement was conducted twice to get the best value (46, 50).

Cardiorespiratory fitness was assessed by 3-min step test, defined as the time that heart rate returns to normal after exercise. Each participant got on and off the bench for 3 min in continuous while maintaining a consistent pace. The height of the wooden bench was 35 cm, and the consistent pace was 96 beats per minute (46, 51).

Statistical analysis

All study parameters were compared before and after the intervention using paired sample *t*-tests when dealing with the whole cohort. Using the Shapiro–Wilk test to assess the normality, descriptive statistics were expressed as mean [standard deviation (SD)] for normally distributed continuous variables, median [interquartile range (IQR)] for skewed variables, and number (proportion) for categorical variables. For within-group comparisons, the paired-samples *t*-test or Wilcoxon signed rank test was used as appropriate. For between-group comparisons, the independent samples *t*-test or Mann–Whitney *U* test was used as appropriate.

Generalized estimating equations (GEEs) were used to compare the differences in the changes of these parameters by cohort subgroups, including sex, age, weight status, and shift-work status. Specifically, each subgroup variable was entered into separate GEEs that included main effects of time (post-intervention vs. pre-intervention) and subgroup variable (e.g., male vs. female), a two-way interaction term of time × subgroup variable, and the main effects of baseline characteristics. A significant interaction effect signified a difference in change between subgroups.

All *p*-values were two-sided and statistical significance was accepted at $p < 0.05$. The data analyses were carried out using IBM SPSS Statistics 25 (International Business Machines Corp., Armonk, NY, United States) and Graph Pad Prism 9.0 for Windows (Graph Pad Software Inc., San Diego, CA, United States).

Results

Characteristics of study participants

During the recruitment period, 659 HCWs registered for the WHP program, among whom 528 eligible participants completed pre-tests. Each participant was encouraged to attend one exercise class per week for 20 weeks (20 classes in total). To assure the internal validity of investigations on effectiveness and response differences of the intervention, those with a participation rate lower than 40% (8 classes) were excluded ($n = 100$). Participants who had no complete data of post-interventional assessments were further excluded ($n = 126$). A total of 302 subjects were enrolled for statistical analysis (**Figure 2**).

Among the 302 participants, median age was 36 years (IQR: 30–45) (**Table 1**), and most (93.0%) were female. Furthermore, 118 (39.1%) participants were older than 40 years of age. The median BMI was 22.6 kg/m^2 (IQR: 20.9–24.7) and 107 (35.4%) of them were overweight (according to a BMI of greater than 24 kg/m^2). Administrative staff and others (45.4%) and nurses (39%) were predominant among participants' professions, and 47 (15.6%) participants served as medical technicians. Approximately one-third (32.8%) of the participants engaged in shiftwork.

Females had significantly lower median BMI, proportion of overweight, proportion of administrative staff and others, and non-shift working compared with males.

Changes in outcome parameters for the whole cohort

Notably, we observed statistically significant differences in all parameters between before and after the intervention (**Table 2**). Specifically, among the anthropometrics, the program led to significant decreases in BMI, WC, WHR, and WHtR (all $p < 0.05$). Likewise, we observed decreased BF% and VFA and increased MW ($p < 0.05$). Regarding PF, we observed significantly better performance at post-intervention in four

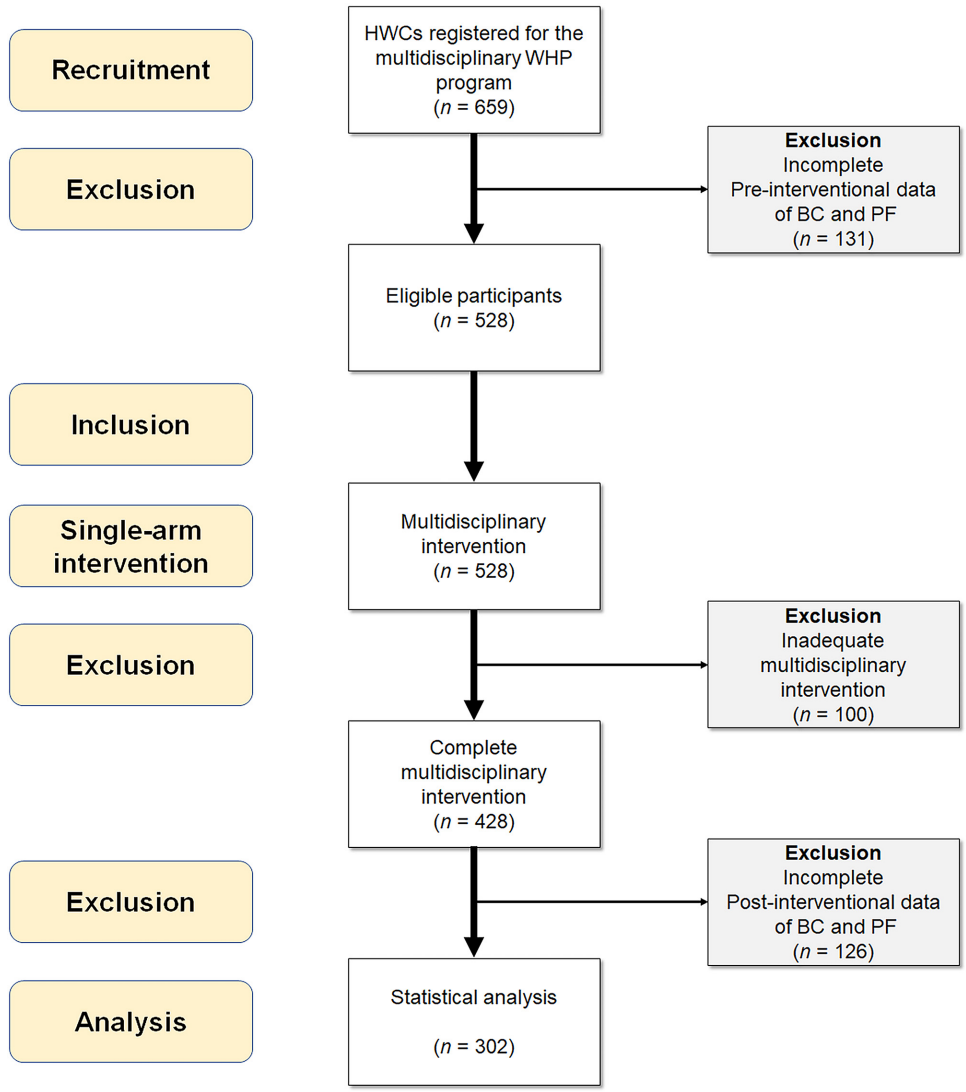

FIGURE 2
Inclusion flow chart of the study participants. BC, body composition; PF, physical fitness; WHP, workplace health promotion.

parameters than at pre-intervention (all $p < 0.05$), except for sit-and-reach ($p = 0.359$).

Furthermore, females had significant improvements in anthropometrics, body composition, and three items of physical fitness (high jump, sit-up, step test) after intervention (Supplementary Table 1) ($p < 0.05$).

Changes in outcome parameters stratified by sex and age

Changes from pre-intervention to post-intervention stratified by sex and age were analyzed with the GEEs (Table 3). After adjustment of the other general characteristics, there was no sex difference in the improvements of anthropometrics (BMI demonstrated in Figure 3A), BC, or PF parameters. No significant differences were observed either between age subgroups (BMI demonstrated in Figure 3B).

Among females, there was no age difference in the improvements of variables of interest after adjustment of the other general characteristics (Supplementary Table 2).

Changes in outcome parameters stratified by weight and shiftwork status

Changes in outcome parameters stratified by weight status and shiftwork status were analyzed with the GEEs (Table 4). We observed no significant difference in the changes

of parameters between the non-overweight and overweight subgroups (BMI demonstrated in Figure 3C). Albeit non-significant, we did observe a borderline ($p < 0.10$) such that participants with overweight showed a slightly greater improvement in step test performance compared to those with non-overweight (3.0 vs. 1.6).

There was a significant difference in the improvement of one parameter—BMI—between participants who worked in shifts and who did not ($p < 0.05$), after adjustment for gender, age, BMI at pre-intervention, and profession. Specifically, while the BMI for the shift and non-shift groups both decreased from pre-intervention to post-intervention, the improvement was substantially greater in the shift group than in the non-shift group (−0.35 vs. −0.19 kg/m^2) (Figure 3D). No significant difference was observed in the changes of other parameters across shift status. Furthermore, these characteristic differences in the improvements of variables of interest between shift

TABLE 1 Characteristics of the study participants.

Variable	Overall	Male	Female	*p*-value[1]
N	302	21	281	
Age, years	36 (30–45)	32 (29–45)	36 (30–45)	0.428
Age group				0.576
< 40 years	184 (60.9)	14 (66.7)	184 (60.9)	
≥ 40 years	118 (39.1)	7 (22.3)	118 (39.1)	
Body mass index, kg/m^2	22.6 (20.9–24.7)	25.5 (23.8–28.1)	22.4 (20.8–24.5)	< 0.001
Weight status				< 0.001
< 24 kg/m^2	195 (64.6)	5 (23.8)	195 (64.6)	
≥ 24 kg/m^2	107 (35.4)	16 (76.2)	107 (35.4)	
Profession				< 0.001
Nurse	118 (39.0)	0 (0.0)	118 (42.0)	
Medical technician	47 (15.6)	3 (14.3)	44 (15.7)	
Administrative staff and others[2]	137 (45.4)	18 (85.7)	119 (42.3)	
Shift status				0.005
Non-shift worker	203 (67.2)	20 (95.2)	183 (65.1)	
Shift worker	99 (32.8)	1 (4.8)	98 (34.9)	

Data are summarized as n (%) or median (interquartile range, as appropriate. [1]For between-group comparisons, the independent samples *t*-test or Mann–Whitney *U* test is used as appropriate. [2]The "others" included mainly staff at payment counters and research assistants and a small number of those who were neither nurses nor medical technicians.

TABLE 2 Changes in outcome parameters for whole cohort (*n* = 302).

Variable	Pre-intervention	Post-intervention	Change[1]	*p*-value[2]
Anthropometrics				
Body mass index (kg/m^2)	22.6 (20.9–24.7)	22.4 (20.6–24.8)	−0.19 (−0.59–0.18)	< 0.001
Waist circumference (cm)	75 (69–81)	74 (68–81)	−1 (−4–3)	0.014
Waist-hip ratio	80.2 (75.9–84.9)	78.9 (74.7–83.8)	−1.0 (−4.0–1.9)	< 0.001
Waist-to-height ratio	47.1 (43.4–51.0)	46.5 (43.0–50.4)	−0.8 (−2.6–1.6)	0.001
Body composition				
Body fat percentage (%)	29.8 (4.7)	29.1 (4.8)	−0.65 (1.19)	< 0.001
Muscle weight (kg)	36.5 (34.0–39.4)	36.7 (31.2–39.9)	0.2 (−0.3–0.6)	< 0.001
Visceral fat area (cm^2)	60.5 (41.8–79.3)	56.0 (38.8–78.0)	−3.0 (−7.0–1.0)	< 0.001
Physical fitness				
Grip strength (kg)	27.0 (23.2–31.0)	27.0 (24.0–31.0)	0.0 (−2.0–2.0)	0.035
High jump (cm)	32.0 (28.0–36.5)	33.0 (29.0–38.0)	2.0 (−1.5–4.0)	< 0.001
Sit-up (count)	26 (20–33)	29 (23–35)	2 (0–4)	< 0.001
Sit-and-reach (cm)	32.1 (26.7–38.5)	32.3 (27.0–38.0)	0.0 (−1.9–2.2)	0.359
Step test	58.4 (53.9–64.3)	60.8 (56.3–66.7)	2.2 (−2.6–6.4)	< 0.001

Data are summarized as mean (standard deviation) or median (interquartile range), as appropriate. [1]Post-intervention minus pre-intervention. [2]Paired sample *t*-test for normally distributed continuous variables or Wilcoxon signed rank test.

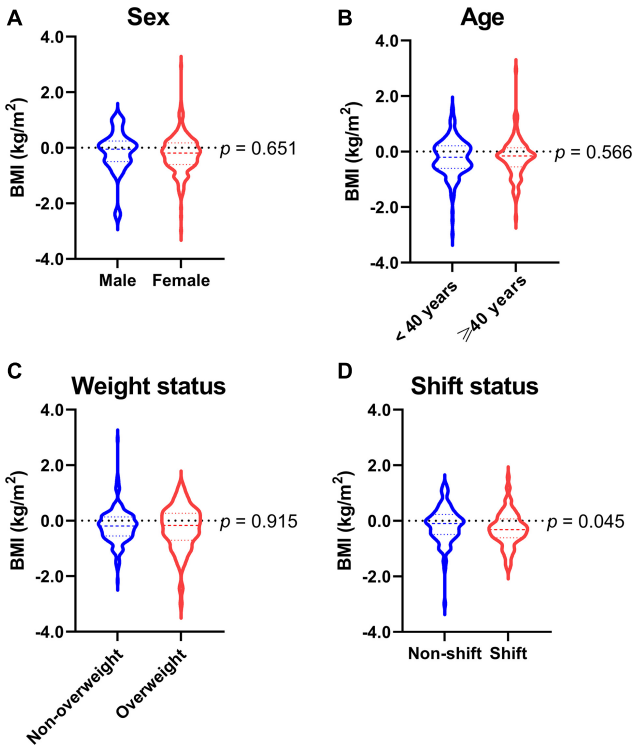

FIGURE 3
Response differences in body mass index of **(A)** sex subgroups, **(B)** age subgroups, **(C)** weight status subgroups, and **(D)** shift status subgroups. BMI, body mass index. Data are summarized as medians, quartiles, and ranges (violin plots) and compared using generalized estimating equation analyses adjusted for age, profession, and shiftwork status.

TABLE 3 Changes in outcome parameters stratified by sex and age.

Variable	Male	Female	*p*-value[1]	Age < 40 years	Age ≥ 40 years	*p*-value[1]
Anthropometrics						
Body mass index (kg/m^2)	−0.1 (−0.5–0.2)	−0.2 (−0.6–0.2)	0.651	−0.2 (−0.6–0.2)	−0.2 (−0.6–0.1)	0.566
Waist circumference (cm)	1 (−4–4)	−1 (−4–3)	0.733	−1 (−4–2.9)	−2 (−4–3)	0.829
Waist-hip ratio	0.6 (−2.4–1.9)	−1.0 (−4.1–2.0)	0.548	−1.0 (−4.1–1.7)	−0.9 (−3.7–2.9)	0.777
Waist-to-height ratio	0.6 (−2.4–1.9)	−0.9 (−2.6–1.5)	0.675	−0.5 (−2.5–1.4)	−1.2 (−2.7–1.7)	0.739
Body composition						
Body fat percentage (%)	−0.3 (−1.6–0.4)	−0.6 (−1.3–0.1)	0.969	−0.6 (−1.3–0.2)	−0.6 (−1.3–0.1)	0.510
Muscle weight (kg)	0.5 (0.1–1.3)	0.2 (−0.3–0.6)	0.105	0.2 (−0.3–0.6)	0.3 (−0.2–0.7)	0.158
Visceral fat area (came)	−1.0 (−8.0–4.0)	−3.0 (−7.0–0.0)	0.157	−2.0 (−0.2–0.7)	−4.0 (−8.0–1.0)	0.281
Physical fitness						
Grip strength (kg)	1.0 (−1.5–4.0)	−2.0 (−3.0–2.0)	0.642	0.0 (−1.0–2.0)	0.0 (−2.0–2.0)	0.820
High jump (cm)	0.0 (−3.0–8.0)	2.0 (−1.0–4.0)	0.721	2.0 (−1.0–4.0)	1.0 (−2.0–4.0)	0.776
Sit-up (count)	3 (−1–5)	2 (0–4)	0.484	2 (0–4)	2 (0–5)	0.858
Sit-and-reach (cm)	−0.8 (−1.2–5.0)	0.1 (−1.9–2.2)	0.345	0.0 (−1.7–2.1)	0.0 (−2.2–3.0)	0.746
Step test	3.7 (−1.4–7.5)	2.0 (−2.6–6.3)	0.332	2.2 (−2.1–6.2)	2.0 (−3.1–6.6)	0.906

Data are summarized as median change (interquartile range). [1]The difference in change (post-intervention minus pre-intervention) between weight or shiftwork subgroups obtained from generalized estimating equation analyses adjusted for sex, age, profession, and/or shiftwork status. The difference in change (post-intervention minus pre-intervention) between sex or age subgroups obtained from generalized estimating equation analyses adjusted for age, BMI at pre-intervention, profession, and shiftwork status.

TABLE 4 Changes in outcome parameters stratified by weight status and shiftwork status.

Variable	Non-overweight	Overweight	*p*-value[1]	Non-shift worker	Shift worker	*p*-value[1]
Anthropometrics						
Body mass index (kg/m^2)	−0.2 (−0.6–0.1)	−0.2 (−0.7–0.3)	0.915	−0.1 (−0.6–0.2)	−0.3 (−0.6–0.1)	0.045
Waist circumference (cm)	−1 (−4–3)	−1 (−4–3)	0.672	−1 (−4–3)	−1 (−3–3)	0.658
Waist-hip ratio	−1.0 (−4.0–2.1)	−0.8 (−4.0 –1.7)	0.855	−1.3 (−4.7–2.1)	−0.8 (−3.2–1.7)	0.340
Waist-to-height ratio	−0.9 (−2.6–1.6)	−0.8 (−2.4–1.4)	0.691	−0.9 (−2.6–1.6)	−0.7 (−2.5–1.5)	0.626
Body composition						
Body fat percentage (%)	−0.7 (−1.4–0.1)	−0.6 (−1.1–0.2)	0.239	−0.7 (−1.3–0.1)	−0.5 (−1.4–0.1)	0.290
Muscle weight (kg)	0.2 (−0.3–0.6)	0.2 (−0.3–0.7)	0.858	0.2 (−0.3–0.7)	0.2 (−0.4–0.5)	0.299
Visceral fat area (came)	−2.0 (−6.0–0.0)	−4.0 (−0.8–2.0)	0.197	−3.0 (−7.0–0.0)	−2.0 (−7.0–1.0)	0.571
Physical fitness						
Grip strength (kg)	0.0 (−1.0–2.0)	1.0 (−2.0–3.0)	0.594	0.0 (−1.3–2.0)	0.0 (−2.0–2.0)	0.902
High jump (cm)	1.0 (−1.0–4.0)	2.0 (−2.0–5.0)	0.608	2.0 (−2.0–5.0)	1.7 (−1.0–4.0)	0.231
Sit-up (count)	2 (0–4)	2 (0–5)	0.471	2 (0–4)	3 (−1–5)	0.367
Sit-and-reach (cm)	0.1 (−2.1–2.0)	0.0 (−1.5–2.8)	0.235	−0.1 (−1.9–2.2)	0.2 (−1.8–2.2)	0.999
Step test	1.6 (−2.8–6.5)	3.0 (−1.7–6.1)	0.067	2.1 (−2.2–6.9)	2.5 (−3.0–5.5)	0.880

Data are summarized as median change (interquartile range). [1]The difference in change (post-intervention minus pre-intervention) between weight or shiftwork subgroups obtained from generalized estimating equation analyses adjusted for sex, age, profession, and/or shiftwork status.

workers and non-shift workers persisted after adjustment of the other general characteristics among females (**Supplementary Table 2**).

Discussion

The overall outcome suggested that the program was effective for improving various anthropometric, BC, and PF parameters. Specifically, we observed significant reductions in BMI, WC, WHR, WHtR, BF%, and VFA, along with an increase in MW, indicating a more preferable BC and fat distribution. As for PF, we noted significant improvements in the explosive muscle strength of the upper and lower limbs, muscular endurance, flexibility, and cardiorespiratory endurance. All of these results are compatible with those of prior studies on health promotion exercises (52–56).

Among all the parameters, we observed no significant differences in intervention effects by sex or age, suggesting that these characteristics have no impact on the intervention outcome. This finding is congruent with those of other studies (57, 58). However, while it did not reach the level of statistical significance, we did observe an interesting tendency for sex: the female sex appeared to show a greater improvement, especially in weight status and BC. Other studies have shown that women had better responses than did men after an exercise intervention (59, 60). One study in 2015 showed similar results to ours; wherein women showed greater improvements in anthropometrics than did men (61). However, another study in 2007 suggested that men showed greater improvements than did women in terms of anthropometrics and BC. Considering these previous inconsistent findings and the lack of a meta-analysis, it remains unclear whether health promotion exercise programs directed at medical personnel show sex differences in their effects. Moreover, our study cohort comprised mainly women (93.0%). According to national data, the number of female HCWs has been persistently much higher than that of males. This data truly reflected the fact that the male/female ratio ranged between 6.0% and 25.2% (mean = 14.4%) in our WHP program from 2014 to 2021 as a result of a higher proportion of women working in the healthcare industry and their higher engagement in WHPs. Future studies that focus specifically on sex differences in intervention response may help design sex-specific interventions.

In the present study, we categorized our cohort into "age $<$ 40 years" and "age $\geq$ 40 years." According to a large prospective cohort study published in 2019, maintaining higher levels of leisure-time physical activity in adults $\geq$ 40 years old was associated with a comparative low risk for all-cause mortality as it in adults $<$ 40 years old (62). Saint-Maurice et al. have recommended that the age of 40 years is a considerable important timepoint to start physical activity (62). We've further analyzed the differences in variables of interest in three age groups: "18–29 years," "30–39 years," and "$>$ 40 years" and found no significant differences existed (data not shown). Therefore, our results supported that the multidisciplinary WHP program can provide comparable benefits of anthropometrics, body composition, and physical fitness to participants with ages $\geq$ 40 years and $<$ 40 years.

Weight status also did not appear to influence the intervention effects. Notably, the subjects with a higher BMI improved to a larger degree than did those with a lower BMI in cardiorespiratory endurance, with a difference almost reaching statistical significance. This somewhat coincides with previous studies, which have indicated that subjects with higher BMIs tend to respond better to exercise interventions in terms of anthropometrics, BC, and cardiorespiratory function (63, 64). Although it is unclear why the response differences existed, possible reasons include individuals with higher BMI having enhanced motivation and compliance with the program, or perhaps an altered physiological response to the intervention co-existing with the obesity itself. Further investigation would be of interest in future studies.

There was a significant difference in BMI improvement between the shiftwork status subgroups. Specifically, the group who engaged in shiftwork showed a more profound weight reduction than did the other subgroup. The association between shiftwork and higher BMI has been robustly demonstrated in the past (65–68). Sleep duration/quality, timing of meals, and timing of light exposure are usually disrupted for shift workers, thereby leading to disruption of circadian rhythms; such a disruption, in turn, can lead to an increased risk of impaired cardio-metabolic function and associated diseases including obesity, diabetes, and cardiovascular disease (69). The underlying pathophysiology of this effect has been suggested to be multifactorial, including inappropriate meal timing (e.g., breakfast skipping or late meals, which can lead to the lower thermic effect of feeding), altered food preferences (e.g., more sugar-sweetened food, which can lead to a higher total calorie intake) (70), and decreased energy expenditure (69). The results of our study imply that while shift workers tend to have higher BMIs, they appear to be able to lower that BMI more efficiently through interventions. We found this effect to be logical, given that the intervention targeted a healthier diet and regular exercise, which can correct the altered eating behavior and decreased energy expenditure caused by the circadian disruption of shift workers. This may be an important finding and suggests that a multidisciplinary WHP program targeting nutrition and exercise is particularly effective and should be prioritized for shift workers.

Overall, this workplace-based intervention appeared to be effective—not only for weight-status outcomes but also for the improvements of BC, fat distribution, and PF. We suggested that the program being multi-faceted, *trans*-disciplinary, and easy-to-access might have contributed to its success. The literature has suggested that the phases of WHP include: needs assessment, planning, implementation, and evaluation (71). Lack of participation is one of the biggest challenges of WHP, especially in the healthcare industry (72). The authors included participants only above a certain level of participation since the current study aimed to assess the effectiveness and response differences to the multidisciplinary intervention. Including all participants with all-ranged participation levels would mix the issues of participation and intervention effectiveness thus possess a threat to internal validity of the research. Incentives and barriers to participation or methods to improve them were not the focus of this study; however, they are certainly critical to the overall success of a WHP and warrant further research. Moreover, mental health is also vital to the well-being of HCWs, and the inclusion of psychological health promotion such as mindfulness-based programs may further broaden the scope of WHP (73).

The advantage of this study includes its comprehensive assessment of anthropometrics and PF. However, there are some limitations. First, since participants volunteered to participate, rather than being selected randomly or with a stratified method from the correspondent population, the generalizability of this program may be limited. Second, the program was conducted in northern Taiwan and might not be representative of the rest of Taiwan. Third, the intervention did not include psychological programs, which should also be considered in future WHPs. Fourth, the study was an efficacy-based research, which is limited in delineating the effects of intervention designs on outcomes. Future prospective research can be more evaluation-based, so lived experiences, feasibility and acceptability of the intervention, and mechanisms of impact in context can be examined. A larger sample size with a control group and a balanced sex distribution can also contribute to a better understanding on the effectiveness of and response differences in WHP among HCWs.

In conclusion, the workplace-based health promotion exercise program was an effective intervention model for hospitals regardless of unfavorable workplace settings for health promotion. Workers with higher BMIs, who engage in shiftwork, and who are at greater risk yet appear more responsive to interventions than their peers, can be considered a priority group for WHP in case of limited resources. Future investigation of response differences and their underlying mechanisms across sex, age, weight, and shiftwork statuses would be interesting.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Chang Gung Medical Foundation. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JJ-CL and H-HC conceived and planned the study. C-TC and JJ-CL enrolled the patients. L-AL and H-HC designed the study, analyzed data, made the statistics, and interpreted results. K-HC, N-KW, C-TC, L-AL, and H-HC participated in manuscript drafting. C-YH, Y-AL, and JJ-CL supervised the study. All authors 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930165/full#supplementary-material

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Effect of healthy lifestyle index and lifestyle patterns on the risk of mortality: A community-based cohort study

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Background: Limited evidence was available on the association of the integrated effect of multidimensional lifestyle factors with mortality among Chinese populations. This cohort study was to examine the effect of combined lifestyle factors on the risk of mortality by highlighting the number of healthy lifestyles and their overall effects.

Methods: A total of 11,395 participants from the Guangzhou Heart Study (GZHS) were followed up until 1 January 2020. Individual causes of death were obtained from the platform of the National Death Registry of China. The healthy lifestyle index (HLI) was established from seven dimensions of lifestyle, and lifestyle patterns were extracted from eight dimensions of lifestyle using principal component analysis (PCA). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using the Cox proportional hazard regression model.

Results: During 35,837 person-years of follow-up, 184 deaths (1.61%) were observed, including 64 from cardiovascular disease. After adjustment for confounders, HLI was associated with a 50% (HR: 0.50, 95% CI: 0.25–0.99) reduced risk of all-cause mortality when comparing the high (6–7 lifestyle factors) with low (0–2 lifestyle factors) categories. Three lifestyle patterns were defined and labeled as pattern I, II, and III. Lifestyle pattern II with higher factor loadings of non-smoking and low-level alcohol drinking was associated with a decreased risk of all-cause mortality (HR: 0.63, 95% CI: 0.43–0.92, P_{-trend} = 0.023) when comparing the high with low tertiles of pattern score, after adjustment for confounders. Every 1-unit increment of pattern II score

was associated with a decreased risk (HR: 0.97, 95% CI: 0.95–0.99) of all-cause mortality. The other two patterns were not associated with all-cause mortality, and the association of cardiovascular mortality risk was observed with neither HLI nor any lifestyle pattern.

Conclusion: The results suggest that the more dimensions of the healthy lifestyle the lower the risk of death, and adherence to the lifestyle pattern characterized with heavier loading of non-smoking and low-level alcohol drinking reduces the risk of all-cause mortality. The findings highlight the need to consider multi-dimensional lifestyles rather than one when developing health promotion strategies.

KEYWORDS

lifestyle, healthy lifestyle index, lifestyle pattern, mortality, cohort study

Introduction

Non-communicable diseases (NCDs) have encroached on many low- and middle-income countries, and become the leading cause of death worldwide (1). Available evidence suggested that lifestyle factors were associated with multiple NCDs (2), and adherence to a healthy lifestyle was associated with a lower risk of NCDs and mortality (3–8). Meanwhile, multiple lifestyle risk factors may have a synergistic effect on adverse health outcomes (9, 10). Hence, reducing exposure to lifestyle risk factors is of great significance for public health prevention and medical resource allocation (11).

Many studies have constructed healthy lifestyle scores to reflect the combined impact of major lifestyle factors, including smoking, alcohol consumption, body mass index (BMI), unhealthy diet, and physical inactivity, on mortality (12–14). A systematic review and meta-analysis found that adherence to the healthiest lifestyles was associated with a 55 and 58% reduced risk of all-cause mortality and cardiovascular mortality, respectively, compared with the least-healthy lifestyles (15). However, other unmentioned factors may also play a significant role in mortality risk. For instance, sleep is a critical bodily function (16), and poor sleep quality has been identified as a risk factor for many adverse health outcomes, such as all-cause mortality, cardiovascular death, etc. (17–19). The mental state is also an important aspect of health, and people with mental disorders have a higher risk of death (20, 21). Pratt and colleagues found that people with anxiety and depression had significantly high mortality than people without such mental disorders (21). In addition, current research mainly reflected the overall impact of lifestyle through the number of lifestyle factors, while ignoring the possible interactions between each factor. Principal component analysis (PCA) is an effective approach to reflect the combined effect of different components by generating different patterns, and using such an approach can avoid ignoring the interaction between some components (22). The human lifestyle is a complex whole with multiple dimensions, and it is important to consider as many of these dimensions as possible when quantifying lifestyle and assessing its impact on health.

Therefore, this prospective cohort study aimed to examine the combined effect of major lifestyle factors, including leisure-time physical activity (LTPA), diet, BMI, smoking, alcohol drinking, sleep quality, and mental status (anxiety, and depression), on the risk of all-cause and cardiovascular mortality, by establishing a healthy lifestyle index (HLI) to reflect the number of healthy lifestyle components and generating the lifestyle patterns to reflect the whole lifestyle profile.

Materials and methods

Study population

Guangzhou Heart Study (GZHS) is an ongoing prospective population-based cohort study in South China. Details of GZHS can be seen in our previous reports (23–25). Briefly, a total of 12,013 permanent residents aged 35 years or more were enrolled using the multistage sampling method; the baseline survey was successfully conducted between July 2015 and August 2017. Participants included met the following criteria: permanent residents in Guangzhou, aged 35 years or older, and had lived in the selected communities for at least 6 months before the survey. Participants with incomplete information of covariates (19 participants) or with a history of cardiovascular diseases including atrial fibrillation, heart failure, myocardial infarction, and valvular heart disease (589 participants) were excluded. Finally, a total of 11,395 participants were available for further analysis.

This study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association and by the Ethical Review Committee for Biomedical Research, School of Public Health, Sun Yat-sen University. The study was performed in line with the Declaration of Helsinki and all participants provided informed consent.

Outcome ascertainment

The outcome of interest was all-cause mortality and cardiovascular mortality. Individual causes of death up to 1 January 2020 were collected from China's National Death Registry, Guangzhou Center for Disease Control and Prevention. The follow-up time was defined as the time from participation in the GZHS to the date of the decedent's death or to the censoring date (1 January 2020) for survivors. The causes of death were coded by professional medical workers according to the 10th revision of the International Classification of Disease and were further classified as all-cause death and death from cardiovascular diseases (I00-I99).

Assessment of lifestyle factors

Structured questionnaires were used to collect information on social demographics, lifestyle, and disease history by using face-to-face interviews. The social demographics included age (years), sex (male, female), education (<high school, high school, >high school), and marital status (married, others). The medical examination was performed on each participant; height and weight were measured to calculate BMI (kg/m^2); a normal BMI was defined as BMI in the range of 18.5–23.9 kg/m^2 according to the Chinese standard (26), otherwise as unhealthy BMI.

The exposure information on cigarette smoking and alcohol drinking was collected using a structured questionnaire. For cigarette smoking, participants who have never smoked or smoked < 100 cigarettes in their lifetime were classified as non-smokers, and those who have currently smoked or smoked ≥ 100 cigarettes in their lifetime were classified as smokers. For alcohol drinking, participants were asked to report their drinking status. Participants who reported "frequent drinking" were considered as high-level alcohol drinking, and those who reported "never drinking or alcohol cessation" or "occasional drinking" were considered as low-level alcohol drinking.

Dietary consumption from each participant was collected using a 22-item food frequency questionnaire (FFQ) (24). Participants were asked to report their intake frequency of each food item (<once per month, 1–3 times per month, 1–3 times per week, 4–6 times per week, and ≥ once per day) over the previous 12 months. A total of 12 major food items in FFQ (cereals, legumes, vegetables, fruit, dairy, nuts, fish and shrimps, poultry, red meat, fried foods, high-salt foods, and sugary beverages) were used to create a diet quality score based on the latest Chinese Dietary Guidelines (27). First, a point was assigned to each category of the intake frequency (**Supplementary Table 1**): for cereals, fruit, dairy, and nuts, 0, 2, 4, 6, and 8 points were assigned to < once a month, 1–3 times a month, 1–3 times a week, 4–6 times a week, and 1–6 times a day, respectively; for legumes, vegetables, fish and shrimps, and poultry, 0, 1, 2, 3, and 4 were assigned to < once a month, 1–3 times a month, 1–3 times a week, 4–6 times a week, and 1–6 times a day respectively; for red meat, fried food, high-salted food, and sugary beverages, 8, 6, 4, 2, and 0 points were assigned to < once a month, 1–3 times a month, 1–3 times a week, 4–6 times a week, and 1–6 times a day, respectively (6, 28). Then, the total score for the diet quality was equal to the sum of points of 12 selected food items. Accordingly, the diet quality score ranged from 0 (lowest) to 80 (highest). If the dietary quality score for a participant was 50 points or more (in the upper two-fifths of all participants), then this participant was considered to have a healthy diet, otherwise have an unhealthy diet.

LTPA was evaluated by a modified Global Physical Activity Questionnaire (29). The total volume of LTPA for each subject was calculated as the sum of volumes of eight categories of most common LTPA including Tai Chi/Qigong, housework, stroll, bicycling, brisk walking/exercises/Yangko, swimming, ball games (basketball, table tennis, badminton, etc.), long-distance running/aerobics dancing. The value of each LTPA was calculated by multiplying the duration of activity by its frequency and then by its intensity (quantified by the value of metabolic equivalent, MET). More details on the assessment of physical activity can be seen in our previous report (25). According to the guidelines on physical activity by World Health Organization (WHO), to attain substantial health benefits, adults should do at least 150–300 min of moderate-intensity aerobic physical activity, or at least 75–150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week (30); this means that conducting activity with at least 10 MET-hours/week is suggested to reach the minimum level of the recommended standard (30).

Sleep quality was assessed with two questions (17). The participants were asked to answer the question "Did you feel tired after waking up in the morning?" If the response of a participant was "yes," then the participant was further required to report the frequency of tiredness after waking up in the morning during the past year, with five choices of "every day," "3–4 times per week," "1–2 times per week," "1–2 times per month," and "never." The participants were considered as

having poor sleep quality if their choice were "every day" or "3–4 times per week"; otherwise, the participants were regarded as having good sleep quality.

Mental status including anxiety and depression were evaluated by the Self-Rating Anxiety Scale (SAS) and the Center for Epidemiologic Studies Depression Scale (CES-D) (31, 32). The SAS index score ranged from 25 to 100 and a participant with a SAS index score $\geq$ 45 was considered as having anxiety. The CES-D score ranges from 0 to 60 and a participant with $\geq$ 16 was considered as having depression. Because the number of participants with depression in our study was small, when establishing the HLI, the participants who had either anxiety neurosis or depression were classified as having an unhealthy mental status, otherwise as having a healthy mental status.

Healthy lifestyle index establishment

The detail of the definition of the HLI was shown in **Table 1**. The HLI was established by using seven dominant factors including BMI, cigarette smoking, alcohol drinking, dietary quality, LTPA, sleep quality, and mental status. These factors were shown as dichotomous variables, and the definitions of these variables were mentioned above. The score for each lifestyle factor was defined as follows: BMI (1 = normal BMI, 0 = unhealthy BMI), alcohol drinking (1 = low-level alcohol drinking, 0 = high-level alcohol drinking), cigarette smoking (1 = non-smoker, 0 = smoker), diet quality (1 = healthy diet, 0 = unhealthy diet), LTPA (1 = reach the minimum level of the recommended standard by WHO, 0 = not reach the minimum level of the recommended standard by WHO), sleep quality (1 = good sleep quality, 0 = poor sleep quality), and mental status (1 = unhealthy mental status, 0 = healthy mental status). The total score for HLI was calculated as the sum of the scores of seven selected factors. The score for HLI ranged from zero to seven (healthiest) points. The HLI was further transformed to the categorical variable: low (0–2 score), moderate (3–5 score), and high (6–7 score).

Lifestyle pattern extraction

The lifestyle pattern was extracted by using the PCA with the varimax-rotated transformation from eight lifestyle components: BMI, diet quality, LTPA, depression (CES-D score), anxiety (SAS index score), cigarette smoking, alcohol drinking, and sleep quality. To perform the PCA, the categorical variables of cigarette smoking, alcohol drinking, and sleep quality were transformed into the continuous variable. For cigarette smoking, a score of 1 and 0 was assigned to the non-smoker and the smoker, respectively; for alcohol drinking, a score of 1 and 0 was assigned to the low-level alcohol drinking and the high-level alcohol drinking, respectively; for sleep quality, a simple score was assigned to each category of the frequency of tiredness after waking up in the morning during the past year: 1 = "every day," 2 = "3–4 times per week," 4 = "1–2 times per week," 5 = "never."

PCA used the correlation matrix of different lifestyle factors to identify common patterns of lifestyle factors within the data to account for the largest amount of variation in lifestyle. The varimax rotation is a statistical technique used to evaluate the relationship among individual factors (22). The Kaiser-Meyer-Olkin (KMO) criterion and Bartlett's test of sphericity were used to evaluate the suitability of using the data for PCA (22). A positive loading for a lifestyle component indicated a direct association with the pattern, while a negative loading showed that this lifestyle component inversely contributed to the pattern. The components in each lifestyle pattern with absolute rotated factor loadings of $\geq$ 0.40 were referred to as "dominant components" hereafter.

Three lifestyle patterns were finally extracted and labeled as pattern I, pattern II, and pattern III (**Supplementary Table 2**). The pattern I was characterized with a higher loading of sleep quality, anxiety, and depression, explaining about 37.7% of total variance; Pattern II was characterized with a higher loading of low-level alcohol drinking and non-smoker, explaining about 32.8% of the total variance; Pattern III was characterized with a higher loading of LTPA, BMI, and diet quality, explaining about 29.5% of the total variance. The score of each pattern was calculated with the weighted approach by using rotated loadings as the weight (33): pattern score = $\sum_{1}^{21} variable_i \ weight_i$; ***variable*** represents each item; ***weight*** means the factor loading. Then the score of each pattern was transformed to categorical variables by using the tertile method.

Statistical analysis

The distribution of baseline social-demographics, lifestyle factors, and other covariables was depicted and the difference among different groups was examined by chi-square test for a categorical variable and *t*-test, or Wilcoxon rank-sum test, or Kruskal-Wallis rank-sum test, or one-way analysis of variance for a continuous variable.

Cox proportional hazard regression model was performed to estimate the hazard ratio (HR) and their 95% confidence interval (Cl) before and after adjustment for confounders, to demonstrate the effects of individual lifestyle factors, HLI, and three lifestyle patterns on all-cause mortality and cardiovascular mortality. The proportional hazard assumption was examined using the Schoenfeld residuals method, and no significant violation of the assumption was observed. The linear exposure-response trend was examined by using Wald statistic.

Two sensitivity analyses were conducted to test the robustness of the results. To eliminate the possible effect of weight loss secondary to preclinical diseases, we excluded the

participants with a BMI below 18.5 kg/m^2. To exclude the possibility of reverse causality, we excluded participants who died within the first year after they finished the baseline survey. A product term between sex and HLI or each lifestyle pattern was added in the model to evaluate the possible multiplicative interaction by using the likelihood ratio test; however, no significant interaction was observed. All analyses were performed with R 4.0.1 (R Development Core Team, Vienna, Austria); the tests were two-tailed, and a *P*-value of less than 0.05 was considered statistically significant.

TABLE 1 The definition of the healthy lifestyle index.

Variable	Points	Description
Diet quality		
	0	Unhealthy diet: dietary quality score < 50
	1	Healthy diet: dietary quality score ≥ 50
Body mass index (BMI)		
	0	Unhealthy BMI: overweight or obese (BMI < 18.5 kg/m^2 or BMI ≥ 24 kg/m^2)
	1	Normal BMI: normal weight (18.5 ≤ BMI < 24 kg/m^2)
Cigarette smoking		
	0	Smoker: current smoker or former smoker (≥100 cigarettes)
	1	Non-smoker: never smoker or former smoker (<100 cigarettes)
Alcohol drinking		
	0	High-level: often drinking
	1	Low-level: no drinking or occasionally drinking
leisure-time physical activity (LTPA)		
	0	Unhealthy: did not achieve the minimum level of the recommended standard
	1	Healthy: achieved the minimum level of the recommended standard
Sleep quality		
	0	Unhealthy: Felt tired after waking up in the morning more than 1–2 times per week
	1	Healthy: felt tired after waking up in the morning less than 1–2 times per week
Mental status		
	0	Unhealthy mental status: either anxiety or depression
	1	Healthy mental status: neither anxiety nor depression
Lifestyle index		
	0–2	Low: score of lifestyle index ranged from 0 to 2
	3–5	Moderate: score of lifestyle index ranged from 3 to 5
	6–7	High: score of lifestyle index ranged from 6 to 7

Results

During 35,837 person-years of follow-up, 184 deaths (1.61%) were observed, including 64 deaths from cardiovascular disease. As shown in Table 2, of all subjects, the mean (*SD*) of age, BMI, diet quality, CES-D score, and SAS index score was 58.36 (11.70) years, 23.97 (3.53) kg/m^2, 48.78 (7.55), 11.95 (2.42), and 43.91 (3.16), respectively. The median (IQR) value of LTPA was 34.65 (41.50) MET-h/week. Most participants were females (65.41%), with an education less than high school (63.0%), married (85.27%), non-smokers (79.61%), and never or occasion drinkers (94.01%).

Individuals with higher HLI were more likely to be female and married (Supplementary Table 3). The proportion of participants with the higher education level increased with the increase of the HLI. With the increase of the HLI, participants had a higher level of healthy diet quality, LTPA, sleep quality, and mental health, and a higher proportion of normal BMI, non-smoking, and non-drinking. The means of lifestyle pattern II score and pattern III score were significantly higher in the lived group ($P < 0.05$), while both lived and death groups had a similar score of lifestyle pattern I ($P > 0.05$) (Supplementary Table 4).

As shown in Table 3, participants with good sleep quality were associated with a 38% (HR: 0.62, 95% CI: 0.43–0.91) reduced risk of all-cause mortality after adjustment for confounders. No significant association was observed between sleep quality and cardiovascular mortality risk. Other individual factors were not observed to be associated with the risk of all-cause and cardiovascular mortality.

Table 4 shows the association of HLI with mortality risk. In comparison to the subjects within the low category of the HLI, those within both the moderate category (HR: 0.48, 95% CI: 0.25–0.93) and the high category (HR: 0.50, 95% CI: 0.25–0.99) were associated with a reduced risk of all-cause mortality after adjustment for confounders. However, no significant association was observed between HLI and cardiovascular mortality risk.

When comparing the highest with lowest tertiles of pattern score, lifestyle pattern II was associated with a 37% (HR: 0.63, 95% CI: 0.43–0.92, $P_{-trend} = 0.023$) reduced risk of all-cause mortality after adjustment for confounders (Table 5). Every 1 score increment of the lifestyle pattern II was associated with a 3% (HR: 0.97, 95% CI: 0.95–0.99) reduced risk of all-cause mortality. No significant association was observed between the other two lifestyle patterns and the risk of all-cause mortality, and between three lifestyle patterns and the risk of cardiovascular mortality.

Two sensitivity analyses were conducted by excluding participants with a BMI lower than 18.5 kg/m2 and by excluding participants who died within the first year during the follow-up. Similar results as the main analyses were obtained for

TABLE 2 The characteristics of participants.

	Total (N = 11,395)	Lived (N = 11,211)	Death (N = 184)	*P-value*
Age, years, mean (*SD*)	58.36 (11.70)	58.16 (11.60)	70.84 (10.98)	< 0.001*
BMI, kg/m^2, mean (*SD*)	23.97 (3.53)	23.98 (3.53)	23.34 (3.81)	0.026*
LTPA, MET-h, median (interquartile)	34.65 (41.50)	34.65 (41.33)	24.50 (34.91)	< 0.001†
Diet quality score, mean (*SD*)	48.78 (7.55)	48.79 (7.53)	48.02 (8.52)	0.223*
CES-D score, mean (*SD*)	11.95 (2.42)	11.95 (2.41)	12.00 (3.05)	0.839*
SAS index, mean (*SD*)	43.91 (3.16)	43.91 (3.16)	43.85 (3.33)	0.811*
Sex, *N* (%)				< 0.001‡
Male	3,941 (34.59)	3,843 (34.28)	98 (53.26)	
Female	7,454 (65.41)	7,368 (65.72)	86 (46.74)	
Education, *N* (%)				0.002‡
< High school	7,179 (63.00)	7,041 (62.80)	138 (75.00)	
High school	2,750 (24.13)	2,723 (24.29)	27 (14.67)	
>High school	1,466 (12.87)	1,447 (12.91)	19 (10.33)	
Material status, *N* (%)				< 0.001‡
Married	9,716 (85.27)	9,587 (85.51)	129 (70.11)	
Others	1,679 (14.73)	1,624 (14.49)	55 (29.89)	
Diet quality, *N* (%)				0.438‡
Unhealthy	6,212 (54.52)	6,106 (54.46)	106 (57.61)	
Healthy	5,183 (45.48)	5,105 (45.54)	78 (42.39)	
Cigarette smoking, *N* (%)				< 0.001‡
Smoker	2,324 (20.39)	2,265 (20.20)	59 (32.07)	
Non-smoker	9,071 (79.61)	8,946 (79.80)	125 (67.93)	
Alcohol drinking, *N* (%)				0.068‡
Low-level	10,713 (94.01)	10,540 (94.01)	173 (94.02)	
High-level	682 (5.99)	671 (5.99)	11 (5.98)	
Mental health, *N* (%)				0.814‡
Unhealthy	4,275 (37.52)	4,208 (37.53)	67 (36.41)	
Healthy	7,120 (62.48)	7,003 (62.47)	117 (63.59)	
BMI, *N* (%)				0.888‡
Unhealthy	5,882 (51.62)	5,792 (51.66)	90 (48.91)	
Normal	5,513 (48.38)	5,419 (48.34)	94 (51.09)	
Sleep quality, *N* (%)				0.214‡
Unhealthy	1,762 (15.46)	1,727 (15.40)	35 (19.02)	
Healthy	9,633 (84.54)	9,484 (84.60)	149 (80.98)	
LTPA, *N* (%)				0.255‡
Unhealthy	1,677 (14.72)	1,644 (14.66)	33 (17.93)	
Healthy	9,718 (85.28)	9,567 (85.34)	151 (82.07)	

BMI, body mass index; LTPA, leisure-time physical activity; MET-h, metabolic equivalent values-hours.
**P-values* of continuous variables were from t-test.
† *P-values* of leisure-time physical activity was from Wilcoxon rank sum test.
‡ *P-values* of categorical variables were from chi-square tests.

HLI (Supplementary Tables 5, 6) and three lifestyle patterns (Supplementary Tables 7, 8).

Discussion

In this large prospective cohort study, we found that both moderate and high levels of HLI were associated with the reduced risk of all-cause mortality, and lifestyle pattern II characterized with higher loadings of low-level alcohol drinking and non-smoker was negatively associated with the risk of all-cause mortality, after adjustment for confounders.

The HLI established in this study considered many aspects of the lifestyle as comprehensively as possible. The five factors used in this study—LTPA, cigarette smoking, alcohol drinking, diet quality, and BMI—have also been considered in many other

TABLE 3 Association of individual lifestyle factors with mortality.

	All-cause mortality			Cardiovascular mortality		
	N (person-years/death)	Crude HR (95% CI)*	Adjusted HR (95% CI)†	*N* (person-years/death)	Crude HR (95% CI)*	Adjusted HR (95% CI)†
Diet quality						
Unhealthy	19,353/106	1.00	1.00	19,353/38	1.00	1.00
Healthy	16,484/78	0.86 (0.64, 1.15)	0.86 (0.63, 1.17)	16,484/26	0.79 (0.48, 1.31)	0.82 (0.49, 1.38)
BMI						
Unhealthy	18,424/90	1.00	1.00	18,424/35	1.00	1.00
Normal	17,413/94	1.10 (0.82, 1.47)	1.11 (0.83, 1.48)	17,413/29	0.87 (0.53, 1.43)	0.90 (0.55, 1.47)
Cigarette smoking						
Smoker	7,290/59	1.00	1.00	7,290/18	1.00	1.00
Non-smoker	28,548/125	0.54 (0.40, 0.74)	0.91 (0.62, 1.32)	28,548/46	0.65 (0.38, 1.12)	0.78 (0.40, 1.54)
Alcohol drinking						
Low-level	2,128/11	1.00	1.00	2,128/1	1.00	1.00
High-level	33,709/173	0.99 (0.54, 1.82)	1.50 (0.80, 2.80)	3,309/63	3.97 (0.55, 28.59)	5.23 (0.71, 38.43)
LTPA						
Unhealthy	5,232/33	1.00	1.00	5,232/14	1.00	1.00
Healthy	30,606/151	0.78 (0.54, 1.14)	0.88 (0.60, 1.29)	30,606/50	0.61 (0.34, 1.10)	0.67 (0.37, 1.23)
Sleep quality						
Unhealthy	5,541/35	1.00	1.00	5,541/9	1.00	1.00
Healthy	30,296/149	0.78 (0.54, 1.13)	0.62 (0.43, 0.91)	30,296/55	1.12 (0.55, 2.26)	0.92 (0.45, 1.89)
Mental health						
Unhealthy	13,297/67	1.00	1.00	13,297/22	1.00	1.00
Healthy	22,541/117	1.02 (0.76, 1.38)	1.11 (0.82, 1.51)	22,541/42	1.12 (0.67, 1.87)	1.24 (0.73, 2.09)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LTPA, leisure-time physical activity; MET-h, metabolic equivalent values-hours.
*Adjustment for age, sex, education, and marital status.
†Adjustment for age, sex, education, marital status, and other lifestyle factors.

similar studies (7, 14, 34). In addition, this study also considered sleep quality and mental status, as they were important elements affecting the occurrence and death of chronic diseases (20, 35–38). Consistently, other studies on the combined or overall effects of lifestyle factors had also highlighted the contribution of sleep condition (9, 10, 13, 39) and mental status (9, 10). Our study found that both moderate level (3–5 score) and high level (6–7 score) of HLI decreased the risk of all-cause mortality, which was consistent with many other studies (13, 34, 39). However, the trend test was not reaching significance; this might be due to the limited death cases during a relatively short-time follow-up.

The multicollinearity and potential synergy were often observed among different individual lifestyle factors. The cumulative impact of multiple lifestyle components in a lifestyle pattern may be detectable. PCA is a multivariate technique that evaluates intercorrelations between individual habits or behaviors and has been widely applied in health science (22). In our study, three lifestyle patterns were successfully extracted by using PCA from eight components of non-smoking, low-level alcohol drinking, BMI, LTPA, diet quality, sleep quality, the SAS index score, and the CES-D score. We found that lifestyle pattern II which was characterized with higher factor loadings of non-smoking and low-level alcohol drinking was inversely associated with the risk of all-cause mortality, no matter the pattern score was regarded as a continuous variable or as a categorical variable. Similarly, Navarro and colleagues used PCA to extract dietary and lifestyle patterns and found that the pattern with the loadings most heavily on alcohol and cigarette use was associated with an increased risk of esophageal cancer (40); Al Thani et al. found that the pattern characterized by smoking, fast foods, sweetened beverages, and sweets was positively related to the risk of elevated blood pressure (41).

Non-smoking and low-level alcohol drinking are two dominant components of lifestyle pattern II. Literature agreed that cigarette smoking was the risk factor of premature mortality and various diseases including respiratory diseases, CVDs, diabetes, and cancer (42–45). Underlying mechanisms were that burning tobacco cigarettes can produce many chemicals that affect many aspects of human health, such as nicotine, nitrosamines, and polycyclic aromatic hydrocarbons. Nicotine affects cardiac contractility and heart rate, increases blood pressure, reduces sensitivity to insulin, aggravates diabetes, and results in endothelial dysfunction (46). Nitrosamines and

TABLE 4 Associations of healthy lifestyle index with mortality.

	N (person-years/death)*	Crude HR (95% CI)†	Adjusted HR (95% CI)‡
All-cause mortality			
Low (0–2 score)	928/10	1.00	1.00
Moderate (3–5 score)	21,460/113	0.49 (0.25, 0.93)	0.48 (0.25, 0.93)
High (6–7 score)	13,449/61	0.42 (0.21, 0.81)	0.50 (0.25, 0.99)
Moderate and high (3–7 score)	34,909/174	0.45 (0.24, 0.87)	0.49 (0.25, 0.93)
P for trend		0.013	0.124
Every 1-score increment		0.88 (0.79, 0.99)	0.95 (0.84, 1.07)
Cardiovascular mortality			
Low (0–2 score)	928/3	1.00	1.00
Moderate (3–5 score)	21,460/40	0.57 (0.18, 1.85)	0.48 (0.15, 1.57)
High (6–7 score)	13,449/21	0.47 (0.14, 1.59)	0.47 (0.14, 1.65)
Moderate and high (3–7 score)	34,909/61	0.53 (0.17, 1.70)	0.48 (0.15, 1.55)
P for trend		0.205	0.344
Every 1-score increment		0.90 (0.74, 1.10)	0.94 (0.76, 1.17)

*N represents the sample size.
†Crude HR, without any adjustment.
‡Adjusted HR, adjustment for age, sex, marital status, educational status.

TABLE 5 The association of lifestyle patterns with mortality.

Patterns*	*N* (person-years /death)*	Crude HR (95% CI)†	Adjusted HR (95% CI)‡
All-cause mortality			
Pattern I			
Tertile 1	12,272/66	1.00	1.00
Tertile 2	11,800/62	0.99 (0.70, 1.40)	1.02 (0.72, 1.45)
Tertile 3	11,766/56	0.90 (0.63, 1.28)	0.91 (0.64, 1.30)
P for trend		0.568	0.621
Every 1-score increment		1.01 (0.97, 1.04)	1.01 (0.97, 1.04)
Pattern II			
Tertile 1	11,860/83	1.00	1.00
Tertile 2	11,939/57	0.68 (0.49, 0.95)	0.76 (0.54, 1.07)
Tertile 3	12,039/44	0.52 (0.36, 0.75)	0.63 (0.43, 0.92)
P for trend		<0.001	0.023
Every 1-score increment		0.96 (0.94, 0.98)	0.97 (0.95, 0.99)
Pattern III			
Tertile 1	11,812/74	1.00	1.00
Tertile 2	11,952/64	0.85 (0.61, 1.19)	0.90 (0.64, 1.27)
Tertile 3	12,073/46	0.60 (0.42, 0.87)	0.70 (0.48, 1.02)
P for trend		0.007	0.065
Every 1-score increment		0.99 (0.98, 0.99)	0.99 (0.98, 1.00)
Cardiovascular mortality			
Pattern I			
Tertile 1	12,272/26	1.00	1.00
Tertile 2	11,800/21	0.86 (0.48, 1.52)	0.89 (0.50, 1.58)
Tertile 3	11,766/17	0.69 (0.38, 1.28)	0.67 (0.36, 1.23)
P for trend		0.818	0.555
Every 1-score increment		1.01 (0.95, 1.07)	1.00 (0.94, 1.06)
Pattern II			
Tertile 1	11,860/30	1.00	1.00
Tertile 2	11,939/20	0.66 (0.38, 1.17)	0.74 (0.42, 1.31)
Tertile 3	12,039/14	0.46 (0.24, 0.86)	0.54 (0.28, 1.04)
P for trend		0.015	0.063
Every 1-score increment		0.97 (0.94, 0.99)	0.97 (0.94, 1.00)
Pattern III			
Tertile 1	11,812/26	1.00	1.00
Tertile 2	11,952/25	0.91 (0.53, 1.57)	0.99 (0.57, 1.71)
Tertile 3	12,074/13	0.43 (0.22, 0.85)	0.49 (0.25, 1.00)
P for trend		0.015	0.050
Every 1-score increment		0.98 (0.97, 0.99)	0.98 (0.97, 1.01)

*N represents the sample size. The pattern I was characterized with a higher loading of sleep quality, anxiety, and depression; Pattern II was characterized with a higher loading of low-level alcohol drinking and non-smoker; Pattern III was characterized with a higher loading of LTPA, BMI, and diet quality.
†Crude HR, without any adjustment.
‡Adjusted HR, adjustment for age, sex, marital status, educational status.

polycyclic aromatic hydrocarbons are proven as carcinogens and CVD enhancers (47). Regarding low-level alcohol drinking, the Global Burden of Disease Study concluded that zero standard drinks per week minimized the overall health risk (48), namely no level of alcohol consumption improves health (49).

Noteworthy, our results found that high sleep quality was associated with a 38% reduced risk of all-cause mortality, which was consistent with previous studies (17–19). The underlying biological mechanism is that poor sleep quality may induce inflammatory cytokines (50), and inflammation has been associated with the incidence of cancer and CVDs (51, 52). No significant associations of diet quality, BMI, cigarette smoking, alcohol drinking, LTPA, and mental status with mortality were observed in this study. However, we found that combined healthy lifestyle factors decreased the risk of all-cause mortality. The possible reason for such discrepancies may be that when multiple lifestyle factors were combined, the synergistic effect of various components might be greater than the effect of each component (9). This further demonstrates the critical importance of considering a variety of healthy lifestyles when maintaining and promoting health.

This study has several strengths. First, participants from community-dwelling residents were recruited by using the multistage sampling method, which can to some degree minimize or reduce selection bias and ensure the population had better representativeness. Moreover, the questionnaire survey was conducted face to face by strictly trained investigators,

which can reduce the information bias to a large degree. Second, we considered a relatively comprehensive range of lifestyle factors, including traditional and emerging lifestyle factors, which could reflect to some extent the complexity of modern life. Third, using indicators of the HLI and lifestyle patterns, we for the first time comprehensively examined the impact of lifestyles on the death from both aspects of the number of healthy lifestyles and their overall effects.

Some limitations also existed. First, the follow-up period in our study was relatively short, resulting in a limited number of death cases; thus, some results did not have enough power to detect significant findings. For example, we found that the association of HLI with cardiovascular mortality risk did not a reach significant level, contradicting the previous reports that showed a negative association between healthy lifestyles and cardiovascular mortality. However, the GZHS is an ongoing cohort study, and further follow-up studies will be performed to examine the association of lifestyle with the risk of cause-specific mortality. Second, dietary information over the past 12 months was collected using the FFQ, which might inevitably lead to recall bias. However, physical examination and questionnaire survey were conducted by trained investigators, which can reduce the bias to some degree. Third, although this study adjusted for several possible confounders, we cannot avoid the possibility of residual confounding due to unmeasured factors.

Conclusion

Our results suggested that the more dimensions of the healthy lifestyle the lower the risk of death, and adherence to the lifestyle pattern characterized with heavier loading of non-smoking and lower alcohol drinking reduces the risk of all-cause mortality. The findings highlight the need to consider multi-dimensional lifestyles rather than one when developing health promotion strategies.

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 the Guangzhou Medical Ethics Committee of the Chinese Medical Association and the Ethical Review Committee for Biomedical Research, School of Public Health, Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XL conceived and designed the study. MZ collected the mortality data. HD, MZ, JH, H-YF, C-JF, H-HR, and Y-SY collected all other data. PH analyzed the data. PH, MZ, and JH drafted the manuscript. HD, XL, WZ, and HW reviewed and edited the manuscript. All authors provided comments and approved the final 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/fmed.2022.920760/full#supplementary-material

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SOOTHER TRIAL: Observational study of an over-the-counter ointment to heal anal itch

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Introduction: Pruritus ani, or rectal or anal itch, is a common perianal disorder that affects ~5% of the population of the developed world. Treatments for this disorder are somewhat limited and include conservative non-medical perianal hygiene care, and topical medical treatments including topical steroids, antibacterial and antifungal agents, and topical anesthetic/analgesics such as lidocaine or capsaicin; astringents and vasoconstrictors such as ephedrine can also be used.

Methods: The study was IRB approved. We assessed the efficacy of a novel, composite, over-the-counter, topical lidocaine ointment that included an epidermal barrier and antimicrobial effect along with the typical lidocaine anesthetizing effect, in a single arm, observational, longitudinal, population of 20 ambulatory pruritus ani patients. Patients applied the ointment twice daily, and were studied for 2 weeks; primary outcomes included time to symptom resolution and clinical exam resolution as measured on a 5-point visual analog scale.

Results: Twenty-nine consecutive patients were screened and 20 patients (12 males; 8 females) were enrolled in the study. Ninety percent of patients achieved 100% symptom resolution by 2 weeks, and most were improved within 72 h of initiating treatment; 95% of patients had a normal visual exam by the 2 week endpoint. There were no significant adverse events attributable to the therapy.

Conclusion: Use of a novel composite topical lidocaine agent, demonstrated rapid and effective relief of pruritus ani in an ambulatory population. Additional studies are underway.

Clinical trial registered: Clinicaltrials.gov, identifier NCT05288907.

KEYWORDS

pruritus ani, anal itch, rectal itch, perianal itch, itch

Introduction

The medical condition known as pruritus ani (commonly referred to as anal itch) is probably the most common ano-rectal disorder in America, and in the developed world. It has been estimated that ∼5% of Americans experience some level of anal itch on a daily basis, so this malady can affect as many as 15 million US residents at any given time (1–3).

Pruritus ani can have multiple causes including diarrhea or frequent liquid stools, multiple loose or soft stools, stool that adheres to the anus and is not entirely cleared post-defecation, leakage of stool from rectal incontinence or frequent passage of gas with some stool leakage, parasites that affect the GI tract, excess anal moisture or perspiration, perianal staph or strep infection, or yeast or candida overgrowth that affects the anal region. Certain diseases or conditions can increase the risk of yeast infections, such as diabetes mellitus, HIV infection or antibiotic usage. Antibiotic use causes alteration of the native intestinal microbiome, potentially leading to yeast overgrowth of the perianal region. Dermatalogical diseases like psoriasis and eczema can also affect the anal region and cause irritation, and systemic diseases such as Crohn's disease, with fistula formation from the small intestine or colon to the skin surrounding the anus can occur allowing leakage of intestinal effluent to the perianal area causing itch. Other comorbid conditions that can contribute to pruritus ani include pinworms, hemorrhoids, anal fissures, and psychogenic causes. Another consideration is that for whatever reason the anal itch initially occurs, a vicious cycle known as the "itch-scratch-itch" cycle can secondarily occur, wherein scratching the itch causes the release of inflammatory chemokines, which secondarily worsens the itch by causing redness, increased itching and dry skin, thereby causing a "rebound" effect (4, 5).

Treatments for pruritus ani are currently limited. The main goal of treatment is to restore the skin in the perianal region to clean, dry, intact, and asymptomatic skin. Repetitively cleaning the region with non-soap warm water then drying the area is the first non-medical treatment that can be tried. If this fails, then steroid ointments can be tried, with or without antifungal or antibiotic additives. Typical antibiotic or antifungal agents contain heavy metals such as zinc oxide or bismuth oxide in varying concentrations. Anesthetic agents like lidocaine or capsaicin can also be tried; lidocaine is commonly available in concentrations from 1 to 5% but capsaicin in therapeutic doses is typically not available commercially. Astringents and vasoconstrictors such as ephedrine can also be used (6).

Lidocaine is a common topical anesthetic agent commercially available in concentrations from 1 to 5%. Lidocaine alters signal conduction in neurons by blocking sodium channels in the neuronal cell membrane thus creating an anesthetic effect (7).

There is a need for newer medical and non-surgical therapies for the treatment of pruritus ani. The ideal therapy would be highly effective at healing itch, with zero to few side effects. This trial assessed a novel, lidocaine-based, composite topical medical therapy for the healing of pruritus ani.

Methods

Study rationale and ointment

The objective and rationale of the trial was to evaluate the efficacy of a novel OTC anal itch ointment on the symptomatic improvement of pruritus ani. This study employed a novel FDA-approved, lidocaine-based, composite topical combination ointment for treating and healing pruritus ani (Rectaid; G&S Labs, Eagan, MN). The composite agent is approved for sale and will be commercially available at retail stores in the United States as an OTC product. As noted above, Lidocaine is a common topical anesthetic agent commercially available in concentrations from 1 to 5%. The composite lidocaine therapy is designed to anesthetize the itch and discomfort associated with pruritus ani, decrease anal sensitivity, improve the epidermal permeability barrier, strengthen keratinocytes and also contains protectant and antibacterial properties. This agent, when used topically will help with pruritus ani primary infection and also the secondary effects of the itch-scratch-itch cycle. The study design was a single arm, uncontrolled, case series. Patients were enrolled consecutively, but not randomly.

Patient population

Any patient male or female, age 18–90, presenting with pruritus ani, in need of treatment, was eligible for the study. Inclusion criteria included presence of pruritus ani (anal itch/discomfort) for at least 2 weeks, and a compatible physical exam. Patients also had to be willing to participate in the study and be capable of understanding the clinical study procedure and be able to give informed consent. Exclusion criteria included inability to understand informed consent, history of inflammatory bowel disease, known venereal disease, or immunodeficiency disease, history of or current anal or perianal abscess, anal or rectal surgery within the past 12 weeks, pregnancy or breastfeeding female, or signs of other rectal diseases such as anorectal fistula, infection, perianal eczema or tumors.

Protocol

This was a single-arm, longitudinal case series of 20 consecutive subjects with pruritus ani. The setting was a private practice colo-rectal surgery clinic, part of a large multi-specialty clinic and located in a suburb of Minneapolis (Voyage Healthcare, Plymouth, MN). The purpose of the study was to investigate the effect of a novel, composite Lidocaine ointment on the healing of pruritus ani. Patients were recruited between October, 2018 to November, 2019; data collection occurred during the same time period.

Any patient presenting with pruritus ani lasting at least 2 weeks was assessed in the standard manner per usual care.

A standard history was taken including current symptoms, past medical history including diarrhea, constipation, fecal incontinence, antibiotic use, inflammatory bowel disease, previous pregnancies and any previous ano-rectal surgery, social history, and medication usage including use of any laxatives. A detailed physical exam was performed including an ano-rectal exam to assess the pruritus ani. Detailed demographic information was captured from each patient specific to pruritus ani. The patients were consecutive but not randomized.

A visual exam of the ano-rectum before and after therapy was carried out per standard practice including anoscopy, flexible sigmoidoscopy and/or colonoscopy on an as-needed basis.

There is no strict definition of pruritus ani, but in this study the following criteria were used:

a) Two weeks or longer persistent itch in the ano-rectal region;
b) consistent physical exam with the presence of erythema, inflammation and/or breaks in the anoderm.

Once pruritus ani was confirmed informed consent was obtained for the study.

Patients applied the novel pruritus ani ointment, in a prespecified amount (per packaged applicator), twice daily for 1–2 weeks or until complete resolution of symptoms. In addition to the novel treatment, patients were also maintained on standard care for pruritus ani, including, but not limited to, a high-fiber diet, laxatives as needed and appropriate maintenance of the region of the anoderm by keeping the area clean and dry using non-soapy water and appropriate drying. Patients were followed in the clinic on an as needed basis, but were specifically assessed at 1–2 weeks following diagnosis and starting the novel ointment. The study ended for each patient at follow-up visit.

Efficacy endpoints

Primary efficacy endpoint

The primary endpoint was the rate of improvement or resolution of symptoms (itch and discomfort) at 2 weeks. At least 50% symptom improvement and 50% exam improvement, both, were necessary for a successful endpoint. Symptoms and physical exam were graded on a 5 point visual analog scale. Standardized case report forms were used to collect study data. Patients were asked to grade their pruritus ani symptoms of itch and discomfort, with 0 being no symptoms and 5 representing the worst symptoms; a similar 5 point scale was used for physical exam assessment, with 0 representing a normal perianal exam with no visible erythema, inflammation or breaks in the anoderm, and 5 representing the most severe exam. Since the exam was a subjective assessment, a single investigator did all of the pre and post-ointment exams (I.F.).

Safety

The ingredients used in the study ointment were deemed as safe, or safer, than existing OTC pruritus ani products, since all of the individual ingredients in the novel preparation are currently available and approved for sale in the US. Study products were compounded under the FDA-approved OTC monograph 21 cfr 346 for Anorectal Topical Products and are commercially approved for use anywhere in the United States. There were no anticipated additional risks beyond that of standard topical pruritus ani OTC therapy. As such, safety was not a primary endpoint of the study; nonetheless all adverse effects related to the study were closely monitored and reported. Any adverse effects were summarized by seriousness, severity, relationship to the ointment, and adverse effect type, and were reported to the IRB.

Study compliance

The study protocol, consent form, case report forms, and all aspects of the conduct of the study were approved and monitored by the Western Institutional Review Board (WIRB; Puyallup, WA). The investigators conducted this study in accordance with all aspects of the protocol, IRB requirements, the Declaration of Helsinki, and the Code of Federal Regulations 21 CFR § 50—Protection of Human Subjects, 21 CFR § 56—and Institutional Review Boards.

Statistical analysis

Each patient served as their own control for statistical analysis. All analyses were performed *via* the intention-to-treat principle. A two-tailed, paired Student's *t*-test or the Wilcoxon signed rank test were used to assess the discrete variables. (Based on a 75% success rate for at least 50% symptom

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TABLE 1 Patient demographics.

Patient #	Age	Weight
1	64	200 lbs.
2	49	148 lbs.
3	46	200 lbs.
4	66	182 lbs.
5	63	165 lbs.
6	50	191 lbs.
7	65	190 lbs.
8	57	142 lbs.
9	61	200 lbs.
10	23	180 lbs.
11	46	150 lbs.
12	76	139 lbs.
13	48	180 lbs.
14	51	130 lbs.
15	68	160 lbs.
16	67	170 lbs.
17	57	200 lbs.
18	64	175 lbs.
19	76	135 lbs.
20	60	189 lbs.

12 males and 8 females.

TABLE 2 Symptom response.

Patient #	Initial symptoms	Follow-up symptoms
1	5	1
2	4	0
3	4	0
4	5	0
5	4	0
6	4	0
7	4	0
8	4	0
9	5	0
10	4	0
11	5	0
12	5	0
13	4	0
14	5	0
15	5	0.
16	5	2
17	5	0
18	4	0
19	3	0
20	4	0

Scale is 0–5 with 5 being the most bothersome.

TABLE 3 Visual exam response.

Patient #	Initial visual exam	Follow-up visual exam
1	3	0
2	2	0
3	5	0
4	4	0
5	4	0
6	3	0
7	4	0
8	4	0
9	3	0
10	4	0
11	5	0
12	4	0
13	3	0
14	4	0
15	3	0
16	4	0
17	2	0
18	3	1
19	4	0
20	2	0

Scale is 0–5 with 0 being normal and 5 being the worst exam.

improvement using the novel ointment, and assuming 30% improvement with standard intervention, 17 patients were required to have a 90% chance of detecting significance at the 5% level, so the study was adequately powered for the outcomes chosen.)

Results

Twenty-nine consecutive pruritis ani patients were screened and 20 patients were enrolled in the study from 2018 to 2019; there were 12 males and 8 females (Table 1). Of the 9 patients not enrolled in the study, 7 chose not to participate and 2 were deemed to not have pruritus ani; of the 20 enrolled patients all completed the study and there were no dropouts. At initial presentation, mean symptoms of itch and discomfort as graded by the patients on a 5 point visual scale, with 0 being no symptoms and 5 being the worst symptoms, were 4.4; the mean symptom score after treatment was 0.15 ($p < 0.008$). Mean visual exam scores (erythema, inflammation, breaks in the anoderm) pre-treatment were 3.5, dropping to 0.1 2 weeks post-treatment ($p < 0.008$). Eighteen of the 20 patients (90%) achieved 100% improvement in symptoms within 14 days of

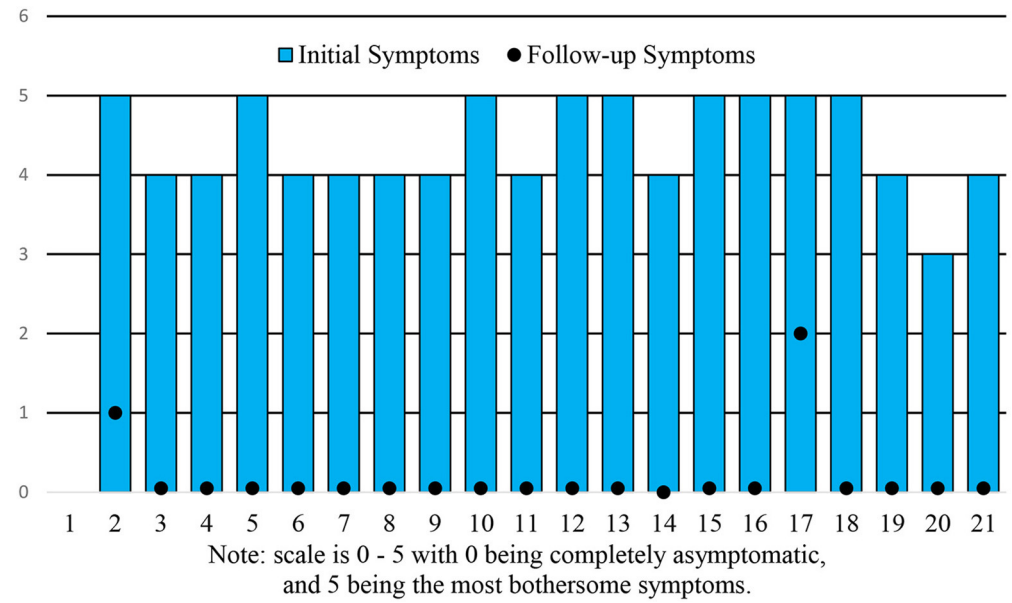

FIGURE 1
SOOTHER TRIAL results-symptoms. Scale is 0–5 with 0 being completely asymptomatic, and 5 being the most bothersome symptoms.

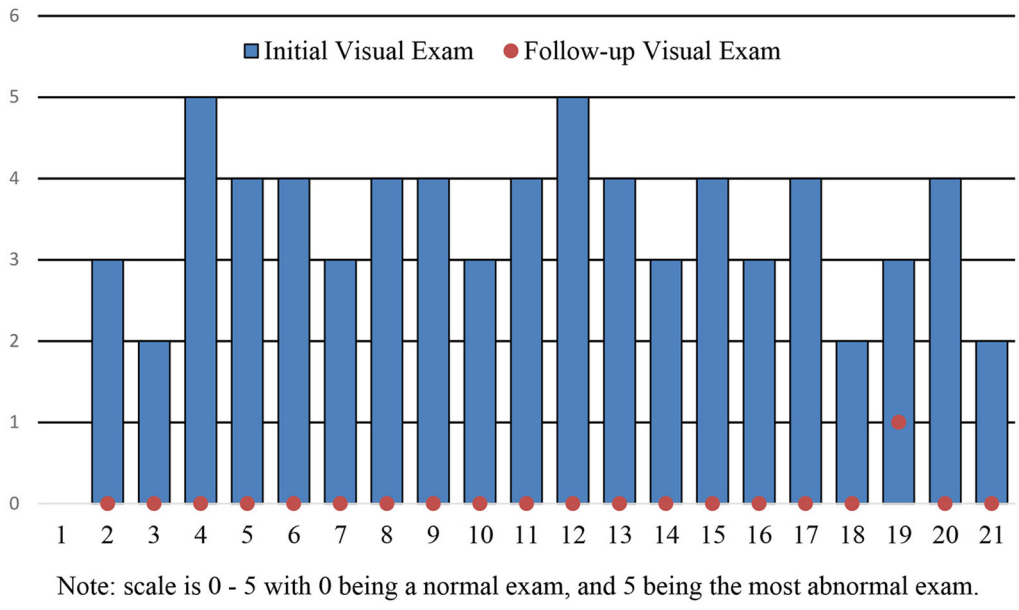

FIGURE 2
SOOTHER TRIAL results-visual exam. Scale is 0–5 with 0 being normal exam, and 5 being the most abnormal exam.

therapy, most within the first 72 h of therapy, and 19 of the 20 patients (95%) had a normal visual exam by 2 weeks (Tables 2, 3). Per intention-to-treat analysis 100% of patients saw at least a 50% improvement both symptomatically and by exam at 2 weeks (Figures 1, 2). There was one adverse event reported, with one female patient developing hives during the study period although it was deemed unlikely to be related to the pruritus ani product; this patient also had a satisfactory symptomatic and visual response to therapy.

Discussion

This trial demonstrates an excellent treatment response of pruritus ani to a novel topical composite lidocaine ointment. Ninety percent of clinic patients were asymptomatic by the end of the 2 week study, with most patients achieving a complete treatment response within the first 72 h. The product was very well-tolerated with no direct adverse events. Limitations of this study include a relatively small number of patients, the non-randomized, uncontrolled population, and the potential bias of single physician assessment. Lidocaine is a well-known over-the-counter topical anesthetic agent at commercially available concentrations of 1–5%. Lidocaine is a weak base with a dissociation constant (pKa) of 7.7, and at standard pH (7.4) about half of the molecules are unionized and able to cross into nerve cells, binding to sodium channels inside the cell membrane, preventing nerve depolarization, thus yielding an anesthesia effect (7). Side effects of topical lidocaine are rare but include irritation, erythema or edema of the skin, hives, or tachycardia. The novel ointment used in this study combines the known anesthetic action of standard lidocaine, with keratinocyte and dermal barrier strengthening effect as well as anti-bacterial, anti-fungal properties leading to good results in anal itch.

There have been very few published therapeutic trials in the field of pruritus ani, even though this is a very common disorder affecting up to 1–5% of the general US population (8). Standard treatment consists of good perianal hygiene by keeping the area of the anus clean and dry, treatment of diarrhea, incomplete evacuation and fecal incontinence, use of fiber preparations such as psyllium and oral anti-histamines. Perianal examination to exclude perianal bacterial or fungal infection is necessary and, if indicated, it can be useful to examine the stool for ova and parasites or obtain bacterial cultures. With good compliance, conservative measures can help the majority of anal itch sufferers (4).

Topical agents like 1% hydrocortisone can be tried and in a small, randomized, controlled crossover trial, 68% of patients improved compared to controls. However, use of steroids can result in skin atrophy and fungal overgrowth. Capsaicin, a natural extract of chili peppers, has also been studied in pruritus ani. Capsaicin causes analgesia by activating TRPV1, a permeable calcium ion channel in nerve cells, and depleting substance P a neuropeptide from sensory neurons, which leads to a decreased pain and itch response to local stimuli. A 44 patient randomized, controlled trial of 0.006% capsaicin ointment in a refractory pruritus ani population, resulted in a 31% response rate. Capsaicin does cause a mild perianal burning sensation however. Other agents have also been studied in limited fashion including injection of methylene blue, a neurotoxic agent, and injection of methylene blue in combination with lidocaine and steroid. This type of therapy, however, has been associated with loss of perianal sensation, occasional fecal incontinence and perianal inflammatory reactions (9).

Consequently, there is a need for novel topical agents for the treatment of pruritus ani, in conjunction with conservative measures. In conclusion, use of a novel, topical, composite lidocaine ointment appears to be a promising new agent for the treatment of pruritus ani. Additional studies are pending.

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 Western IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IF helped draft the study protocol, recruited patients, and did all exams. RG conceived the project and helped with study design, drafted the study protocol, helped with data analysis, and drafted the manuscript. MS helped with product design, study design, drafting the protocol, and helped with data analysis. WC helped with product design and study design. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Authors MS and WC work for Bell International Labs. RG serves as a consultant to G&S Labs, Inc., a subsidiary of Bell International Labs.

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Efficacy of electro-acupuncture in postpartum with diastasis recti abdominis: A randomized controlled clinical trial

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Background: Electro-acupuncture (EA) has promising effects on diastasis rectus abdominis (DRA), defined as a separation of the two muscle bellies of rectus abdominis. To study, there is scant knowledge or scarce high-quality evidence.

Objective: We aimed to evaluate the long-term efficacy and safety of EA in treating DRA during postpartum. It was assumed that the improvement of DRA was more obvious in the EA group than in the control group.

Design: Randomized, controlled, blinded trial (Clinical Trial Registration: ChiCTR2100041891).

Setting: Hangzhou Hospital of Traditional Chinese Medicine in China.

Participants: Females aged 20–45 years without a past medical history of pathological rectus abdominal dissection were recruited from DRA inclusion criteria from 42 days to 1 year postpartum.

Intervention: 110 participants were randomly assigned in a 1:1 ratio to a control group with no EA intervention ($n = 55$), and EA group ($n = 55$). The EA group received ten sessions of EA combined with physical exercise or only physical exercise for 2 weeks with a 26-week follow-up.

Measurements: Outcomes were assessed at baseline, week 2, and week 26. The primary outcome was the change of the inter recti distance (IRD) and electromyographic evaluation of the pelvic floor. Secondary outcomes included elasticity of linea alba (LA), paraumbilical subcutaneous adipose tissue (SAT) measurement, body mass index (BMI), percentage body fat (F%), dyspepsia symptoms, menstrual symptoms, quality of life (QoL), pain performance of patients with lower back pain, postnatal depression symptoms (PDS), postpartum self-image, and DRA-related symptom assessment including urine leakage, frequency, and urgency, constipation, sexual dysfunction, and chronic pelvic pain.

Results: A total of 110 maternal (55 in each group) were recruited. The mean difference in IRD from baseline to week 2 and week 26 in all states of the two groups were reduced compared with those before treatment, with statistical significance ($P < 0.05$). The mean of IRD at the horizontal line of the umbilicus in the end-expiratory state was smaller in the EA group than in the control group, but the difference was not statistically significant ($P > 0.05$) at week 2. The mean of IRD at the horizontal line of the umbilicus in head-up and flexed knee state was smaller in the EA group than in the control group, and the difference was statistically significant ($P < 0.05$) at week 26. Five (9.1%) and thirteen (23.64%) adverse events were reported in EA and control groups, respectively. No serious adverse events were reported.

Limitation: The frequency intensity of EA parameters was selected between 4 and 6 because of individual tolerance differences.

Conclusion: EA is an effective approach to improve IRD, electromyographic evaluation of the pelvic floor, BMI, the elasticity of LA, paraumbilical SAT, and symptoms of DRA, with durable effects at 26 weeks.

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Clinical trial registration: http://www.chictr.org.cn/index.aspx, identifier: ChiCTR2100041891.

KEYWORDS

acupuncture, diastasis recti abdominis, postpartum, intra-abdominal stimulation, randomized controlled trial

Introduction

Diastasis recti abdominis (DRA) is defined as a separation of the rectus abdominal muscles disintegrating to the sides, accompanied by the extension of the linea alba (LA) tissue and bulging of the abdominal wall (1, 2). Diastasis recti abdominis is diagnosed when the inter-rectus distance is > 2 cm (3, 4). It affects 30–70% of women during pregnancy (5), and 35–70% of pregnant women do not recover after giving birth without treatment or exercise (6). In addition, 39–45% of women continue to have DRA at 26 weeks postpartum, and the incidence of DRA at 1 year postpartum is 23–32% (1). The negative effects of DRA manifest in physical function, abdominal trunk function, and impairment of quality of life (QoL) in postpartum women. Women with DRA primarily receive the application of support band and abdominal band during pregnancy and postpartum (6), electrical stimulation, surgical repair (7), and physical exercise (8). There is a lack of a unified and effective treatment plan. There are few studies on the efficacy and safety of current treatments (7, 9); careful follow-up for adverse events must be considered with long-term use. As a worldwide alternative therapy, acupuncture has received wide attention in preventing and treating issues related to pregnancy and childbirth.

Acupuncture therapy is rooted in a complex practice ritual, especially the acupuncture needle procedure, particularly when coupled with EA stimulation. Electro-acupuncture applies electrical stimulation to acupuncture needles (10), which generates improved tissue excitability (11) and adjusts the mechanical balance of the postpartum abdominal muscle group. However, the long-term efficacy of EA is still unclear, and

Abbreviations: AE, Adverse Event; BMI, Body Mass Index; DRA, Diastasis Recti Abdominis; OR, Odds Ratio; PASS, Power Analysis and Sample Size; IRD, Inter Recti Distance; PRI, Pain Rating Index; PPI, Present Pain Intensity; WHR, Waist-to-Hip Ratio; LDQ, Leeds Dyspepsia Questionnaire; MDQ, Menstrual Distress Questionnaire; SF-36, The MOS Item Short Form Health Survey; PT, physical therapists; LA, Linea Alba; SF-MPQ-2, Short-Form McGill Pain Questionnaire-2; EPDS-10, 10 Items of Edinburgh Postnatal Depression Scale; MBIS, The Modified Body Self-Image Scale; ICIQ-SF, International Consultation Incontinence Questionnaire Short-Form; HerQles, Hernia-Related Quality-of-Life Survey; SE, Side Effects.

there is a lack of solid objective evidence. To date, there are no RCT studies on the impact of EA on DRA or evaluating the standardized EA application for DRA. This study comprehensively evaluates the effectiveness and safety of EA in the treatment of postpartum DRA. It provides a reference for the clinical treatment of postpartum DRA.

Methods

Design overview

This was a single-center, randomized, and controlled clinical trial, following the Consolidated Standards of Reporting Trials (CONSORT) statement (12), the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (13), and the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (14). It involved females aged 20–45 years without a past medical history of pathological rectus abdominal dissection, who were recruited from DRA inclusion criteria in 42 days to 1 year postpartum.

The trial was carried out in accordance with the Declaration of Helsinki (15). The Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine reviewed this study's protocol and gave its approval and consent (approval code 2020KY082, Supplementary material 1), which agreed with the Declaration of Helsinki (Version Fortaleza 2012). Clinical Trial Registration: Chinese Clinical Trial Registry, ChiCTR2100041891. All data generated or analyzed in this study will be fully available without restriction through the Clinical Trial Management Public Platform (www.medresman.org.cn, Supplementary material 2). All study patients provided informed consent.

Sample size

According to previous similar reports (16), the mean value of inter recti distance (IRD) in the control group was 2.09 after treatment. The mean value of IRD in the EA group was expected to be 1.43 after treatment in this study. Two groups were set up in this study. The test level was $\alpha = 0.05$ with a test efficiency of $1 - \beta = 0.90$. A two-sided test was also conducted. PASS (Power Analysis and Sample Size) 15.0 software (17) estimated the sample size and effect size as 0.313269. Considering 2-sided *P*-values to be deemed statistically significant at $P < 0.05$ and a power of 90%, 50 patients would be required per group (NQuery Advisor, version 4.0; Statistical Solutions). Estimating that 10% of patients might be lost to follow-up, we planned to enroll 110 patients, with 55 in each group.

Setting and patients

The study was conducted in the outpatient department of Hangzhou Hospital of Traditional Chinese Medicine. Volunteers were recruited *via* hospitals' WeChat (Version 8.0.27) public platform and hospital posters. Patients were recruited using the following inclusion criteria:

(1) Female aged 20–45 years;
(2) 42 days to 1 year postpartum;
(3) The use of ultrasound to evaluate DRA (18) in (a) the midpoint of the umbilicus and xiphoid process, (b) the horizontal line of the umbilicus, and (c) the midpoint of the umbilical and pubic symphysis line. If at any point of the three measurements, IRD is $\geq$2 cm (3) at the resting state;
(4) No cognitive barriers, and able to understand and communicate correctly;
(5) Those who sign the informed consent, cooperate with the treatment, and commit to completing all therapy as planned.

Note: Patients who met the above five criteria were included in this study.

The study also had the following exclusion criteria:

(1) Patient is suspected or diagnosed with severe spinal lesions (such as spinal fractures, metastases, inflammatory or infectious diseases, or cauda equina syndrome/widespread neurological disease) and neurological injury.
(2) Patient has motor contraindications or severe infectious diseases such as fractures, severe heart disease, hypertension, and cancer.

Patients with any of the above were to be excluded.

Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to EA or control group *via* a random-number table (Supplementary material 3) to balance known and unknown confounding factors and thus improve comparability between the two groups. The third-party operator (Lijuan Xiao) put the grouping list into a sequentially numbered, opaque, sealed envelope and delivered it to the operator (Li Sun) to complete the subject intervention assignment. The study leader (Liyuan Jiang) generated allocation numbers, Ying Zhu recruited subjects, and Li Sun assigned interventions. Patient recruiters, outcome assessors, and statisticians did not touch these envelopes until data processing was complete. Participants and the acupuncture provider were not blind to the groups because of the specificity of the EA treatment (19). Outcome assessors, physical therapists (PT), and statisticians were blinded to treatment assignments. Guesstimates of EA group assignment were completed by outcome assessors, PT, and statisticians at the end of the study follow-up. Statistical blinding assessments were performed using the Bang's index and James index (20).

Interventions

The intervention protocol was based on the previous literature and clinical experience of DRA (21). The treatment was administered by a certified acupuncturist (Yingying Shi) who had 23 years of clinical experience in EA. The selection of acupoints was based on Chinese literature and clinical experience. The acupuncture locations are described in The National Standards for Acupoint Location (22).

For the EA group (electro-acupuncture + physical exercise), the patient was placed in the supine position, exposing the abdomen and acupoints Zhongwan (RN12), Xiawan (RN10), bilateral Tianshu (ST25), bilateral Dai Mai (GB26), Qi Hai (RN6), and Guanyuan (RN4) were selected (Figure 1A).

The skin at the acupoints was routinely disinfected, and disposable sterile acupuncture needles were used for vertical acupuncture of 25–40 mm. The acupoints were Zhongwan (RN12), Xiawan (RN10), bilateral Tianshu (ST25), bilateral Dai Mai (GB26), Qi Hai (RN6), and Guanyuan (RN4). The needles were manipulated until the patient felt a "de qi" sensation (23), and were connected to EA (the instrument was Great Wall KWD-808I (Figure 1B) continuous wave (CW) tuning knob of pulse rate "2". The intensity was adjusted to 4–6 mA, which was appropriate if the abdominal muscles contract without feeling pain. The treatment was for 30 min once/day, five times a week for 2 weeks. Physical exercise was the same as the control group.

The control group received the following (only physical exercise, Figure 1C): (a) Fascial abdominal breathing (Figure 1D): The patient was kept at the supine position, lower limb hip, and knee flexion, with foam bricks clamped between the legs. The abdomen was humped when inhaling and was forced to the navel when exhaling. Abdominal muscles and pelvic floor muscles was forced to contract at the same time. This was to be repeated ten times per set and a total of three sets for this exercise. (b) Supine head training: The patient was asked to assume a supine position, lower limb hip, and knee flexion, with foam brick between the legs, and directed to do abdominal breathing increasing abdominal muscle contraction force during exhalation. The head was then held up, and the parts below the lower edge of the scapula cannot leave the bed surface. This was to be repeated ten times per set and a total of three sets for this exercise. (c) Left and right-side leg rotation: The patient was asked to adopt a buckling posture, supine, and legs down to the right. The patient was then asked to inhale with the abdominal bulge, exhale with abdomen muscle contraction, and move both legs in a buckled posture to the left (engage the core abdominal muscles and not engage excessive leg muscles.). The therapist placed one hand on the right side of the external oblique muscle of the patient during muscle contraction, and with the other hand, the therapist applied counter resistance at the side of the knees according to the strength of the patient's exertion. The patient was to repeat this movement alternating on both sides and do it ten times each. (d) Supine cycling: In the supine position, with foam placed at the lumbosacral axis, and arms on both sides of the body, the patient was asked to lift the legs off the bed surface and perform a cycling action. The patient had to complete the cycling action ten times for one set and repeat the set three times. Each exercise was designed for about 5 min, and a total of 20 min, once/day, five times a week for 2 weeks. Patients in both groups started their treatment on the day of randomization and received ten sessions for two consecutive weeks: 5 sessions every week (ideally five consecutive days) until ten sessions. All patients were followed up for 26 weeks.

The same acupuncturist (Yingying Shi) delivered the treatment with standardized operating procedures (Figures 1A,B). Patients were encouraged to refrain from using other therapies for the management of DRA throughout the trial. If other therapies were used, details were documented on a concomitant therapy form. Any adverse event (AE), or side effects (SE) (e.g., bleeding, post stitch, needle blocking) were to be documented in detail on the form and reported to the project leader (Liyuan Jiang). Serious adverse events were to be immediately reported to the institutional review board at the clinical sites within 26 h. Subjects with adverse events were to be treated in the hospital where the project was being implemented, and the project team was to bear the treatment and examination costs.

Assessments and outcomes

The primary outcome was the amelioration of the inter recti distance (IRD) determined by ultrasound at weeks 2 and 26. The response was assessed immediately after the 2-week treatment (week 2) and 24 weeks after treatment (week 26). The between-group difference had to be statistically significant at both time points for us to conclude the efficacy for at least 26 weeks.

IRD is the distance between the rectus abdominal muscles (18). An ultrasound scanner (LOGIQ E9) with a 6–15 MHz high-frequency probe with ML6-15 was used to collect images (MSK Gen mode). Patients were asked to take the supine position and fully expose the upper abdomen. Three measurement sites were selected (the midpoint of the umbilicus and xiphoid process, the horizontal line of the umbilicus, and the midpoint between umbilicus and pubic symphysis at resting state), and wide-field imaging was used when necessary. The mean value of three results from each was taken as the reference value.

IRD and electromyographic evaluation of the pelvic floor by Creative Medical Biofeedback System (AM1000B) were evaluated as the primary endpoint using an ultrasound (18).

The secondary outcomes included: (1) The elasticity of linea alba is assessed by strain elastography (24). The elastic mode is selected at two sites (the horizontal line of the umbilicus, and the midpoint of the umbilicus and xiphoid process). The elastic

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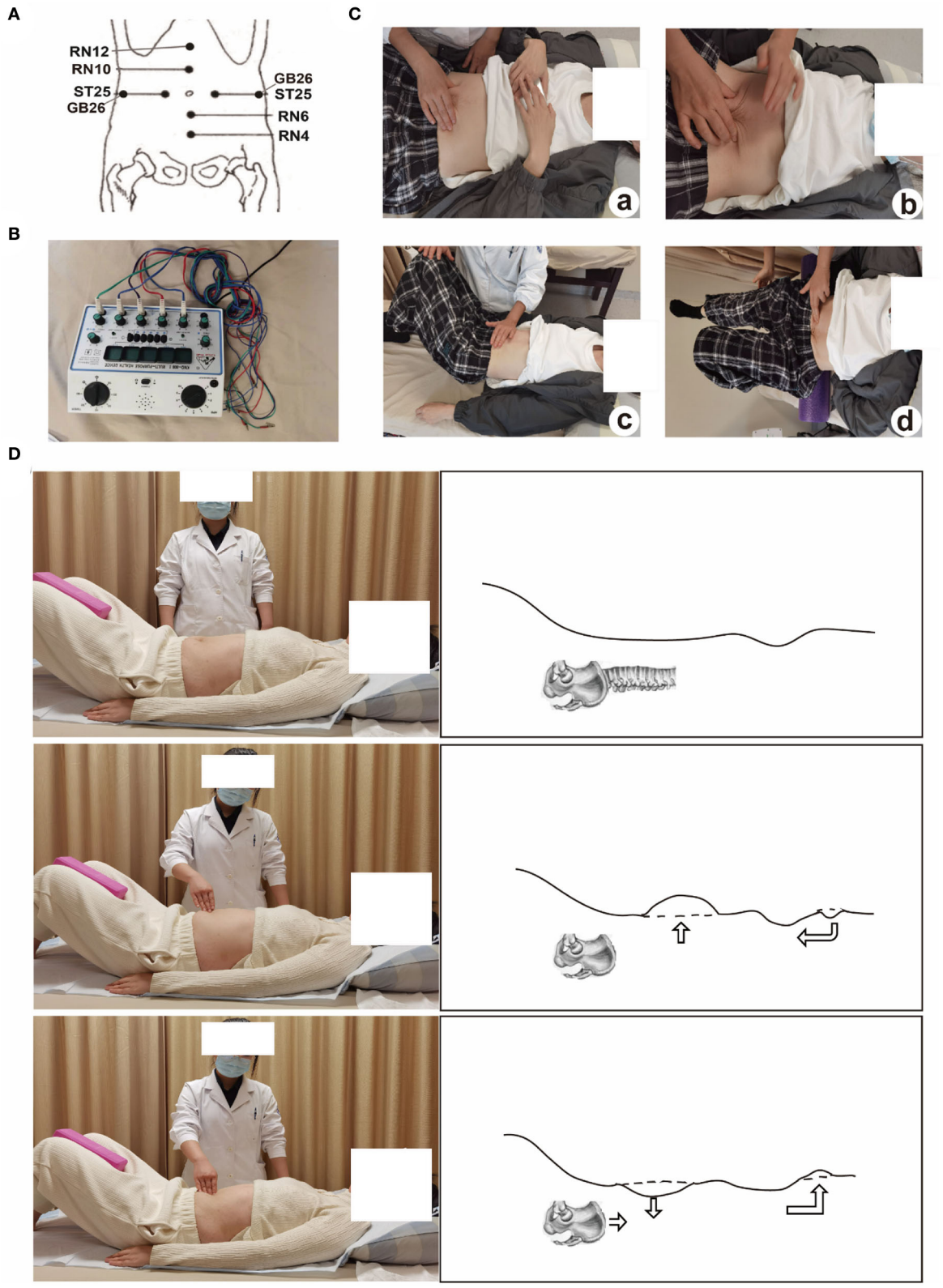

FIGURE 1
(A) the location of the acupoint; **(B)** the EA instrument Great Wall KWD-808I; **(C)** the graphic representation of physical exercise; **(D)** the fascial abdominal breathing at rest (from the authors' own archives, reprinted with the patient's permission).

zone of interest includes the LA and surrounding tissues, and the zone of interest is adjusted to more than twice the area of the LA and as far as possible the mass scale color is kept fluctuating smoothly within the range of 1/3 to 2/3. Mass scale yellow or green is preferred. The smoothness lasts at least 5s. (2) Body mass index (BMI); (3) Paraumbilical subcutaneous adipose tissue (SAT) measurement (25); (4) Percentage body fat (F%) (26).

Other outcomes: (1) Dyspepsia symptoms were evaluated using the Leeds dyspepsia questionnaire (LDQ). LDQ has six grades based on the severity and frequency of the symptoms. The higher the score is, the more serious the symptoms are. LDQ has qualified validity, reliability, reactivity, and internal unity. Therefore, this study chose LDQ as the evaluation index of dyspepsia symptoms to evaluate the difference in efficacy of electro-acupuncture and the control group in treating DRA from the improvement of dyspepsia symptoms. (2) Menstrual symptoms were measured by the Menstrual Distress Questionnaire (25). (3) Quality of life (QoL) was assessed by the Short Form 36 (SF-36®) questionnaire (27, 28) where eight dimensions of health-related quality of life are assessed: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). In addition, the reported health transition (HT) is included. (4) Overall improvement as measured by the short-form McGill pain questionnaire (SF-MPQ) or symptom scale based on the Clinical Study Guideline for New Developed Chinese Medicine (29–31). The questionnaire can be used to assess the pain performance of patients with lower back pain, including the Pain Rating Index (PRI) calculated from the SF-MPQ scale where the PRI is the sum of sensory item scores and emotional item scores; the Visual Analog Scale (VAS) (27, 32); and the Present pain intensity (PPI). (5) Postnatal depression symptoms (PDS) were assessed with Edinburgh postnatal depression scale (EPDS). (6) Postpartum self-image was assessed using the Modified Body Self-Image Scale (MBIS). (7) DRA-related symptom assessment of urine leakage, frequency, and urgency; constipation; sexual dysfunction; and chronic pelvic pain. (8) The main idea of the Hernia-Related Quality of Life Survey (HerQLes) (33) questionnaire was adapted to ask subjects how they felt about the separation of the rectus abdominis muscle and how it affected their lives.

For the evaluation of compliance and adverse events, the patients were instructed to perform physical exercise every day for 26 weeks. Their compliance (number of physical exercises per day, duration of physical exercise per day, movements per day, reasons for not being able to adhere to them) and other conditions (whether they had received other treatment for rectus abdominal separation in the past 26 weeks, whether they had received related treatment for other diseases in the past 26 weeks, whether they had weight-bearing exercises and the frequency of weight-bearing in the past 26 weeks) were statistically evaluated at the end of the follow-up period (Table 1).

Statistical analysis

Data were analyzed using Python 3.8 software. Categorical variables were presented by frequency (percentage) and analyzed with the chi-squared test or Fisher's exact test. If they met normal distribution, continuous variables were presented as mean ± standard deviation (M ± SD). Otherwise, they were presented as medians ± interquartile range (M ± IQR). The demographic characteristics were compared between the groups by independent *t*-tests at baseline. To evaluate the safety of acupuncture, we used a Fisher exact test to report the relative risk of an adverse effect. Analysis of the correlation between the elasticity of linea alba and IRD was undertaken using Spearman's correlation analysis. All tests were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

Patients

The study's flow chart is shown in Figure 2. Between 18 January 2021 and 24 January 2022. A total of 31 patients were not enrolled, of whom 21 (67.7%) met exclusion criteria and 10 (32.3%) were eligible but not enrolled for other reasons (Figure 2). A total of 110 randomized patients enrolled in the study of which 55 were randomized to the EA group and 55 to the control group. Only one patient (1 [who withdrew with low back pain] in the control group) did not receive the study's consecutive treatment. The follow-up to 26 weeks was incomplete for 3 patients (due to COVID-19, there was no way to follow up on time in other places). Thus, data for 106 patients (54 in the EA group and 52 in the control group) were used in the final analysis (Figure 2). Attendance in the study was similar between groups.

Baseline characteristics are presented in Table 2. There were no differences between the two groups regarding patient characteristics, IRD, LDQ, and menstrual symptoms as measured by the Menstrual Distress Questionnaire, QoL, EPDS, and so on.

Briefly, EA and control groups were comparable with respect to demographic characteristics at baseline (Table 2). Minor adverse events (bruising and bleeding from sites of needle insertion) occurred in five (9.1%) patients from the EA group (Supplementary material 2), and minor adverse events (a little lumbar acid) occurred in thirteen (23.64%) control group patients (Supplementary material 2). There were no serious

TABLE 1 The analysis of compliance.

Questions	Grade	EA group	Control group	*P*-value
Number of exercises per day	0 time	19 (35.20%)	19 (36.50%)	0.479
	<1 time on average	27 (50.00%)	30 (57.70%)	
	1 time	7 (13.99%)	3 (5.80%)	
	2 times	1 (1.90%)	0 (0.00%)	
	3 times	1 (0.50%)	0 (0.00%)	
	>3 times	0 (0.00%)	0 (0.00%)	
Daily exercise movements (multiple choice)	No	20 (37.00%)	19 (36.50%)	0.958
	Fascial abdominal breathing	32 (59.30%)	32 (61.50%)	0.811
	Supine head training	6 (11.10%)	5 (9.6%)	0.802
	Left and right-side leg rotation	4 (7.40%)	2 (3.80%)	0.430
	Supine cycling	3 (5.60%)	2 (3.80%)	0.680
Daily exercise time	0	19 (35.20%)	18 (34.60%)	0.647
	<5 min	14 (25.90%)	17(32.70%)	
	5-10 min	12 (22.20%)	11 (21.20%)	
	10-20 min	6 (11.10%)	5 (9.60%)	
	> 20min	3 (5.60%)	1 (1.90%)	
Reasons for not being able to exercise consistently (multiple choice)	Forget	27 (50.00%)	30 (57.70%)	0.429
	No time	31 (57.40%)	39 (75.00%)	0.057
	Unwillingness	7 (13.00%)	12 (23.10%)	0.177
	Not necessary	1 (1.90%)	0 (0.00%)	0.326
	Not mastering the method	0 (0.00%)	0 (0.00%)	1.000
Any other treatment for separation of the rectus abdominis muscle in the last 24 weeks	No	51 (94.40%)	47 (90.40%)	0.431
	Yes	3 (5.60%)	5 (9.60%)	
Any related treatment for other illnesses in the last 6 months	No	51 (94.40%)	43 (82.70%)	0.057
	Yes	3 (5.60%)	9 (17.30%)	
Any weight-bearing activities (carrying children/heavy objects) in the last six months	No	4 (7.40%)	10 (19.20%)	0.113
	Yes	50 (92.60%)	42 (80.80%)	
Weight frequency, if any	≥20 times/week	39 (78.00%)	38 (90.50%)	0.109
	<20 times/week	11 (22.08%)	4 (9.50%)	

adverse events that were attributed to the study intervention in either group.

Blinding assessments

Outcome assessors and physical therapists (PT) responded to the assessment of blinding questions at week 2. Statisticians responded to the assessment of blinding questions at week 26 (Table 3). For the three categories of responders, the majority reported: "don't know". The PT had six (10.91%) accurate guesses for the EA group, and three (5.45%) correct guesses were for the control group. For the Bang index where values between −0.2 and 0.2 indicate successful blinding, values for the EA group and control group were 0 and 0, respectively for outcome assessors. For the PT, the Bang index values were 0.109 (95% CI = 0.031–0.187) for the EA group, and 0.115 (95% CI = −0.004 to 0.114) for the control group. For statisticians, the Bang index values were 0 for the EA group, and 0 for the control group. James' Blinding index (BI) assesses the overall degree of disagreement between treatment allocation and guess, where BI < 0.5 represents unblinding. James' Blinding index (BI) was 1, 0.959 (95% CI = 0.920–0.998), and 1, respectively, for outcome assessors, physical therapists (PT), and statisticians. Blinding index values suggest that blinding was achieved for outcome assessors, physical therapists (PT), and statisticians.

At 2 weeks, the mean of IRD at the horizontal line of the umbilicus, the midpoint of the umbilicus, and the xiphoid process in all states of the two groups were reduced compared with those before the treatment, with statistical significance ($P < 0.05$). For the difference of IRD at the horizontal line of the umbilicus in end-expiratory state, the EA group was better than the control group, with a statistically significant $P < 0.05$. The mean of IRD at the horizontal line of the umbilicus in the

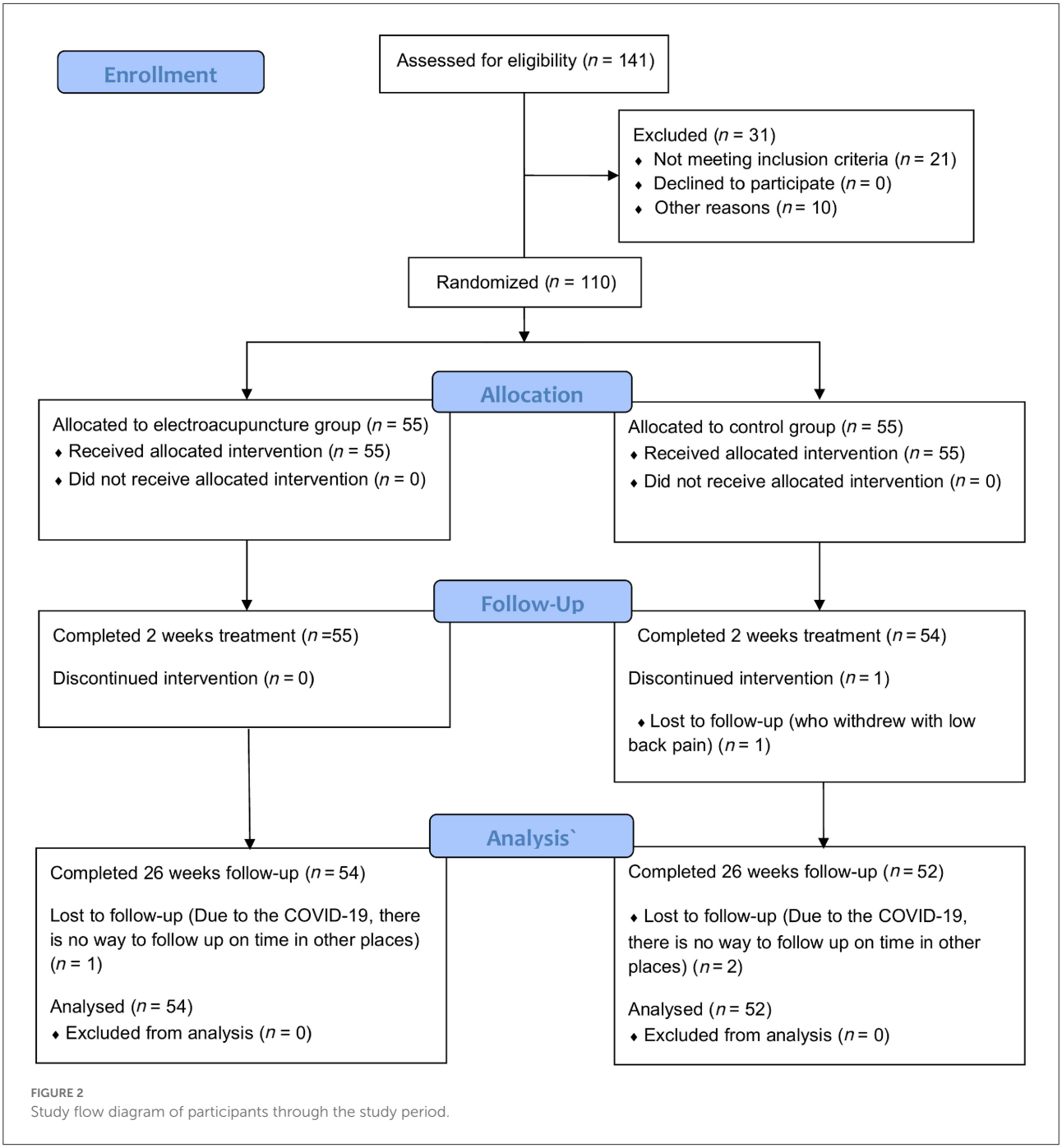

FIGURE 2
Study flow diagram of participants through the study period.

end-expiratory state was smaller in the EA group than in the control group, but the difference was not statistically significant ($P > 0.05$) (Table 4).

At 26 weeks follow-up, the mean of IRD at all status in the midpoint of umbilicus and xiphoid process, at the horizontal line of umbilicus in the resting state, and the horizontal line of umbilicus in the end-expiratory state in both groups were reduced compared with those at 26 weeks, and the difference was statistically significant ($P < 0.05$). The mean of IRD at the horizontal line of the umbilicus in head-up and flexed knee state was smaller in the EA group than in the control group, and the difference was statistically significant ($P < 0.05$). The IRD difference at the horizontal line of the umbilicus in head-up and flexed knee state was higher in the EA group than in the control group, but the difference was not statistically significant ($P > 0.05$). The between-group differences in the mean change from baseline in the IRD followed similar trends of stabilizing during follow-up (Table 4).

TABLE 2 Baseline characteristics of the study population*.

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
Age, y				0.054
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	32.60 ± 3.93	32.56 ± 4.27	32.77 ± 3.58	
Min–Max	24–42	24–42	23.61–40.43	
Median (IQR)	32.0 (5.0)	32.10 (6.78)	33.44 (4.90)	
Height, m				0.443
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	160.35 ± 4.88	160.00 ± 5.33	160.69 ± 4.41	
Min–Max	150–171	150–171	150–170	
Median (IQR)	160 (7.3)	160 (8)	160 (6)	
Mean weight before this pregnancy, kg				0.268
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	53.92 ± 6.97	52.98 ± 7.20	54.85 ± 6.67	
Min–Max	42–75	42–70	42–75	
Median (IQR)	53 (11)	52 (9)	55 (10)	
Weight before this prenatal, kg				0.823
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	68.51 ± 8.07	67.71 ± 7.96	69.31 ± 8.17	
Min–Max	52–98	53–89	52–98	
Median (IQR)	68.0 (8.9)	68 (9.2)	70 (8)	
Weight after childbirth, kg				0.729
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	61.32 ± 7.95	59.99 ± 7.39	62.65 ± 8.32	
Min–Max	44–89	44–80	46–89	
Median (IQR)	60.0 (9.25)	60.0 (10.5)	62.0 (10.0)	
Mean BMI before this pregnancy, kg/m^2				0.598
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	20.99 ± 2.41	20.67 ± 2.42	21.48 ± 2.86	
Min–Max	16.41–27.34	17.01–27.34	16.41–31.22	
Median (IQR)	20.50 (3.06)	20.31 (2.77)	21.64 (4.02)	
BMI before this prenatal, kg/m^2				0.921
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	26.62 ± 2.68	26.42 ± 2.53	27.18 ± 3.86	
Min–Max	20.96–35.56	20.96–33.20	20.31–40.79	
Median (IQR)	26.37 (2.92)	25.89 (2.52)	27.24 (4.86)	
BMI after childbirth, kg/m^2				0.453
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	23.83 ± 2.74	23.40 ± 2.41	24.57 ± 3.83	
Min–Max	17.42–32.30	18.31–28.76	18.07–37.04	
Median (IQR)	23.44 (3.35)	23.03 (2.88)	24.38 (4.44)	
Baby's birth weight, kg				0.330
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	3.42 ± 0.51	3.42 ± 0.47	3.42 ± 0.55	
Min–Max	2.07–6.0	2.07–4.56	2.5–6.0	
Median (IQR)	3.4 (0.7)	3.42 (0.71)	3.40 (0.64)	
Delivery mode, *n* (%)				0.529

(Continued)

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TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
Spontaneous vaginal delivery	59 (53.6)	28 (50.9)	31 (56.4)	
Cesarean section	51 (46.4)	27 (49.1)	24 (43.6)	
Past medical history, *n* (%)				0.782
Yes	15 (13.6)	7 (12.7)	8 (14.5)	
No	95 (86.4)	48 (87.3)	47 (85.5)	
Medication history, *n* (%)				0.697
Yes	7 (6.4)	3 (5.5)	4 (7.3)	
No	103 (93.6)	52 (94.5)	51 (92.7)	
Allergic history, *n* (%)				0.142
Yes	13 (11.8)	4 (7.3)	9 (16.4)	
No	97 (88.2)	51 (92.7)	46 (83.6)	
Previous abdominal surgery, *n* (%)				0.708
Yes	55 (50.0)	30 (54.5)	25 (45.5)	
No	55 (50.0)	25 (45.5)	30 (54.5)	
Number of pregnancies				0.868
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	1.91 ± 1.09	1.93 ± 1.21	1.89 ± 0.96	
Min–Max	1–7	1–7	1–5	
Median (IQR)	2 (1)	1 (1)	2 (1)	
Number of deliveries				0.478
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	1.47 ± 0.57	1.45 ± 0.57	1.49 ± 0.57	
Min–Max	1–3	1–3	1–3	
Median (IQR)	1 (1)	1 (1)	1 (1)	
Multiple or twin pregnancies, *n* (%)				0.978
Yes	2 (1.8)	1 (1.8)	1 (1.8)	
No	108 (98.2)	54 (98.2)	54 (98.2)	
Exercise habits, *n* (%)				0.912
Yes	28 (25.5)	13 (23.6)	15 (27.3)	
No	82 (74.5)	42 (76.4)	40 (72.7)	
Weight-bearing activity, *n* (%)				0.619
Yes	105 (95.5)	53 (96.4)	52 (94.5)	
No	5 (4.5)	2 (3.6)	3 (5.5)	
Fetal head circumference, mm				0.159
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	33.15 ± 0.62	33.18 ± 0.50	33.13 ± 0.72	
Min–Max	32.0–38.0	32.0–35.5	32–28	
Median (IQR)	33 (0)	33 (0)	33 (0)	
Supraumbilical IRD, cm§				0.920
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	1.41 ± 1.27	1.26 ± 1.13	1.56 ± 1.39	
Min–Max	0–7	0–3	0–7	
Median (IQR)	1.5 (2.0)	1.0 (2.0)	1.5 (3.0)	
IRD at the horizontal line of umbilicus, cm				0.051
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	2.84 ± 0.80	2.74 ± 0.75	2.94 ± 0.85	
Min–Max	1.0–7.0	1.5–5.0	1.0–7.0	

(Continued)

TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
Median (IQR)	3.0 (0.5)	3.0 (1.0)	3.0 (0.5)	
IRD at the midpoint of the umbilical and pubic symphysis line, cm				0.654
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	0.18 ± 0.59	0.18 ± 0.62	0.18 ± 0.57	
Min–Max	0–3	0–3	0–3	
Median (IQR)	0 (0)	0 (0)	0 (0)	
Time to pregnancy, weeks				0.524
N (Nmiss)	109 (1)	55 (0)	55 (0)	
Mean±SD	38.87 ± 1.31	38.85 ± 1.38	54.85 ± 6.67	
Min–Max	34–42	34–42	42–75	
Median (IQR)	39 (2)	39 (2)	55 (10)	
Time to postpartum, days				0.875
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	116.98 ± 78.05	118.07 ± 78.83	115.89 ± 77.97	
Min–Max	43–363	43–346	43–363	
Median (IQR)	87.0 (83.8)	87.0 (77.0)	88 (88)	
Educational level, *n* (%)				0.161
Primary education or less	5 (4.5)	4 (7.3)	1 (1.8)	
Secondary education	9 (8.2)	6 (10.9)	3 (5.5)	
Tertiary education	96 (87.3)	45 (81.8)	51 (92.7)	
Occupation before this pregnancy, *n* (%)				0.797
Yes (including the women who were on sick leave)	107 (97.3)	54 (98.2)	53 (96.4)	
No (homemaker, job seeker or student)	3 (2.7)	1 (1.8)	2 (3.6)	
Low back pain, *n* (%)				0.068
Yes	94 (85.5)	46 (83.6)	48 (87.3)	
No	16 (14.5)	9 (16.4)	7 (12.7)	
Pelvic girdle pain, *n* (%)‡	109 (1)	55 (0)	54 (1)	0.792
Yes	59 (53.6)	26 (47.3)	33 (60.0)	
No	50 (45.5)	29 (52.7)	21 (38.2)	
Urine leakage, *n* (%)				0.248
Yes	59 (53.6)	28 (50.9)	31 (56.4)	
No	51 (46.4)	27 (49.1)	24 (43.6)	
Urinary frequency, *n* (%)				0.061
Yes	49 (44.5)	21 (38.2)	28 (50.9)	
No	61 (55.5)	34 (61.8)	27 (49.1)	
Sexual dysfunction, *n* (%)				0.487
Yes	34 (30.9)	15 (27.3)	19 (34.5)	
No	76 (69.1)	40 (72.7)	36 (65.5)	
Chronic pelvic pain, *n* (%)				0.548
Yes	10 (9.1)	5 (9.1)	5 (9.1)	
No	100 (90.9)	50 (90.9)	50 (90.9)	
Constipation, *n* (%)				0.847
Yes	54 (49.1)	28 (50.9)	26 (47.3)	
No	56 (50.9)	27 (49.1)	29 (52.7)	
Urinary urgency, *n* (%)				0.098
Yes	27 (24.5)	16 (29.1)	11 (20.0)	

(Continued)

TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
No	83 (75.5)	39 (70.9)	44 (80.0)	
Pelvic organ prolapses, *n* (%)				0.467
1	42 (38.2)	21 (38.2)	21 (38.2)	
2	65 (59.1)	34 (61.8)	31 (56.4)	
3	3 (2.7)	0	3 (5.5)	
Supraumbilical AC at supine position, cm§				0.645
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	79.64 ± 6.30	78.27 ± 5.45	81.0 ± 6.82	
Min–Max	64.0–97.5	66.0–95.5	64.0–97.5	
Median (IQR)	79.5 (6.0)	79.0 (4.5)	81.0 (8.7)	
AC at the horizontal line of umbilicus in supine position, cm				0.927
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	83.16 ± 6.93	81.56 ± 6.26	84.77 ± 7.24	
Min–Max	66.5–102.8	68.0–96.0	66.5–102.8	
Median (IQR)	83.0 (7.8)	82.8 (6.5)	85.5 (9.8)	
AC at the midpoint of the umbilical and pubic symphysis line in supine position, cm				0.726
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	85.39 ± 6.47	83.80 ± 5.59	86.97 ± 6.93	
Min–Max	70–105	72–101	70–105	
Median (IQR)	85.5 (6.9)	84.3 (6.8)	86.0 (9.0)	
HC at supine position, cm				0.876
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	91.42 ± 5.58	90.06 ± 5.10	92.78 ± 5.76	
Min–Max	78.0–106.5	78.0–104.7	81.0–106.5	
Median (IQR)	91.0 (6.63)	90.0 (5.5)	93.5 (6.5)	
Supraumbilical AC at standing position, cm§				0.261
N (Nmiss)	85 (25)	44 (11)	41 (14)	
Mean±SD	78.44 ± 6.68	77.28 ± 6.08	79.67 ± 7.14	
Min–Max	64.0–96.5	64.0–94.8	65.0–96.5	
Median (IQR)	77.5 (7.9)	77.0 (7.9)	79.0 (8.85)	
AC at the horizontal line of umbilicus in standing position, cm				0.509
N (Nmiss)	85 (25)	44 (11)	41 (14)	
Mean±SD	88.38 ± 7.45	87.25 ± 7.14	89.60 ± 7.67	
Min–Max	70–109	70–103	71–109	
Median (IQR)	88.0 (9.1)	88.0 (7.8)	89.0 (10.8)	
AC at the midpoint of the umbilical and pubic symphysis line in standing position, cm				0.717
N (Nmiss)	85 (25)	44 (11)	41 (14)	
Mean±SD	91.91 ± 6.35	90.43 ± 5.52	93.50 ± 6.84	
Min–Max	75.0–110.5	79.5–106.0	75.0–110.5	
Median (IQR)	92.0 (7.5)	90.3 (6.7)	93.5 (8.9)	
HC at standing position, cm				0.086

(Continued)

TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
N (Nmiss)	84 (26)	44 (11)	40 (15)	
Mean±SD	93.36 ± 6.06	91.82 ± 5.90	95.07 ± 5.84	
Min–Max	78.0–111.5	78.0–105.5	84.0–111.5	
Median (IQR)	93.5 (7.8)	92.3 (6.9)	95.3 (7.3)	
Abdominal static endurance, s				0.902
N (Nmiss)	76 (34)	41 (14)	35 (20)	
Mean±SD	8.49 ± 22.16	9.95 ± 26.84	6.77 ± 15.17	
Min–Max	0–150	0–150	0–71	
Median (IQR)	0 (4.5)	0 (3)	0 (10)	
Abdominal dynamic endurance				0.062
N (Nmiss)	74 (36)	40 (15)	34 (21)	
Mean±SD	3.31 ± 7.03	3.00 ± 6.34	3.68 ± 7.84	
Min–Max	0–28	0–22	0–28	
Median (IQR)	0 (0)	0 (0)	0 (1.75)	
Left side of umbilics skinfold thickness, mm				0.667
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	40.48 ± 14.93	39.42 ± 15.30	41.55 ± 14.61	
Min–Max	10–90	11–90	10–74	
Median (IQR)	39.5 (20.0)	36 (23)	40 (20)	
Right side of umbilics skinfold thickness, mm				0.974
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	41.84 ± 14.79	40.02 ± 15.45	43.65 ± 14.0	
Min–Max	11–90	11–90	13–73	
Median (IQR)	41.5 (19.3)	37 (17)	44 (17)	
Right skinfold thickness of triceps brachii, mm				0.347
N (Nmiss)	81 (29)	42 (13)	39 (16)	
Mean±SD	37.67 ± 9.38	39.21 ± 10.50	36.0 ± 7.79	
Min–Max	15–65	15–65	15–52	
Median (IQR)	38.0 (13.0)	40.0 (16.3)	37.0 (9.0)	
Right skinfold thickness of scapula, mm				0.219
N (Nmiss)	81 (29)	42 (13)	39 (16)	
Mean±SD	36.07 ± 10.30	36.93 ± 10.44	35.15 ± 10.21	
Min–Max	15–62	20–62	15–60	
Median (IQR)	35.0 (14.5)	35.5 (15.3)	34.0 (14.0)	
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm Δ				0.445
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	22.21 ± 10.83	20.60 ± 7.38	23.81 ± 13.31	
Min–Max	7–97	10–36	7–97	
Median (IQR)	21 (12)	20 (12)	23 (12)	
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm Δ				0.544
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	18.13 ± 9.67	17.32 ± 6.88	18.95 ± 11.84	
Min–Max	4–90	5–34	4–90	
Median (IQR)	17 (10)	17 (9)	16 (11)	
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm Δ				0.288
N (Nmiss)	110 (0)	55 (0)	55 (0)	

(Continued)

TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
Mean±SD	23.88 ± 11.84	21.95 ± 8.00	25.81 ± 14.55	
Min–Max	7–104	10–40	7–104	
Median (IQR)	22 (14)	22 (13)	24 (15)	
IRD at the horizontal line of umbilicus in the resting state, cm Δ				0.749
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	36.57 ± 13.73	34.88 ± 9.78	38.26 ± 16.70	
Min–Max	21–114	21–69	21–114	
Median (IQR)	34 (14)	34 (12)	34 (16)	
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm Δ				0.540
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	26.94 ± 9.75	26.06 ± 8.67	27.83 ± 10.73	
Min–Max	10–80	14–65	10–80	
Median (IQR)	25.0 (9.3)	25 (9)	25 (9)	
IRD at the horizontal line of umbilicus in end-expiratory state, cm Δ				0.708
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	38.38 ± 14.69	36.49 ± 11.04	40.27 ± 17.50	
Min–Max	21–118	21–72	22–118	
Median (IQR)	35 (14)	35 (13)	28 (16)	
IRD at the midpoint of between umbilicus and pubic symphysis, cm Δ				–
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	0	0	0	
Min–Max	0	0	0	
Median (IQR)	0 (0)	0 (0)	0 (0)	
Left abdominal skinfold, mm Δ				0.454
N (Nmiss)	15 (95)	4 (51)	11 (44)	
Mean±SD	20.47 ± 4.44	20.25 ± 1.50	20.55 ± 5.18	
Min–Max	14–30	19–22	14–30	
Median (IQR)	20.0 (6.0)	20.0 (2.8)	20 (8)	
Right abdominal skinfold, mm Δ				0.260
N (Nmiss)	15 (95)	4 (51)	11 (44)	
Mean±SD	19.93 ± 3.58	19.75 ± 0.96	20.0 ± 4.20	
Min–Max	15–26	19–21	15–26	
Median (IQR)	19.0 (7.0)	19.5 (1.8)	19 (8)	
The mean values of pre-baseline at the period of calm				0.043
N (Nmiss)	109 (1)	55 (0)	54 (1)	
Mean±SD	7.10 ± 3.91	7.02 ± 4.43	7.18 ± 3.35	
Min–Max	0.58–23.16	1.14–23.16	0.28–14.91	
Median (IQR)	6.2 (5.1)	5.7 (5.8)	6.81 (4.54)	
The mean values of fast muscle at the period of systolic				0.427
N (Nmiss)	109 (1)	55 (0)	54 (1)	
Mean±SD	27.88 ± 11.42	28.55 ± 10.37	27.20 ± 12.46	
Min–Max	5.09–49.61	9.12–48.83	5.09–49.61	

(Continued)

TABLE 2 (Continued)

Characteristic	All ($n = 110$)	EA ($n = 55$)†	Control ($n = 55$)†	*P*-value
Median (IQR)	28.2 (18.2)	28.5 (17.8)	27.1 (20.66)	
The mean values of comprehensive muscle at the period of systolic				0.005
N (Nmiss)	109 (1)	55 (0)	54 (1)	
Mean±SD	20.74 ± 10.74	20.48 ± 10.20	21.01 ± 11.35	
Min–Max	3.16–43.76	3.19–40.84	3.16–43.76	
Median (IQR)	18.6 (17.2)	18.2 (17.1)	18.7 (18.42)	
The mean values of slow muscle at the period of systolic				0.001
N (Nmiss)	109 (1)	55 (0)	54 (1)	
Mean±SD	18.13 ± 9.72	17.40 ± 9.06	18.87 ± 10.39	
Min–Max	2.85–40.50	2.85–40.50	4.12–38.97	
Median (IQR)	16.4 (14.2)	16.1 (13.3)	16.61 (15.77)	
The mean values of post-baseline at the period of calm				0.225
N (Nmiss)	109 (1)	55 (0)	54 (1)	
Mean±SD	6.47 ± 3.78	6.24 ± 3.66	6.70 ± 3.69	
Min–Max	0.58–19.12	1.21–19.12	0.58–16.52	
Median (IQR)	6.5 (5.2)	5.8 (4.3)	6.6 (4.9)	
Leeds dyspepsia questionnaire				0.716
N (Nmiss)	110	55	55	
Mean±SD	6.55 ± 1.22	6.49 ± 1.09	6.60 ± 1.34	
Min–Max	6–13	6–12	6–13	
Median (IQR)	6.0 (0.25)	6.5 (0)	6.0 (1)	
SAT in the paraumbilical region				0.069
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	41.16 ± 14.84	39.38 ± 15.38	43.01 ± 14.09	
Min–Max	10–90	11–90	10–74	
Median (IQR)	40 (20)	36 (20)	43 (18.5)	
SAT in right triceps region				0.124
N (Nmiss)	81 (29)	41 (14)	40 (15)	
Mean±SD	37.67 ± 9.38	39.21 ± 10.50	36 ± 7.79	
Min–Max	15–65	15–65	15–52	
Median (IQR)	38 (13)	40 (16.25)	37 (9)	
SAT in the right subscapular region				0.442
N (Nmiss)	81 (29)	41 (14)	40 (15)	
Mean±SD	36.07 ± 10.31	36.93 ± 10.44	35.15 ± 10.21	
Min–Max	15–62	20–62	15–60	
Median (IQR)	35 (14.5)	35.5 (15.25)	34 (14)	
F%				0.380
N (Nmiss)	110 (0)	55 (0)	55 (0)	
Mean±SD	0.32 ± 0.20	0.34 ± 0.21	0.30 ± 0.19	
Min–Max	0.02–0.73	0.02–0.73	0.02–0.62	
Median (IQR)	0.37 (0.44)	0.39 (0.40)	0.35 (0.41)	

AC, abdominal circumference; EA, electroacupuncture; BMI, body mass index; SD, Standard Deviation; HC, hip circumference; IQR, Inter-Quartile Range; IRD, inter recti distance.
*The only one patient (1 [who withdrew with low back pain] in control group) did not receive the study consecutive treatment. The follow-up to 26 weeks was incomplete for 3 patients (Due to the COVID-19, there is no way to follow up on time in other places).
† There were no significant differences between two groups.
‡ The pelvic girdle includes inguinal, pubic symphysis, coccyx, sacrum, and either side of the pelvis.
§ The midpoint of umbilicus and xiphoid process.
Δ At the supine position.

TABLE 3 Guesstimate vs. treatment assignment.

Treatment assignment	Outcome assessors ($n = 110$)		Physical therapists ($n = 110$)		Statisticians ($n = 110$)	
	EA group	Control group	EA group	Control group	EA group	Control group
Guesstimate[a]						
EA group	0	0	6 (10.91)	3 (5.45)	0	0
Control group	0	0	0	0	0	0
Don't know	55	55	49 (89.09)	52 (94.55)	55	55
Degree of confidence in response[a]						
Correct guesstimate						
Extremely confident	0	0	0	0	0	0
Reasonably confident	0	0	0	1	0	0
Slightly confident	0	0	6 (10.91)	2	0	0
Missing	55	55	49 (89.09)	52 (94.55)	55	55
Incorrect guesstimate						
Extremely confident	0	0	0	0	0	0
Reasonably confident	0	0	0	0	0	0
Slightly confident	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Blinding indices						
James' Blinding Index[b]	1		0.959 (0.920, 0.998)		1	
Bang Blinding Index[b]						
EA group	0		0.109 (0.031, 0.187)		0	
Control group	0		0.115 (−0.004, 0.114)		0	

James' Blinding index (BI) assesses overall degree of disagreement between treatment allocation and guess, where a BI<0.5 represents unblinding.
Bang Blinding index assesses the degree of disagreement in each treatment group, where a BI>0.2 represents unblinding and a BI<-0.2 represents Opposite Guess or 'Wishful thinking'.
[a]Parentheses denote percentages.
[b]Parentheses denote 95% confidence interval.

The results of the electromyographic evaluation of the pelvic floor show the following: After treatment, the mean of pre-baseline during the period of calm in both groups was lower than that before treatment, and the difference was statistically significant ($P < 0.05$). The mean value of the fast muscle during systole, the comprehensive muscle during systole, and the slow muscle during systole in both groups increased compared with that before treatment, and the difference was statistically significant ($P < 0.05$). The difference in slow muscle during systole before and after treatment in the EA group was higher than that in the control group, and the difference was statistically significant ($P < 0.05$). After 26 weeks of follow-up, the mean of pre-baseline during the period of calm in the EA group was lower than those after treatment, and the difference was statistically significant ($P < 0.05$). The mean of the fast muscle during systole, the comprehensive muscle during systole, and the slow muscle during systole in the EA group were increased compared with that after treatment, and the difference was statistically significant ($P < 0.05$). At 26 weeks, the differences in the mean of slow muscle during systole were higher in the EA group than in the control group, and the difference was statistically significant ($P < 0.05$). At 26 weeks, the mean of the pre-baseline during the period of calm of the EA group was lower than that of the control group, and the difference was statistically significant ($P < 0.05$). Compared with the control group, the mean of the fast muscle during systole, the comprehensive muscle during systole, and the slow muscle during systole in the EA group were increased, and the differences were statistically significant ($P < 0.05$) (Table 4).

In the control group, the elasticity of linea alba was smaller than that of the EA group at two sites (the horizontal line of the umbilicus, and the midpoint of the umbilicus and xiphoid process) at week 2 and week 26 ($P < 0.05$). In terms of the correlation between the elasticity of linea alba and IRD, the LA elasticity score was negatively correlated with IRD ($rs = -0.356$, $P < 0.05$). As recognized by week 2, a greater decrease in BMI in the EA group compared with the control group indicate the presence of variation in response to treatment ($P < 0.05$) (Table 4).

After treatment, the mean of SAT at the paraumbilical and right triceps of the two groups, and the mean of SAT at the right subscapular of the EA group were reduced compared with those before treatment, with statistical significance ($P < 0.05$), but the difference was not statistically significant ($P > 0.05$) between

TABLE 4 Primary and secondary outcomes*.

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	*P*-value##
Primary outcome				
IRD				
IRD at the horizontal line of umbilicus in the resting state, cm Δ†	Before the treatment	3.49 ± 0.98	3.83 ± 1.67	
	After the treatment	2.85 ± 0.86	3.08 ± 1.43	
	P-value #	0.000	0.000	
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm Δ†	Before the treatment	2.61 ± 0.87	2.78 ± 1.07	
	After the treatment	1.96 ± 0.61	2.17 ± 0.81	
	P-value #	0.000	0.000	
IRD at the horizontal line of umbilicus in end-expiratory state, cm Δ†	Before the treatment	3.65 ± 1.10	4.03 ± 1.75	
	After the treatment	3.21 ± 0.96	3.43 ± 1.57	
	P-value #	0.000	0.000	
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm Δ†	Before the treatment	2.06 ± 0.74	2.38 ± 1.33	
	After the treatment	1.60 ± 0.72	1.82 ± 1.24	
	P-value #	0.000	0.000	
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm Δ†	Before the treatment	1.73 ± 0.69	1.90 ± 1.18	
	After the treatment	1.33 ± 0.62	1.41 ± 0.80	
	P-value #	0.000	0.000	
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm Δ†	Before the treatment	2.20 ± 0.80	2.58 ± 1.46	
	After the treatment	1.76 ± 0.78	2.03 ± 1.39	
	P-value #	0.000	0.000	
IRD at the midpoint of between umbilicus and pubic symphysis, cm Δ†	Before the treatment	0.00 ± 0.00	0.00 ± 0.00	
	After the treatment	0.00 ± 0.00	0.00 ± 0.00	
	P-value #	1.000	1.000	
IRD at the horizontal line of umbilicus in the resting state, cm Δ†	After the treatment	2.85 ± 0.86	3.08 ± 1.43	
	At 24 weeks follow-up after treatment	2.59 ± 0.84	2.89 ± 1.31	
	P-value #	0.000	0.000	
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm Δ†	After the treatment	1.96 ± 0.6	2.17 ± 0.81	
	At 24 weeks follow-up after treatment	1.77 ± 0.67	2.08 ± 0.82	
	P-value #	0.167	0.001	
IRD at the horizontal line of umbilicus in end-expiratory state, cm Δ†	After the treatment	3.21 ± 0.96	3.43 ± 1.57	
	At 24 weeks follow-up after treatment	3.00 ± 1.02	3.25 ± 1.30	
	P-value #	0.001	0.000	
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm Δ†	After the treatment	1.60 ± 0.72	1.82 ± 1.24	
	At 24 weeks follow-up after treatment	1.37 ± 0.72	1.50 ± 1.24	
	P-value #	0.000	0.000	
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm Δ†	After the treatment	1.33 ± 0.62	1.41 ± 0.80	
	At 24 weeks follow-up after treatment	1.12 ± 0.63	1.17 ± 0.74	
	P-value #	0.000	0.000	
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm Δ†	After the treatment	1.76 ± 0.78	2.03 ± 1.39	
	At 24 weeks follow-up after treatment	1.56 ± 0.83	1.68 ± 1.39	
	P-value #	0.000	0.000	
IRD at the midpoint of between umbilicus and pubic symphysis, cm Δ†	After the treatment	0.00 ± 0.00	0.00 ± 0.00	
	At 24 weeks follow-up after treatment	0.00 ± 0.00	0.00 ± 0.00	
	P-value #	1.000	1.000	

(Continued)

TABLE 4 (Continued)

Outcome	EA group ($n = 54$)	Control group ($n = 52$)	P-value[##]
Week 2[##]			
IRD at the horizontal line of umbilicus in the resting state, cm [Δ‡]	−7.56 ± 3.82	−6.37 ± 3.67	0.084
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm [Δ‡]	−6.20 ± 5.37	−6.48 ± 5.05	0.884
IRD at the horizontal line of umbilicus in end-expiratory state, cm [Δ‡]	−6.09 ± 3.91	−4.44 ± 4.62	0.017
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm [Δ‡]	−5.58 ± 3.24	−4.64 ± 2.11	0.212
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm [Δ‡]	−4.89 ± 5.89	−4.06 ± 3.62	0.472
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm [Δ‡]	−5.43 ± 3.94	−4.32 ± 2.74	0.128
IRD at the midpoint of between umbilicus and pubic symphysis, cm [Δ‡]	0 ± 0	0 ± 0	1.000
Week 26[##]			
IRD at the horizontal line of umbilicus in the resting state, cm [Δ‡]	−2.57 ± 3.12	−2.17 ± 3.31	0.361
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm [Δ‡]	−1.94 ± 4.22	−0.88 ± 4.01	0.146
IRD at the horizontal line of umbilicus in end-expiratory state, cm [Δ‡]	−1.98 ± 4.27	−2.08 ± 4.54	0.429
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm [Δ‡]	−2.37 ± 2.08	−3.42 ± 3.31	0.153
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm [Δ‡]	−2.09 ± 2.58	−2.48 ± 3.46	0.932
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm [Δ‡]	−2.17 ± 2.89	−3.69 ± 3.91	0.056
IRD at the midpoint of between umbilicus and pubic symphysis, cm [Δ‡]	0 ± 0	0 ± 0	1.000
Week 2[##]			
IRD at the horizontal line of umbilicus in the resting state, cm [Δ†]	2.85 ± 0.86	3.08 ± 1.43	0.736
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm [Δ†]	1.96 ± 0.61	2.17 ± 0.81	0.194
IRD at the horizontal line of umbilicus in end-expiratory state, cm [Δ†]	3.21 ± 0.96	3.43 ± 1.57	0.851
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm [Δ†]	1.60 ± 0.72	1.82 ± 1.24	0.401
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm [Δ†]	1.33 ± 0.62	1.41 ± 0.80	0.593
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm [Δ†]	1.76 ± 0.78	2.03 ± 1.39	0.338
IRD at the midpoint of between umbilicus and pubic symphysis, cm [Δ†]	0.00 ± 0.00	0.00 ± 0.00	1.000
Week 26[##]			

(Continued)

TABLE 4 (Continued)

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	P-value[##]
IRD at the horizontal line of umbilicus in the resting state, cm [Δ†]		2.59 ± 0.84	2.89 ± 1.31	0.224
IRD at the horizontal line of umbilicus in head-up and flexed knee state, cm [Δ†]		1.77 ± 0.67	2.08 ± 0.82	0.027
IRD at the horizontal line of umbilicus in end-expiratory state, cm [Δ†]		3.00 ± 1.02	3.25 ± 1.30	0.450
IRD at the midpoint of umbilicus and xiphoid process in the resting state, cm [Δ†]		1.37 ± 0.72	1.50 ± 1.24	0.704
IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm [Δ†]		1.12 ± 0.63	1.17 ± 0.74	0.562
IRD at the midpoint of umbilicus and xiphoid process in end-expiratory state, cm [Δ†]		1.56 ± 0.83	1.68 ± 1.39	0.756
IRD at the midpoint of between umbilicus and pubic symphysis, cm [Δ†]		0 ± 0	0 ± 0	1.000
Electromyographic evaluation of pelvic floor				
Week 2#	Before the treatment	7.02 ± 4.43	7.17 ± 3.32	
The mean value of pre-baseline during the period of calm[†]				
	After the treatment	5.55 ± 3.58	6.56 ± 3.64	
	P-value #	0.000	0.050	
Fast muscle during systole[†]	Before the treatment	28.55 ± 10.37	27.37 ± 12.40	
	After the treatment	35.41 ± 10.59	32.86 ± 12.48	
	P-value #	0.000	0.000	
The comprehensive muscle during systole[†]	Before the treatment	20.48 ± 10.20	20.48 ± 10.20	
	After the treatment	27.33 ± 10.38	25.86 ± 10.52	
	P-value #	0.000	0.000	
Slow muscle during systole[†]	Before the treatment	17.40 ± 9.06	18.77 ± 10.32	
	After the treatment	24.82 ± 9.70	23.54 ± 0.81	
	P-value #	0.000	0.000	
The mean value of post-baseline during the period of calm[†]	Before the treatment	6.24 ± 3.88	6.70 ± 3.65	
	After the treatment	6.76 ± 4.18	7.37 ± 3.70	
	P-value #	0.463	0.149	
Week 26#	Before the treatment	5.55 ± 3.58	6.56 ± 3.64	
The mean value of pre-baseline during the period of calm[†]				
	After the treatment	4.44 ± 2.29	6.25 ± 3.87	
	P-value #	0.004	0.348	
Fast muscle during systole[†]	Before the treatment	35.41 ± 10.59	32.86 ± 12.48	
	After the treatment	46.08 ± 14.91	39.64 ± 19.76	
	P-value #	0.000	0.008	
The comprehensive muscle during systole[†]	Before the treatment	27.33 ± 10.38	25.86 ± 10.52	
	After the treatment	39.64 ± 19.76	28.67 ± 16.07	
	P-value #	0.002	0.120	
Slow muscle during systole	Before the treatment	24.82 ± 9.70	23.54 ± 0.81	
	After the treatment	29.10 ± 10.80	23.02 ± 11.22	
	P-value #	0.003	0.579	
The mean value of post-baseline during the period of calm[†]	Before the treatment	6.76 ± 4.18	7.37 ± 3.70	
	After the treatment	5.95 ± 2.55	7.38 ± 5.31	

(Continued)

TABLE 4 (Continued)

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	*P*-value[##]
	P-value #	0.213	0.289	
Week 2[##]		−1.47 ± 3.43	−0.64 ± 2.90	0.225
The mean value of pre-baseline during the period of calm[‡]				
The mean value of fast muscle during systole[‡]		6.86 ± 7.50	5.59 ± 9.51	0.178
The mean value of the comprehensive muscle during systole[‡]		6.86 ± 7.14	4.87 ± 7.82	0.074
The mean value of slow muscle during systole[‡]		7.42 ± 6.39	4.63 ± 8.21	0.019
The mean value of post-baseline during the period of calm[‡]		0.51 ± 3.32	0.62 ± 2.93	0.630
Week 26[##]		−1.21 ± 2.74	−0.41 ± 3.54	0.355
The mean value of pre-baseline during the period of calm[‡]				
The mean value of fast muscle during systole[‡]		10.36 ± 12.7	7.07 ± 16.02	0.102
The mean value of the comprehensive muscle during systole[‡]		5.54 ± 11.77	3.05 ± 12.66	0.191
The mean value of slow muscle during systole[‡]		4.03 ± 9.30	−0.19 ± 9.29	0.013
The mean value of post-baseline during the period of calm[‡]		−0.91 ± 3.44	0.01 ± 4.75	0.970
Week 2[##]		5.55 ± 3.58	6.56 ± 3.64	0.116
The mean value of pre-baseline during the period of calm[†]				
The mean value of fast muscle during systole[†]		35.41 ± 10.59	32.86 ± 12.48	0.212
The mean value of the comprehensive muscle during systole[†]		27.33 ± 10.38	25.86 ± 10.52	0.486
The mean value of slow muscle during systole[†]		24.82 ± 9.70	23.54 ± 0.81	0.575
The mean value of the mean value of post-baseline during the period of calm[†]		6.76 ± 4.18	7.37 ± 3.70	0.211
Week 26[##]		4.44 ± 2.29	6.25 ± 3.87	0.006
The mean value of pre-baseline during the period of calm[†]				
The mean value of fast muscle during systole[†]		46.08 ± 14.91	39.64 ± 19.76	0.006
The mean value of the comprehensive muscle during systole[†]		33.15 ± 12.66	28.67 ± 16.07	0.016
The mean value of slow muscle during systole[†]		29.10 ± 10.80	23.02 ± 11.22	0.002
The mean value of post-baseline during the period of calm[†]		5.95 ± 2.55	7.38 ± 5.31	0.235
Secondary Outcomes				
The elastic of linea alba				
Week 2[##]		3.08 ± 0.43	2.24 ± 0.74	0.000
The elastic of linea alba in the horizontal line of umbilicus				
The elastic of linea alba in the midpoint of umbilicus and xiphoid process		2.34 ± 0.65	1.24 ± 0.48	0.000
Week 26[##]		3.94 ± 0.72	3.16 ± 0.93	0.000
The elastic of linea alba in the horizontal line of umbilicus				
The elastic of linea alba in the midpoint of umbilicus and xiphoid process		3.23 ± 0.85	2.72 ± 1.01	0.010
BMI at week 2		21.97 ± 0.05	23.25 ± 0.42	0.013
The paraumbilical SAT				
SAT in the paraumbilical region[†]	Before the treatment	39.38 ± 15.38	43.01 ± 14.09	
	After the treatment	35.02 ± 11.97	37.85 ± 12.05	
	P-value #	0.000	0.000	
SAT in right triceps region[†]	Before the treatment	39.21 ± 10.50	36 ± 7.79	
	After the treatment	34.58 ± 7.03	33.04 ± 6.65	

(Continued)

TABLE 4 (Continued)

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	P-value[##]
	P-value[#]	0.001	0.024	
SAT in the right subscapular region[†]	Before the treatment	36.93 ± 10.44	35.15 ± 10.21	
	After the treatment	31.64 ± 7.51	33.62 ± 8.56	
	P-value[#]	0.000	0.604	
F% [†]	Before the treatment	0.34 ± 0.21	0.30 ± 0.19	
	After the treatment	0.31 ± 0.16	0.34 ± 0.14	
	P-value[#]	0.142	0.067	
SAT in the paraumbilical region[†]	After the treatment	35.02 ± 11.97	37.85 ± 12.05	
	At 24 weeks follow-up after treatment	31.64 ± 7.51	31.77 ± 8.83	
	P-value[#]	0.000	0.000	
SAT in right triceps region[†]	After the treatment	34.58 ± 7.03	33.04 ± 6.65	
	At 24 weeks follow-up after treatment	28.89 ± 7.26	30.08 ± 5.97	
	P-value[#]	0.002	0.040	
SAT in the right subscapular region[†]	After the treatment	31.64 ± 7.51	33.62 ± 8.56	
	At 24 weeks follow-up after treatment	32.22 ± 9.05	31.32 ± 8.95	
	P-value[#]	0.218	0.216	
F% [†]	After the treatment	0.31 ± 0.16	0.34 ± 0.14	
	At 24 weeks follow-up after treatment	0.34 ± 0.10	0.33 ± 0.11	
	P-value[#]	0.246	0.723	
Week 2[##]				
SAT in the paraumbilical region[†]		35.02 ± 11.97	37.85 ± 12.05	0.084
SAT in right triceps region[†]		34.58 ± 7.03	33.04 ± 6.65	0.285
SAT in the right subscapular region[†]		31.64 ± 7.51	33.62 ± 8.56	0.244
F% [†]		0.31 ± 0.16	0.34 ± 0.14	0.362
SAT in the paraumbilical region[‡]		−5.60 ± 9.93	−5.16 ± 9.03	0.726
SAT in right triceps region[‡]		−0.81 ± 9.33	1.38 ± 9.43	0.084
SAT in the right subscapular region[‡]		−1.13 ± 8.44	1.94 ± 9.00	0.010
F% [‡]		−0.01 ± 0.10	0.02 ± 0.09	0.019
Week 26[##]				
SAT in the paraumbilical region[†]		29.23 ± 8.66	31.77 ± 8.83	0.038
SAT in right triceps region[†]		28.89 ± 7.26	30.08 ± 5.97	0.365
SAT in the right subscapular region[†]		32.22 ± 9.05	31.32 ± 8.95	0.611
F% [†]		0.34 ± 0.10	0.33 ± 0.11	0.586
SAT in the paraumbilical region[‡]		−11.19 ± 19.44	−13.59 ± 17.12	0.332
SAT in right triceps region[‡]		−0.78 ± 15.38	0.93 ± 13.86	0.390
SAT in the right subscapular region[‡]		1.69 ± 14.74	1.81 ± 13.79	0.951
F% [‡]		0.00 ± 0.16	0.01 ± 0.15	0.599

AC, abdominal circumference; EA, electroacupuncture; BMI, body mass index; SD, Standard Deviation; HC, hip circumference; IQR, Inter-Quartile Range; IRD, inter recti distance; BMI, Body Mass Index; SAT, subcutaneous adipose tissue; F%, percentage body fat.

*Data for 106 patients (54 randomized to the EA group and 52 to the control group) were used in the final analysis.

[#]Comparisons of means within group.

[##]Comparisons were carried out between groups.

[†]The mean value.

[‡]The difference.

[§]The midpoint of umbilicus and xiphoid process.

[Δ]At the supine position.

groups. The F% difference and the right subscapular SAT were reduced in the EA group than in the control group on the front-to-back difference between groups, with statistical significance ($P < 0.05$) (Table 4). The comparison within the group suggested that the total LDQ score of the EA group improved compared with that before treatment and was statistically significant (P

TABLE 5 Other outcomes*.

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	*P*-value##
LDQ				
Week 2†		6.34 ± 0.14	6.29 ± 0.12	0.840
	P-value#	0.005	0.300	
Week 26†		6.11 ± 0.07	6.65 ± 0.25	0.057
	P-value#	0.134	0.147	
	P-value of difference between post-follow-up and pre-treatment#	0.017	0.548	
	P-value of difference between post-follow-up and post-treatment#	0.134	0.147	
	upper abdominal pain	1 ± 0	1.06 ± 0.05	0.147
	postprandial fullness	1.02 ± 0.02	1.16 ± 0.07	0.081
	early satiety	1.04 ± 0.04	1.08 ± 0.05	0.301
	upper abdominal cauterization	1 ± 0	1.04 ± 0.03	0.147
	postprandial nausea	1.02 ± 0.02	1.04 ± 0.03	0.537
	belching	1.04 ± 0.03	1.27 ± 0.11	0.020
Menstrual symptoms				
Week 26		10.97 ± 0.59	20.15 ± 0.60	0.801
QoL		6.34 ± 0.14	6.29 ± 0.12	0.840
Week 26				
PF†.		95.19 ± 1.03	92.84 ± 1.19	0.025
PF‡		12.17 ± 2.08	12.35 ± 1.79	0.946
RP†		96.23 ± 2.22	96.08 ± 1.66	0.492
RP‡		41.04 ± 6.43	25 ± 5.22	0.062
BP†		87.13 ± 1.79	88.82 ± 1.65	0.500
BP‡		16.77 ± 2.57	15.86 ± 1.95	0.770
GH†		76.26 ± 2.60	72.33 ± 3.09	0.410
GH‡		13.43 ± 3	9.53 ± 2.28	0.291
VT†		78.11 ± 2.10	78.24 ± 1.74	0.865
VT‡		13.21 ± 2.36	8.82 ± 2.62	0.134
SF†		116.75 ± 2.09	114.71 ± 2.29	0.242
SF‡		12.97 ± 3.16	11.52 ± 2.93	0.529
RE†		89.31 ± 3.15	93.46 ± 2.15	0.456
RE‡		28.3 ± 6.19	28.76 ± 5.82	0.936
MH†		76.53 ± 2.18	75.61 ± 1.83	0.722
MH‡		7.7 ± 2.53	6.82 ± 2.31	0.794
SF-MPQ				
Week 2- Pain rating Index (PRI)‡		1.38 ± 0.23	1.22 ± 0.20	0.562
	P-value#	0.000	0.000	
Week 2- sensory item scores‡		0.85 ± 0.15	0.86 ± 0.15	0.997
	P-value#	0.000	0.000	
Week 2- emotional item scores‡		0.53 ± 0.12	0.35 ± 0.11	0.181
	P-value#	0.000	0.000	
Week 2-VAS scores‡		0.87 ± 0.58	1.00 ± 0.16	0.587
	P-value#	0.000	0.000	
Week 2- present pain intensity (PPI) ‡		1.17 ± 0.05	1.33 ± 0.07	0.055
	P-value#	0.000	0.001	

(Continued)

TABLE 5 (Continued)

Outcome		EA group ($n = 54$)	Control group ($n = 52$)	*P*-value##
Week 26				
Week 26- Pain rating Index (PRI)‡		1.04 ± 0.17	1.49 ± 0.27	0.322
	P-value#	0.129	0.307	
Throbbing pain		0	0.08 ± 0.04	0.039
Tingling		0	0.02 ± 0.02	0.308
Cutting pains		0	0	1
Sharp pain		0	0	1
Spasmodic pain		0	0	1
Biting pain		0	0	1
Burning pain		0	0	1
Soreness		0.55 ± 0.08	0.69 ± 0.10	0.311
Cramping and swelling pain		0.04 ± 0.03	0.14 ± 0.06	0.125
Tender		0	0.02 ± 0.02	0.308
Cleavage pain		0	0.04 ± 0.04	0.308
Week 26-sensory scores‡		0.58 ± 0.10	0.98 ± 0.18	0.185
	P-value#	0.125	0.468	
Week 26- emotional item scores‡		0.45 ± 0.13	0.51 ± 0.12	0.642
	P-value#	0.502	0.202	
Week 26- VAS scores‡		0.57 ± 0.09	1.12 ± 0.17	0.051
	P-value#	0.035	0.472	
Week 26- present pain intensity (PPI) ‡		1.06 ± 0.03	1.16 ± 0.06	0.160
	P-value#	0.058	0.039	
EPDS				
Week 2†		6.53 ± 0.58	5.80 ± 0.52	0.455
	P-value#	0.005	0.002	
Week 26†		5.3 ± 0.65	6 ± 0.76	0.475
	P-value#	0.001	0.000	
Week 2‡		−1.23 ± 0.57	0.20 ± 0.77	0.222
	P-value#	0.319	0.101	
Week 26‡		−2.64 ± 0.66	−1.67 ± 0.76	0.469
	P-value of difference between post-follow-up and pre-treatment#	0.001	0.004	
	P-value of difference between post-follow-up and post-treatment#	0.029	0.773	
MBIS				
Week 2		16.39 ± 5.60	14.94 ± 4.55	0.328
	P-value#	0.002	0.050	
Week 26		14.21 ± 6.03	13.02 ± 5.57	0.554
	P-value#	0.001	0.001	
HerQles				
Week 2		15.96 ± 10.25	14.24 ± 10.89	0.267
	P-value#	0.000	0.000	
Week 26		13.36 ± 4.35	12.96 ± 4.96	0.824
	P-value#	0.001	0.001	
DRA-related symptom				
Urine leakage				

(Continued)

TABLE 5 (Continued)

Outcome	EA group ($n = 54$)	Control group ($n = 52$)	P-value[##]
Week 2	5 (9.3%)	9 (16.7%)	0.29
Week 26	7 (13.0%)	14 (26.9%)	0.104
Urinary frequency			
Week 2	4 (7.4%)	4 (7.4%)	0.74
Week 26	0	3 (5.8%)	0.072
Urinary urgency			
Week 2	3 (5.6%)	2 (3.7%)	0.33
Week 26	2 (3.7%)	1 (1.9%)	0.594
Constipation			
Week 2	12(0.22%)	7 (13.0%)	0.22
Week 26	5 (9.3%)	7 (13.5%)	0.677
Sexual dysfunction			
Week 2	6 (11.1%)	8 (14.8%)	0.45
Week 26	6 (11.1%)	15 (28.8%)	0.02
Chronic pelvic pain			
Week 2	0	0	1.00
Week 26	0	1 (1.9%)	0.303

AC, abdominal circumference; EA, electroacupuncture; BMI, body mass index; SD, Standard Deviation; HC, hip circumference; IQR, Inter-Quartile Range; IRD= inter recti distance; SAT, subcutaneous adipose tissue; F%, percentage body fat; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; HT, health transition.
*Data for 106 patients (54 randomized to the EA group and 52 to the control group) were used in the final analysis.
[#]Comparisons of means within group.
[##]Comparisons were carried out between groups.
[†]The mean value.
[‡]The difference.
The pelvic girdle includes inguinal, pubic symphysis, coccyx, sacrum, and either side of the pelvis.
[§]The midpoint of umbilicus and xiphoid process.
[Δ]At the supine position.

< 0.05). However, the difference between the control group after and before treatment was not statistically different ($P > 0.05$), and the comparison between the groups suggested that the total LDQ score after treatment was not statistically different between the two groups ($P > 0.05$). At 26 weeks follow-up, the intra-group comparison suggested that the difference in the total LDQ scores between the EA group after follow-up and before treatment improved and was statistically significant ($P < 0.05$), and the difference between the EA group after follow-up and after treatment was not statistically significant ($P > 0.05$). Comparisons between groups suggested no statistical difference ($P > 0.05$). At 26 weeks, 38 in the control group and 39 in the EA group had menstruated. Comparison between the groups suggested no significant difference in menstrual symptoms between the two groups. At follow-up, a comparison between groups suggested that the EA group had better PF than the control group, which was statistically significant ($P < 0.05$). No statistically significant differences were seen in the remaining dimensions. The intra-group comparisons suggested that the SF-MPQ total score and entry change values for the low back at that time were significantly better in both groups after treatment than before treatment, and inter-group comparisons suggested that there was no statistically significant difference ($P < 0.05$) in the SF-MPQ total score and entry change values for the low back after treatment in both groups. The intra-group comparison suggested a statistical difference in the total EPDS score between the two groups ($P < 0.05$), but the inter-group comparison suggested no statistical difference in the total EPDS score between the two groups ($P > 0.05$) (Table 5).

At 26 weeks follow-up, the mean of SAT in paraumbilical and right triceps of the two groups in both groups were reduced compared with those before treatment at 26 weeks, and the difference was statistically significant ($P < 0.05$). The SAT difference in paraumbilical was reduced in the EA group than in the control group on the front-to-back difference between groups, with statistical significance ($P < 0.05$) (Table 4). The comparison between groups suggested that picking pain was less frequent in the EA group than in the control group and the difference was statistically significant ($P < 0.05$). VAS scores for the difference between follow-up and post-treatment in the EA group, and present pain intensity (PPI) for the difference between follow-up and post-treatment in the control group

all decreased and were statistically different ($P < 0.05$). The comparison between the two groups suggested that there was no statistical difference in the total EPDS score between the two groups ($P > 0.05$). Within-group comparisons suggested a statistically significant difference between the two groups after follow-up and before treatment ($P < 0.05$), but there was a statistically significant difference between the EA group after follow-up and after treatment ($P < 0.05$), and no statistically significant difference between the control group after follow-up and after treatment ($P > 0.05$) (Table 5).

At the end of treatment and the end of follow-up, within-group comparisons suggested a statistical difference between the two groups in terms of total MBIS and HerQles scores after treatment ($P < 0.05$), but between-group comparisons suggested no statistical difference between the two groups ($P > 0.05$) (Table 5).

In DRA-related symptom assessment, there was no statistical difference in any of the symptoms after treatment ($P > 0.05$) at week 2. The EA group was better than the control group in the improvement of sexual dysfunction at week 26, and the difference was statistically significant ($P < 0.05$); constipation, chronic pelvic pain, and urine leakage, frequency, and urgency, were not statistically significant ($P > 0.05$) at week 26 (Table 5).

In addition, exploratory subgroup and *post hoc* analyses were performed to determine whether cesarean delivery was performed. The study found that the EA group had a statistically significant difference in IRD at the midpoint of umbilicus and xiphoid process in head-up and flexed knee state, cm Δ† compared to the control group (OR = 0.904, 95% CI: 0.820-0.998, $P = 0.046 < 0.05$) (Supplementary material 5).

Discussion

This randomized, controlled clinical trial was carried out at Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, China.

DRA is a common complication during pregnancy and the postpartum period. Postpartum DRA may cause a decrease in the tension of the elastic LA, resulting in a decrease in the ability to transmit abdominal forces across the midline, which in turn may affect abdominal muscle function. A severe decrease in the tension of the elasticity of LA may cause bulging of the abdominal organs, which may alter the appearance of the abdomen, seriously affecting the aesthetics of the body and reducing the woman's perception of her self-image. Postnatal DRA reduces the strength of the abdominal muscles and significantly reduces the support for the low back, affecting the mechanical balance of the low back muscles (7), resulting in a tilted pelvis, increasing the physiological curvature of the lumbar spine and increasing the incidence of low back pain and accumulation of abdominal fat. Therefore, postpartum DRA presents both psychological and physiological obstacles to the mother. However, there is a lack of ideal treatment options for postpartum DRA, and existing treatments such as physical rehabilitation, electrophysiological stimulation, and surgical treatment are still being developed. EA originating from traditional acupuncture around the 1930s has been verified to significantly improve the therapeutic effects of traditional acupuncture in a variety of diseases (31). This randomized trial showed that, compared with the control group, 10 sessions of EA for 2 weeks provided a higher improvement in IRD, especially at the horizontal line of the umbilicus in the end-expiratory state. Physical exercise has therapeutic effects on activation and induces transverse abdominis contraction and tightening of LA, and the different values of IRD are all changed, but the more obvious effect of the EA group may be related to EA therapy and the selection of acupoints.

The abdominal selection of acupoints treated in this study include bilateral Tianshu (ST25) and bilateral Dai Mai (GB26) at the horizontal line of the umbilicus, but Zhongwan (RN12) and Xiawan (RN10) in linea alba at the midpoint of umbilicus and xiphoid processor. Qi Hai (RN6), and Guanyuan (RN4) in linea alba at the midpoint between the umbilicus and pubic symphysis, may be related to the number of acupoints and curative effect (32). IRD was measured in the end-expiratory state to assess the width of the abdominal linea alba under transverse abdominis contraction.

The difference in IRD was only in the end-expiratory state, which might be related to the activation and enhancement of transverse abdominis tension by physical exercise and the EA group. The rectus sheath wraps the rectus abdominal muscles and is divided into two layers: the anterior is formed by the healing of the aponeurosis of the external oblique muscle and the aponeurosis of the internal oblique muscle, and the posterior rectus sheaths are formed by the healing of the aponeurosis of the internal oblique muscle and the aponeurosis of the transverse abdominis. The posterior rectal sheath is functionally more related to transverse abdominis than rectus abdominal muscles, and activation of transverse abdominis plays an important role in the etiology of the DRA (34, 35). Physical exercises adopted in this study, such as left and right-side leg rotation, are more effective in activating deep transverse abdominis, external oblique muscle, and internal oblique muscle (36, 37), and posterior rectus fascia sheath formed by transverse abdominis tendon sheath has better efficacy in maintaining abdominal wall tension stability. On the other hand, previous studies (38) found that electro-acupuncture had a more significant activation effect on transverse abdominis, which accelerated the adjustment of alba and transverse abdominis fascia tension to the normal level on the basis of rehabilitation exercise. However, it may not be reflected due to insufficient sample size or a short course of EA.

In addition, to further determine whether there are other influencing factors, such as fascia tension imbalance of transverse abdominis, fascia tension imbalance of muscles

around the linea alba, or fascia tension imbalance of pelvic floor muscles, we added the normal population as a control group (Supplementary material 4) and found that these factors were present in the end-expiratory state compared with the normal population. These unbalance factors were corrected by EA; IRD and pelvic floor muscle status were improved. Therefore, the EA group was superior to the control group in improving IRD at all sites and states at 26 weeks. Only IRD at the midpoint of the umbilicus and xiphoid process in end-expiratory showed statistically significant changes, which to some extent indicated that EA corrected these imbalance factors and achieved long-term improvement.

Previous studies have shown that women with DRA in the first year postpartum have a significantly lower trunk muscle rotational moment and a significantly lower score on the sit-up test and that rectus abdominis spacing is negatively associated with trunk rotational moment and sit-up test scores (39). It is possible that these changes are related to the widening and thinning of the elasticity of LA during pregnancy, resulting in an imbalance in tension. When DRA occurs, the tension of the wide and thin LA decreases, the stabilization of the abdominal muscle and the conduction of abdominal wall force are reduced, and the abdominal wall is relaxed. Lee et al. (40) proposed the deformation index as a means of assessing the elasticity of LA, suggesting that the greater the deformation index the less elastic it is, whereas in this study the elasticity of LA was assessed by strain-based elastography. This study found that: In the control group, the elasticity of linea alba was smaller than that of the EA group at two sites (the horizontal line of the umbilicus, and the midpoint of the umbilicus and xiphoid process) at week 2 and week 26 ($P < 0.05$). In terms of the correlation between the elasticity of linea alba and IRD, the elasticity of the LA score was negatively correlated with IRD ($rs = -0.356$, $P < 0.05$) (Table 4). Beamish et al. (41) suggested that the elasticity of linea alba was worse when the IRD was greater in patients with DRA, which is consistent with the study. Reducing linea alba deformation and increasing the elasticity of linea alba or making this a goal is important for subsequent DRA rehabilitation.

The tension of the anterior abdominal wall (including the LA) in patients with DRA is influenced by the entire abdominal wall myofascia, and an imbalance in the tension of the anterior abdominal wall myofascia caused by DRA can also cause changes in the tension of the entire abdominal myofascia (42). The specific morphological alterations of the lateral abdominal muscle groups and other muscle and fascia tissues throughout the body in patients with DRA have not been reported in the literature. Some studies have analyzed the correlation between DRA and abdominal muscle dysfunction, and a study by Liaw et al. (43) found that abdominal muscle function showed a negative correlation with the mean IRD, which is consistent with the results of the present study. Narrowing IRD may lead to an increase in trunk flexion and rotation strength and endurance to some extent.

In addition, this study takes into account that postpartum DRA causes changes in overall trunk biomechanics, which is more conducive to understanding the pathophysiological changes of DRA and clarifying the coordination and unity of the abdomen and pelvic floor (40), and that treatment cannot address only a single muscle or symptom. Even the combined thoracoabdominal breathing of the control group is called to emphasize the opening of the thorax and the inward retraction of the abdomen. Combined with the elastography results, comparison between groups suggested an advantage of the elasticity of linea alba in the EA group compared to the control group ($P < 0.05$) at week 2, this could provide an important basis for the improvement of rectus abdominis spacing, i.e., the improvement of elasticity in the short term and an improvement of distance in the long term. The same is true for the pelvic floor results, both at 2 weeks and 26 weeks, the EA group showed an improvement compared to the control group, except that the results were more significant in slow muscle during systole ($P < 0.05$). The same is true for the electromyographic evaluation of pelvic floor results, where both at 2 and 26 weeks, the EA group showed an improvement compared to the control group, except that the results were more significant in the mean value of slow muscle during systole ($P < 0.05$). Postpartum women often have pelvic floor dysfunction, and there is no consensus on whether DRA is associated with pelvic floor dysfunctional disorders (44, 45). In the supine position with low intra-abdominal pressure, contraction of the abdominal musculature activates contraction of the pelvic floor musculature (46), as advocated in the control group with combined thoraco-abdominal breathing, emphasizing the opening of the thorax and the internal retraction of the abdomen. The "abdominal tank" theory suggests the coordination and unity of the abdomen and pelvic floor (40) and that treatment should not address only a single muscle or symptom. EA enhances pelvic floor innervation and muscle support (47), thereby improving pelvic floor muscle strength.

In general, obesity is determined by the body mass index (BMI) (48). BMI has been suggested as a possible risk factor for DRA, due to excess fat in the abdominal cavity exerting excessive pressure on the abdominal wall, thus causing further separation of DRA on both sides (49). And on the other hand, it has been suggested that muscle loss may co-exist (50), thus raising the idea that obese people are more likely to have DRA (51). The results of the study showed that the EA group was better than the control group at reducing BMI and when the patients' DRA treatment improved, BMI was also reduced compared to the previous one. The paraumbilical SAT and F% better represent the fat distribution of the body. DRA reduces the strength of the abdominal muscles and significantly reduces the support for the low back, affecting the mechanical balance of the low back muscles, increasing the accumulation of abdominal fat, and increasing the paraumbilical SAT (52). Therefore, postnatal DRA, in turn, increases the degree of abdominal laxity, affecting

the aesthetics of the shape. The interconnection between the separation of the rectus abdominis muscle and abdominal obesity affects each other.

Postpartum abdominal skin laxity is a natural manifestation of skin aging and may be associated with increased skin collagen gaps, weak skin elastic fibers, and weak skin contraction (53). The maternal experience of pregnancy and childbirth causes mechanical strain on the abdominal muscles, especially the rectus abdominis, resulting in increased muscle tension and poor elasticity. EA can reduce the muscle tension of the abdominal muscles in patients with rectus abdominis detachment by using the corresponding points in the abdomen, increasing the proportion of type I collagen and a decrease in the proportion of type III collagen in the tendon fascia, thus causing a change in the expression form of collagen and achieving a repair of the damaged rectus abdominis muscle (54, 55). The EA helps to improve abdominal laxity by inhibiting the expression of pro-inflammatory cytokines (TGF-β1), allowing the TGF-β1/CTGF pathway to function properly and promoting the regeneration of myoelastin fibers (56).The probability of persistent abdominal laxity in the postpartum period is 30–40%. Pregnancy and childbirth cause the LA to widen and weaken, and the abdominal skin to loosen and sag and bulge in the midline, making the abdominal core unstable and leading to low back pain (1). During the SF-MPQ analysis, we found that pick pain was less frequent in the EA group than in the control group in terms of long-term effects (at week 26) and the difference was statistically significant ($P < 0.05$).

When DRA is studied, some scholars examine the interrelationship between diseases, and the abdominal canal theory (40) considers other symptoms of the abdominopelvic muscles when describing pelvic-abdominal coordination, thus linking the mechanisms of disease occurrence in tandem, or forming a hypothesis. Indigestion, low back pain, postpartum depression, quality of life, and menstrual changes are common problems in postpartum women, but the association with DRA is unknown (1, 51, 57), so this study continues to develop reported research on these factors. LDQ scores suggested that digestive symptoms were better in the EA group than in the control group both after treatment and after follow-up, and the improvement was more prominent in the symptoms of belching. Menstrual symptoms scores suggested that 24 weeks after the end of treatment, 38 people in the rehabilitation group and 39 people in the acupuncture group had menstruated. Comparison between groups suggested no significant difference in menstrual symptoms between the two groups. Due to the need to breastfeed during the puerperium, not all postpartum women's menstruation returned, so a pre- and post-group comparison was not possible. It has also been shown Gluppe et al. (58) that after 10 sessions of conventional Tui Na combined with physiotherapy for postpartum DRA, the patient's IRD shrank and QoL improved significantly, and no recurrence or worsening of postpartum DRA was found after more than 12 weeks of follow-up. The SF-36 score was for 1 month, and 1 month after the end of 10 treatments partially overlapped in time with the first filling, so we chose to compare during the follow-up period with the pre-treatment period, reflecting the fact that QoL in women with postpartum DRA was 24 weeks after the end of treatment compared to the pre-treatment period A trend toward improvement, especially PF was significantly improved. The degree of improvement in daily functional limitations treated with EA was better than in the control group, with better results for the long-term effects of EA. The health status of patients at 24 weeks after the end of treatment correlated with the presence of DRA at 24 weeks after the end of treatment.

Some researchers have investigated the correlation between DRA and low back pain, with Sperstad et al. (1) reporting no difference in the incidence of chronic lower back pain and pelvic girdle pain between DRA and non-DRA patients. EA could effectively activate the TrA, RA, and internal and external oblique abdominal muscles, promote the restoration of proprioception, release the fascia, and accelerate the improvement of muscle strength and elasticity repair of the abdominal muscles. The study effectively reflected whether the patients' current low back pain was caused by pain or by psychological effects using the SF-MPQ. The results showed an improvement in both groups compared to pre-treatment, with less pain provocation in the follow-up period after EA treatment than in the control group, indicating an advantage of EA in improving low back pain and a more pronounced long-term effect of EA treatment. The changing role of women in modern society requires them to recover quickly after childbirth and integrate into society, and the physical changes brought about by pregnancy often cause psychological changes. The impact of the physical changes brought about by DRA on maternal self-perception and emotions is of concern. EPDS and MBIS scores were significantly better in both groups after treatment and at follow-up, but the difference between the two was not significant, suggesting an improvement in postnatal depression and self-image valuing issues regardless of the method, although the efficacy outcomes were similar.

Patients with DRA have a wider and thinner LA, a reduced elastic component, and decreased tension, resulting in a reduction in the ability to transmit abdominal muscle forces across the midline (40), affecting abdominal wall morphology and abdominal muscle function. In this study, HerQles scores were found to be significantly better in both groups after treatment and at follow-up, but the difference between the two was not significant, suggesting that abdominal wall valuation problems improved regardless of the method used, although the efficacy results were similar. Postpartum-related symptoms (leakage, constipation, urinary frequency, urgency, sexual dysfunction, changes in chronic pelvic pain) were extracted from previous literature (1) and used to see if there was a correlation between DRA and the following symptoms. However, the results of the study suggested that no significant differences were seen

between the two. This is consistent with the findings of previous scattered literature (1, 57, 58). In contrast, symptoms of sexual dysfunction were less frequent in the EA group after treatment than in rehabilitation during follow-up, suggesting that EA has a unique advantage in this regard.

The study aimed to determine whether EA was effective in DRA, we wanted to find out further during the study whether it would be more effective in patients who had a cesarean delivery, given that the presence or absence of a cesarean delivery might interact with the trial intervention (p for interaction), an exploratory subgroup analysis was conducted based on the presence or absence of cesarean delivery. It was found that there was an interaction between the presence or absence of cesarean delivery compared to the control group on the difference in umbilical level flexion at follow-up and that EA had a more significant improvement in IRD in patients who had a cesarean delivery, which may be more applicable to patients who had a cesarean delivery ($P < 0.05$).

This study investigated the therapeutic effect of EA combined with physical exercise on postnatal DRA and compared it with only physical exercise to objectively evaluate the clinical efficacy of both on postnatal DRA from multiple perspectives. The study provides an objective evaluation, guidance, and new ideas and methods for the clinical treatment of postpartum DRA, and will have scientific significance and practical value for the study of DRA and the promotion of EA.

Limitation

1. Random errors during the trial: (1) Unavoidable individual differences, e.g., frequency intensity of EA parameters were selected between 4 and 6 because of individual tolerance differences. (2) Errors caused by uncontrollable factors in the research process, e.g., since the treatment was not blind to patients, we could not rule out that the clinical improvement in DRA was due to the expected value or placebo effect. In addition, although the therapist did not know the purpose of the experiment and did not have knowledge of acupuncture and moxibustion, she performed the blind method. However, some marks were left on the abdomen after electro-acupuncture, so the patient received rehabilitation treatment first and then electro-acupuncture. 2. Selection bias: Berkson rate bias due to the single-center study. 3. Recall bias of patients with DRA: as the questions in the questionnaire involved the collection of past information, the research results were biased due to the incomplete memory of the subjects. 4. Confounding bias may exist during subgroup analysis, because subgroup analysis of trials neutralizes the benefits of randomization, which leads to potentially biased results (59). 5. Because of the degree of bladder filling, the patient's position has been shown to affect the results of the measurements. In addition, it is occasionally difficult to obtain a valid Valsalva maneuver, so there is no clear and uniform reference measurement to date. 6. Examination means. Although ultrasound is a cost-effective and confirmatory means of detecting IRD, the results are influenced by the ultrasonographer's experience and the angle of incision of the ultrasound placement, the measurement duration, and despite the availability of intercepted images as evidence, it is not possible to observe the respiratory coordination. The muscle changes during the movement were not observed, and a way of monitoring dynamic changes was lacking.

Conclusion

Compared with the control group (only physical exercise), ten sessions in the EA group for 2 weeks resulted in improvement in IRD, electromyographic evaluation of the pelvic floor, WHR, the elasticity of LA, paraumbilical SAT, symptoms of DRA, abdominal tension, and strengthening of abdominal muscles with durable effects 26 weeks.

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 Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine reviewed this study protocol and gave its approval and consent (Approval Code 2020KY082). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL: data analyses, figure preparation, and manuscript preparation. YZ: recruit subjects. LYJ: responsible for the design of randomization, project funding, and study initiation. CL and MYG: ultrasound evaluation. LJX: responsible for the design of randomization. LS: random allocation. JYC and TW: responsible for manual data measurement before treatment. LJD: physical therapists. YYS: acupuncture treatment. TTZ and MF: responsible for

guidance and statistics. All authors approved the final version of 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1003361/full#supplementary-material

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Baduanjin improves neck pain and functional movement in middle-aged and elderly people: A systematic review and meta-analysis of randomized controlled trials

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Background: Neck pain (NP), one of the most common musculoskeletal diseases, exercises a great influence on the daily life of individuals, especially the elderly. Baduanjin is a traditional Qigong therapy from China, but there is no evidence for its use in the treatment of neck pain in middle-aged and elderly people.

Objective: We hope to summarize the efficacy evidence of Baduanjin in the treatment of middle-aged and elderly patients with neck pain (NP) for the first time, conduct a systematic review and meta-analysis, and provide basic evidence-based evidence for clinical practice.

Methods: Two researchers collectively searched PubMed, Web of Science, Embase, Cochrane Library, China Biology Medicine disk (Sino-Med), China National Knowledge Infrastructure (CNKI), Wanfang database, and China Science and Technology Journal Database (VIP). The search time is set from initial to 27 September 2022, to find out RCT articles that may meet the criteria. The risk bias assessment tool Cochrane was applied to assess the methodological quality of involved studies. RevMan 5.3 was used for the meta-analysis with a mean difference (MD) and 95% confidence interval (CI), and the model type was a random effects model. The VAS scores of the intervention and control groups were extracted and the results of the meta-analysis were presented using a forest plot.

Results: In total, 13 randomized controlled trials were meta-analyzed, including 840 patients. The results turned out that the VAS score in the intervention group was below the control group, which was statistically significant [MD = −1.15, 95% CI (−1.39, −0.92) and $P < 0.001$]. The result of general efficiency suggests that the Baduanjin group was better than the control group [RR = 1.19, 95% CI (1.10, 1.29), $P < 0.001$].

Conclusion: The existing results seem to show that Baduanjin is safe and has a trend of positive benefits in the treatment of neck pain in middle-aged and elderly people. However, considering the limitations of this study, we need to be cautious in our conclusions, and more studies are needed to verify it in future.

KEYWORDS

Baduanjin, neck pain, cervical pain, cervical spondylosis, meta-analysis

1. Introduction

Neck pain (NP), one of the most common musculoskeletal diseases, exercises a great influence on the daily life of individuals, especially the elderly (1–3). NP usually refers to pain between the neckline and the spinous process of the first thoracic vertebra (4). In the general population, the overall occurrence of NP ranges between 0.4 and 86.8%, and point prevalence can be as high as 41.5% (5). NP can be divided into acute (<6 weeks), subacute (6–12 weeks), and chronic (>12 weeks) according to the classification of symptoms (6, 7). Further differentiated by the International Statistical Classification of Diseases and Related Health Problems, NP also includes cervical vertebra pain, head and neck pain, and radiation pain in skin segments (6, 8). There was evidence that the development of NP is associated with inappropriate lifestyle, female gender, advanced age, faulty posture, and high demands for work (9–14). There is also a study which suggested that psychology may be a major factor in triggering neck pain (10). In general, NP can result in limited cervical spine functional range of motion (15), increase muscle burden, induce adverse posture, and affect proprioception (15, 16). It not only consumes healthcare resources to alleviate these symptoms but can also impose huge social and economic burdens (17, 18).

Relevant practice guidelines indicate that conservative treatments, such as health education, cervical spine mobility technique, muscle stretching, muscle strength training, and manual massage, can be served as the preferred treatment for NP (6, 19). However, although physical therapy and manual therapy are commonly recognized as mainstream treatments and have considerable efficacy, they usually cost an amount of money and time and need therapist care (20–23). Therefore, some accessible and cost-effective therapeutic interventions are urgently needed.

As a traditional Chinese Qigong therapy, Baduanjin is characterized by symmetrical body posture and actions, breathing control, meditative state, and concentration (24). Compared to traditional treatment methods, Baduanjin typically emphasizes a physical and mental integration of exercise to regulate the breath and coordinate psychology to balance Yin and Yang for general wellbeing (25–27). Additionally, the Baduanjin exercise routine includes eight independent movements, which are comparatively convenient to learn with little requirement for space. Patients can build up independently at home or out of doors (27). Many studies have found that Baduanjin can safely and effectively relieve pain intensity in various parts of NP patients (28, 29). Yang et al. randomly divided 55 patients with neck pain into the control group and the observation group. Based on the same treatment, the observation group received Baduanjin training and found that the VAS score of the observation group was significantly lower than that of the control group after 2 weeks of treatment (28).

So far, there has not been a systematic review of this topic using meta-analysis. Thus, we summarized data from randomized controlled trials (RCT) in recent years to analyze the therapeutic effects of Baduanjin on pain degree and total efficacy.

2. Materials and methods

2.1. Data sources and retrieval strategy

Two review authors, XJL and XW, conducted a comprehensive article search on 27 September 2022. The search database includes China National Knowledge Infrastructure (CNKI), China Biology Medicine disk (Sino-Med), Wanfang database, China Science and Technology Journal Database (VIP), PubMed, Embase, Web of Science, and Cochrane library. The time limit is from the time of their inception to 27 September 2022. For a comprehensive search of studies that might meet the criteria, the literature search focused on "Baduanjin" and "Neck Pain." The basic search terms are: (Baduanjin OR Eight-section Brocade OR Ba duan jin) AND (Neck Pains OR Neck Ache OR Neck Aches OR Cervical Pain OR Posterior Cervical Pain OR Posterior Neck Pains OR anterior neck pain OR anterior cervical pain).

Detailed search strategies for all databases are shown in **Supplementary Data Sheet 1**.

2.2. Inclusion criteria and study selection

2.2.1. Types of studies

The current meta-analysis researched the RCTs of Baduanjin that were intended to study the efficacy of Baduanjin in alleviating pain degree in middle-aged and elder patients with NP.

2.2.2. Types of participants

According to the age classification standards of the World Health Organization (30), the patients included in this study were middle-aged and elderly with an average age of 45–90 years. To prevent insufficient effect sizes due to small number of studies, we set the age as at least one group with an average age of 40 years or more.

2.2.3. Types of intervention

In addition to single Baduanjin treatment, the observation group also combined with Chinese medicine, traction, electroacupuncture, massage manipulation, or other treatment methods, respectively. The control group received intervention measures corresponding to the observation group except for Baduanjin. In summary, Baduanjin must be used as the only exposure factor (variable), and any of the other interventions were the same in both groups.

2.2.4. Types of measured outcomes

The outcome indicators mainly used pain intensity and total efficiency. The Visual Analog Scale (VAS) (31) was mainly adopted to evaluate pain intensity. Neck Disability Index (NDI) (32) and Neck Pain Questionnaire (NPQ) (33) were used to

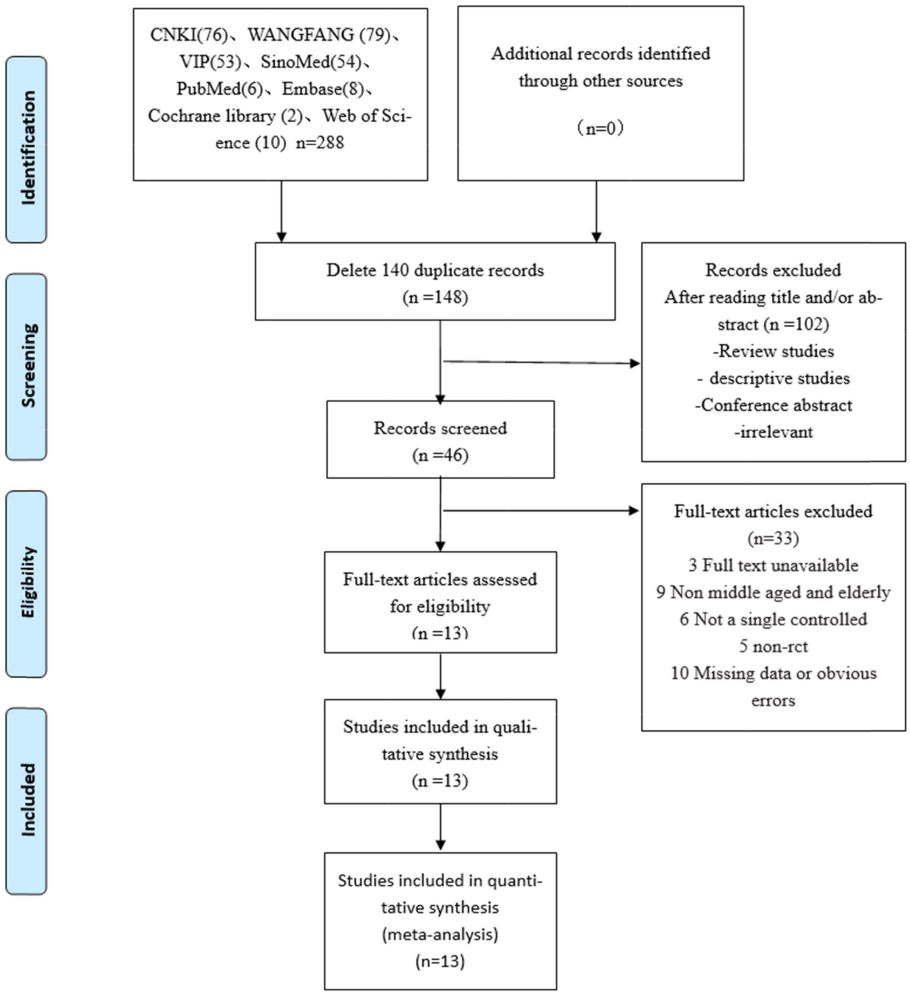

FIGURE 1
Flowchart of the study search and selection process.

assess the cervical spine range of motion. Besides, according to the Diagnostic and Therapeutic Criteria of TCM Diseases and Syndromes (34), Integrative Efficacy was used as an outcome indicator. The specific criteria are as follows: (1) Healing: clinical symptoms disappear, neck and limb function return to normal, can participate in normal labor and work, and no recurrence for 3 months; (2) obvious effect: original pain, shoulder, and other symptoms; and (3) improvement: original symptoms and signs are not improved.

2.2.5. Exclusion criteria

The following types of literature will be excluded: (1) the full text is not available; (2) duplicate publication; (3) significant number of evidence missing or seriously erroneous literature; (4) review articles, purely descriptive studies, conference abstracts, and other non-randomized controlled trials; and (5) contains multiple intervention variables.

2.3. Data synthesis and extraction

According to the study purpose and inclusion and exclusion criteria, two researchers HH and ZCL screened the literature independently. If any disagreement exists, there will be a third researcher HYL to participate in the discussion to decide whether to include the literature. The researchers extracted the literature data according to a unified data extraction table, including first author and year of publication, age, gender, sample size, intervention method, and outcome indicators. Duplicate articles were excluded using the EndnoteX9 software.

2.4. Literature quality assessment

Two researchers, HH and ZCL, collectively evaluated the quality of the included literature based on the methodological quality evaluation standard of Cochrane manual 5.1.0 (35) and similarly sought a third researcher HYL to judge if there is any point of disagreement to obtain final results. The contents include random sequence generation, allocation concealment, blindness, completeness of outcome data, selective reporting, and other biases. "Low" represents a low risk of bias, "Unclear" indicates a lack of relevant information or uncertainty of bias, and "High" suggests a high risk of bias.

2.5. Statistical analysis

Review manager 5.3 (Cochrane) is applied to analyzing all statistical data. Forest plots are used to show the results of individual Baduanjin studies and meta-analyses. I^2 statistical tests were used to determine data heterogeneity. The I^2 value indicates the heterogeneity of the study; when I^2 is equal to 0, there is no heterogeneity, the value of I^2 less than 25% is considered as low heterogeneity, between 25 and 50% is recognized as moderate heterogeneity, and over 50% indicates high heterogeneity (36). During the meta-analysis, the between-group mean differences were converted to mean differences (MD) with 95% confidence intervals (CIs). To better cope with clinical heterogeneity, a random effects model was used. Meta-analyses that included more than nine trials were tested for publication bias using funnel plots. Statistical significance was determined by $p < 0.05$. Our research is informed by PRISMA Statement (37).

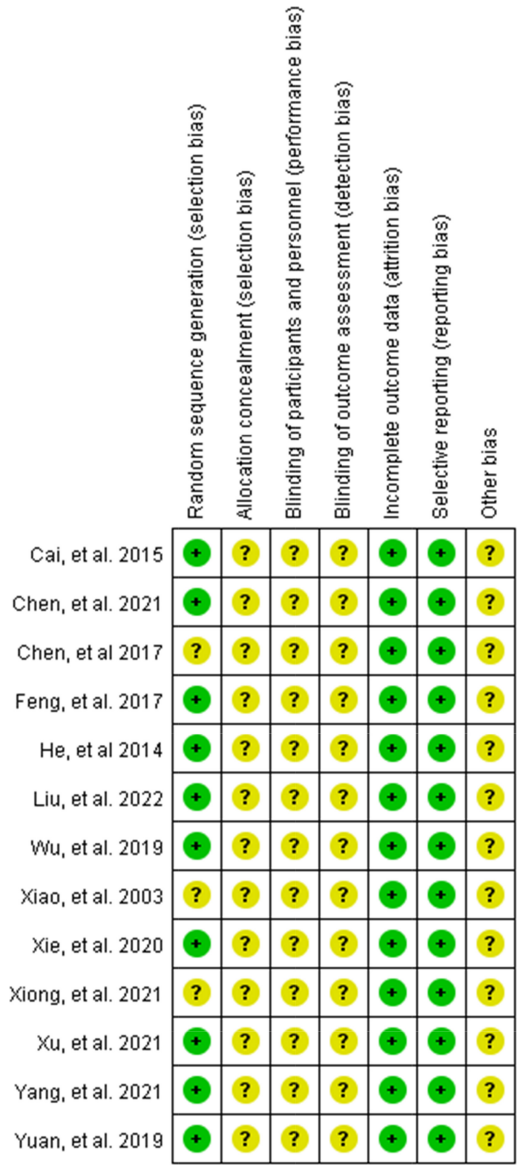

FIGURE 2
Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

3. Results

3.1. Study search results

Initially, we obtained 288 possibly related articles from the following databases (CNKI, Wanfang, VIP, Sino-Med, PubMed, Embase, Web of Science, and Cochrane Library). In that, 140 duplicate articles were excluded by using EndNote software to check up. Through reading titles or/and abstracts, 102 non-confirming articles were excluded and 46 studies were obtained after initial screening. After reading the full text, 13 studies (28, 38–49) were finally included, including 840 patients. The specific inclusion process is shown in **Figure 1**.

3.2. Quality assessment of the included literature

The literature quality results are shown in **Figures 2**, **3**. Eight studies used the random number table method (28, 38–40, 43–45, 47), one study used computer Excel randomization (48), and four studies were just verbal randomization (41, 42, 46, 49), so nine studies were rated as low risk and four studies as unclear in terms of randomization. Blinding and allocation concealment were not reported in any of the studies, and it is unclear whether third-party personnel evaluated, so all risks of three sections were rated unclear. All studies had low risk in completeness of outcome data and Selective outcome reporting, all of them explained the reason and confirmed that it did not affect the results. Out of caution, we did not see detailed reports of Other Biases in the original text, so all studies were rated as unclear about Other Biases. We found that most Chinese studies do not seem to report the habit of blinding, which seems to be widespread in Chinese academia. However, this may lead to a certain bias.

3.3. Basic features of included studies

The basic features of the 13 studies that were finally included are summarized in **Tables 1**, **2**. All 13 RCTs compared the baseline data of age, frequency, and the difference between the intervention group and control group. The average age of trial participants was more than 40 years, with more women than men. In most studies, intervention groups tended to be treated with Baduanjin combined with other treatments (including traditional therapies, stretching, acupuncture, and medicine therapy) to intervene. They were compared with the corresponding traditional treatment methods implemented in the control group. The frequency of the treatment in the intervention group ranged from three times a week to two times per day. The total duration of the treatment ranged from 2 weeks to 6 months. Most studies used clinical general effectiveness based on Diagnostic and Therapeutic Criteria of TCM Diseases and Syndromes (34) to assess disease synthesis efficacy. Other outcome measures included VAS to evaluate pain, NDI or SF-MPQ or NPQ to evaluate cervical motion function, CROM to measure cervical motion range, and SF-12 to evaluate the quality of life.

3.4. Effectiveness

3.4.1. Effects of Baduanjin on neck pain degree

Ten studies (28, 29, 38–40, 42–45, 47–49) used VAS to assess NP intensity. Although Xiao et al. (49) also used the VAS score,

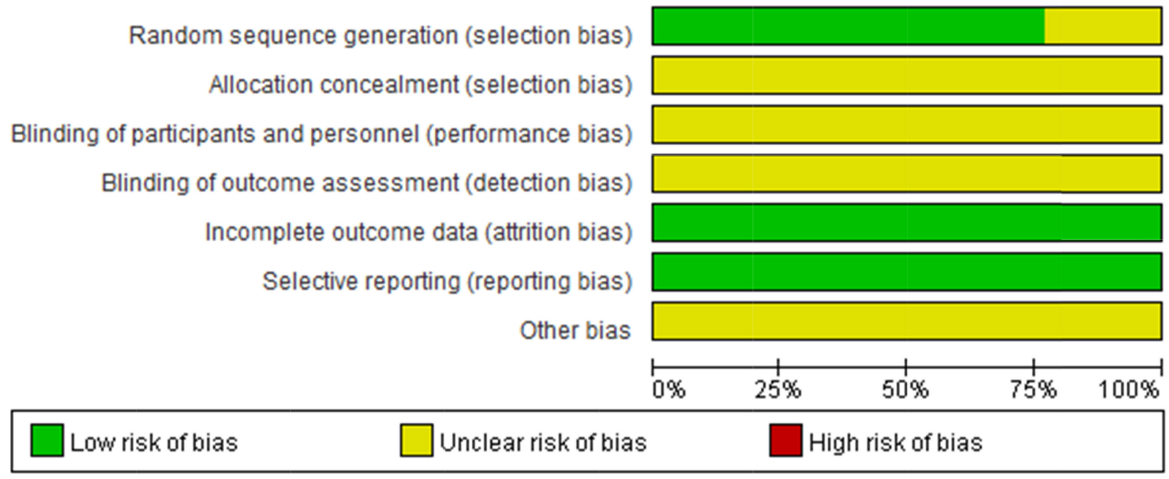

FIGURE 3
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

TABLE 1 Baseline features of the included studies (1).

References	Characteristics of participants		
	T	Age, mean	Sex
Xiao et al. (49)	44	$I = 52.0$, $C = 50.0$	Unclear
He (48)	60	$I = 43.23 \pm 8.01$, $C = 41.50 \pm 7.45$	$F = 26$, $M = 34$
Cai et al. (47)	60	$I = 50.8 \pm 8.0$, $C = 49.9 \pm 8.0$	$F = 27$, $M = 33$
Feng (45)	100	$I = 45.55 \pm 7.33$, $C = 50.22 \pm 4.68$	$F = 49$, $M = 51$
Chen and Yang (46)	60	$I = 51.1 \pm 8.3$, $C = 50.4 \pm 9.4$	$F = 47$, $M = 13$
Wu and Chen (44)	68	$I = 57.8 \pm 5.6$, $C = 56.3 \pm 5.3$	$F = 37$, $M = 31$
Yuan et al. (43)	60	$I = 67.5 \pm 5.6$, $C = 67.0 \pm 7.2$	$F = 44$, $M = 16$
Xie et al. (50)	84	$I = 56.3 \pm 6.5$, $C = 60.0 \pm 6.7$	$F = 32$, $M = 52$
Chen (39)	60	$I = 39.27 \pm 9.40$, $C = 40.00 \pm 7.89$	$F = 36$, $M = 24$
Xiong (41)	60	$I = 52.1 \pm 10.8$, $C = 51.7 \pm 10.$	$F = 33$, $M = 27$
Xu and Wang (40)	60	$I = 54.93 \pm 11.21$, $C = 55.27 \pm 9.84$	$F = 37$, $M = 23$
Yang et al. (28)	55	$I = 49.6 \pm 7.8$, $C = 46.5 \pm 9.9$	$F = 28$, $M = 27$
Liu and Zhu (38)	69	$I = 41.5 \pm 8.26$, $C = 41.8 \pm 7.3$	$F = 41$, $M = 28$

T, total population; I, intervention group; C, control group; F, female; M, man.

we did not include it in the meta-analysis because the scale versions were inconsistent. Meta-analysis using the random-effect model showed that the VAS score in the treatment group was below the control group, which was statistically significant [MD = −1.17, 95% CI (−1.55, −0.80) and $P < 0.001$] (see Figure 4), but the result showed high significant heterogeneity among studies ($I^2 = 74\%$, $P = 0.0002$). We plotted VAS correlation funnel plots and found that two studies were outside the funnel line (Figure 5). Through sensitivity analysis, the two studies were identified as those of Liu et al. (38) and Feng et al. (45), respectively. After removing the two studies, all the studies were in the funnel (Figure 6), and the VAS forest plot showed that the results were still stable [MD = −1.15, 95% CI (−1.39, −0.92) and $P < 0.001$] with low heterogeneity ($I^2 = 0\%$, $P = 0.54$) (see Figure 7). In addition, through visual inspection of the funnel plot (Figure 6), it can be found that it is roughly symmetric, and all points are in the funnel and at the top, indicating that publication bias is small.

3.4.2. General efficiency

According to the Diagnostic and Efficacy Standard of TCM Disease (34), a total of 10 studies (39, 41, 42, 44–50) reported the percentage of total efficacy. The results showed that the treatment group was better than the control group [RR = 1.17, 95% CI (1.10, 1.25), $P < 0.001$] in the Heterogeneity test ($P = 0.50$, $I^2 = 0\%$, see Figure 8).

3.4.3. Other outcome indicators

There were other measures of NP and cervical motor function in the included studies, such as NDI, NPQ, and SF-MPQ. Owing to the small number of studies containing these indicators and the lack of sufficient data, these indicators were not included in the analysis.

3.4.4. Safety

None of the 13 studies-suggested participants experienced any significant adverse reaction or uncomfortable symptoms.

4. Discussion

This study mainly summarized the evidence of Baduanjin in the treatment of middle-aged and elderly NP from a large number of RCT trials. Preliminary meta-analysis seems to indicate that Baduanjin has some efficacy in the treatment of NP, while our results need to be interpreted with caution because when there are fewer studies, the power of the tests is too low to distinguish chance from real effect. However, these results can provide some basic trends and give clinicians a trend judgment. In addition, none of the 13 studies found any adverse effects of Baduanjin on middle-aged and elderly patients with neck pain. This initially shows that the Baduanjin treatment is relatively safe and reliable. General efficiency also shows that Baduanjin can indeed be used as a treatment strategy to relieve NP.

Neck pain is a common condition that reduces the individual quality of life and causes economic loss and mental burden, gaining increasing concerns (6, 51). Baduanjin is an ancient traditional Chinese medicine method that regulates and improves the respiratory, metabolic, digestive, circulatory, and motor systems (52–54). As an adjunctive treatment, in recent years, Baduanjin has gradually been used to treat NP in the middle-aged and elderly group (7, 55). Zou et al. (24) showed that Baduanjin exercise can effectively relieve musculoskeletal pain and improve overall sleep quality in patients with chronic diseases. The study by Kong et al. (29) showed positive evidence that Baduanjin can be used as a complementary therapy for neck pain in middle-aged and elderly patients.

According to the available literature, Baduanjin relieving NP may currently be the following mechanism. As a kind of self-exercise treatment method, Baduanjin includes stretching actions such as flexion and extension and left and right twisting (56). While fully exercising the neck and back muscles, Baduanjin can pull the cervical spine by the deep static stretching of the muscles in various action directions, thereby alleviating muscle spasms, reducing pain, and restoring and

TABLE 2 Baseline features of the included studies (2).

References	Invention methods I/C		Frequence, follow-up time	Outcome
	I	*C*		
Xiao et al. (49)	Baduanin + routine comprehensive treatment	Routine compre-hensive treatment	2 times/d, 40 min/sessions, 1 m	①②
He (48)	Baduanin + tuina	Tuina	Baduanin: 50–60 min/session, 84 sessions, 12 w	①②
Cai et al. (47)	Baduanjin + medication and traction therapy	Medication and traction therapy	2 times/day, 30 min/sessions, 6 m	①②
Feng (45)	Baduanjin + massage	Massage	20 min/session, 48 sessions, 4 w	①②
Chen and Yang (46)	Baduanjin + acupuncture and fire cans	Acupuncture and fire cans	3 sessions/w, repeat the sets 3 times each session, 3 w	①⑥
Wu and Chen (44)	Baduanjin + routine comprehensive treatment	Routine compre-hensive treatment	5 sessions/w, 40 min/sessions, 8 w	①②③④
Yuan et al. (43)	Baduanjin + routine comprehensive treatment	Routine compre-hensive treatment	5 sessions/w, 40 min/sessions, 12 w	②
Xie et al. (50)	Baduanjin + acupuncture and medicine	Acupuncture and medicine	7 sessions/w, 30 min/sessions, 3 m	①⑤
Chen (39)	Baduanjin + electroacupuncture	electroacupuncture	12 sessions, 4 w	①②③④
Xiong (41)	Baduanjin + routine comprehensive treatment	Routine compre-hensive treatment	5 sessions/w, 40 min/sessions, 8 w	①⑤⑥
Xu and Wang (40)	Baduanjin + acupuncture	Acupuncture	56 sessions, 4 w	②
Yang et al. (28)	Baduanjin + routine comprehensive treatment	Routine compre-hensive treatment	3 times/d, 5 min, 2 w	②
Liu and Zhu (38)	Baduanin + thunder fire moxibustion	Thunder fire moxibustion	1 times/d 40 min/d, 5 d/w, 4 w	①②

I, intervention group; C, control group; routine comprehensive treatment-including health education, cervical spine mobility technique, muscle stretching, muscle strength training, and manual massage; ①-general efficiency. ②-VAS score. ③-Cervical Range of Motion (CROM). ④-Neck Disability Index (NDI). ⑤-Neck Pain Questionnaire (NPQ). ⑥-SF-MPQ. d, day; m, month; w, week.

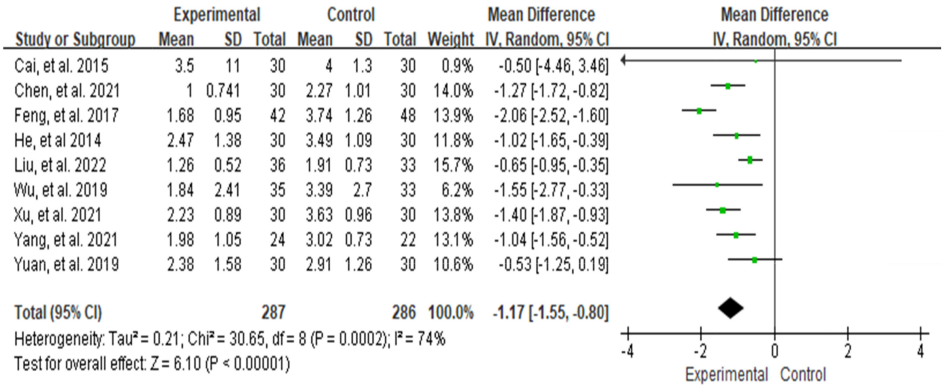

FIGURE 4
Analysis chart of comparison of VAS scores.

improving cervical spine motor function (57, 58). Compared with other effective treatment options (traction, acupuncture, medicine, and so on), there are amount of advantages to using Baduanjin exercise as an adjunct therapy to treat patients with NP, such as easy access, low cost, no side effects, and unlimited venues (23, 59). It is especially important for groups that cannot tolerate the side effects or afford the high cost of conventional medical treatment.

Although the relevant Baduanjin research data are relatively abundant, there is a lack of international consensus on the therapeutic schedule of Baduanjin for NP currently. Previous research has focused more on the efficacy of Baduanjin for pain throughout the body or the comprehensive effects of Baduanjin on sleep, pain, respiratory function, or other aspects (24, 27, 59). At present, systematic evaluation and meta-analysis on the efficacy of Baduanjin for middle-aged and elderly patients with NP are still lacking. Hence, our study is the first to highlight the efficacy of Baduanjin against NP, which owns a certain degree of innovation and creation. Compared to previous systematic reviews and analyses (50), Our study focused on Baduanjin as an intervention mode, and the population was biased toward the middle-aged and elderly, which was more

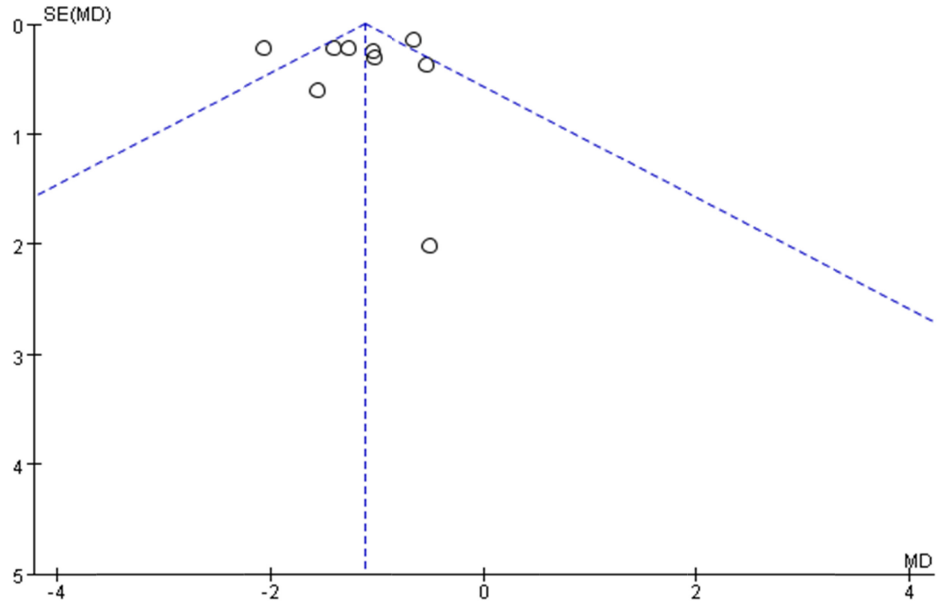

FIGURE 5
Funnel plots for detection of publication bias (VAS).

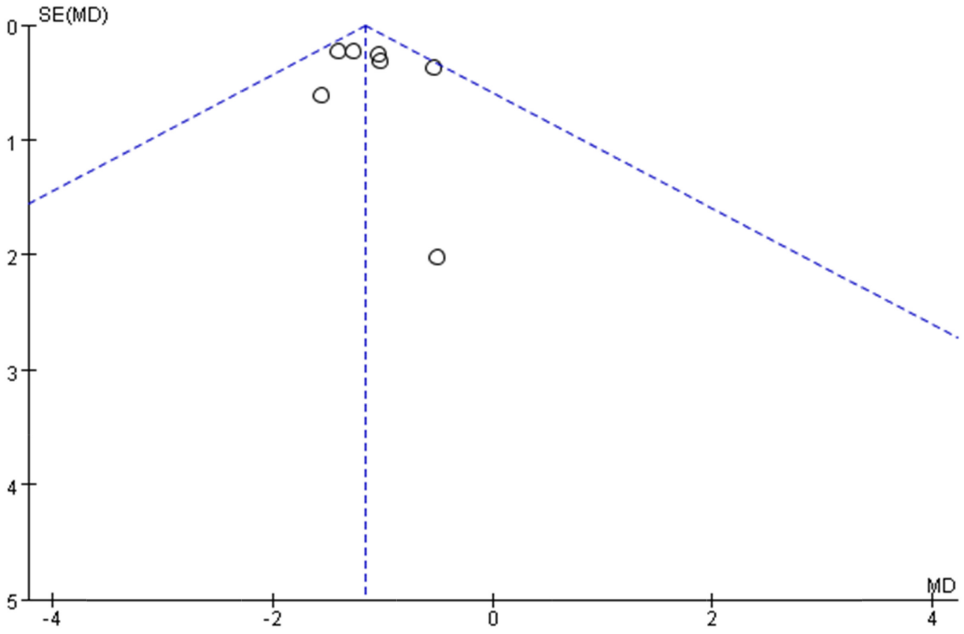

FIGURE 6
Funnel plots (VAS) after removing two biased studies after sensitivity analysis.

specific. Moreover, our study also has stricter inclusion and exclusion criteria and expands the sample size, making it more convincing.

Future research not only needs to improve the research quality in terms of research methods but also needs to explore the differences in efficacy for people in different regions and find out the most appropriate intervention frequency and optimal intervention time. Which specific action of Baduanjin is the most effective? How long the long-term effect lasts also needs to be explored.

The research also has some limitations. One of the primary disadvantages is that most existing articles lack blinding,

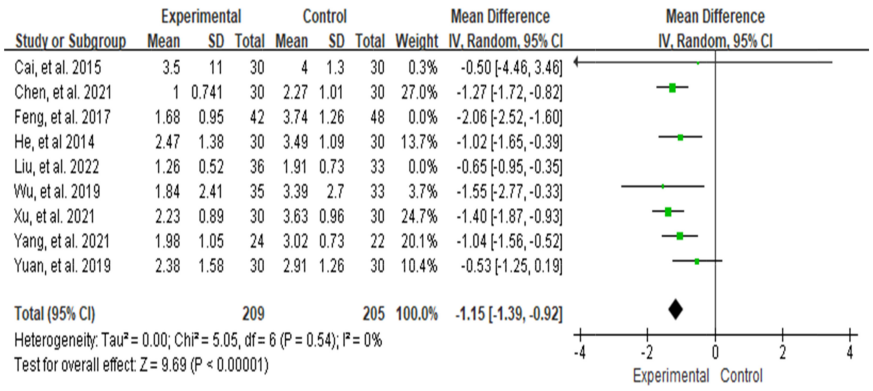

FIGURE 7
Forest plot of the effect of Baduanjin on reducing VAS after sensitivity analysis.

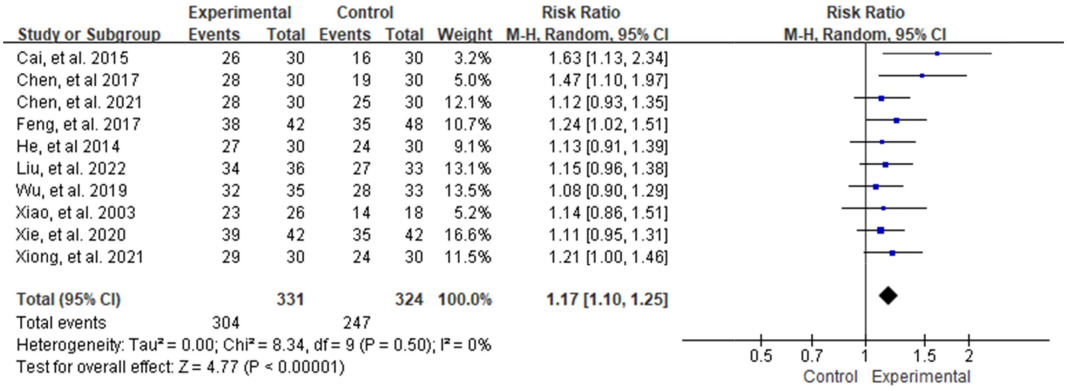

FIGURE 8
Analysis of the comparison of general efficiency.

which may result in the emergence of subjective biases, yet this seems to be a common phenomenon in most Chinese documents; due to the local characteristics of Baduanjin in China, there are still few relevant randomized controlled trials in other countries. Most of the participants in the study were from the Chinese region, thus leading to geographical limitations. Second, many variables affect the outcome, leading to the high heterogeneity of included studies, such as the intervention time, frequency, and specific actions of Baduanjin; although sensitivity analysis was performed to identify the source of heterogeneity, more research is needed to determine the optimal Baduanjin intervention. Third, there may be publication bias and reporting bias in the included studies. Since gray literature was not included, statistically significant outcomes are probability to be fully reported, thus making the therapeutic benefits of Baduanjin exaggerated. Finally, the sample size included in this study is still comparatively small and statistical power may be insufficient, thereby reducing the persuasiveness of evidence.

In conclusion, our systematic review and meta-analysis preliminarily provided positive evidence that Baduanjin alleviated NP in middle-aged and elderly people, and it also confirms the safety of Baduanjin in treating the middle and the old with NP. However, given the limitations of this study, more large, high-quality RCTs still be needed to demonstrate it in future.

Data availability statement

All data from this study are based on online RCT studies.

Author contributions

HH and ZL: conceptualization, methodology, software, writing – original draft, and writing – review and editing. XL and XW: data management. ZW and XX: investigation. XL and ZW: resources. XW, HL, and LL: supervision. HL: funding

sources. 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/fmed.2022.920102/full#supplementary-material

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The positive effect of mother-performed infant massage on infantile eczema and maternal mental state: A randomized controlled trial

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Objective: To observe the influence of MPIM on infantile eczema, quality of life, growth and maternal mental state.

Methods: This trial was a randomized controlled study. Sixty-six full-term infants with eczema were randomly divided into eczema control group (EC group, $n = 33$) and eczema with MPIM group (EM group, $n = 33$), along with healthy full-term infants in the healthy control group (HC group, $n = 31$). The mothers in the EC group received the instruction of routine care, while the mothers in the EM group applied massage on the infants plus receiving the same instruction of the routine care. HC group received none of any specific intervention. Data were collected in the three groups at the baseline and at the end of 2- and 5-month intervention. Before and at the end of 2-month intervention, the following indexes were investigated in infants including the growth indexes, eczema area severity index (EASI), infantile dermatitis quality of life index (IDQOL). And the scores of self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were investigated in mothers at the same timepoints. At the end of 5-month intervention, the infants' growth and relapse condition of eczema were observed.

Results: Overall, 31 cases in HC group, 31 in EC group and 32 in EM group were included for data analysis. There were no significant differences in the indexes of infantile growth among the three groups (all $P > 0.05$). The scores of EASI and IDQOL significantly lowered (both $P < 0.001$) in EC group following the instruction of routine care, along with reduced maternal scores of SAS and SDS (both $P < 0.05$). Compared with the EC group, the EM group showed significantly lower scores of EASI and IDQOL (both $P < 0.001$) and lower relapse rate ($P < 0.01$) in infants with eczema, along with significantly lower scores of SAS and SDS in mothers (both $P < 0.01$). Moreover, none of obvious adverse reaction was reported following MPIM, to which most of the mothers could adhere.

Conclusion: MPIM could effectively promote the remission of infantile eczema and reduce its relapse, along with relieving maternal anxiety and depression mood.

Clinical trial registration: Identifier: ChiCTR2200066246.

KEYWORDS

family massage, infant eczema, postpartum, anxiety, depression

Introduction

Eczema, also known as atopic eczema or atopic dermatitis, is a chronic relapsing inflammatory dermatosis characterized by pruritus, xerosis and a close association with immunoglobulin E (IgE)- mediated sensitization to aeroallergens and foods (1). The incidence of eczema in children has reached 15–20% (2), with the highest incidence in infants between the ages of 3 and 6 months old (2). A substantial portion of cases with eczema can go into complete remission by 2 years of age, while there are about 40% of cases with a prolonged duration and the highest risk for the atopic march (3). Moreover, infantile eczema obviously impairs infantile quality of life and potentially influence growth (4, 5). Current treatments for eczema aim to relieve symptoms since there is no cure for it (6, 7). General measures include the application of emollients and topical agents and avoidance of infections and trigger factors (2).

It is noteworthy that eczema in infants also negatively influences maternal mood (4). Postpartum mothers are especially susceptible to depressive and anxious episodes (8). It is reported that 8.5% of postpartum mothers experienced anxiety disorder (9) and 13% or higher experienced depression in their first postpartum year (10–12). Moreover, the mothers of infants with eczema are more susceptible to the psychological distress such as frustration, depression and anxiety, the level of which is often correlated to the eczema severity (4).

Infant massage, as a common traditional practice, is widely used all over the world for both preterm and full-term infants nowadays (13, 14). A series of studies have revealed its benefits to infants, such as enhancing growth and development, improving sleep and increasing interactions with parents (15–17). Previous trials also demonstrated that massage could relieve eczema symptoms in young children (18, 19). In China, infant massage is often applied on certain meridians and acupoints based on the theory of traditional Chinese medicine (TCM), which effectively relieves eczema in infants and toddlers (20–22). As we all know, infant massage can be performed not only by professionals in clinical setting, but also by parents at home (23). Systematic reviews recommend that parents can perform massage on low-risk infants for promoting mental and physical health due to its cost-effectiveness and no evidence of any risk (13, 14). Moreover, a series of studies indicated that mother-performed infant massage (MPIM) improved maternal depression, stress or negative mood during postpartum period (24–26). However, few trials have simultaneously observed the outcomes of both mothers and infants following MPIM. So far, there is also no trial to investigate whether MPIM can improve infantile eczema and whether MPIM influences the growth of infants with eczema.

Therefore, this trial was designed to observe the potential influence of MPIM on infantile eczema, growth and maternal mental state, which may be a beneficial health-care method for mother-infant dyads.

Methods

Trial design

The study used a prospective block-controlled randomized design shown in Figure 1. Given convenient and practical implement, participants were recruited through publicity in Dingshan street community (Nanjing in Jiangsu province, China). This study was conducted in the health service center of Dingshan street community and at home, respectively based on the intervention protocol between April 2020 and March 2021. The optimal sample size of 87 (29 per group) was calculated by using PASS software (version 15.0, NCSS, USA) based on the following assumptions: $\beta = 0.10$, $\alpha = 0.05$, $\sigma 1 = 1.8$, $\sigma 2 = 0.4$, $\mu 1 = 1.6$, and $\mu 2 = 0.3$, with 90% power, a two-sided alpha of 5%, and an estimated 20% loss to follow-up (27). Thirty-one healthy full-term infants and 66 full-term infants with acute eczema were enrolled in this study. Thirty-one healthy full-term infants were enrolled in the healthy control group (HC group, $n = 31$) for the comparison of infants' growth and mothers' mental state with eczema groups. By using a random number list produced by Excel software (version 2016, Microsoft, US), 66 infants with eczema were randomly divided into eczema control group (EC group, $n = 33$) and eczema with MPIM group (EM group, $n = 33$) in a 1:1 ratio by one investigator, who didn't participate in the following intervention or assessment. Participants were not blinded due to the nature of the intervention. The investigators responsible for the assessment of the infantile growth and eczema severity were blinded. However, the investigators responsible for the instruction of routine care and MPIM as well as regular supervision were not blinded due to the nature of the intervention.

Inclusion criteria

For the infants with eczema:(1) full-term infant at or under 12 months old; (2) diagnosed as infantile eczema based on the clinical criteria for pediatric atopic dermatitis (28); (3) with informed consent and voluntary compliance with the study arrangement from the infant's mother.

For the healthy infants: (1) same as (1) and (3) for the infants with eczema above; (2) infants without any history of obvious visceral and functional diseases; (3) infants without eczema and other atopic diseases.

Exclusion criteria

For the infants with eczema: (1) preterm infants or infant over 1 year old; (2) infant with any visceral disease or dysfunction except for eczema; (3) infant with infection, or the history of topical and systemic application of corticosteroids,

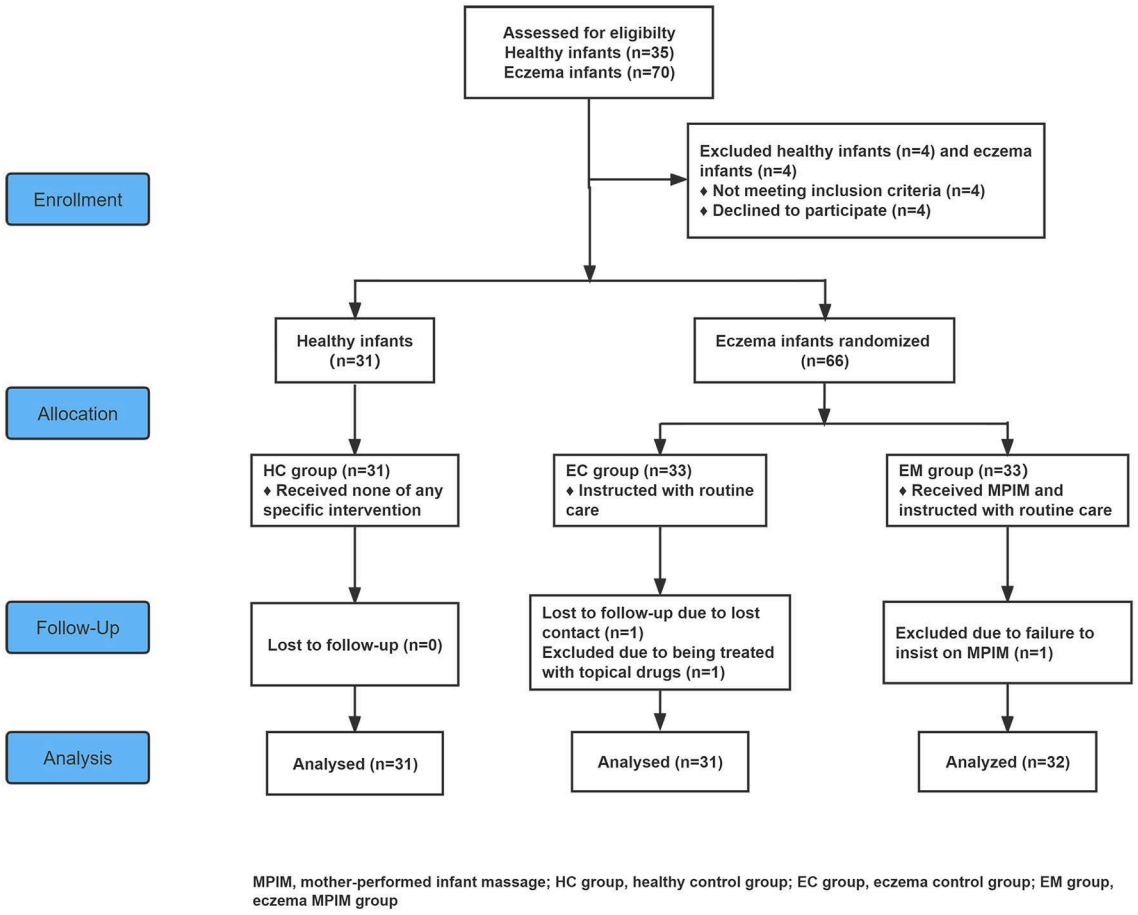

FIGURE 1
Flowchart of this study. MPIM, mother-performed infant massage; HC group, healthy control group; EC group, eczema control group; EM group, eczema MPIM group.

antihistamines, antibiotics agents, traditional Chinese herbs or other specific intervention during the last 2 weeks; (4) infants with severe eczema, i.e., eczema area and severity index (EASI) score > 21 (2); (5) infant with obvious eczema or skin lesion on the back where massage is applied; (6) mother with diagnosed severe mental disorders or the scores of Zung's self-rating anxiety scale (SAS) and self-rating depression scale (SDS)≥70; (7) mother unable to follow study protocol.

For the healthy infants: same as (1), (3), (5), (6) and (7) for the infants with eczema above.

Interventions

This study was a 5-month-long intervention study, which included the first 2-month intervention with regular supervision and the latter 3-month intervention without any supervision (shown in Figure 2). This kind of design aimed to have a knowledge of the feasibility and maternal adherence of MPIM, which is very important for promoting its application as a home-based healthcare method in the community. Data in the three groups were collected at the baseline and at the end of 2- and 5-month intervention to evaluate and analyze the outcome difference among groups. One investigator communicated with the mothers in the EC and EM group to enhance the adherence to the respective instruction by wechat communication once a week and by face to face once a month during the first 2-month intervention. During the latter 3-month intervention, the mothers in the EC and EM group were advised to record the adherence of respective intervention without any contact from investigators until the last assessment.

Protocol in the HC group

Infants and mothers in the HC group received none of any specific intervention, except for the assessment at the three timepoints.

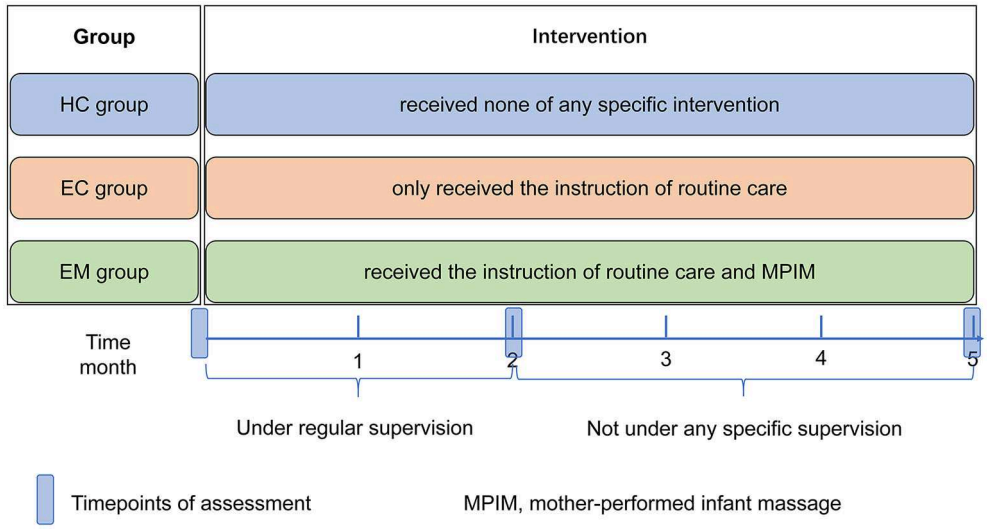

FIGURE 2
The protocol of the study.tif.

Protocol in the EC group

The mothers in the EC group only received the instruction of routine care from one investigator for about half an hour in a small group of 3–5 mothers according to their convenience after the baseline observation. The tips of routine care for infantile eczema included the avoidance of skin irritants and allergens, avoidance of allergenic food in maternal and infantile diet, breast-feeding as much as possible and the application of emollient. For avoiding the confounder caused by using different emollients in this study, Pigeon skin lotion (Pigeon, Shanghai, CNH) was recommended in this study since it is popularly used on infants in China. It was advised to apply the skin lotion on the whole body of the infant except for the scalp at least twice daily, once during day time and once either after bathing or before sleep (if no bathing that day) in the evening. The used amount of the skin lotion was not fixed but determined by the body surface area and dry condition of skin in individual infant, which aimed to achieve the lubricant effect. In addition, let the infant lie on his/her stomach safely and comfortably for 10 min after the application of skin lotion before bedtime, for controlling the massaging position and time in EM group. The mothers in the EC group were instructed about infant massage by investigators after this study observation ended based on the voluntary rule.

Protocol in the EM group

The mothers in the EM group were also instructed with the same routine care as the EC group and infant massage. The mothers were instructed with infant massage by the investigator for about 1 h in a small group of 3–5 mothers according to their convenience after the baseline observation, following the instruction about the same routine care as the EC group. The whole procedure of massage was determined according to the clinical application and textbook (29–32). The whole procedure took about 10 min as follows: Let the infant lie safely and comfortably on his/her stomach; the mother washed her hands and applied some skin lotion (Pigeon, Shanghai, CNH) to lubricate her hands and infant's back; firstly, the mother stroked the infant's back longitudinally along the middle line with finger bellies from shoulder level down to the sacrum level for 10 times; secondly, horizontally rubbed the back swiftly and gently with a palm for 20 times respectively at upper, middle, lower back levels; thirdly, applied traditional back-pinching manipulation (BP) for 6 repeats with the finger bellies; lastly, kneaded top-down on both sides of the back slowly and gently with a palm for 5 repeats. The details of one-repeat BP were as follows: pinched the skin located on the middle sacrum with the finger bellies and lifted to twist and move forward swiftly upward to the should level. The intensity of pinching and twisting would be increased gradually to avoid intolerable discomfort. For infants beyond 6 months, BP was performed for 9 repeats. After the instruction and learning, the mothers performed the whole procedure of infant massage on their infants for about 10 min in the presence of the investigator at the health care center. Afterwards, the mothers performed infant massage once daily at home 6 times per week. It was recommended to massage infants before bedtime in the evening as previous reports due to its beneficial effect on infantile sleep pattern (25). The investigator also communicated with the mothers on massage practice during wechat communication once a week and by face

to face once a month. The mothers were also provided with massage video.

Outcome observation

Weight, length, head circumference and BMI in infants

The weight, length and head circumference in infants were measured to assess infant's physical growth at the baseline, at the end of the 2- and 5-month intervention by one investigator, who was blinded from group division. The weight and length were measured by using an intelligent physical examination instrument (WS-RTG-ID, Wuhan Computer Software Development Co. LTD, China). Body mass index (BMI) was also calculated by using the following formula: BMI= weight (kg) /length $(m)^2$. Head circumference was measured by a measuring tape (Guoshi measuring tape Co., LTD, China).

Eczema severity

Eczema severity was assessed by using the eczema area and severity index (EASI) at the baseline and the end of the 2-month intervention, which was conducted by one blinded investigator. EASI is a simple, reliable and easily understood system, which can be used by practitioners and investigators as a baseline evaluation and to track changes of eczema condition over time (2, 33, 34). EASI assesses the key signs of eczema including redness, thickness, excoriation, lichenification and the percentage of skin involving four areas (the head and neck, the trunk, the upper and lower extremities) (2, 33, 34). The scores are summed to achieve a total score ranging from 0 to 72. An EASI score $\leq$7 is considered as mild, 8–21 moderate, 22–50 severe, 51–72 very severe (2).

Quality of life in infants with eczema

The quality of life (QOL) in infants with eczema was evaluated by their mothers using the infants' dermatitis quality of life index (IDQOL) at the baseline and the end of the 2-month intervention. IDQOL is an easy and sensitive method with good reproducibility for parents to assess QOL impairment in infants with eczema (35). IDQOL contains 11 questions about current dermatitis severity, symptoms such as itching and scratching, mood, sleep, play, family activities, mealtimes, treatments, dressing and bathing. Ten questions present with the scores ranging from 0 to 3 and 1 question from 0 to 4 (35). In addition, the sleep condition in infants was also evaluated by the total scores of 2 questions involving sleep in IDQOL.

Mental state in mothers

Maternal anxiety and depression levels were evaluated, respectively by using SAS and SDS to investigate their mental state. Mothers in the three groups completed SAS and SDS questionnaires at the baseline and the end of the 2-month intervention. SAS and SDS were designed to quantify the severity of anxiety and depression symptoms, which is widely used as a common and effective self-assessment method (36–39). SDS is often used for perinatal women in China (40, 41). Both of SAS and SDS are 20-item self-reported assessment scales. The total score multiplied by 1.25 provides a standard score. The severity of symptoms was determined based on the standard scores of SAS and SDS as follows: $<$ 50 (normal), 50–59 (mild), 60–69 (moderate), and $\geq$70 (severe). The score below 50 also indicates the levels of depression and anxiety mood (42, 43).

Adverse event

During the study, the mothers and investigators observed whether there were any adverse events in the infants after intervention, including any local impairment of skin, continuous crying, any abnormal change in sleep, eating and bowel movement.

Observation on the relapse of eczema

Since infantile eczema is a chronic relapsing inflammatory dermatosis (1), this study also observed the relapse condition of eczema in infants at the end of the 5-month intervention comparing with eczema condition at the end of the 2-month intervention. Persistent zero score of EASI from the end of 2-month to 5-month interventions was considered as complete remission. Eczema recurred after complete remission at the end of 2-month intervention was considered as a relapse. Persistent eczema without complete remission from the end of 2-month to 5-month interventions was considered as non-complete-remission. The general condition of infantile eczema was evaluated by a blinded investigator.

Statistical analysis

The one-way ANOVA and $\chi 2$ test were performed to compare baseline data among groups. The repeated-measures ANOVA was performed to compare infantile growth data among groups. The student's *t*-test was used to compare the scores of EASI, IDQOL and sleep in infant-mother dyads pre- and post-intervention among groups. The rank sum test was used to analyze the infantile eczema condition and the level of maternal anxiety and depression among groups. The SAS score and SDS score among groups were analyzed by one-way ANOVA and *t*-test for the comparison of pre- and post-intervention. Finally, we used spearman's rank correlation to assess the correlation between EASI score and the scores of

IDQOL, sleep, SAS and SDS. All analyses were done by using Statistical Package for Social Sciences version 25.0 (SPSS, IBM, Armonk, NY, USA) and figures by using GraphPad Prism 6 (GraphPad Software Inc., La, Jolla, CA, USA). $P < 0.05$ were considered as statistical significance.

Results

Demographical data of infant-mother dyads

Thirty-one dyads and 63 dyads completed the study. The demographical profile of these infant-mother dyads is shown in Table 1. The age and the gender ratio in infants were not significantly different among the three groups ($F = 0.464$, $P = 0.630$; $\chi^2 = 0.663$, $P = 0.718$). There were no significant differences in the age, education background, primiparity and breast-feeding condition among the mothers in the three groups ($F = 2.637$, $P = 0.077$; $\chi^2 = 1.274$, 0.141 and 1.005, $P = 0.693$, 0.932 and 1.000).

Weight, length, head circumference and BMI in infants

As shown in Figures 3A–D, there were no significant differences in the baseline values of infantile weight, length, BMI and head circumference in the three groups ($F = 0.222$, 0.768, 0.246 and 0.612; $P = 0.802$, 0.467, 0.782, and 0.544). The increasing in the infantile weight, length and head circumference was not significantly different among the three groups during this study ($F = 1.752$, 1.010 and 1.030; $P = 0.172$, 0.381 and 0.370). Moreover, the change in the infantile BMI value was not significantly different among the three groups ($F = 0.490$, $P = 0.699$).

Improvement on infantile eczema

The severity of infantile eczema was evaluated by EASI and IDQOL scores as shown in Table 2. At the baseline, the scores of EASI and IDQOL in infants were not significantly differenct between the EC and EM groups (t = 1.389, $P = 0.172$; t= 0.349, $P = 0.728$). There were significantly lower scores of EASI (t = 8.749 and 15.460; both $P < 0.001$) and IDQOL (t = 5.981 and 8.132; both $P < 0.001$) after the 2-month intervention in both groups. Moreover, the EM group had significantly lower scores of EASI and IDQOL than the EC group (t = 3.953 and 3.797; both $P < 0.001$). Meanwhile, as shown in Table 3, the EM group had significantly lower scores involving sleep state following MPIM than the EC group (t = 3.969, $P < 0.001$). In addition, there was a significantly positive correlation of EASI scores with IDQOL scores before ($\gamma = 0.348$, $P = 0.005$, Figure 4A) and after 2-month intervention ($\gamma = 0.709$, $P < 0.001$, Figure 4E). There was also a significant correlation of EASI scores with sleep scores after 2-month intervention ($\gamma = 0.559$, $P < 0.001$, Figure 4F), but not at the baseline ($\gamma = 0.171$, $P = 0.180$, Figure 4B). At the end of 5-month intervention, the EM group had significantly more cases of complete remission and fewer relapse cases than the EC group ($Z = 3.124$, $P = 0.002$, Table 4).

Improvement on mental state in mothers

The mental state in mothers was evaluated by SAS and SDS scores as shown in Table 5. Compared with the HC group, the mothers in the EC and EM groups showed significantly higher scores of SDS ($P = 0.032$, $P = 0.010$) and non-significantly higher scores of SAS ($P = 0.158$, $P = 0.236$). At the end of 2-month intervention, there were significantly lower scores of SAS and SDS in the EC group (t = 2.087, $P = 0.046$; t = 2.695, $P = 0.011$) and EM group (t = 6.066 and 7.972, both $P < 0.001$). The EM group had significantly lower scores of SAS and SDS than the EC group ($P = 0.003$, $P = 0.002$). Intriguingly, the scores of SAS and SDS in EM group were significantly lower at the end of 2-month intervention than those in the HC group ($P = 0.031$, $P = 0.039$). The scores of SAS and SDS in the HC group didn't show significant change (t = 0.220, $P = 0.827$; t = 0.000 $P = 1.000$). Moreover, compared with the EC group, the ratio of cases with mild-to-moderate depression to normal cases lowered significantly ($Z = 2.349$, $P = 0.019$), but the ratio of cases with mild-to-moderate anxiety to normal cases didn't change significantly ($Z = 1.016$, $P = 0.310$, Table 6). Meanwhile, the correlation of maternal scores of SAS and SDS with infantile EASI scores showed significantly positive before ($\gamma = 0.294$, $P < 0.019$; $\gamma = 0.267$, $P < 0.035$; Figures 4C,D) and after 2-month intervention ($\gamma = 0.495$, $P < 0.001$; $\gamma = 0.524$, $P < 0.001$, Figures 4G,H). In addition, as shown in Table 3, maternal sleep state got improved remarkably in the EC and EM groups after 2-month intervention (t = 2.160, $P = 0.039$; t = 4.923, $P < 0.001$,). MPIM further improved maternal sleep state (t = 2.468, $P = 0.018$).

Safety observation of MPIM

During the study, none of any obviously adverse events was observed and reported following MPIM or routine care except for temporal crying during BP only on the first several days in 4 cases in the EM group.

TABLE 1 Demographical data of infant-mother dyads.

	HC group($n = 31$)	EC group($n = 31$)	EM group($n = 32$)	*P*-value
Infant				
Age (month)	4.3 ± 3.1	3.7 ± 2.9	3.6 ± 2.7	0.630
Male/female	14/17	17/14	17/15	0.718
Mother				
Age (year)	28.8 ± 2.6	27.8 ± 2.8	29.6 ± 3.6	0.077
Education background (high school and above/below)	30/1	28/3	29/3	0.693
Primiparity/multiparity	22/9	21/10	23/9	0.932
Breast-/mixed-/artificial feeding	27/2/2	27/3/1	28/2/2	1.000

Data are presented as the mean ± standard deviation or n/n.
HC, healthy control; EC, eczema control; EM, eczema with mother-performed infant massage.

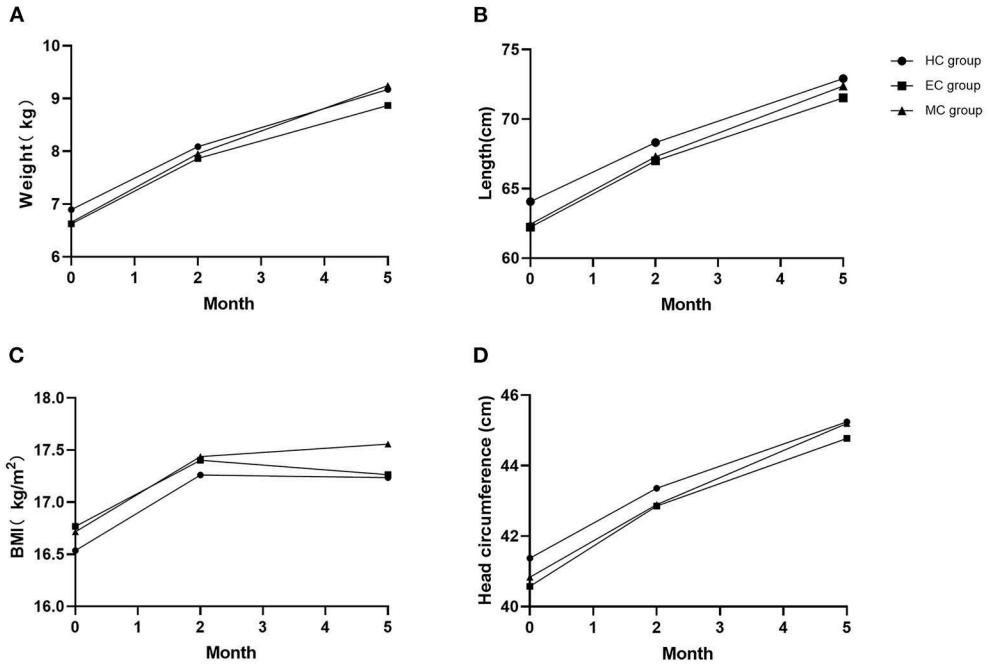

FIGURE 3
Comparison of infantile growth indexes at three timepoints. **(A)** Weight; **(B)** Length; **(C)** BMI; **(D)** Head circumference. No significant difference in all indexes among the three groups ($P_A = 0.172$, $P_B = 0.381$, $P_C = 0.699$, $P_D = 0.370$).

Adherence in routine care or MPIM

This study was also designed to observe maternal adherence condition during the latter 3-month intervention without any supervision from investigators. The investigator asked about (1) whether the mothers persisted in following instructed routine care in the EC and EM groups; (2) how often MPIM was conducted in the EM group. It was found that routine care was followed by all mothers in both groups. Nineteen mothers performed MPIM at least 6 days a week, 12 mothers 1 or 2 days a week, and only 1 mother discontinued for no special reason.

Discussion

This study aimed to observe the potentially positive effect of MPIM on infantile eczema, growth and the mental state in mothers. This study indicated that infantile eczema impaired infantile quality of life and negatively influenced maternal mental state. Infantile eczema improved over time after mothers followed the instructions about the routine care for infantile eczema, along with improved depressive and anxious mood in mothers. More importantly, this study demonstrated that MPIM further enhanced eczema remission and decreased its relapse

TABLE 2 Comparison of infantile eczema condition.

	EC group ($n = 31$)	EM group ($n = 32$)	*P*-value
EASI score			
Baseline	7.0 ± 4.2	5.9 ± 1.9	0.172
2 Month	2.2 ± 2.7	0.3 ± 0.7	<0.001***
P-value	<0.001***	<0.001***	/
IDQOL score			
Baseline	4.8 ± 3.4	5.1 ± 3.1	0.728
2 Month	3.0 ± 2.4	1.1 ± 1.4	<0.001***
P-value	<0.001***	<0.001***	/

Data are presented as the mean ± standard deviation.
EASI, eczema area severity index; IDQOL, infantile dermatitis quality of life index.
*** $P<0.001$.

TABLE 3 Comparison of sleep scores in infant-mother dyads.

	EC group ($n = 31$)	EM group ($n = 32$)	*P*-value
Infant			
Baseline	1.42 ± 1.12	1.75 ± 1.02	0.224
2 Month	1.16 ± 0.90	0.38 ± 0.66	<0.001***
P-value	0.030*	<0.001***	/
Mother			
Baseline	5.61 ± 2.28	5.56 ± 1.98	0.919
2 Month	4.90 ± 1.76	4.03 ± 0.90	0.018*
P-value	0.039*	<0.001***	/

Data are presented as the mean ± standard deviation.
* $P < 0.05$, *** $P < 0.001$.

rate, together with further improved mental state in mothers. However, the growth in infants with eczema was not affected by MPIM.

Eczema is typically the first allergic manifestation to appear (44). Precipitating or aggravating factors of eczema include food allergens, environmental allergens or irritants, climatic condition, stress and genetic predisposition, although the exact cause of eczema is not clear (45). Infantile emollient is inexpensive, widely available, and used extensively for relieving eczema (46), which can improve the function of skin barrier and reduce itch and irritation (45). About 35% to 40% of children with moderate to severe eczema have food allergy, and eczema can be improved significantly by eliminating the causative food from their diet (46). Previous studies demonstrated that breastfeeding was associated with lower incidences of allergic diseases, eczema included (47, 48). Breast-feeding is proved to prevent allergy due to the immune mediators and oligosaccharides in maternal milk, which facilitates balanced gut microbiota to induce tolerance (44). In this study, infantile eczema improved after the mothers followed these instructions about the routine care for infantile eczema. Itching, the cardinal symptom of eczema, obviously impairs infantile QOL, therefore, IDQOL is widely used in conjunction with EASI for assessing clinical severity of eczema (4, 5). This study also demonstrated that QOL of infants with eczema was impaired by eczema and improved along with relieved eczema after the mothers followed the instruction of routine care.

As we all know, postpartum mothers are susceptible to depression and anxiety episodes (9–12), whose mood is negatively influenced by infant eczema (4). This study showed that the respective prevalence of anxiety and depression among these postpartum mothers was 1/31 and 3/31 in HC group, 3/31 and 5/31 in EC group, 2/32 and 7/32 in EM group at baseline, which are consistent with previous reports (10–12). The mothers in the EC and EM groups had significantly higher levels of depression and anxiety mood than those in the HC group at baseline. Moreover, the mothers in the EC and EM groups had higher rates of depression symptoms than those in the HC group

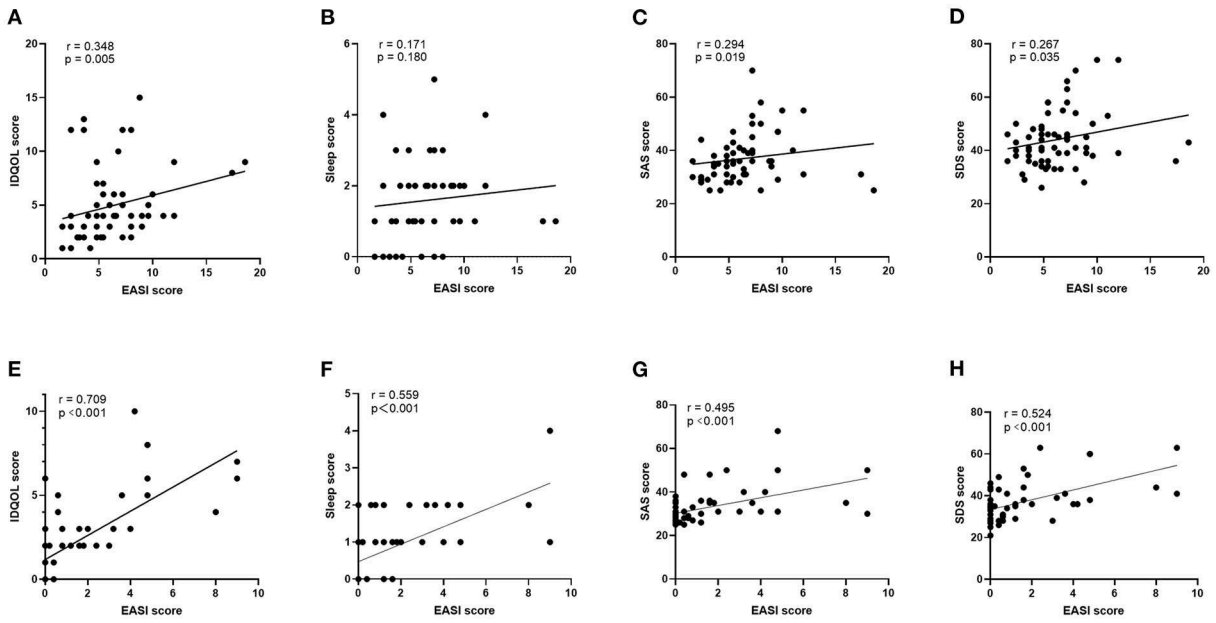

FIGURE 4
Correlation between EASI score in infant and indexes in infant-mother dyads at baseline and after 2-month intervention. Baseline/ After 2-month intervention: **(A,E)** EASI score and IDQOL score in infants; **(B,F)** EASI score and sleep score in infants; **(C,G)** EASI score and SAS score in mothers; **(D,H)** EASI score and SDS score in mothers.

TABLE 4 Comparison of infantile eczema condition at the end of 5-month intervention.

Group	Complete remission	Relapse	Non-complete-remission	*P*-value
EC group ($n = 31$)	6 (19.35)	10 (32.26)	15 (48.39)	0.002**
EM group ($n = 32$)	15 (46.88)	13 (40.63)	4 (12.5)	

Data are presented as n (%).
** $P < 0.01$.

at baseline, but not higher rates for anxiety symptom. This result indicated that infantile eczema might increase the susceptibility of mothers to depression, which is consistent with previous study (4).

Two previous trials demonstrated that mother-performed massage could relieve eczema symptoms in young children (18, 19). One trial showed that the children with eczema were massaged with skin oil on the whole body (except for head and face) by the therapist once a week and by mothers every day for 8 weeks, which decreased night-time disturbance score (18). The other one demonstrated that mother-performed massage on the whole body (except for head) for 1 month after the first instruction by therapist could relieve eczema symptoms in children and reduce the anxiety of mothers and children. In China, infant massage is applied based on the theory of TCM, which is performed on the specific areas to relieve eczema in infants and toddlers (20–22). So far, there is no trial to investigate whether mother-performed massage can relieve infantile eczema. It is well-known that the development of eczema is associated with Th2-skewed inflammation, which is closely related with intestinal dysbiosis (49, 50). Our previous experiments demonstrated that BP, the major manipulation in MPIM, attenuated Th2-skewed inflammation and regulate the intestinal dysbiosis in immature rats with allergic airway inflammation (51, 52). In TCM, the back is the location where Du vessel and Bladder meridian run, which can be stimulated to regulate visceral function and relieve allergic symptoms (29, 32). Based on our previous trials and animal experiments, this study was designed to massage the back (29–31). This study demonstrated that MPIM further enhanced eczema remission and decreased its relapse rate, along with improved infantile QOL. It is worth mentioning that MPIM remarkedly improved the sleep state of infants with eczema and their mothers, which is consistent with previous studies (53–56). Our previously trial showed mother-performed massage improved the depression and anxiety state of the mothers of asthmatic children (31). This study indicated that MPIM also significantly reduced the levels of maternal depression and anxiety mood, including obvious

TABLE 5 Comparison of SAS and SDS scores.

	HC group ($n = 31$)	EC group ($n = 31$)	EM group ($n = 32$)	*P*-value	*P*-value[a]	*P*-value[b]	*P*-value[c]
SAS score							
Baseline	34.1 ± 8.3	37.3 ± 9.6	36.7 ± 8.6	0.316	0.158	0.236	0.809
2 Month	33.7 ± 8.2	35.4 ± 9.3	29.5 ± 4.9	0.009**	0.390	0.031*	0.003**
P-value	0.827	0.046*	<0.001***	/	/	/	/
SDS score							
Baseline	37.7 ± 10.7	43.6 ± 2.1	44.8 ± 9.7	0.023	0.032	0.010	0.663
2 Month	37.7 ± 10.8	40.3 ± 10.2	32.9 ± 6.2	0.007**	0.275	0.039*	0.002***
P-value	1.000	0.011*	<0.001***	/	/	/	/

Data are presented as the mean ± standard deviation.
SAS, self-rating anxiety scale; SDS, self-rating depression scale.
[a,b and c] represent P-values for comparisons between HC and EC group, HC and EM group, EC and EM group, respectively.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

TABLE 6 Comparison of maternal depression and anxiety condition.

	group	Severity					
		Normal	Mild-to-moderate	*P*-value	Normal	Mild-to-moderate	*P*-value
		Pre-intervention			Post-intervention		
Anxiety	EC group ($n = 31$)	28 (90.32)	3 (9.68)	0.618	30 (96.77)	1 (3.23)	0.310
	EM group ($n = 32$)	30 (93.75)	2 (6.25)		32 (100)	0 (0)	
Depression	EC group ($n = 31$)	26 (83.87)	5 (16.13)	0.565	26 (83.87)	5 (16.13)	0.019*
	EM group (n=32)	25 (78.13)	7 (21.88)		32 (100)	0 (0)	

Data are presented as n (%).
*$P < 0.05$.

depression symptom, which consist with previous trials (24–26, 57, 58).

Further investigation in this study revealed the positive correlation between the levels of depression and anxiety and the severity of infant eczema. Therefore, on one side, the sleep state of infants got better with eczema improvement, which might beneficially influence the mothers sleep and mood. On the other hand, skin-to-skin contact during MPIM might trigger oxytocin (OT) production and release, which contributed to anti-stress effect and improving sleep state in mothers as previous reports (59–61). OT is synthesized and released from the magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus (62). OT has positive central effects on psychological adjustment and maternal behaviors during postpartum period (63–67). It is also believed that tactile contact between mother and child during massage could reduce the levels of stress-related hormones (cortisol and norepinephrine) in children and mothers and led to relieved eczema and maternal anxiety (19, 68). The placebo effect could also play a role due to a beneficial expectation (18).

Few trials investigated the outcomes of both infants and mothers following MPIM. To our knowledge, only one trial did investigate the physical status of preterm infants and the psychological state in the mothers following MPIM, which led to greater weight, motor development, and larger bicep and thigh circumference in infants as well as increased maternal attachment and decreased anxiety compared to the control group (69). However, our study showed that the growth of the infants with eczema was not affected by eczema during 5-month observation in this study. MPIM didn't significantly enhance the infantile growth although it improved infantile eczema. Previous reports also demonstrated inconsistent results about the effect of MPIM on enhancing infantile growth in preterm infants and healthy infants. Gonzalez (70) and Zhang (71) reported that MPIM could enhance the growth of preterm infants while Abedi (72) reported that MPIM didn't enhance the growth of healthy neonates. In this study, most of infants had mild eczema and thus their growth might not be affected by eczema, which might explain the result.

In addition, the correlations of EASI score with infantile scores of IDQOL and sleep and maternal scores of SAS and

SDS were more significant after 2-month intervention compared with those at baseline. This result suggests that infantile quality of life and sleep and maternal mood might be affected easily by surrounding complicated factors during early postpartum stage, which may change overtime.

Previous study showed that parents preferred to learn and practice infant massage on their own babies either in a class, in a hospital or at home under the investigators' supervision and instruction (24–26, 30, 31, 73). However, for the feasibility and practicality, the adherence of MPIM at home without any specific supervision of investigators should be investigated, which is the minor aim of this study. This study demonstrated good adherence of MPIM without persistent supervision from investigators, which indicated that MPIM is feasible and convenient to implement at home after the relative training in the community background.

Limitations

There are some limitations in this study. Firstly, for the convenient implementation in this pilot study, it was designed to enroll participants from one community, which might influence the real intervention effects. Secondly, this study was designed not to supervise the implementation of MPIM during the latter 3 months, aiming to observe the feasibility and adherence of MPIM. Therefore, the outcomes of infant-mother dyads at the end of 5-month intervention might be affected by the various performing frequency of MPIM. Thirdly, due to the small sample size, this study didn't analyze the potentially different effects caused by various frequency of MPIM at the end of 5-month intervention. Fourthly, this pilot study only enrolled infants and their mothers to observe the potential effect on maternal mental state. It can also extend to fathers of eczema infants who also experience worse mental state during postpartum. Fifthly, due to the study feature, mothers could not be blinded and they also assessed their own mental state and infantile quality of life, which might bring certain placebo effect. In the future, multi-centered randomized controlled trials with larger size are warranted to further investigate the potential benefits of parent-performed infant massage on the outcomes of infant-parent dyads for a prolonged time.

Conclusion

In conclusion, this study demonstrated for the first time that MPIM enhanced the remission of infantile eczema, reduced the relapse rate and improved maternal depression and anxiety mood. Given its safety, cost-effectiveness and feasibility, MPIM may be recommended as a routine home healthcare method for infants with eczema in the community background.

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 Ethics Committee of Jiangsu Provincial Hospital of Intergrated Chinese and Western Medicine. Number of ethics approval: 2020LWKY010. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YX contributed to the conception and design of the study. LY and JL participated in the design of the manuscript and collected data. LL and YX drafted the manuscript. LL and SZ analyzed data. All authors contributed to manuscript revision, read, 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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The association between isometric strength and cognitive function in adults with cerebral palsy

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Background: The literature supports quantifying the maximum force/tension generated by one's forearm muscles such as the hand grip strength (HGS) to screen for physical and cognitive frailty in older adults. Thus, we postulate that individuals with cerebral palsy (CP), who are at higher risk for premature aging, could benefit from tools that objectively measure muscle strength as a functional biomarker to detect frailty and cognitive decline. This study assesses the clinical relevancy of the former and quantifies isometric muscle strength to determine its association with cognitive function in adults with CP.

Methods: Ambulatory adults with CP were identified from a patient registry and were enrolled into this study. Peak rate of force development (RFD) and maximum voluntary isometric contraction of the quadriceps were measured using a commercial isokinetic machine, while HGS was collected with a clinical dynamometer. Dominant and non-dominant side were identified. Standardized cognitive assessments, including the Wechsler Memory and Adult Intelligence Scales IV, Short Test of Mental Status, and the Patient-Reported Outcomes Measurement Information System (PROMIS®) were used to evaluate cognitive function.

Results: A total of 57 participants (32 females; mean age 24.3 [SD 5.3]; GMFCS levels I–IV) were included in the analysis. Although dominant and non-dominant RFD and HGS measures were associated with cognitive function, non-dominant peak RFD showed the strongest associations with cognitive function.

Conclusion: RFD capacity may reflect age-related neural and physical health and could be a better health indicator than HGS in the CP population.

KEYWORDS

cerebral palsy - diagnosis, cognitive function, isometric strength measurement, rate of force development (RFD), hand grip dynamometer, aging, frailty, gross motor function classification scale (GMFCS)

1. Introduction

Cerebral Palsy (CP) is characterized by damage or injury to the developing brain sustained before, during, or shortly after birth, and affects roughly 3.5 individuals per 1,000 live births (1). This makes CP the most common physical disability in children (1). Although CP is considered a childhood condition, adults with CP experience chronic, lifetime disability and often develop a variety of secondary health conditions that could be a sign of premature aging (2). Premature aging is characterized by the development of common geriatric health conditions such as cardiovascular disease, hypertension, cognitive decline, and frailty syndrome at an earlier age (2–5).

Frailty syndrome is a common geriatric condition associated with disease severity and mortality in the older adult population (6, 7). In the absence of a standardized clinical definition, frailty syndrome has been operationalized as cumulative deficits in key musculoskeletal systems such as weak grip strength, low energy, slow walking speed, challenges in performing physical activities, and/or unintentional weight loss (6, 7). Individuals with CP often have difficulty performing physical activities including routine daily tasks due to musculoskeletal impairments, sarcopenia, and pain (1, 3, 5). This may contribute to experiencing signs of frailty much earlier compared to adults without any pathology as is often reported (5–7). Therefore, there is a need for research evaluating innovative screening, diagnostics, biomarkers, and interventions to delay disease development, decrease frailty, and the subsequent risk for early co-morbidities and mortality in adults with CP (2–5).

Hand grip strength (HGS) is recognized as an important health indicator and is commonly used to measure upper body neuromusculoskeletal function (8–10). Substantial evidence supports that HGS is a strong predictor of disability and frailty in the older adult population (11). HGS is also strongly correlated with cognitive function in the older population (12). Additionally, HGS has been associated with function and activities of daily living in children and adults with CP (13). While HGS is a good measurement tool to evaluate neuromuscular function in the upper extremities, it might not be the most sensitive measure to capture physical frailty and functional health decline in adults with CP. HGS is a simple and unidimensional measure of maximum strength and does not assess the speed of muscle contraction (14–16). This limits the assessment of neurofunctional abilities for individuals with CP (13), as many individuals with CP have hypertonicity, including spasticity and dystonia (1). The physical metric known as Rate of Force Development (RFD) has the potential to be a more multidimensional measure of neuromuscular health for populations with musculoskeletal impairments because it includes a measure of both the speed and magnitude of a muscle group's force output (14–16). RFD measures the rate at which force, or torque, is produced during a specific amount of time and is dependent on muscle strength, type of muscle fibers, muscle size, and motor neuron function (17). Moreau and colleagues (14, 15) reported the importance of RFD when assessing fatigue and functional ability in individuals with CP and concluded that RFD may be of greater importance than maximal strength for specific tasks. They also stated that interventions focused on improving RFD would also improve the functional ability of individuals with CP (14, 15). Similarly, other studies have reported that high RFD values are needed to counteract the effects of sudden changes in balance (17), which pertains to adults with CP as they have reduced overall balance and are at an elevated risk for falling (18, 19).

While RFD is a promising neuromuscular health assessment tool for adults with CP, there is limited literature reporting the associations between RFD and important neurologic and functional outcomes associated with frailty in adults with CP. Specifically, whether RFD could be a good correlate of physical and cognitive outcomes in adults with CP is unknown; as such, this study aimed to evaluate the associations between RFD, HGS, and cognitive function in adults with CP to shed light on the potential integration of these instruments as a potential health screening tool to capture early physical and cognitive frailty in adults with CP before they develop severe frailty syndrome and disability (20).

2. Materials and methods

2.1. Setting and study design

This report analyzed data collected from the parent study; "The Cerebral Palsy Adult Transition Study" (CPAT) which has been previously described (2, 3, 21, 22). The CPAT study was performed at a clinical motion analysis laboratory in a regional children's hospital that has been serving the health needs of individuals with CP for over 20 years (2, 3, 21, 22). The facility is accredited by the Commission for Motion Laboratory Accreditation (CMLA[1]) and is composed of a multidisciplinary team of clinicians and researchers. The study was approved by the university's Institutional Review Board and all participants signed informed consent prior to participation.

2.2. Participants

Participants with a confirmed diagnosis of CP over the age of 18 years were identified from an internal patient registry and were invited to participate in a short telephone screening survey to determine if they were (1) interested and able to participate in the study, and (2) able to walk across a 35-foot (10.6 m) walkway, with or without assistive devices, at least three times. A total of 72 ambulatory participants passed the study inclusion criteria and participated in the parent CPAT study (2, 3, 21, 22). For this study evaluating the associations between peak RFD of the quadriceps, HGS, and cognitive function in ambulatory adults with CP, data from 57 participants out of the 72 were used for the analysis. A total of 15 participants did not complete the cognitive and physical performance assessments and were not included in the analysis (Table 1).

Abbreviations: CP, Cerebral Palsy; HGS, Hand grip strength; RFD, Rate of Force Development; MVIC, Maximum Voluntary Isometric Contraction; CPAT Study, Cerebral Palsy Adult Transition Study; WMS-IV, Wechsler Memory Scale IV; WAIS-IV, Wechsler Adult Intelligence Scale IV; PROMIS®, Patient-Reported Outcomes Measurement Information System; STMS, Short Test of Mental Status.

1 www.CMLAinc.org

TABLE 1 Demographics.

Age	
Mean Age (SD) [range]	24.3 (5.3) [18–48]
Gender (*n*)	
Male	25
Female	32
Ethnicity (n)	
African-American	3
Asian/Pacific Islander	1
Hispanic/Latino	7
White	39
Mixed/Multiethnic	6
Other	1
CP Diagnosis (n)	
Right hemiplegia	9
Left hemiplegia	13
Diplegia	30
Triplegia	3
Quadriplegia	2
Education Level	
Mean Years (SD)	13.8 (2.4)
GMFCS (*n*)	
I	25
II	18
III	13
IV	1

2.3. Assessment tools and outcomes

2.3.1. Isometric knee extension strength assessment

Calculation of isometric strength outcome variables was performed in compliance with guidelines published by Moreau and colleagues (14). Testing was performed during an isometric knee extension activity using the HUMAC NORM isokinetic dynamometer (CSMi, Stoughton, MA). Participants were seated and stabilized at an 85° back angle with a fixed 60° knee flexion angle. Each subject was instructed to push as hard as they could for 5 s followed by 60 s of rest between exercise trials. Three exercise trials were collected. The maximum voluntary isometric contraction (MVIC) of each trial was identified from the knee extension torque vs. time curve, and the slope of the rising edge (rate of force development, RFD) was calculated at 0–30, 0–50, 0–100, and 0–200 ms, where *t0* was defined as the time when muscle torque either met or first exceeded 2.5% of the maximum torque value. The peak RFD corresponds to the single highest slope value between 0–30, 0–50, 0–100, and 0–200 ms intervals. Additionally, RFD50 was calculated as the slope at 50% of MVIC. Successful trials were initially identified as having a starting torque of 0. If an offset was present, in which the trial had a non-zero resting torque, the measured offset was subtracted from the MVIC to adjust for this residual force, and the procedure described above was performed. Trials were excluded from analysis if they did not follow the Moreau et al. protocol (14) or if the trial did not have a definite offset. If multiple trials for a given leg were successful, the trial with the largest Peak RFD was used in the analysis. These tests were performed on both limbs, in which the right and the left side were analyzed separately (14–16).

2.3.2. Cognitive function assessments

Cognitive function was measured using the Wechsler Memory Scale-IV (WMS-IV) (23, 24), the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (23, 24), the Short Test of Mental Status (STMS) (25), and the Patient-Reported Outcomes Measurement Information System (PROMIS®) Applied Cognition–Executive Function (26, 27). PROMIS® is a large measurement information system initiative funded by the National Institutes of Health that has been extensively evaluated, validated, and used in reported outcomes research (26). The following WMS-IV subtests were used to evaluate a participant's memory (23): the Visual Reproduction I, Logical Memory I, Verbal Paired Association I, Category Fluency Test, Visual Reproduction II Delayed Recall, Visual Reproduction II Recognition, Logical Memory II Delayed Recall, Logical memory II, Visual Reproduction II Delayed Recall, Visual Reproduction II, and Visual Reproduction II Word Recall. The WAIS-IV subtests were used to evaluate a person's overall cognitive ability, which consisted of Block Design, Digit Span, Symbol Search, and Picture Completion (24). The STMS was used to evaluate the global cognition and the overall cognitive status of the study participants (25). Qualified and trained research staff administered the neuropsychological protocol.

2.3.3. Hand grip strength

Bilateral hand grip strength (HGS) was obtained by a trained research staff member using a Jamar digital hand dynamometer (model number 5030J1, Patterson Medical, Warrenville, IL, United States). This model of dynamometer was chosen due to its proven value in CP patient populations (28). After adjusting for hand size, participants were instructed and verbally encouraged to grip the handle of the dynamometer as hard as possible with their dominant and non-dominant hands; participants performed this test while seated, shoulders adducted and neutrally rotated, elbow flexed at 90, with forearms in a neutral position and wrist between 0 and 30 degrees of dorsiflexion. Three trials were collected and averaged for analysis. This procedure for HGS data collection follows the recommendations of the The American Society of Hand Therapists (29).

2.3.4. Dominant side identification

For individuals who were diagnosed with hemiplegia, a form of unilateral CP, the non-dominant side was identified as the affected side. For those who had a diagnosis of diplegia, triplegia, or quadriplegia, forms of bilateral CP, dominant and non-dominant sides were identified by asking participants which hand they wrote with, in which their writing hand was considered their dominant side (20). For those who were not able to write and unable to communicate which side was their dominant side, the values from their left and right side were averaged, in which the average value was used as both their dominant and non-dominant values.

2.4. Statistical analysis

With a power of 80% to detect statistical significance at a 5% alpha level, the study was powered to detect significant correlations (≥ 0.33). Mean plus standard deviation and percentage distribution summarized continuous and categorical outcomes, respectively. Isokinetic values were calculated for both the dominant and non-dominant side using the methods published by Moreau et al. (16). The predictor variables (Peak RFD, MVIC, RFD50, and HGS) were correlated with the WMS-IV raw scores, WAIS-IV raw scores, and STMS total scores to identify associations using Pearson's correlation coefficient. After the bivariate analysis, a comparison between dominant and non-dominant Peak RFD, MVIC, RFD50, and HGS was performed to identify which variable showed the strongest correlations (determined by the largest r2 value) and had the greatest number of correlations with all cognitive outcome variables. Subsequently, a multi-variable linear regression was performed, in which the outcome variables used were the cognitive functional assessment sub-tests that had the strongest correlations with the isometric knee extension strength assessment and the hand grip strength variables. A backward selection method was used to determine which predictor variables significantly impacted the final model, in which non-significant variables were taken out of the model, one predictor at a time, until only the statistically significant variables were left in the model. The predictor variables included in the full model were dominant and non-dominant MVIC, Peak RFD, RFD50, and HGS. In step 1 of the analyses, due to the exploratory nature of the bivariate analyses, no statistical adjustments were performed. In step 2 of the analyses, for the multi-linear regression, significance was adjusted using the Bonferroni correction, in which a value of p under 0.00625 (0.05/8) was considered statistically significant. SAS 9.4 (SAS Institute Inc., Cary, NC, United States) was used as the program for all analyses.

3. Results

A total of 57 participants were included in this study. The demographics of this cohort comprised 25 males and 32 females, who had a mean age of 24.3 [SD 5.3] with a GMFCS level between I–IV. Full demographic information is provided in Table 1.

3.1. Association between isometric assessment and cognitive function

Results on the correlations between the dominant and non-dominant MVIC, Peak RFD, and RFD50 with tests of cognitive function are summarized in Table 2 and Figures 1, 2. Additionally, Supplementary Tables S1 and S2 report the overall results of the analysis. The analysis revealed that all isometric knee extension strength assessment variables had at least one statistically significant correlation with one of the cognitive tests ($p < 0.05$). Upon analyzing the dominant side, it was found that Peak RFD on the dominant side had the greatest number of correlations with the cognitive tests compared MVIC and RFD50 on the dominant side (Table 2). Additionally, Peak RFD had the strongest correlation compared to MVIC and RFD50 on the dominant side, which was indicated by the largest Pearson's R value. This correlation was between Peak RFD and the Symbol Search sub-test (Pearson's R value = 0.49) within the WAIS-IV (Table 2, Figure 1, and Supplementary Table S1). Furthermore, it was found that Peak RFD on the dominant side showed strong correlations ($p < 0.001$ and Pearson's R > 0.40) with all the cognitive sub-tests within the WAIS-IV (Figure 1 and Supplementary Table S1).

Upon analyzing the non-dominant side, it was found that Peak RFD on the non-dominant side had the greatest number of correlations with the cognitive tests compared to MVIC and RFD50 on the non-dominant side (Table 2). Additionally, the analysis revealed that the strongest correlations, which were indicated by the largest Pearson's R value, were observed from Peak RFD and RFD50 variables. These correlations were with the Symbol Search sub-test (Pearson's R value with Peak RFD = 0.55; Pearson's R value with RFD50 = 0.56) within the WAIS-IV (Table 2, Figure 2, and Supplementary Table S2). Furthermore, while Peak RFD had the greatest number of correlations with the cognitive test on the non-dominant side, the strong correlations on the non-dominant side ($p < 0.001$ and Pearson's R > 0.40) were not associated with a single cognitive test (Figure 2 and Supplementary Table S2).

3.2. Association between HGS and cognitive function

Results analyzing HGS on the dominant and non-dominant side are summarized and presented in Table 2, Figure 3, and Supplementary Table S3. It was observed that dominant and non-dominant HGS had the same number of correlations (total of 9 correlations) with cognitive function (Table 2 and Supplementary Table S3). It was also found that the strongest correlations observed were between non-dominant grip strength and the Digit Span sub-test (Pearson's R value = 0.46; value of $p<0.05$) (Figure 3 and Supplementary Table S3). Furthermore, the strong correlations for the HGS on the dominant and non-dominant side ($p < 0.001$ and Pearson's R > 0.40) were not associated with a single cognitive assessment test (Figure 3 and Supplementary Table S3).

3.3. Comparison and multi-variable linear regression analysis

Comparison between dominant and non-dominant MVIC, Peak RFD, RFD50, and HGS with the cognitive assessment variables can be summarized in Table 2. This comparison revealed that Peak RFD on the non-dominant side had the second strongest correlations and the highest number of correlations with all the cognitive function tests (WMS/ STM, WAIS-IV and PROMIS®) compared to HGS, MVIC, and RFD50 on either the dominant or non-dominant hand.

Since the Digit Span subtest in the WAIS-IV showed the strongest correlation with the HGS assessment variables (Pearson's R value = 0.46; value of $p<0.05$), and since the Symbol Search sub-test within the WAIS-IV showed the strongest correlations with the isometric strength assessment variables, these cognitive sub-tests were used as our outcome variables for the multi-variable linear regression analysis. For the model with Digit Span as the outcome variable, the backward selection method excluded every predictor variable except

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TABLE 2 Overall summary of all correlation based on sidedness.

Sidedness	RFD/HGS	Number of statistically significant correlations Pearson (out of 17)	Range of statistically significant correlations Pearson	Cognitive tests correlations		Cognitive function Domain
				Smallest Pearson's *R*	Largest Pearson's *R*	
Dominant	MVIC	6	0.27–0.34	Visual Paired Associates I - Immediate Recall Raw Score	Picture Completion Raw Score	Visual Perception/ Perceptual Organization
	Peak RFD	10	0.32–0.49	Visual Reproduction II-Recognition Raw Score	Symbol Search Raw Score	Processing Speed
	RFD at 50% MVIC	8	0.27–0.39	Visual Reproduction I - Immediate Recall Raw Score	Picture Completion Raw Score	Visual Perception/ Perceptual Organization
	HGS	9	0.30–0.45	Total Logical Memory I - Immediate Recall Raw Score	STMS Total Score	Global Cognition
Non-Dominant	MVIC	7	0.23–0.34	Visual Reproduction I - Immediate Recall Raw Score	Digit Span Raw Score	Working Memory
	Peak RFD	16	0.26–0.55	Visual Reproduction II - Recognition Raw Score	Symbol Search Raw Score	Processing Speed
	RFD at 50% MVIC	13	0.27–0.56	Verbal Paired Associates II - Recognition Raw Score	Symbol Search Raw Score	Processing Speed
	HGS	9	0.25–0.46	Symbol Search Raw Score	Digit Span Raw Score	Working Memory

RFD, Peak Rate of force development; MVIC, Maximum Voluntary Isometric Contraction; HGS, Hand Grip Strength.
This summarizes the dominant and non-dominant MVIC, Peak RFD, RFD at 50% MVIC, and HGS univariate correlations with cognitive function, in which specific cognitive tests with the smallest and largest Pearson's R value are displayed.

the non-dominant Peak RFD. This resulted in the following final model: Digit Span Score = 19.10052 + 0.03252 x [Non-dominant Peak RFD] (model value of $p = 0.0006$; $r^2 = 0.204$). Similarly, for the model with Symbol Search as the outcome variable, the backward selection method excluded every predictor variable except the non-dominant Peak RFD. This resulted in the following final model: Symbol Search Score = 13.81751 + 0.06363 x [Non-dominant Peak RFD] (model value of $p < 0.0001$; $r^2 = 0.3055$).

4. Discussion

The main findings of this study reveal that higher isometric strength, defined by MVIC, Peak RFD, RFD50, and HGS, was associated with higher cognitive function scores, especially in the executive function domain. Executive function is a set of mental skills that include working memory, attention, speed, flexible thinking, and self-control, which are skills essential for learning, working, and managing daily life. More specifically, Peak RFD and RFD50 showed the strongest association with the Symbol Search Test, which could indicate that higher isometric strength is associated with better processing speed ability such as mental speed defined by the time it takes a person to do a mental task. In other words, processing speed is the time between receiving and responding to a stimulus. These findings support current literature, as multiple studies have found that measures of strength or tasks that are associated with strength and speed have been correlated with cognitive function in other populations (30–32). However, there is limited literature on cognitive function and HGS for individuals with CP. In this population, there have been multiple references showing that HGS and strength are associated with participation and quality of life (33, 34). Additionally, HGS and hand impairments are not directly related to functional ability but do indirectly affect functional skills, as it is one of many contributing factors that impact daily activities and functional ability (13, 34, 35). Current literature has also analyzed the impact of increasing upper and lower body strength in children and adults with CP, in which it is recommended that both children and adults with CP include physical activity in their lives, as it has immense health

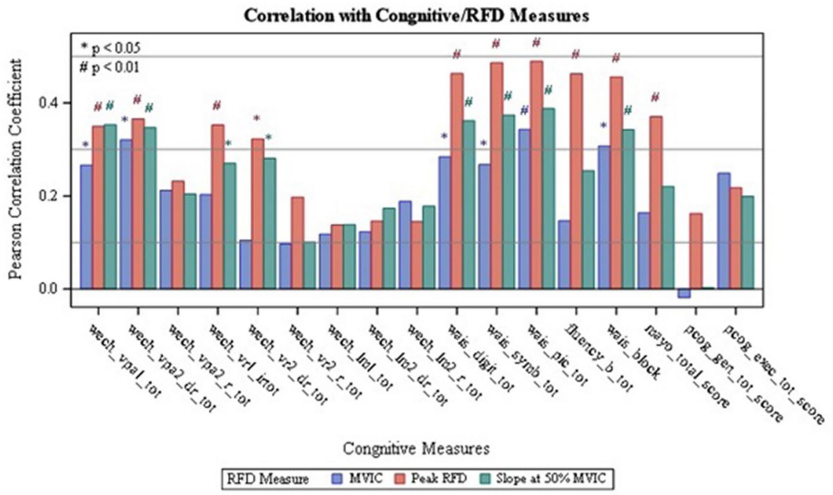

FIGURE 1
Correlation of Dominant RFD with Cognitive Measures: wech_vpal_tot — Total Visual Paired Associates I — Immediate Recall Raw Score; wech_vpa2_dr_tot — Total Verbal Paired Associates II-Delayed Recall Raw Score; wech_vpa2_r_tot — Total Verbal Paired Associates II- Recognition Raw Score: wech_vrl_irtot — Total Visual Reproduction I - Immediate Recall Raw Score; wech_vr2_dr_tot — Total Visual Reproduction II — Delayed Recall Raw Score; wech_vr2_r_tot — Total Visual Reproduction II - Recognition Raw Score; wech_lm1_tot — Total Logical Memory I- Immediate Recall Raw Score; wech_lm2_dr_tot — Total Logical Memory II-Delayed Recall Raw Score; wech_lm2_r_tot — Total Logical Memory II-Recognition Raw Score; wais_digit_tot — Total Digit Span Raw Score (forward+backward+sequencing); wais_symb_tot — Total Symbol Search Raw Score, wais_pic_tot — Total Picture Completion Raw Score; fluency_b_tot — Category Test Raw Score; wais_block — Total Block Design Raw Score; mayo_total_score — STMS Total Score; pcog_gen_tot_score — PROMIS Applied Cognition - General Concerns Short Form 8a; pcog_exec_tot_score — Neuro-QOL Applied Cognition-Executive Function.

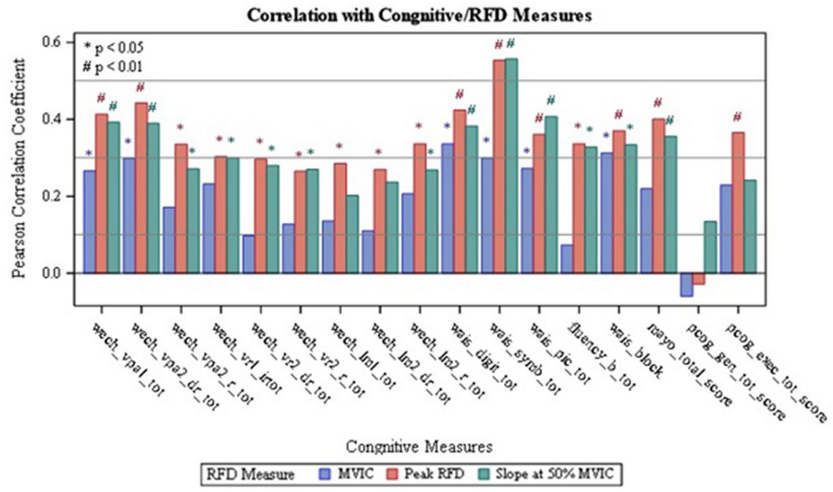

FIGURE 2
Correlation of Non-dominant RFD with Cognitive Measures; wech_vpal_tot — Total Visual Paired Associates I — Immediate Recall Raw Score; wech_vpa2_dr_tot — Total Verbal Paired Associates II — Delayed Recall Raw Score; wech_vpa2_r_tot — Total Verbal Paired Associates II- Recognition Raw Score; wech_vrl_irtot — Total Visual Reproduction I - Immediate Recall Raw Score; wech_vr2_dr_tot — Total Visual Reproduction II - Delayed Recall Raw Score; wech_vr2_r_tot — Total Visual Reproduction II — Recognition Raw Score: wech_lm1_tot — Total Logical Memory I — Immediate Recall Raw Score; wech_lm2_dr_tot — Total Logical Memory II — Delayed Recall Raw Score, wech_lm2_r_tot — Total Logical Memory II- Recognition Raw Score; wais_digit_tot — Total Digit Span Raw Score (forward+backward+sequencing), wais_symb_tot — Total Symbol Search Raw Score; wais_pic_tot — Total Picture Completion Raw Score; fluency_b tot Category Test Raw Score; wais_block_Total Block Design Raw Score; mayo_total_score — STMS Total Score; pcog_gen_tot_score — PROMIS Applied Cognition - General Concerns Short Form 8a; pcog_exec_tot_score — Neuro-QOL Applied Cognition - Executive Function.

benefits (36–38). While strength measures are important and have been extensively reported in the CP population, there is no evidence supporting the association between cognitive function and HGS in adults with CP. Many studies focus on whether strength and cognition impact certain areas, such as quality of life and mortality, but very few studies focus on relating HGS and cognition (39, 40). As such, this

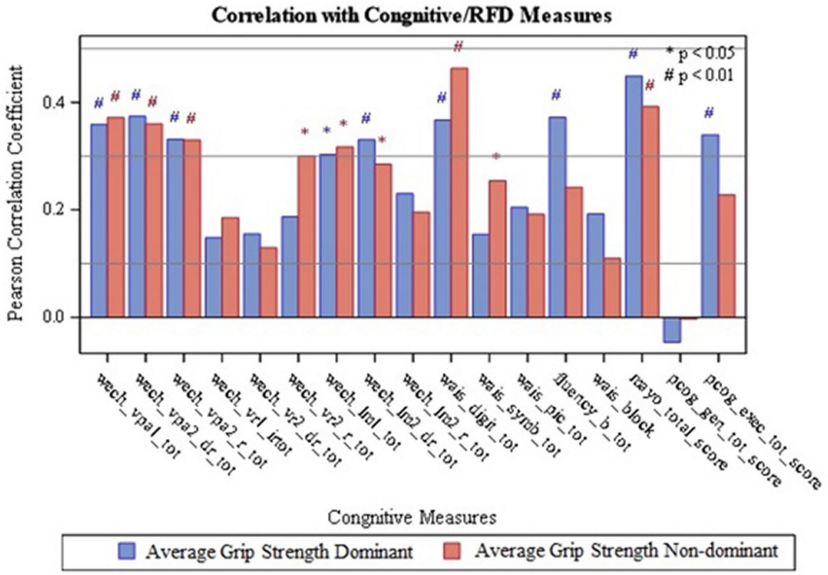

FIGURE 3
Correlation of Grip strength with Cognitive Measures; wech_vpal_tot — Total Visual Paired Associates I — Immediate Recall Raw Score; wech_vpa2_dr_tot — Total Verbal Paired Associates II-Delayed Recall Raw Score; wech_vpa2_r_tot — Total Verbal Paired Associates II- Recognition Raw Score; wech_vrl_irtot — Total Visual Reproduction I — Immediate Recall Raw Score; wech_vr2_dr_tot — Total Visual Reproduction II - Delayed Recall Raw Score; wech_vr2_r_tot — Total Visual Reproduction II — Recognition Raw Score; wech_lm1_tot — Total Logical Memory I- Immediate Recall Raw Score; wech 1m2_dr_tot — Total Logical Memory II — Delayed Recall Raw Score; wech_lm2_r_tot — Total Logical Memory II — Recognition Raw Score; wais_digit_tot — Total Digit Span Raw Score (forward+backward+sequencing); wais_symb_tot — Total Symbol Search Raw Score, wais_pic_tot - Total Picture Completion Raw Score; fluency_b_tot — Category Test Raw Score; wais_block — Total Block Design Raw Score; mayo_total_score — STMS Total Score: pcog_gen_tot_score — PROMIS Applied Cognition - General Concerns Short Form 8a; pcog exec_tot_score — Neuro-QOL Applied Cognition-Executive Function.

study is original and innovative in extending the knowledge of current literature by focusing on grip strength, RFD, and cognitive function outcomes in ambulatory adults with CP (see Table 3)

Another major finding from this study is related to the non-dominant Peak RFD. This study revealed that compared to dominant Peak RFD, MVIC, RFD50, and HGS, non-dominant Peak RFD had the second strongest correlations and the highest number of correlations with all the cognitive function tests (WMS/STM, WAIS-IV, and PROMIS®). Furthermore, upon performing the multi-variable linear regression using the backward selection method, dominant Peak RFD, non-dominant HGS, MVIC, and RFD50 were taken out of the model, revealing that Peak RFD on the non-dominant side was the only statistically significant predictor variable that correlated with the cognitive assessment variables. These results suggest that Peak RFD on the non-dominant side is a better predictor of cognitive function compared to all other strength assessment variables, as it is the strongest predictor variable correlated with cognitive function, and Peak RFD is correlated with a broad spectrum of cognitive domains. Similar findings have been reported in the literature, as Moreau et al. (14) also found that Peak RFD on the non-dominant side correlated with functional ability in individuals with CP. An explanation as to why these results were observed could be due to a hierarchical relationship among performance measures used to characterize physical and cognitive function. From the General Systems Performance Theory model of human performance developed by Kondraske (41, 42), higher-level physical and cognitive tasks, such as walking and information processing speed, respectively, require sufficient amounts of more basic elements of human performance, such as strength or speed, to achieve a specified level of performance in the higher-level task. The theory further suggests that higher-level task performance may be limited by any one of the more basic performance "resources" such as strength, balance, and coordination, suggesting that it is the weaker or less dominant side that more greatly influences the overall task performance (41, 42). When applying these theories to the study findings, we believe Peak RFD shows a stronger correlation with cognitive function outcomes compared to the HGS because it reflects the subject's ability to accomplish two fundamental human tasks, force production and rate (speed) of force production simultaneously, whereas HGS only reflects force production ability without regard to how quickly the force can be applied or removed. For individuals with CP, who have greater challenges with fine motor control and characteristically may have greater difficulty with complex and high-level tasks, overall cognitive performance may be better characterized by RFD than HGS, and subsequently may be a more robust screening tool than the unidimensional assessment provided by HGS test.

Regardless, our results reveal that compared to HGS, non-dominant Peak RFD has a stronger correlation with cognitive function, especially with cognitive tests that required mental speed and attention. This may indicate that non-dominant RFD has the potential as a biomarker or index for cognitive decline. In the literature, adults with CP are showing signs of accelerated aging (2, 43) such as developing secondary health conditions earlier in life (2–5). We also previously showed that several neurocognitive functions were at comparable levels between the two groups (2). To identify these changes earlier, we would need precise and accurate

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TABLE 3 Overall summary of Mean (SD) data for subgroups.

Variable name	*N*	Mean±SD	Mean(SD), Females (*N*=32)	Mean(SD), MALES (*N*=25)	Mean(SD), BILATERAL CP (*N*=35)	Mean(SD), Unilateral CP (*N*=22)
Age	57	24.3 ± 5.3	24.31 ± 6.67	24.20 ± 2.96	24.11 ± 4.82	24.50 ± 6.17
Years of education (highest year of school completed)	57	13.8 ± 2.4	13.66 ± 2.22	13.88 ± 2.57	13.63 ± 2.07	13.95 ± 2.80
Weight (kg)	57	64.2 ± 15.7	60.59 ± 11.93	68.81 ± 18.75	64.44 ± 16.14	63.80 ± 15.33
Height (in)	57	162.8 ± 11.5	156.36 ± 8.49	171.09 ± 9.55	161.75 ± 12.33	164.53 ± 10.23
Body Mass Index (BMI)	57	24.2 ± 4.9	24.87 ± 5.13	23.23 ± 4.42	24.66 ± 5.29	23.34 ± 4.08
RFD 0–30 ms slope Non-Dominant Leg	57	101.8 ± 78.5	92.87 ± 73.94	113.22 ± 84.13	96.36 ± 71.45	110.43 ± 89.68
RFD 0–50 ms slope Non-Dominant Leg	57	107.3 ± 82.4	96.29 ± 75.47	121.29 ± 90.13	105.44 ± 79.12	110.16 ± 89.21
RFD 0–100 ms Slope Non-Dominant Leg	57	108.0 ± 83.7	97.63 ± 80.12	121.30 ± 87.81	108.31 ± 82.97	107.54 ± 86.69
RFD 0–200 slope Non-Dominant Leg	57	107.4 ± 81.8	94.11 ± 73.17	124.47 ± 90.26	107.49 ± 76.59	107.32 ± 91.29
RFD 0–100 ms slope Dominant Leg	53	152.0 ± 119.3	137.04 ± 112.26	171.45 ± 127.79	121.34 ± 104.61	198.65 ± 127.50
RFD 0–200 slope Dominant Leg	53	137.3 ± 93.6	120.01 ± 86.88	159.78 ± 99.01	117.80 ± 90.62	166.94 ± 92.20
RFD 0–30 ms slope Dominant Leg	53	149.6 ± 135.3	132.89 ± 121.00	171.34 ± 151.97	110.85 ± 101.85	208.60 ± 159.57
RFD 0–50 ms slope Dominant Leg	53	156.8 ± 133.0	138.60 ± 118.30	180.56 ± 149.43	120.48 ± 108.60	212.18 ± 149.64
Total Visual Paired Associates I – Immediate Recall Raw Score	57	29.9 ± 15.5	30.88 ± 14.00	28.56 ± 17.48	31.23 ± 15.35	27.68 ± 15.89
Total Verbal Paired Associates II – Delayed Recall Raw Score	55	9.1 ± 4.2	9.16 ± 3.84	9.13 ± 4.77	9.52 ± 4.39	8.59 ± 4.01
Total Verbal Paired Associates II – Recognition Raw Score	55	36.4 ± 6.2	37.35 ± 4.54	35.17 ± 7.73	36.97 ± 4.95	35.55 ± 7.71
Total Visual Reproduction I – Immediate Recall Raw Score	57	29.5 ± 10.2	33.00 ± 7.61	25.08 ± 11.46	29.23 ± 9.99	30.00 ± 10.75
Total Visual Reproduction II – Delayed Recall Raw Score	57	22.5 ± 11.7	26.56 ± 10.03	17.28 ± 11.80	21.34 ± 11.27	24.32 ± 12.40
Total Visual Reproduction II – Recognition Raw Score	57	5.2 ± 1.8	5.69 ± 1.45	4.48 ± 2.00	5.14 ± 1.85	5.18 ± 1.76
Total Logical Memory I – Immediate Recall Raw Score	57	26.2 ± 9.7	27.41 ± 8.12	24.56 ± 11.45	27.63 ± 9.38	23.82 ± 10.03
Total Logical Memory II – Delayed Recall Raw Score	57	22.8 ± 10.2	24.03 ± 8.15	21.12 ± 12.25	23.86 ± 9.64	21.00 ± 10.93
Total Logical Memory II – Recognition Raw Score	56	22.7 ± 3.8	23.44 ± 3.37	21.79 ± 4.15	23.06 ± 3.01	22.23 ± 4.76
Total Digit Span Raw Score (forward+backward+sequencing)	56	23.1 ± 7.2	23.13 ± 5.15	23.08 ± 9.36	23.91 ± 6.46	21.86 ± 8.17
Total Number Correct	55	24.0 ± 10.3	26.03 ± 10.28	21.26 ± 9.88	22.59 ± 10.41	26.38 ± 9.91
Total Symbol Search Raw Score	55	22.6 ± 10.8	24.97 ± 10.40	19.35 ± 10.68	20.94 ± 11.03	25.33 ± 10.06
Total Picture Completion Raw Score	57	9.9 ± 4.0	10.44 ± 3.77	9.32 ± 4.31	9.60 ± 4.05	10.50 ± 3.99
Overall Total words F + S + A	55	32.0 ± 16.0	31.78 ± 14.07	32.26 ± 18.62	32.06 ± 12.88	31.86 ± 20.36
Total Block Design Raw Score	56	27.8 ± 15.5	31.06 ± 13.98	23.33 ± 16.60	23.94 ± 14.89	34.10 ± 14.71
STMS total score	57	30.8 ± 5.0	31.80 ± 3.66	29.44 ± 6.21	31.11 ± 4.77	30.20 ± 5.50
Total Score of PROMIS Applied Cognition	57	16.8 ± 7.4	15.31 ± 6.82	18.64 ± 7.78	16.54 ± 5.73	17.14 ± 9.58
Total score of executive function of Neuro-QOL Applied Cognition	57	48.8 ± 11.5	50.72 ± 10.92	46.28 ± 12.05	48.17 ± 11.52	49.73 ± 11.78

indicators to help monitor or measure changes in performance as individuals with CP age. While HGS is unidimensional as a screening tool (8, 9, 11, 12), peak RFD's ability to describe both the magnitude and speed of force development may be a more robust and comprehensive tool, and better suited for screening for cognitive decline and secondary health conditions; especially so in individuals with CP, which uniquely affects physical and muscular health, necessitating more complex assessments/instruments (20). RFD is unique in that it is a quantitative measure that also directly describes an individual's functional ability and task performance (18, 20).

Previous studies support the cognitive and motor function relationship in individuals with cerebral palsy (44, 45). Rooijen et al. (44) showed that the cognitive and motor predictors were positively correlated with each other in a sample of children with CP. Their study showed that word decoding task and fine motor skills were the strongest predictors of arithmetic performance among children with CP. This pioneering work by Rooijen's group combined with the results of our study will help future research to evaluate the relationships between measures of physical strength and cognitive function in other populations. Specifically, an idea for future research into RFD and cognitive function amongst the pediatric and pre-teenager CP populations could give valuable insight into the growth and development of individuals with CP as they transition to adult healthcare. Thus, the authors would be interested in furthering this research with other tests of cognitive function, physical performance, and quality of life (44, 45).

An earlier study by our research team (43) supported the association between mobility performance and participation and executive function in adults with CP. Therefore, integrating screening and measures that capture early changes in functional performance, may assist practitioners in the identification of key functional deficits associated with diseases as well as premature cognitive decline in adults with CP. Thus, healthcare practitioners should adopt screenings that can identify early markers associated with physical and cognitive frailty to intervene and prescribe personalized interventions that will increase and include individuals with CP in physical activities. Their participation in these interventions could improve their cognitive and motor function and could assist and increase the quality of life of individuals with CP.

By screening for changes in performance that may be linked to deficits in function and premature cognitive aging in adults with CP, clinicians can develop targeted interventions to increase participation in physical activities, which may simultaneously improve cognitive outcomes and more fully engage individuals with CP in their communities. This group would be interested in exploring further investigations into relationships between measures of physical strength and cognition in other populations. Specifically, an idea for future research into RFD and cognition amongst the pediatric and teen CP populations could give valuable insight into the growth and development of individuals with CP. Previous studies have shown the relationship between word development, fine motor skill development, and arithmetic performance in children with CP; the authors would be interested in furthering this research with other tests of cognitive function and physical performance (44).

5. Limitations

A limitation of the current investigation is that while the parent CPAT study is relatively large for a longitudinal functional outcome study of adults with CP, the cross-sectional adult cohort represents a sample that is relatively small and diverse for determining prevalence across the CP population. Due to the cross-sectional study nature, we could not conclude the directions of causality for the associations detected. Larger sample size with multiple time points would address this limitation and could possibly reveal differences in key markers associated with premature disease and aging. Another limitation of this study is the generalizability of the study. Since the parent study focused on gait performance and secondary disease development in individuals who are ambulatory, individuals at GMFCS levels IV and V were underrepresented. As such, further validation of these findings would require similar investigation in individuals with CP who rely primarily on wheeled mobility. Another limitation would be how the dominant side is defined. Since dominance was determined by asking participants with bilateral CP, there could be errors in which dominance was identified. To address this issue, a more rigorous definition of defining the dominant side should be used in future studies. Lastly, owing to the pilot and exploratory nature of this study, we did not control for multiple testing. These considerations suggest that while noteworthy, this work is a starting point for additional research evaluating RFD in a broader sample of adults with CP.

6. Conclusion

This study found an association between RFD, HGS, and cognitive function in ambulatory adults with CP. Upon comparison between RFD and HGS, Peak RFD was correlated with a higher number of cognitive function measures and had a stronger correlation with common cognitive tests than the HGS. Because RFD is a higher-level functional task than HGS and provides information about both magnitude and rate of force production, it could be used as a promising screening tool for measuring both functional and cognitive decline in this vulnerable population.

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 Colorado Multiple Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PH, TR, ZP, and JC: conceptualization methodology. ZP: software and formal Analysis. PH, AT, ZP, TR, and JC: validation, investigation, writing – Review & Editing, and visualization. PH and AT: data Curation and writing – original draft preparation. PH and JC: supervision, project administration, and funding acquisition. 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/fmed.2023.1080022/full#supplementary-material

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