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Interprofessional approaches for the management of chronic diseases

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Interprofessional approaches for the management of chronic diseases

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Table of contents

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Editorial: Interprofessional approaches for the management of chronic diseases

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Editorial on the Research Topic
Interprofessional approaches for the management of chronic diseases

Background

Chronic diseases, as long-lasting conditions that require ongoing medical attention, can often be controlled, but not cured, and tend to limit daily life activities. These are the leading causes of death and disability, accounting for nearly 75% of all deaths globally (1), and represent the main drivers of increased healthcare costs and decreased productivity. Clinical management of chronic conditions such as cardiorespiratory diseases, stroke, mental health issues, diabetes, or cancer, among others, require an interdisciplinary, collaborative, and person-centered workforce (2). Common modifiable risk factors, including dietary habits, lack of physical activity, and tobacco and alcohol use, are responsible for most of these diseases. Urgent action is needed to support innovative and effective preventive strategies to reduce the associated socioeconomic burden. Toward this, aspects related to promote self-management and self-efficacy can help patients to successfully cope with their conditions and improve their general wellbeing and quality of life.

Research

This editorial summarizes the contributing articles to the Research Topic "*Interprofessional Approaches for the Management of Chronic Diseases*". We received a total of 23 manuscripts and one manuscript summary and were able to approve thirteen of them for publication. Out of these papers, eight were original research, two were study protocols, one was an umbrella review, another was a retrospective analysis, and the last paper was a co-creation workshop.

Overall, the included studies highlighted the multifaceted aspects of chronic diseases in diverse populations and clinical settings, reflecting the importance of prevention and individual self-management and the complex relationship

between various biopsychosocial factors in the development and persistence of chronic diseases.

Three studies including participants with chronic musculoskeletal conditions assessed the impact of self-efficacy as an outcome measure. Perez-Dominguez et al. translated and culturally adapted the Spanish Version of the Pain Self-Efficacy Questionnaire. This study analyzed 107 patients with rotator cuff injuries and found the questionnaire had good psychometric properties, with high validity, test-retest reliability, and internal consistency. In 68 outpatients with rheumatoid arthritis, a longitudinal study developed by Hayashi et al. observed if discordances between patients and physicians in global assessment may influence pain-related outcomes at 9 years of follow-up. They found that patients who showed a worse perception in their global assessment, in comparison to physicians assessment at baseline, reported higher pain intensity and pain catastrophizing, and lower quality of life and pain self-efficacy at the follow-up. Further, a clinical trial conducted by Fu et al. evaluated the effects of a multidisciplinary treatment plan in patients who received surgery for cervical spondylosis. This study highlighted the benefits of this type of interprofessional treatment in improving important aspects such as neck disability, self-efficacy, quality of life and patient satisfaction, compared with routine care.

Two of the papers were developed as study protocols. Huon et al. proposed a secondary study in primary care by addressing the combined effect of an interprofessional intervention delivered by general practitioners and community pharmacists to deprescribe benzodiazepines and related drugs in older adults. For this purpose, the pharmacists will be trained in motivational interviewing and the impact of the intervention will be measured in terms of acceptability, appropriateness, cost, and fidelity. The second was a protocol of a randomized controlled trial conducted by Martínez-Miranda et al. that aims to evaluate the efficacy of a physiotherapy-focused individualized program using pain neuroscience education and graded exposure to movement in breast cancer survivors. The ultimate goal of this approach was to reinforce individual self-management and empower women throughout cancer care.

A comprehensive overview of current evidence on integrative medicine treatments, e.g., diet, mind-body therapies, and herbal medicine, for chronic, inflammatory, and autoimmune diseases such as rheumatoid arthritis, spondylarthritis, and gout, was provided by Lin et al.. After including 52 reviews, this umbrella review concluded that exercise was effective and, therefore, should be prescribed for this population. Chang et al. delved into nurse-led case management in addition to usual care in 96 adults with rheumatoid arthritis. Results from the study demonstrated that the multimodal approach was helpful to reduce pain and fatigue, offering a new perspective to provide tailored care for these individuals. From a preventive viewpoint, Zhang et al. explored the predictive role of visceral adipose tissue in people with osteoarthritis using a two-sample Mendelian randomization method. Their findings suggested that decreasing the accumulation of visceral adipose tissue could reduce the incidence of osteoarthritis, whether at the hip, knee, or spine. In a sample of 112 individuals with ankylosing spondylitis, Cortes-Rodríguez et al. investigated the impact of foot health on the quality of life. They observed that adults with ankylosing spondylitis present lower quality of life concerning foot health and overall wellbeing compared to healthy population, which highlights the importance of a podiatrist involvement for regular foot checks.

In a retrospective analysis of 411 patients with fibromyalgia, Rivera et al. investigated the possible association of different comorbidities with functionality, pain, and depression in this cohort. Obesity was the most robust significant predictor since obese patients were twice more likely to have poorer functional status. The authors suggest that it is important to address obesity in people with fibromyalgia in order to manage this condition. Kassaw et al. conducted a hospital-based cross-sectional study to investigate whether medication regimen complexity was associated with medication adherence in patients with multimorbidity. They found that nearly half of the 416 participants had low medication adherence, and that medication complexity was negatively associated with medication adherence, thus healthcare providers should develop effective strategies to improve this lack of adherence to pharmacological treatments in people with multiple chronic diseases. Exercise is a key strategy for non-communicable chronic diseases, but the problem of low levels of physical activity in adults with intellectual disability is well-recognized. Kwan et al. conducted a multicentre controlled trial to examine the effectiveness of a video-based exercise programme in promoting physical activity in this population. They included 160 participants who underwent an 8-week exercise intervention and observed positive changes in the physical condition. Finally, chronic pain, a health condition that requires a biopsychosocial approach and a person-centered interprofessional care, was investigated by Berryman et al.. These authors have developed a co-creation workshop to generate ideas about how to provide evidence-based and efficient care in a pediatric chronic pain service. Thirty-four multidisciplinary skateholders participated in this collaborative activity and provided a launch pad for innovative clinical and research ideas. This study highlights the importance of creating interprofessional networks to improve the management of chronic conditions.

Summary

To summarize, chronic diseases have a multifactorial etiology, which makes them difficult to manage in the clinical setting. Strengthening the collaboration among healthcare professionals, while always respecting individual differences among professionals and patients, is likely the best approach to provide an evidence-based response to the preventive and therapeutic treatment of chronic diseases.

Author contributions

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Conflict of interest

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Discordance of global assessment between the patients and physicians predicts 9-year pain-related outcomes in rheumatoid arthritis patients

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Introduction: Perspectives regarding the disease state often differ between patients with rheumatoid arthritis (RA) and physicians. The aim of the present longitudinal cohort study was to investigate the impact of the discordance in global assessments between patients and physicians on 9-year pain-related outcomes in patients with rheumatoid arthritis.

Method: Sixty-eight consecutive outpatients with rheumatoid arthritis on their first visit to a tertiary center were included. Baseline measurements included demographic data, drugs used, disease activity, and a modified Health Assessment Questionnaire (mHAQ). Discordance in global assessment between patients and physicians at baseline was defined as 10 mm higher in the patient global assessment (PGA) than in the physician global assessment. A 9-year follow-up assessment included pain intensity, the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) scale, Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS), Pain Disability Assessment Scale (PDAS), and Pain Self-Efficacy Questionnaire (PSEQ).

Results: The number of patients with discordance was 26 (38%) in 68 patients. Patients with a 10 mm higher PGA than the physician global assessment at baseline measurements had significantly worse pain intensity, PCS score, PSEQ score, and EQ-5D-3L score measurements at the 9-year follow-up than those with concordance. A higher mHAQ score and 10 mm higher PGA at baseline were significantly independently associated with the EQ-5D-3L scale score and pain intensity at the 9-year follow-up.

Conclusion: This longitudinal cohort study suggested that discordance in global assessment between patients and physicians modestly predicted worse 9-year pain-related outcomes in patients with rheumatoid arthritis.

KEYWORDS

arthritis rheumatoid, communication, physicians, prognosis, quality of life

1. Introduction

Rheumatoid arthritis (RA) is classified based on joint distribution, serology, symptom duration, and acute-phase reactants according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (1). RA has an incidence of 0.5–1%, affects women two to three times more often than men, and occurs at any age (2, 3). RA involves chronic inflammation of the synovial membrane, with attendant worsening in physical function, cumulative comorbid risk, ability to work, and quality of life (2–7). The experience of pain in RA is multifactorial, and it can be due to structural changes in the joint as well as pain-related psychological factors (8). Treatment options include education complemented by physical activity and exercise, psychological and social interventions, sleep hygiene education, weight management, orthotics, pharmacological and joint-specific treatment options such as a local injection, and interdisciplinary treatment (9). The prognosis factors in RA are gender, disease activity, psychological factors, and education level (10–12). Routine care for RA includes a comprehensive assessment of specific symptoms (13, 14).

The global assessment of disease by patients and physicians constitutes a part of the disease activity measures for RA (1). Interestingly, the perspective regarding disease state often differs between patients and physicians (15, 16). The frequency of discordance in global assessments between patients and physicians is 36–51% (17). The cutoff defining discordance is inconsistent among countries and studies, ranging from 5 mm to 30 mm on a 0–100 mm visual analog scale (17). Forty-five percent of Asian patients with RA showed a discordance of 10 mm higher in patients than physicians (18). The discordance is influenced by the tender joint count, swollen joint count, pain, fatigue, health literacy, and depressive symptoms (15–18). One longitudinal study showed that discordance before treatment was significantly associated with pain, disease activity, and activity of daily living after treatment (18). This suggests the importance of discordance in treatment outcomes in patients with RA, although the association was based on a univariable test over 12 months. The impact of discordance on treatment outcomes should be considered along with confounding factors, including age and disease activity. However, no studies have evaluated the association between the discordance in global assessment between patients and physicians and long-term treatment outcomes in patients with RA.

This longitudinal cohort study aimed to investigate the hypothesis that discordance in global assessments between patients and physicians predicts worse 9-year pain-related outcomes in patients with RA.

Abbreviations: RA, rheumatoid arthritis; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level; DAS28-ESR, Disease Activity Score 28 joint count and erythrocyte sedimentation rate; PGA, patient global assessment of disease activity; mHAQ, modified Health Assessment Questionnaire; NRS, Numerical Rating Scale; HADS, Hospital Anxiety and Depression Scale.

2. Materials and methods

2.1. Study design

Baseline measurements were assessed face-to-face during the first visit to a tertiary center by a doctor. Follow-up measurements were assessed by mail survey 9 years after the first visit.

The sample size was calculated using the G*Power software (version 3.1.9.2; Franz Faul, Kiel University, Kiel, Germany). The minimum number of subjects was estimated to be 68 for an α-level of 0.05, and a power (1–β) of 0.80 (18).

All methods of the present longitudinal cohort study were performed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (19). This study was approved by the Research Ethics Committee of Hayaishi Hospital and all the patients provided written informed consent for this study.

2.2. Participants

Participants were purposively and consecutively recruited during their doctor visits at our tertiary center between November 2012 and February 2013. Inclusion criteria were as follows: (1) older than 20 years of age, (2) first visit to our tertiary center, and (3) a diagnosis of established RA, more than 1 year of disease duration, by a medical doctor, based on the American College of Rheumatology/European League Against Rheumatism classification criteria (1).

Exclusion criteria were as follows: (1) cancer-related pain, neurological disease, and evidence of bone fractures; (2) recent surgery within the past 6 months; (3) consuming medication associated with dementia; (4) poor Japanese language comprehension; and (5) not returning or not completing the follow-up measurement by mail. All inclusion and exclusion criteria were assessed by the referring physicians.

2.3. Treatment

All patients received the usual treatment following recommendations from the clinical practice guidelines (20). Treatment in the clinic was performed at least once every 3 months by orthopedics and physical therapists. The treatment included advice to remain active with education and reassurance as first-line care. If patients needed second-line care, non-pharmacological

treatment was attempted before pharmacological treatment. Pharmacological treatments were administered at the lowest effective dose for the shortest period possible.

2.4. Baseline measurement

All baseline measurements were collected during the first visit to the tertiary center. Demographic data included age, sex, body mass index, disease duration of RA, Steinbrocker-class classification (21), and drug use (non-steroidal anti-inflammatory drugs, glucocorticoids, methotrexate, and biological agents).

Disease activity was assessed using the Disease Activity Score 28 joint count, erythrocyte sedimentation rate (DAS28-ESR), and Simplified Disease Activity Index (22). Calculation of the DAS28-ESR and Simplified Disease Activity Index was used in the outcome parameters: tender joint count and swollen joint count based on a 28-joint assessment, patient global assessment of disease activity (PGA) with a visual analog scale of 0–100 mm, physicians global assessment of disease activity with a visual analog scale of 0–100 mm, C-reactive protein, and ESR. The questions of global assessment of disease activity are "How do you estimate your disease activity?" The discordance of the global assessment between patients and physicians was defined as a 10 mm higher PGA than in the physician global assessment (17, 18).

Patient satisfaction regarding the activities of daily living was assessed using a modified Health Assessment Questionnaire (mHAQ) (23). The mHAQ score was calculated as the mean of the scores for eight activities of daily living.

2.5. Follow-up measurement

All follow-up measurements were performed by mail 9 years after the first visit. The sender and return addresses were tertiary centers. The patients were instructed by a letter included in the questionnaire package.

Quality of life and pain intensity were the primary outcome measures. Quality of life was measured using the European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) scale, a generic scale used worldwide that assesses health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (13, 14). Each domain was assessed using a single question with three possible responses: no problems, problems, and serious health problems. The combination of all the possible dimensions and levels resulted in 243 unique health states. It can be converted into EQ-5D-3L scale scores ranging from −0.111 to 1.00. A score of 0 represents death, and 1.00 represents a state of full health. Pain intensity was measured using a 0–10 pain numerical rating scale (NRS) (24). The scale, which ranged from 0 to 10, was used as an indicator of the average level of pain during the day. The scale was labeled at the anchor points, with 0 indicating "no pain" and 10 indicating "worst possible pain."

Secondary outcomes were measured using the Japanese version of the following questionnaires: Pain Catastrophizing Scale (PCS) (25, 26), Hospital Anxiety and Depression Scale (HADS) (27, 28), Pain Disability Assessment Scale (PDAS) (29), Pain Self-Efficacy Questionnaire (PSEQ) (30, 31), and working status.

The PCS consists of 13 items (25, 26). The participants rated how frequently they experienced emotions such as rumination (e.g., "I keep thinking about how much it hurts"), magnification (e.g., "I wonder whether something serious may happen"), and helplessness (e.g., "There is nothing I can do to reduce the intensity of the pain"). The total PCS score ranged from 0 to 52, with higher scores indicating higher levels of catastrophizing.

The HADS was designed to assess two separate dimensions: anxiety and depression (27, 28). The HADS consists of 14 items, and the anxiety and depression subscales each include seven items. A four-point response scale (from 0 representing the absence of symptoms to 3 representing maximum symptoms) was used, with possible scores for each subscale ranging from 0 to 21.

The PDAS assesses the degree to which chronic pain interferes with various daily activities during the past week (29). The PDAS includes 20 items reflecting pain interference in a broad range of daily activities, and respondents indicate the extent to which pain interferes. Scores on the total PDAS ranged from 0 to 60, with higher scores indicating higher levels of pain interference.

The PSEQ scores were designed to assess the degree of confidence in performing several activities despite pain (30, 31). The PSEQ consisted of 10 items. The total PSEQ score ranges from 0 to 60, with lower scores indicating lower levels of self-efficacy for functioning despite the pain.

2.6. Statistical analysis

All continuous data are expressed as means and standard deviations. The normality of the distribution was evaluated using the Shapiro-Wilk test for the continuous variables. Univariate and multivariate tests were used for comparisons. The categorical variables included dummy variables. The correlation between variables was analyzed using Pearson's correlation coefficient test. Multivariate analysis was used to investigate variables with $p < 0.1$ in the univariable analysis. Four variables were analyzed in the multivariable analysis for the EQ-5D-3L scale score: mHAQ, 10 mm PGA higher, biological agents, and Simplified Disease Activity Index scores. Three variables were analyzed in the multivariate analysis for Pain-NRS value: mHAQ, 10 mm PGA higher, and biological agents. The multicollinearity of the variables was also assessed (correlation coefficient < 0.9).

Data were analyzed using SPSS (version 27.0 for Microsoft Windows; SPSS, Chicago, IL, USA). A p-value of < 0.05 was considered to be statistically significant.

3. Result

The survey response rate was 63% (n = 68 of 107). The patient characteristics are shown in **Table 1**. The mean patient age was 62 years. Of the 68 patients, 62 (91%) were women. The mean PGA value was 42.55 mm, while the mean physician global assessment value was 35.13 mm (7.42 mm higher in the patient than the physician). The physician's global assessment value was significantly correlated with the mean PGA value with a moderate correlation coefficient (r = 0.506, $p < 0.001^*$) (**Figure 1**). The number of patients with 10 mm higher PGA than the physician's global assessment was 26 of 68 (38%).

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TABLE 1 Comparison of data between patients with concordance and those with 10 mm PGA higher than physician global assessment.

	Overall (n = 68)	Concordance (n = 42)	10 mm PGA higher (n = 26)	Odds ratio (95% CI)	p-value
Baseline					
Age (years)	62.69 (10.46)	62.57 (10.09)	62.88 (11.24)	0.313 [−4.940 to 5.566]	0.906
≤49 [n (%)]	9 (13%)	5 (11%)	4 (15%)	0.035 [−0.136 to 0.206]	0.686
50–59 [n (%)]	14 (20%)	8 (19%)	6 (23%)	0.040 [−0.164 to 0.245]	0.695
60–69 [n (%)]	28 (41%)	20 (47%)	8 (30%)	−0.168 [−0.414 to 0.077]	0.175
≥70 [n (%)]	17 (25%)	9 (21%)	8 (30%)	0.093 [−0.124 to 0.311]	0.395
Women [n (%)]	62 (91%)	38 (90%)	24 (92%)	0.018 [−0.125 to 0.162]	0.799
Body Mass Index (kg/m^2)	22.4 (3.3)	22.8 (3.4)	21.8 (3.2)	−0.941 [−2.622 to 0.741]	0.268
Disease duration (years)	11.57 (11.14)	12.73 (11.42)	9.692 (10.61)	−3.046 [−8.591 to 2.499]	0.277
1–2 [n (%)]	19 (27%)	12 (28%)	7 (26%)	−0.016 [−0.243 to 0.210]	0.885
3–9 [n (%)]	19 (27%)	9 (21%)	10 (38%)	0.170 [−0.053 to 0.393]	0.132
10–19, n (%)	15 (22%)	9 (21%)	6 (23%)	0.016 [−0.193 to 0.226]	0.876
≥20 [n (%)]	15 (22%)	12 (28%)	3 (11%)	−0.170 [−0.376 to 0.035]	0.103
Steinbrocker class [n (%)]				−0.068 [−0.418 to 0.282]	0.700
1	46 (67%)	27 (64%)	19 (73%)	0.088 [−0.148 to 0.324]	0.459
2	16 (23%)	11 (26%)	5 (19%)	−0.070 [−0.283 to 0.144]	0.518
3	5 (7%)	4 (9%)	1 (3%)	−0.057 [−0.188 to 0.074]	0.391
4	1 (1%)	0 (0%)	1 (3%)	0.030 [−0.022 to 0.099]	0.206
Drugs in use [n (%)]					
Non-steroidal anti-inflammatory drugs	38 (55)%	24 (79%)	14 (53%)	−0.033 [−0.284 to 0.218]	0.794
Glucocorticoids	33 (48%)	18 (24%)	15 (57%)	0.148 [−0.102 to 0.398]	0.241
Methotrexate	48 (70%)	27 (15%)	21 (80%)	0.165 [−0.062 to 0.392]	0.152
Biologic agents	20 (29%)	11 (46%)	9 (34%)	0.084 [−0.145 to 0.314]	0.466
Tender joint count (number)	3.54 (3.97)	3.61 (4.45)	3.42 (3.13)	−0.196 [−2.193 to 1.801]	0.845
Swollen joint count (number)	2.38 (3.30)	2.69 (3.87)	1.88 (2.04)	−0.806 [−2.453 to 0.842]	0.332
Patient global assessment (PGA) (mm)	42.55 (26.74)	30.45 (24.07)	62.11 (17.97)	31.663 [20.721 – 42.605]	<0.001*
Physician global assessment (mm)	35.13 (24.93)	39.5 (28.38)	28.07 (16.13)	−11.423 [−23.619 to 0.773]	0.066
C-reactive protein (mg/dL)	1.20 (1.91)	1.41 (2.15)	0.85 (1.42)	−0.562 [−1.513 to 0.388]	0.242
ESR (mm/hour)	30.95 (26.44)	31.80 (27.24)	29.57 (25.57)	−2.233 [−15.496 to 11.031]	0.738
DAS28-ESR (points)	3.97 (1.23)	3.85 (1.28)	4.16 (1.13)	0.306 [−0.307 to 0.919]	0.322
Simplified Disease Activity Index (points)	14.90 (10.09)	14.72 (12.04)	15.18 (5.936)	0.460 [−4.609 to 5.529]	0.857
mHAQ (points)	0.47 (0.59)	0.42 (0.56)	0.56 (0.62)	0.142 [−0.153 to 0.436]	0.341
Nine-year follow-up					
Working [n (%)]	21 (30%)	12 (28%)	9 (34%)	0.060 [−0.173 to 0.294]	0.607
Presence of pain [n (%)]	65 (95%)	39 (16%)	26 (16%)	0.071 [−0.031 to 0.174]	0.168
Knee	38 (55%)	23 (54%)	15 (57%)	0.029 [−0.222 to 0.280]	0.816
Hand	32 (47%)	18 (42%)	14 (38%)	0.110 [−0.141 to 0.361]	0.385
Neck	30 (44%)	18 (42%)	12 (46%)	0.033 [−0.218 to 0.284]	0.794
Back	27 (39%)	15 (35%)	12 (46%)	0.104 [−0.142 to 0.351]	0.400
Foot	25 (36%)	11 (26%)	14 (38%)	0.277 [0.042 – 0.511]	0.021*
Ankle	12 (17%)	8 (19%)	4 (15%)	−0.037 [−0.229 to 0.156]	0.705
Wrist	9 (13%)	6 (14%)	3 (11%)	−0.027 [−0.199 to 0.144]	0.750
Elbow	9 (13%)	5 (11%)	4 (15%)	0.035 [−0.136 to 0.206]	0.686

(Continued)

TABLE 1 (Continued)

	Overall (n = 68)	Concordance (n = 42)	10 mm PGA higher (n = 26)	Odds ratio (95% CI)	p-value
Shoulder	6 (8%)	5 (11%)	1 (3%)	−0.081 [−0.223 to 0.061]	0.262
Pain-NRS (points)	3.29 (2.19)	2.71 (1.97)	4.23 (2.25)	1.516 [0.477 – 2.556]	0.005*
PCS (points)	19.22 (13.49)	15.69 (12.08)	24.92 (13.91)	9.233 [2.851 – 15.614]	0.005*
Rumination (points)	9.17 (5.78)	7.85 (5.41)	11.30 (5.81)	3.451 [0.675 – 6.226]	0.016*
Helplessness (points)	6.01 (5.27)	4.83 (4.90)	7.92 (5.39)	3.090 [0.551 – 5.628]	0.018*
Magnification (points)	4.02 (3.14)	3 (2.66)	5.69 (3.19)	2.692 [1.257 – 4.127]	<0.001*
HADS (points)	10.38 (6.88)	9.52 (6.22)	11.76 (7.74)	2.245 [−1.164 to 5.655]	0.193
Anxiety (points)	4.60 (3.60)	4.14 (3.20)	5.34 (4.12)	1.203 [−0.582 to 2.988]	0.183
Depression (points)	5.77 (3.98)	5.38 (3.88)	6.42 (4.11)	1.042 [−0.940 to 3.024]	0.298
PDAS (points)	18.01 (14.18)	15.73 (11.63)	21.69 (17.15)	5.954 [−1.013 to 12.921]	0.093
PSEQ (points)	37.73 (12.80)	40.21 (11.67)	33.80 (13.73)	−6.412 [−12.674 to −0.150]	0.045*
EQ-5D-3L (points)	0.73 (0.19)	0.77 (0.16)	0.66 (0.23)	−0.110 [−0.206 to −0.014]	0.025*

DAS, Disease Activity Score; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level; ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale; PDAS, Pain Disability Assessment Scale; PGA, Patient global assessment; PSEQ, pain self-efficacy questionnaire. Data from continuous variables are presented as mean (standard deviation). Data for categorical variables are presented as numbers (%). *Significance level was set at <5%.

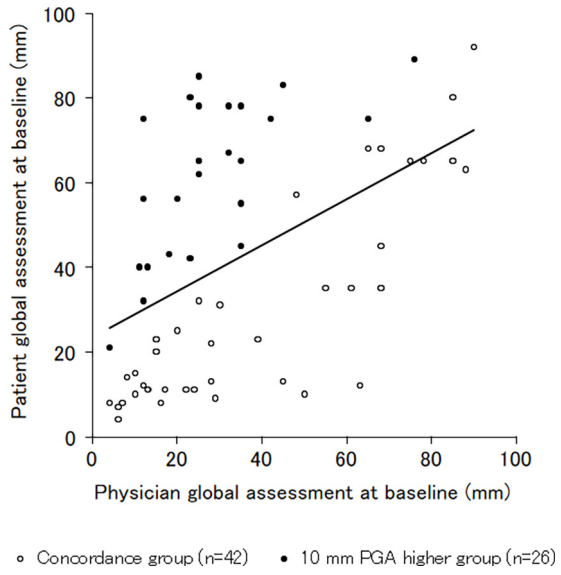

FIGURE 1
Correlation of the patient and physician global assessment. The physician global assessment value was significantly correlated with the mean patient global assessment value, with a moderate correlation coefficient (r = 0.506, p < 0.001). *Significance level was set at <5%.

At the 9-year follow-up measurement, 65 of the 68 patients (95%) experienced pain. The mean scores were 3.29 for Pain-NRS, and 0.73 for EQ-5D-3L at the 9-year follow-up measurement. The patients with a 10 mm higher PGA than the physician global assessment at baseline measurements had significantly worse pain rating scale, PCS, PSEQ, and EQ-5D-3L scores at the 9-year follow-up measurement compared to those with concordance (Table 1; Figure 2). There were significant differences of 1.5 points and 0.11 points in the NRS values and EQ-5D-3L scale scores between groups, respectively.

The correlations of the EQ-5D-3L scale scores and Pain-NRS scores at the 9-year follow-up with the independent variables at baseline are shown in Table 2. The 10 mm higher PGA and mHAQ values were significantly correlated with the EQ-5D-3L scale scores and Pain-NRS values in the univariable analysis.

The results of the multivariate analysis for the EQ-5D-3L scale scores and Pain-NRS values are shown in Table 3. The mHAQ score and 10 mm higher PGA at baseline were significantly independently associated with the EQ-5D-3L scale score and Pain-NRS score at the 9-year follow-up in the multivariable analysis. No multicollinearity was observed for any of the tested independent variables.

4. Discussion

4.1. Overview

The present longitudinal cohort study suggested that discordance in the global assessment between patients and physicians modestly predicted worse 9-year pain-related outcomes in patients with RA. These findings suggest that the presence of discordance between patients and physicians could predict the treatment outcome of patients with RA.

4.2. Discordance between patients and physicians

Many patients are unable to express their disease burdens and treatment goals (32). The patient global assessment is usually worse than the physician global assessment (17). There was moderate discordance between the observed functional disability and self-report questionnaires in patients with RA (33). Increased pain leads to a discrepancy toward worse patient global assessment, while an

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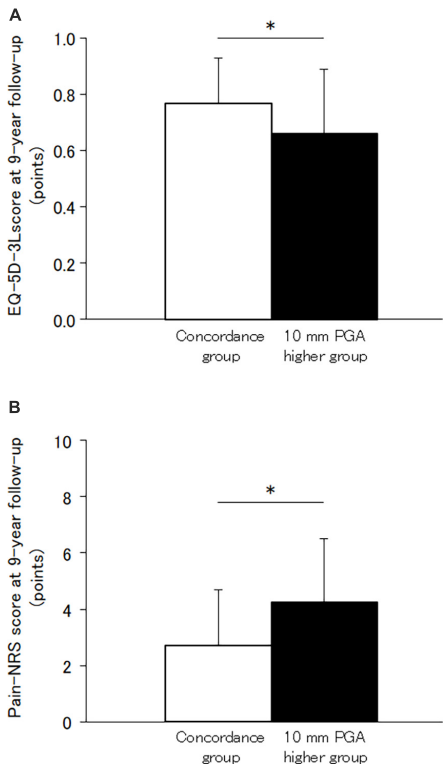

FIGURE 2
Difference of scores between those with concordance and 10 mm PGA higher than physician global assessment. **(A)** EQ-5D-3L score. **(B)** Pain-NRS values. The EQ-5D-3L score and Pain-NRS values at 9-year follow-up measurement were significantly worse in the 10 mm PGA higher group than the concordance group. *Significance level was set at <5%. EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level; NRS, Numerical Rating Scale; PGA, patient global assessment of disease activity.

TABLE 2 Correlations of the EQ-5D-3L scale scores and Pain-NRS value at 9-year follow-up measurement with independent variables at baseline.

	EQ-5D-3L at 9-year follow-up		Pain-NRS at 9-year follow-up	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Baseline				
Age	−0.121	0.326	0.045	0.716
Women	0.049	0.691	0.137	0.266
Body Mass Index	−0.038	0.759	0.097	0.433
Disease duration	−0.207	0.090	0.103	0.402
Steinbrocker class	−0.114	0.356	0.121	0.325
Non-steroidal anti-inflammatory drugs	−0.004	0.972	−0.057	0.646
Glucocorticoids	−0.158	0.199	0.152	0.215
Methotrexate	0.099	0.422	0.013	0.916
Biologic agents	−0.219	0.073	0.209	0.088
Tender joint count	−0.167	0.173	0.162	0.186
Swollen joint count	−0.190	0.120	0.165	0.179
Patient global assessment (PGA)	−0.186	0.129	0.182	0.137
Physician global assessment	−0.044	0.723	−0.012	0.922
10 mm PGA higher	−0.271	0.025*	0.338	0.005*
C-reactive protein	−0.200	0.103	0.189	0.122
ESR	−0.035	0.776	−0.056	0.647
DAS28-ESR	−0.161	0.189	0.145	0.238
Simplified Disease Activity Index	−0.226	0.064	0.199	0.104
mHAQ	−0.492	<0.001*	0.368	0.002*

DAS, Disease Activity Score; EQ-5D-3L, Euro Quality of life-5 Dimensions-3 level; ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; NRS, Numerical Rating Scale; PGA, Patient global assessment. Data were analyzed using Pearson's correlation coefficient test. Categorical variables included dummy variables. The 10 mm PGA higher and mHAQ values were significantly correlated with EQ-5D-3L scale scores and Pain-NRS in the univariate analysis. *Significance level was set at <5%.

increased number of swollen and tender joints lead to a discrepancy toward worse physician global assessment (34). High pain, general health, and C-reactive protein levels before treatment are associated with discordance in assessment between patients and physicians after treatment (35). The number of patients with discordance has either not resolved or has increased over time (18, 35). Physician global assessment is often decreased during treatment, whereas patient global assessment is sometimes unchanged (18). The discordance between the patients and physicians is hypothesized to result in patient dissatisfaction, difficulties regarding treatment decision-making, poor adherence, and worse treatment outcomes (17, 34, 35). The patients with discordance had significantly worse pain and pain-related psychological factors at the 9-year follow-up measurement in the present study. A combination of subjective and objective clinical measurements is useful for patients with RA (1). This information may help in the treatment and prognosis of patients with RA.

4.3. Physician-patient communication

Physician-patient communication is associated with accurate care as well as with more satisfied patients (36). The clinical expectations for analgesia between patients and physicians are in agreement, with some discordance (37). Most physician-patient communication focuses on symptoms and treatment options rather than the patients' perspective of quality of life (32). RA remissions of tenderness, swelling, and pain are consistently associated with physician assessment but not patient-reported outcomes (38). Physicians should initiate more detailed discussions with patients regarding expectations and carefully explain treatment-to-target approaches and other goal-setting strategies (32). Specifically, patients with inadequate health literacy are likely to report poor communication in the domains of general clarity, explanation of their condition, and processes of care (39). Physician-patient communication is expected to be a shared control in patients with adequate health literacy; however, physician dominance and patient passivity sometimes occur in patients with inadequate health literacy (40). The sex of the patient and physician could impact the physician-patient interaction and its outcomes (41). Discordance was more common in female patients, regardless of the sex or age

TABLE 3 Multivariable analysis.

Independent variables	*B*	SE	Beta	*p*-value	R^2
A) Analysis for EQ-5D-3L scale at 9-year follow-up measurement					
mHAQ	−0.159	0.033	−0.497	<0.001*	0.308
10 mm PGA higher	−0.087	0.042	−0.212	0.043*	
Biologic agents				0.714	
Simplified Disease Activity Index				0.822	
B) Analysis for Pain-NRS at 9-year follow-up measurement					
mHAQ	1.232	0.409	0.328	0.004*	0.230
10 mm PGA higher	1.411	0.488	0.314	0.005*	
Biologic agents				0.588	

B, non-standard regression coefficient; Beta, standardized regression coefficient; EQ-5D-3L, Euro Quality of life-5 Dimensions-3 level; mHAQ, modified Health Assessment Questionnaire; NRS, Numerical Rating Scale; PGA, Patient global assessment; R^2, multiple correlation coefficient adjusted for degrees of freedom; SE, standard error. These data were analyzed using multivariate analysis. The multicollinearity of the variables was also assessed (correlation coefficient < 0.9). The higher mHAQ score and 10 mm PGA higher at baseline were significantly independently associated with the pain NRS and EQ-5D-3L scale scores at the 9-year follow-up in the multivariable analysis. *Significance level was set at <5%.

of the physician (42). Many physicians tend to overestimate their communication (36). Physicians with better communication and interpersonal skills can detect problems earlier, prevent medical crises and expensive interventions, and provide better support to their patients (36). Furthermore, wearable activity trackers provide objective data for healthcare providers and for patients to educate themselves (43). The objective measurements of physical activity and sleep might resolve the discordance between patients and physicians. Encouraging and educating patients may play a key role in improving psychological disturbance and emotional wellbeing (44). The evaluation of a bio-psychosocial framework enhances the evaluation of the health-related quality of life and disability in the clinical management of patients (8).

4.4. Variety of discordance between patients and physicians

The impact of discordance between patients and physicians on treatment outcomes has been shown in Asian patients with early RA (18), and is further established for RA in the present study. Ethics and sociocultural contexts are associated with pain and health perceptions in patients (45). The discordance between patient and physician ratings varies widely across different countries (17). The degree of discordance in the global assessment was relatively small in the present study, which is consistent with the results of previous studies (18). Patients with osteoarthritis are more likely to be discordant (46), similar to those with RA (47). Physicians mainly assess the patient's experience of pain and other symptoms of osteoarthritis because laboratory findings are not informative for the diagnosis and management of osteoarthritis (46). The effect of discordance between physicians and patients on treatment outcomes has not been demonstrated across different diseases, countries, and cultures.

4.5. Study limitations

The present study has several limitations. First, the courses of the global assessment of disease by patients and physicians, disease activity, physical and psychological disturbances, and objective measurements were not investigated. Second, the present study excluded the participants who were not returning or not completing the follow-up measurement by mail. Third, the follow-up measurements were by mail and not face-to-face, which had a response bias. Fourth, the present study included patients with established RA at different stages of disease activity. Finally, this study included only a small number of patients. Therefore, the observations should be interpreted with caution.

5. Conclusion

In conclusion, discordance in global assessment between patients and physicians modestly predicted worse 9-year pain-related outcomes in patients with RA. This finding suggests the importance of discordance in global assessment between patients and physicians in patients with RA.

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 Research Ethics Committee of Hayaishi Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KH and KM designed the study and wrote the main manuscript. KS, MY, MH, and YH prepared and supervised the

analyses. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work as a whole, and have approved this version to be published.

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Conflict of interest

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

Publisher's note

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Psychometric properties of the translated Spanish version of the Pain Self-Efficacy Questionnaire

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Introduction: Some patients with rotator cuff injuries do not report significant changes in pain-related outcomes. Pain self-efficacy, which is commonly assessed using the Pain Self-Efficacy Questionnaire, may contribute toward this outcome. However, a Spanish adaptation of this questionnaire is currently lacking. Therefore, this study's purpose was developing the Spanish version of this questionnaire, and assess its psychometric properties.

Methods: The Spanish version of the Pain Self-Efficacy Questionnaire was translated and culturally adapted, and a sample of 107 patients with rotator cuff injuries completed the questionnaire to examine its convergent validity (analyzing its correlation with the Tampa Scale of Kinesiophobia), its test–retest reliability, for which a subset of 40 participants completed again the questionnaire, and its internal consistency.

Results: Translation was conducted without any problems, and 107 participants completed the study. Mean scores for the Pain Self-Efficacy Questionnaire were 45.2 points (standard deviation, 11.4). The Pain Self-Efficacy Questionnaire showed a moderate negative correlation with the Tampa Scale of Kinesiophobia (Pearson's correlation index r=−0.48) supporting its convergent validity. High test–retest reliability (Intraclass Correlation Coefficient of 0.90) and excellent internal consistency (Cronbach's α value of 0.92) were also found.

Discussion: The Spanish version of the Pain Self-Efficacy Questionnaire presents high validity, test–retest reliability, and internal consistency to assess pain self-efficacy in patients suffering rotator cuff injuries in Spanish-speaking settings.

KEYWORDS

cross-cultural adaptation, pain self-efficacy questionnaire, reliability, Spain, validity

1. Introduction

Rotator cuff injuries account for 80% of primary care consultations for shoulder pain (1), and their incidence increases with age (2). These injuries, among other problems such as weakness and loss of function, can cause significant levels of pain that are crucial when deciding

treatment strategies (3). Despite the development of many effective interventions to improve symptoms, around 30% of the patients report no significant change in pain-related outcomes, and psychosocial, occupational and lifestyle factors have been identified as possible reasons for this (1).

One of these factors is pain self-efficacy. Originally defined by Albert Bandura, self-efficacy is one's confidence or belief in their capacity goal achievement or activity performance (4). Higher levels of self-efficacy are suggested as predictors of better prognosis in patients with musculoskeletal pain (5), less disability, pain, fatigue, or emotional distress (6). Self-efficacy, therefore, determines the willingness to persist when obstacles are faced, avoids shying away from a complicated task, and shows commitment to achieving a goal (7).

The assessment of self-efficacy, as it is a belief, must be self-administered. To assess self-efficacy, many tools have been developed. Some of them are specific to a condition, such as the Arthritis Self-Efficacy Scale (ASES) or the Chronic Disease Self-Efficacy Scale, and some are related to pain and altered pain states, such as the Chronic Pain Self-Efficacy Scale or the Pain Self-Efficacy Scale (PSEQ) (8, 9). When dealing with clinical settings involving musculoskeletal disorders, the PSEQ is the preferred scale used by clinicians (10). It is a short and comprehensive questionnaire composed with 10 items first developed in English, aimed to assess the confidence or ability people with pain have to achieve activities despite their pain (11). The PSEQ assesses several dimensions, including physical functioning, social interaction, and participation in activities of the daily living when pain is present (11).

Translated and adapted versions of the PSEQ have assessed its psychometric properties in several languages, such as Amharic (7), Arabic (12), Canadian-French (1), Catalan (13), Chinese-Hong Kong (14), Chinese-Mainland (15), Danish (16), Italian (17), Farsi (18), Japanese (19), Marathi (20), Mongolian (21), Portuguese-Brazilian (22), Portuguese-European (23), and Yoruba (24). All of these translations were performed rigorously, and several of them adapted items from the questionnaire to their culture. Despite this, a validated version of this questionnaire in Spanish is lacking, limiting its access to healthcare professionals who develop their practice in Spanish-speaking settings. Therefore, this study aimed to translate and culturally adapt the Spanish version of the PSEQ, and examine its psychometric properties.

2. Materials and methods

2.1. Participants

This cross-sectional study was conducted at a private practice Hospital in Valencia, Spain, and included a sample of patients with rotator cuff injuries that were considered for surgical repair. Recruitment of participants was conducted between March and May 2023. Participants were included based on the following eligibility criteria: (1) adults >18 years old, (2) with a medically diagnosed rotator cuff injury considered for surgical repair, and (3) willingness to participate in the study. Participants were excluded if they had any cognitive impairments that could interfere with the completion of the assessment or if they were illiterate in Spanish. A briefing on the purpose of the study was given to the participants by a member of the research team during consultation with the surgeon, and gave written consent before being considered for enrollment in this study.

2.2. Measures

Baseline demographic characteristics from the sample were obtained for descriptive purposes, including sex, age, if the involved side was dominant or not, educational level (uneducated, primary, high school, college) and work status (part-time, full-time, unemployed, or retired).

The PSEQ is a 10-item questionnaire aimed to assess the confidence or ability people with pain have to achieve activities despite their pain. It includes lifestyle, social and daily activity questions the participant has to rate from 0 (not at all confident) to 6 (completely confident) in a Likert-style scale. Scores range from 0 to 60, with higher values indicating stronger self-efficacy levels (11). The psychometric properties, such as a high internal consistency, a high degree of stability, and construct validity of this assessment tool have been previously reported (7, 10).

The Tampa Scale of Kinesiophobia (TSK) was used as a validity criterion. It assesses fear-avoidance behaviors related to pain, and it has been previously translated and adapted in Spanish (25). In each item, patients have to answer in a 4-item Likert-style scale if they strongly agree (1) or strongly disagree (4) with the given statement. The total score ranges from 17 to 68 points, with higher values indicating stronger fear-avoidance behaviors. The preliminary Spanish version of the TSK was reviewed by a group of bilingual experts, including healthcare professionals and researchers familiar with the target population. They assessed the clarity, comprehensibility, and appropriateness of the translated items in the Spanish context. Any necessary modifications or adjustments were made based on their feedback and consensus.

2.3. Procedures

2.3.1. Translation and cultural adaptation

Before starting the translation and cross-cultural adaptation process, the original developer of the PSEQ (Professor Michael K. Nicholas) was contacted for the permission to translate and adapt the original English version of the PSEQ into Spanish. Established guidelines must be followed to translate and culturally adapt a questionnaire to a new language and cultural setting (26). The following steps were followed in the translation process: (1) The first author, bilingual in Spanish and English, translated every item from its original English version to Spanish, (2) a forward translation was then conducted twice by two independent authors who were also fluent in both languages, and to solve any differences between those authors, consensus was obtained. Finally (3) a back translation from Spanish to English was conducted twice by two independent authors fluent in both languages. Once the final version of the Spanish translation was approved by every member in the research team through consensus, a preliminary testing for cognitive debriefing was conducted in a small sample of 30 patients with rotator cuff injuries to assess comprehensiveness and clarity of the translated items.

2.3.2. Data collection

Data collection was carried out by two experienced physiotherapist members of the research team from March to May 2023, and was registered in a spreadsheet for further analysis. During their medical visit, participants were asked to complete a short form with their

sociodemographic and clinical information, the Spanish version of the PSEQ, and the TSK. To assess test–retest reliability, a subset of 40 participants was asked to complete again the PSEQ within a week after completing it for the first time.

2.4. Statistical analysis

To conduct statistical analyses, SPSS Statistics (IBM, Armonk, NY, United States) software, in its 23.0 version for MacOS was used. Baseline demographic information was described as means (standard deviations) for continuous data, and counts (percentages) for categorical data. The Kolmogorov–Smirnov test was used to check for data normal distribution. Missing values were handled using mean imputation. This method involved replacing missing values with the mean value of the available data for each respective variable. Floor and ceiling effects were established and determined by calculating if >15% of the responses given by participants corresponded to the minimum possible score of 0 or the maximum possible score of 60 (27).

2.4.1. Sample size estimation

Published guidelines with established requirements for the validation of a survey-like instrument were followed to conduct the sample size estimation (10 participants per item in the tool) (28). Also, the COSMIN recommendation for the selection of health-status measurement instruments were followed (29), establishing that the sample should at least be seven times the total number of items and ≥ 100. A sample of a minimum of 100 respondents was required, as the PSEQ is a 10-item questionnaire.

2.4.2. Validity

An exploratory factor analysis (EFA) was conducted to assess validity through an exploratory principal component analysis (PCA) with Varimax rotation, establishing the number of generated domains using the Scree test criteria (30). Keyser-Meyer-Olkin (KMO) measure was used for sampling adequacy at >0.8 to be considered good, and the Bartlett test for sphericity was used to determine the level of significance (31, 32). Similar to what previous studies have reported (1, 11–19, 22, 23), a one-factor solution is hypothesized to be found in the factorial analysis.

Additionally, convergent validity was also assessed, and it is defined as how close a measurement tool is related to other measurement tools that assess the same (or similar) constructs. To conduct convergent validity analysis, our *a priori* hypothesis was that the PSEQ would have a significant negative correlation with fear-avoidance behaviors related to pain, assessed through the Tampa Scale of Kinesiophobia (TSK) (25), as shown in similar studies (12, 15, 17). This outcome has been previously associated with pain-self efficacy, and has been also recommended as a core pain-related assessment in pain clinical trials (33). Pearson's correlation coefficient was used to establish correlation levels between these tools. As reported in similar studies that aimed to validate a translated version of the PSEQ (14, 18), absolute values above 0.3 are sufficient to support the tool's validity.

2.4.3. Test–retest reliability

Stability over time is assessed by conducting a test–retest reliability analysis, by assessing the same outcome twice in the same group of people and establishing the level of correlation between responses. To assess test–retest reliability, the Intraclass Correlation Coefficient (ICC) was used (model alpha, 2-way random effects model). ICC establishes a coefficient that ranges from 0 to 1, being 0 no correlation and 1 the highest correlation possible. Scores ranging from 0 to 0.4 are considered to have low correlation, from 0.4 to 0.6 moderate correlation, 0.6 to 0.8 average correlation and scores above 0.8 show excellent correlation (34). A subset of 40 participants was asked to complete again the PSEQ within a week after completing it for the first time. Additionally, a Bland–Altman graph was also created to plot the mean differences of the measurements with their limits of average difference corresponding limits ± the standard deviation's difference (35).

Absolute reliability measures were also calculated through the standard error of measurement (SE) and the minimal detectable change (MDC). The MDC represents the smallest change in scores that can be considered beyond measurement error and is required to confidently conclude that a meaningful change has occurred in an individual's pain self-efficacy. To calculate the SE, the following formula was used: $SD \times \sqrt{(1\text{-}R)}$, where SD is the Standard Deviation and R is the reliability coefficient of the instrument (36). To calculate the MDC, the following formula was used: $1.96 \times \sqrt{2} \times SE$.

2.4.4. Internal consistency

Internal consistency is the degree of relatedness between the items of an assessment tool (12). To assess the internal consistency of the PSEQ, Cronbach's α was calculated. Cronbach's α values range between 0 and 1, and an α value >0.9 was considered excellent, > 0.8 was considered good, and > 0.7 was considered acceptable (37). Corrected-total item correlation was also assessed to establish association levels between the items and the total score of the PSEQ.

3. Results

107 participants completed the questionnaire. Researchers in charge of the translation reached an agreement during the translation and adaptation process of the PSEQ into Spanish (PSEQ-Sp) and in a Spanish context. None of the items of the original were removed during the translation process.

3.1. Descriptive statistics

Demographic and clinical data of the study sample is shown in Table 1. Data was normally distributed. 112 participants met inclusion criteria and were enrolled in the study. However, 5 of them failed to complete all of the outcome measures and were excluded from the final analyses, leaving a total final sample of 107 participants. The sample included 48 males and 59 females, and the mean age was 49.4 years (SD 12.9). The vast majority of participants had a high educational level (97% had at least a High School degree), and were currently employed (91%).

The PSEQ-Sp mean score was 45.2 points (SD 11.4), and the TSK mean score was 46.6 points (SD 8.2). The PSEQ ranges from 0 to 60, and the TSK ranges from 17 to 68 points. None of the participants reported the lowest possible score 0, and only 3 (3%) of them reported the maximum score possible 60, so no significant floor and ceiling effects were found.

3.2. Validity

Results for the EFA are presented in Table 2. The value for the KMO assessing sampling adequacy was 0.90 and the score for Bartlett's test was $X^2 = 1{,}866.08$ ($p < 0.001$), suggesting that sampling was adequate, and data was appropriate for factor analysis. The exploratory factor analysis yielded for the PSEQ-Sp a one-factor solution, which accounted for 66% of the variance, as every item's factor loading was >0.5. Additionally, every participant completed the PSEQ-Sp and the TSK measures, and the convergent validity analysis found a significant moderate negative correlation between the PSEQ-Sp and the TSK (Pearson's correlation index $r = -0.48$, $p < 0.001$).

TABLE 1 Baseline demographic characteristics from the sample.

Outcome	*n* (%) or mean (SD)
Gender (%)	
Male	48 (45%)
Female	59 (55%)
Age (years)	49.4 (12.9)
Involved side (%)	
Dominant	63 (59%)
Non-dominant	44 (41%)
Educational level (%)	
Uneducated	0 (0%)
Primary	3 (3%)
High School	41 (38%)
College	63 (59%)
Work status (%)	
Part-time	39 (36%)
Full-time	59 (55%)
Unemployed	7 (7%)
Retired	2 (2%)

3.3. Test–retest reliability

Results for the test–retest reliability analysis are shown in Table 3. Every participant invited to respond to the PSEQ-Sp for a second time completed the questionnaire. The overall ICC for the PSEQ was 0.90 (95% CI 0.88–0.93), showing excellent correlation levels. ICC's for each individual item ranged from 0.77 to 0.86. The SE was 1.23 and the MDC was 3.05 points, respectively. Additionally, most of the pair differences are between the agreement limits, as shown in the Bland–Altman plot graph (Figure 1). This implies that test–retest measure of the PSEQ-Sp have a high concordance.

3.4. Internal consistency

Results for the internal consistency analysis are shown in Table 3. The PSEQ-Sp showed overall excellent internal consistency, with a Cronbach's α value of 0.92. Moreover, the Corrected-item total correlation values for Cronbach's α if an item was deleted were also excellent, ranging from 0.90 to 0.93. These findings indicate that there is a strong association between the items and the total score.

4. Discussion

The aim of the present study was to translate and culturally adapt the Spanish version of the PSEQ, and examine its psychometric properties, being this the first study to perform such translation and analysis. Our results show that PSEQ-Sp has excellent test–retest reliability and excellent internal consistency. Also, our hypothesis stating that the PSEQ-Sp and the TSK were associated was confirmed, supporting the validity of the PSEQ-Sp.

The PSEQ is a relatively short and feasible questionnaire that can easily be administered during a regular assessment, and can provide valuable information to understand the patient's clinical presentation from a biopsychosocial perspective. Authors have discussed its form and how can it be improved. For instance, respondents in the study conducted by Chala et al. (7) suggested to include every possible

TABLE 2 Exploratory factor analysis results of the Spanish version of the PSEQ.

Description	Mean (SD)	Factor loading
Item 1. Puedo disfrutar de las cosas, a pesar del dolor	4.91 (1.31)	0.780
Item 2. Puedo realizar la mayoría de las tareas del hogar (recoger, lavar los platos…) a pesar del dolor	4.85 (1.80)	0.774
Item 3. Puedo socializar con amigos y familia tanto como solía hacer, a pesar del dolor	5.39 (1.20)	0.825
Item 4. Puedo gestionar mi dolor en la mayoría de las situaciones	4.40 (1.39)	0.811
Item 5. Puedo realizar alguna forma de trabajo a pesar del dolor (incluye trabajo doméstico, remunerado y no remunerado)	3.81 (2.82)	0.702
Item 6. Todavía puedo hacer muchas cosas que disfruto hacer, como hobbies o actividades de ocio, a pesar del dolor	4.53 (2.13)	0.882
Item 7. Puedo gestionar mi dolor sin medicación	4.95 (1.10)	0.644
Item 8. Todavía puedo alcanzar la mayoría de mis objetivos en la vida a pesar del dolor	4.84 (2.10)	0.776
Item 9. Puedo tener un estilo de vida normal a pesar del dolor	4.83 (2.43)	0.846
Item 10. Puedo volverme más activo gradualmente a pesar del dolor	4.11 (2.72)	0.758

TABLE 3 Descriptive statistics, internal consistency values, and intraclass correlations of the items in the PSEQ.

Description	Mean (SD)	ICC	95% CI	Cronbach's α (if item deleted)	SE	MDC
Item 1. Puedo disfrutar de las cosas, a pesar del dolor	4.91 (1.31)	0.83	0.70–0.89	0.91		
Item 2. Puedo realizar la mayoría de las tareas del hogar (recoger, lavar los platos...) a pesar del dolor	4.85 (1.80)	0.79	0.63–0.88	0.92		
Item 3. Puedo socializar con amigos y familia tanto como solía hacer, a pesar del dolor	5.39 (1.20)	0.79	0.63–0.87	0.92		
Item 4. Puedo gestionar mi dolor en la mayoría de las situaciones	4.40 (1.39)	0.77	0.70–0.82	0.92		
Item 5. Puedo realizar alguna forma de trabajo a pesar del dolor (incluye trabajo doméstico, remunerado y no remunerado)	3.81 (2.82)	0.85	0.73–0.93	0.93		
Item 6. Todavía puedo hacer muchas cosas que disfruto hacer, como hobbies o actividades de ocio, a pesar del dolor	4.53 (2.13)	0.86	0.78–0.94	0.90		
Item 7. Puedo gestionar mi dolor sin medicación	4.95 (1.10)	0.80	0.70–0.88	0.93		
Item 8. Todavía puedo alcanzar la mayoría de mis objetivos en la vida a pesar del dolor	4.84 (2.10)	0.82	0.73–0.90	0.90		
Item 9. Puedo tener un estilo de vida normal a pesar del dolor	4.83 (2.43)	0.81	0.71–0.86	0.91		
Item 10. Puedo volverme más activo gradualmente a pesar del dolor	4.11 (2.72)	0.78	0.68–0.80	0.91		
Overall	45.2 (11.4)	0.90	0.88–0.93	0.92	1.23	3.05

number in the scale, instead of including numbers only at every limit. However, authors in this study decided that such modification would have a significant influence in the performance of the scale, and opted not to conduct such modification.

The exploratory factor analysis yielded a one-factor solution, coinciding with previous studies (1, 11–19, 22, 23). Contrary to this, several studies did not report results for factorial analysis (20, 21, 24) and one study (7) showed a two-factor solution instead, alluding there may have been underlying factors in the cultural setting they assessed their translated version in Ethiopia. Also, the construct convergent validity of the PSEQ-Sp was assessed by performing a correlation analysis with the TSK. The moderate negative correlation found in our study between the PSEQ-Sp and the TSK is consistent with other studies that conducted the same analysis. Chiarotto et al. (17), Almutairi et al. (12), and Yang et al. (15) found moderate negative correlations of $r = -0.48, -0.41, -0.45$, respectively. All of these studies conducted their validity analysis in patients that suffered low back pain, unlike our study, but we can consider this positively, as the correlation between these tools seems to be consistent despite the clinical condition. However, our validity analysis could have been further developed by correlating the PSEQ with other tools that similar studies used, such as the Short-Form 36 (SF-36) assessing health-related quality of life (7, 12, 14, 18, 19, 23), or other indices of validity, such as discriminant (13), or factorial (7, 18) validity. Future studies could consider these analyses.

Both the Bland–Altman plot and ICC values showed excellent reliability levels for the PSEQ-Sp. Other studies have also used the ICC to establish correlation values for the PSEQ. The Arabic and Chinese-Hong Kong versions (12, 14) found average ICC correlation values of 0.79 and 0.75, respectively, and the Amharic, Canadian-French, Danish, Farsi, Italian, Japanese, and Marathi versions (1, 7, 16, 20) found high ICC correlation values that ranged from 0.80 to 0.96. However, we have to consider the possible incurring in a recall bias, as the high test–retest reliability might've been influenced by the interval between assessments.

The level of internal consistency of the PSEQ-Sp was excellent. Other language translations of the PSEQ have found excellent internal consistency levels too. The Amharic (7), Arabic (12), and Portuguese-Brazilian (22) versions had internal consistencies of $\alpha = 0.90$, the Canadian-French (1) version of $\alpha = 0.91$, the original English (11), Catalan (13), and Farsi (18) versions of $\alpha = 0.92$, the Chinese-Hong Kong (14), and Marathi (20) versions of $\alpha = 0.93$, the Italian (17), Japanese (19), and Mongolian (21) versions of $\alpha = 0.94$, and the

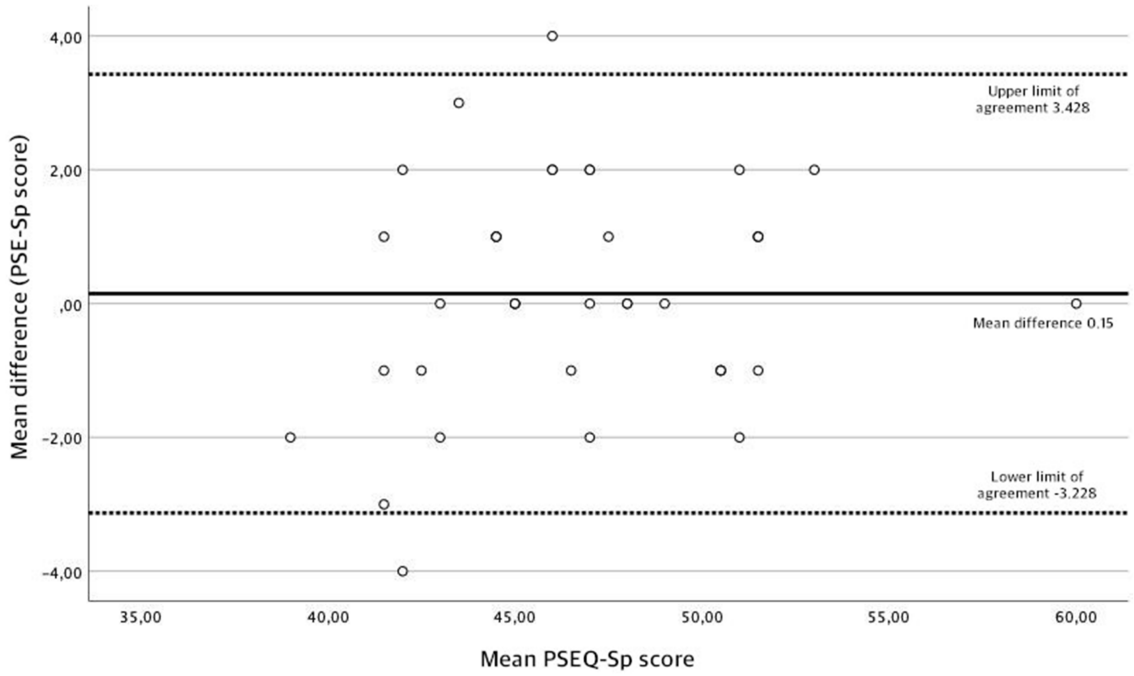

FIGURE 1
Results for the Bland-Altman plot graph.

Chinese-Mainland (15) version of $\alpha = 0.95$. The Portuguese-European (23) and Danish (16) versions had good levels of internal consistency, both $\alpha = 0.88$. Only the Yoruba (24) version had inferior, but still acceptable levels of consistency of $\alpha = 0.79$. Therefore, this tendency appears to be a psychometric property of the PSEQ across different languages and cultural contexts.

Limitations were also present in our study. First, results from this study are limited to patients suffering rotator cuff injuries, so conclusions should be interpreted cautiously. Also, our sample was of convenience, it was not randomly selected from the general population, meaning the generalizability cannot be assumed for all patients suffering rotator cuff injuries. Finally, we translated and cross-culturally adapted the PSEQ in Spain, and even though the version is easily understood by any Spanish speaker, cross-cultural adaptations to other Spanish-speaking countries, as the ones in South America, could report different results. Additional limitations to be considered include response biases, as our assessment was self-administered, and the potential recall bias on the test–retest assessment.

However, our study also presents strong points. This is the first translation of the PSEQ in Spanish, the world's second most spoken native language, and the official language in 20 countries. Therefore, the development of the PSEQ-Sp could imply an important addition for so many clinicians and researchers. Future research could conduct cross-cultural adaptations of the PSEQ-Sp in different Spanish-speaking countries to explore potential variations in psychometric properties and cultural influences. Cross-cultural adaptations of the PSEQ-Sp in different Spanish-speaking countries to explore potential variations in psychometric properties and cultural influences.

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 Ethics Committee of University of Valencia (protocol code 2537824 and date of approval March 9, 2023). The patients/participants provided their written informed consent to participate in this study.

Author contributions

BP-D and MB-D contributed to the conception and design of the study. SP-M and IE-P organized the database. AR-R performed the statistical analysis. BP-D wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

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

Publisher's note

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Evaluation of the effectiveness of a joint general practitioner-pharmacist intervention on the implementation of benzodiazepine deprescribing in older adults (BESTOPH-MG trial): protocol for a cluster-randomized controlled trial

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Background: Deprescribing benzodiazepines and related drugs (BZDR) is a challenge due to a lack of time on physicians' part, a lack of involvement of other health professionals, and the need for adapted tools. This study is based on primary care collaboration, by evaluating the effectiveness of a joint intervention between general practitioners and community pharmacists on the implementation of BZDR deprescribing in older adults.

Methods: This is a cluster randomized controlled trial in which each cluster will be formed by a physician-pharmacist pair. Within a cluster allocated to the intervention, the pharmacist will be trained in motivational interviewing (MI), and will offer the patient 3 interviews after inclusion by the physician. They will base their intervention on validated deprescribing guidelines. The pharmacist will receive methodological support during the first interviews. Interprofessional collaboration will be encouraged by writing reports for the physician after each interview. The following implementation outcomes will be evaluated: acceptability/adoption, appropriateness, cost, and fidelity. They will be measured by means of sociological interviews, observations, logbooks, and cost-utility analysis. Focus groups with physicians and pharmacists will be carried out to identify levers and barriers experienced in this collaboration. Observations will be conducted with pharmacists to assess their approach of the MIs. Effectiveness outcomes will be based on medication (discontinuation or reduction of BZDR) and clinical outcomes (such as quality of life, insomnia or anxiety), assessed by health insurance databases and validated questionnaires.

Discussion: This study will determine whether collaboration in primary care between physicians and pharmacists, as well as training and coaching of pharmacists in motivational interviewing, allows the implementation of BZDR deprescribing in the older adults.

This study will provide an understanding of the processes used to implement deprescribing guidelines, and the contribution of collaborative practice in implementing BZDR discontinuation. The cluster methodology will allow to assess the experience of the relationship between the different primary care actors, and the related obstacles and levers.

The results obtained will make it possible to produce guidelines on the involvement of community pharmacists in the management of substance abuse in older adults, or even to legislate new missions or care pathways.

Clinical trial registration: ClinicalTrials.gov, identifier, NCT05765656.

KEYWORDS

primary care, collaborative practice, implementation, deprescribing, benzodiazepines

Background

According to a 2017 report from the French National Agency for the Safety of Medicines and Health Products (ANSM), 13.4% of the French population used a benzodiazepine or related drug (BZDR) at least once in 2015 (1). These drugs are consumed for hypnotic or anxiolytic purposes in most cases. As per the recommendations, BZDR should not be prescribed for more than 28 days when for hypnotic use and for 8 to 12 weeks, including withdrawal, when for anxiolytic purpose. Indeed, these drugs have shown a real, but mediocre, short-term efficacy on anxiety and sleep disorders (2). Moreover, their long-term effectiveness is almost nil. However, literature shows that nearly one patient out of six taking a BZDR is a long-term user (3) and that the proportion of patients for whom the indication is questionable can reach 2/3 (4). The consequences of BZDR are multiple with an increased risk of daytime sedation, balance disorders leading to falls and fractures, cognitive disorders, road accidents and dementia (1, 2). Also, given their comorbidities, physiological changes, and multiple medications, the older adults are more at risk of experiencing from BZDR adverse events, like falls, driving accidents, dementia or even death (5–9). The majority of patients are unaware of these potential risks and continue to use these medications over the long term. They overestimate the benefits of BZDR and underestimate their harmful effects. The consequences are substantial, both from a health and financial perspective: in France, BZDR represent more than 4% of total drug consumption (10), and 117 million euros in sales (excluding taxes) per year.

At the national level, numerous actions have been taken by the health authorities to reduce the use of BZDR: information for health professionals, pictograms on drug boxes, recommendations by health authorities, incentive measures, and regulatory measures. However, despite these numerous initiatives, the consumption of BZDR remains high. Their deprescribing, defined as discontinuing or reducing under the supervision of a health care professional the dose of medications that are no longer needed, for which risks outweigh the benefits (11, 12) has difficulties being implemented in real life.

Literature shows that many levers can facilitate the implementation of actions for the appropriate use of drugs. Especially, interprofessional collaboration has shown efficacy in improving prescribing appropriateness and affect patients outcomes positively (13–15). As concluded by Nurchis et al., policy makers should promote the widespread adoption of a collaborative approach (15). This may address the discomfort of general practitioners (GPs) who report not feeling fully capable of implementing interventions to deprescribe BZDR if they have to rely solely on guidelines (16), and because of issues such as lack of time to re-assess these treatments, availability of mental health resources, and multiplicity of prescribers (17, 18). Yet, current international deprescribing studies remain mainly based on actions only directed at the prescriber (19), whereas collaboration between primary care professionals appears to be a solution for implementing a decision to stop treatment (17). In addition, BZDR users are very often described as reluctant to stop their medication for fear of a return of anxiety or insomnia (20). In this context, another lever usable to achieve the implementation of deprescribing is the use of techniques that enhance patients' motivation to change and their engagement in the intervention proposed by their GPs. As such, motivational interviewing (MI) may reduce the extent of substance abuse compared to no intervention (21). Developing and promoting training for healthcare professionals in MI may be a simple and pragmatic implementation strategy to reduce inappropriate BZDR use.

For this study, an interprofessional collaboration between the GP and the pharmacist will be held within primary care setting, with a specific training of pharmacists in MI, allowing the implementation of BZDR deprescribing in the older adults. The acronym BESTOPH-MG stands for "*BEnzodiazépines STOp PHarmacien Médecin Généraliste*"(= "*BEnzodiazepines STOp PHarmacist General*

Abbreviations: BZDR, Benzodiazepines and related drugs; CUA, Cost-utility analysis; CP, Community pharmacist; DDD, Daily drug dose; GP, General practitioner; HAS, Health high authority; MI, Motivational interview; QALY, Quality adjusted life year; SNDS, National health data system.

Practitioner"). Clusters composed of a general practitioner and community pharmacist pair will be made and both cluster and patient level objectives will be addressed. The specific aims are (1) to examine implementation outcomes like patient's factors of receptivity to the intervention, effects of the program on the professional practices of GPs and pharmacists, or reduction in health care consumption, economic efficiency and effectiveness of the intervention on inappropriate BZDR deprescribing rate, and (2) to evaluate if this intervention is associated with improvement in patients reported outcomes and use of other substances following the cessation of BZDR.

Methods

Design and setting

This is an open cluster-randomized pragmatic trial with parallel groups and conducted in primary care setting. The study is led by the Nantes University Hospital and is being conducted in the "Pays de la Loire" Region of France. Each cluster will be made up of a GP-Community Pharmacist pair (GP-CP), both of whom already have regular professional exchanges about patients, in order to respect an existing territorial organization. A clustered design was chosen to avoid potential contamination between the intervention and control arms. Indeed, a GP-CP pair applying both the intervention and control condition could lead to patients from the control condition being treated as if they were in the intervention condition. The GP-CP pairs will be randomized with a 1:1 ratio (intervention/control), and all patients handled by the pair will receive the same intervention. If necessary, several physicians from the same practice will be grouped together in the same cluster, and associated with the same pharmacy, in order to be randomized in the same arm and avoid potential contamination between physicians. Figure 1 illustrates the flow chart.

Study population and recruitment

Patients

In order to minimize the risk of subjective pre-selection of patients by the GP, a predefined list of eligible patients per cluster will be sent out to each GP by the Health Insurance according to the inclusion criteria detailed below, before randomization of the clusters and on the basis of the GP's request. The study population will consist of patients aged 65 years and older, monthly users of at least one anxiolytic or hypnotic BZDR for more than 3 consecutive months (ATC classes N05BA, N05CD and N05CF). Patients meeting the eligibility criteria will be recruited by GPs during their medical encounters.

The inclusion criteria will be: outpatients aged 65 and over, followed by the GP and being delivered their medications by the pharmacist of the GP-CP pair, having a prescription for an anxiolytic or hypnotic BZDR prescribed at least 4 times in the past year, the last prescription being dispensed in less than 3 months and having been dispensed monthly during the last 3 months, affiliated to a social security scheme, and having given consent to participate in the research.

Non-inclusion criteria will be: patients living in an institution, participating in another clinical trial, with any medical condition that contraindicates BZDR discontinuation on the physician's opinion, unable to participate in an interview or answer a questionnaire and with insufficient autonomy to carry out the steps inherent in the study. Patients living in an institution will be excluded because an unknown part of them have their BZDR not traced in the SNDS database (for administrative reasons), which could induce bias in our study.

If eligible, the patient will be offered to enroll in the study during a standard medical consultation. If he agrees to participate, signed informed consent will then be obtained, and the patient will be assigned a patient number automatically upon inclusion.

Primary healthcare professionals

This study will involve GPs and pharmacists practicing in primary care, i.e., in medical practices or community pharmacies. GP and CPs in the Pays de Loire region will be contacted by e-mail through multiple channels like research networks and professional associations. An evening webinar regarding BZDR misuse will be held for physicians and pharmacists in the Region. The objective will be to raise awareness of the problem and to explain the study to professionals. If a GPs shows interest, he/she will be asked to reach out the pharmacist (or vice versa) in order to form a pair (cluster). Pre-existing interactions between healthcare professionals of the same area is a major driver regarding the optimal implementation of the intervention within the cluster. Moreover, as in the context of a pragmatic trial, this way of conducting recruitment is the most coherent regarding the evaluation of what would be observed in practice when deploying the intervention to a larger scale. If both GP and CP agrees to participate, signed informed consent will then be obtained, and the cluster will be randomized.

Randomization

A schedule for enrollment, randomization and allocation, interventions, and assessments for the study is presented in Table 1. The randomization will be performed by cluster of GP-CP pairs in open without stratification with a ratio of 1:1 using the *Ennov clinical* software via a secure connection to the servers of the Nantes University Hospital. The information necessary for communication will be provided to the recruiting GPs by a data manager of the Nantes University Hospital. The randomization will be computer-generated by blocks of 6 as the clusters are recruited. The trial statistician and the researchers assessing the outcomes will be blinded to the randomization results.

Intervention

Deprescribing will be implemented through 3 successive steps, the cornerstones of which are interprofessional collaboration between GPs and CPs, and training and methodological support for CPs.

Step 1: medical encounter with the GP and submission of documents

Patients in the GP-CP clusters randomized to the intervention arm will be offered a joint GP-CP deprescribing intervention by their GP. The physician will present the study schedule to the patients and inform them of the planned follow-ups.

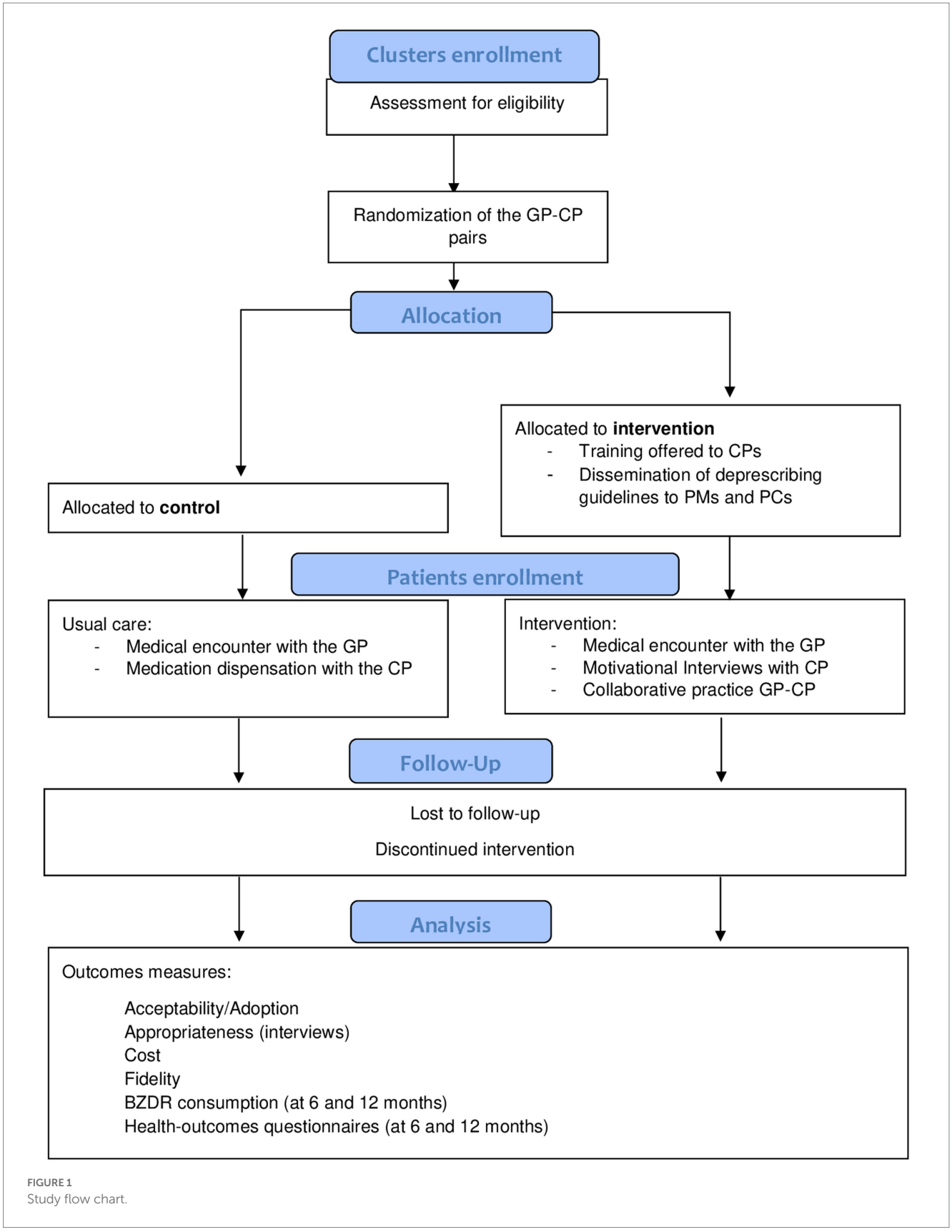

FIGURE 1
Study flow chart.

Step 2: medication treatment dispensing and MI

Following the medical consultation, the patients will go to the pharmacy to get their medication treatment dispensed. They will be given a kit of patient education materials addressing the risks of BZDs and the benefits of reducing/stopping their use. This kit will be designed on the basis of patient education materials produced by

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TABLE 1 Schedule of enrollment, interventions, and assessments.

	2022	2023			2024		
	June-Dec.	Jan.-Feb.	March-Sept.	Oct.-Dec.	Jan.-March	April–June	July-Sept.
Enrollment							
Recruitment and GP-CP clusters forming	X	X	X				
Eligible patients' identification			X				
Clusters allocation		X	X				
Intervention							
CP training in MI performing		X	X				
Patients enrollment and MI 1 to 3			X	X			
Monthly reports to GP			X	X	X		
Assessments							
Acceptability/Adoption		X	X				
Appropriateness (interviews)				X		X	
Cost						X	
Fidelity			X	X	X	X	
BZDR consumption				X	X		
Health-outcomes questionnaires				X	X		
Dissemination							X

the Canadian Deprescribing Society[1] and adapted to the French context. The pharmacist will then plan with the patients 3 MIs to be carried out within the next 3 months. These interviews will last 30 to 60 min and will address the risks of using BZDR, as well as the benefits and modalities of stopping them. MI is a client-centered, semi-directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence (22). It is intended to work through four main principles: express empathy, support self-efficacy, roll with resistance, and develop discrepancy. During these interviews, the pharmacist will provide information about non-pharmacological ways to improve sleep or reduce anxiety, prevention of rebound phenomena, and will provide an example of de-escalation of doses (i.e., progressive reduction). The pharmacist will identify the patients' representations of their medication and pathology (insomnia, anxiety), and will understand the barriers and facilitators for deprescribing. Any question the patients may have will be addressed. The choice to stop or reduce the dose of the BZDR will be the result of a shared medical decision (trio patient – GP – PC). To facilitate implementation, the pharmacists of the intervention arm will receive a 2-day specifically designed training course in MI by a certified organization prior to the intervention (Table 2). They will be given guidelines on the risks associated with BZDR, their deprescribing, and the management of patients who were deprescribed. If required, the pharmacists will be supported by the interventional public health department of the promoting center which will accompany them in their first MI. To avoid contamination, pharmacists working in pharmacies randomized in the control group will not be trained in MI and in deprescribing until after the study is completed.

Step 3: interprofessional communication

Following each interview, the pharmacist will inform the physician by means of a formalized report of the points discussed and of the relevant information concerning the objective of deprescribing (barriers, facilitators, etc.), using the patient's comments when appropriate. The report will include the data collected from the patient during the interviews (expressed needs) as well as the pharmacist's conduct (initiation of de-escalation, associated advice, dispensing of therapeutic alternatives). The pharmacist will inform the GP of the patient's choice or not to get involved in a deprescribing process and of the protocol followed, if applicable. The objective of this exchange is to formalize the joint GP-CP intervention and to secure the deprescribing of BZDR for the patients.

Patients included in the control group clusters (non-interventional) will not benefit from the joint GP-CP intervention but will be managed in the usual way: medical consultation followed by dispensing of medication treatments. Blinding of participants for this type of intervention is not possible.

1 Deprescribing.org

TABLE 2 Objectives and program of the pharmacist's training course in Motivational Interview.

Pedagogical objectives	
- To discover Motivational Interviewing (MI) - To become imbued with the spirit of the MI and to identify the corrective/repairing reflex - To Mobilize the skills of the MI - To use specific tools to share information in a motivational way - To identify the change discourse - To begin to focus questions and reflections to promote discourse-change - To practice and receive feedback on MI practice in a training context	
Pedagogical means	
The training uses a variety of media (video, summary document, presentation, written exercises, workshops and oral role plays, brainstorming, exchanges between participants)	
Training program	
Day 0	- Reading of a summary of MI: history, key elements of MI and definitions
Day 1	- Creating the group dynamic – introduction to Engagement in MI - Review of theory - Ambivalence - The corrective/repairing reflex - Introduction to empathy and reflective listening - Open questions - Summarizing - DDPD tool (motivational information sharing) - Valuation - Practice around a polycephalous interview (with several people) to building the alliance and engaging the relationship - Conclusion
Day 2	- Renewal of group dynamics and commitment - The different types of simple and complex reflections - Introduction to sustaining and changing discourses - The different types of discourse-change - Introduction to evocation strategies - Observation of a live MI by the trainer on the subject of deprescribing BZDR - Practice of a MI by each participant and feedback from the trainer with the elements congruent with the MI and one or two possible areas for improvement - Conclusion and evaluation

Data sources and collection

The implementation outcomes will be measured by different procedures detailed below (see Outcomes section).

The sociological study will consider the variability of practice locations to be more representative: rural, urban, peri-urban. Depending on the location of the practice, the patient may have different social characteristics that will probably require professionals to adapt (vocabulary, arguments, conduct of the interview, etc.). Four days of observations will be conducted with pharmacists who have just been trained in MI to study, in action, how they conduct their first interviews with the older adults. These same pharmacists will be observed a second time at the end of the study, to see how their approach to MI has evolved.

A first wave of ten semi-structured interviews will be conducted with older adults who have already been seen by their pharmacist, to see what effects the pharmacist has had on their representations of BZDR and on their consumption.

Finally, three focus groups will be carried out, one with CPs, one with GPs and one with pairs. The first two will allow to identify any difficulties experienced in this interprofessional collaboration, but also what has been facilitated. The last focus group will allow the pairs to exchange and compare their point of view on multidisciplinary work and relevance of the collaboration.

Regarding the effectiveness of the intervention, the consumption of reimbursed drugs and the co-payments of the system will be assessed using the National Health Data System (SNDS) (23). This database provides access to all reimbursed healthcare, including drugs dispensed in pharmacies.

The outcomes concerning the clinical evolution of the patients will be measured using questionnaires administered to the patients by telephone by a clinical research associate.

Data analysis

Outcomes

Aim 1: implementation and effectiveness outcomes

Implementation outcomes will be assessed according to Proctor et al. classification (24) as described below: acceptability/adoption, appropriateness, cost and fidelity (Table 3). All qualitative data will be transcribed in full before being analyzed. The interviews and focus groups will be subject to thematic and structural discourse analysis. No software will be used.

Acceptability/adoption

The achievement of the number of clusters and patients included planned in the protocol will be evaluated. A short questionnaire will be sent to a sample of GPs and pharmacists who refused to participate in order to understand the reasons for not participating in the study.

The patients' factors of receptivity to the intervention (gender, age, couple, socio-economic level, last diploma, literacy level, frequency of consultations with the GP, duration of prescription, indications for BZDR) will be studied in order to identify a typical profile of the patient responding to the intervention.

Appropriateness

The sociological study will allow to analyze the appropriateness of this work in pairs on the deprescribing of BZDR among the older adults. We will study the impact of this collaboration on GPs and CPs, and in particular analyze the extent to which it allows for an increase

TABLE 3 Implementation and effectiveness outcomes.

	General Practitioners and Community Pharmacists	Patients
Implementation outcomes		
Acceptability/Adoption	Nb of clusters included/Nb of clusters planned Reason for refusal	Nb of patients included/Nb of patients eligible Factors of receptivity
Appropriateness	GP & CP Sociological interviews CP Observations	Sociological interviews
Cost	Cost-Utility and Budgetary impact analysis	
Fidelity	Nb of clusters completing the study/Nb of clusters Rate of CP's reporting to GP	Nb of appointments/ Nb of planned appointments
	Nb, duration and frequency of MI	
Effectiveness outcome		
Medication		Cessation or reduction of BZDR at M12
Clinical		Patient reported outcomes

CP, Community Pharmacists; GP, General Practitioners; MI, Motivational interview; Nb, Number.

in the competence of the professionals. Based on a field survey that will put the discourse (interviews) into perspective with the practices (observations), the effects of this arrangement on all parties and the effectiveness of this collaboration will be assessed, while identifying how each party has lived this experience, what they have learned and any resistance to change. In this way, how pharmacists use motivational interviews, how they conduct them, and what this multidisciplinary collaboration brings them will be studied, but also how they transmit new norms to the older adults and the concrete effects of these motivational interviews.

Furthermore, by observing the way in which these motivational interviews are constructed and conducted according to the different practitioners, and by putting these practices into perspective with the discourses of the doctors and pharmacists, we will be able to question the appropriateness of this multidisciplinary vision, and how it upsets the socialization and professional logics of the two.

Cost-utility

Economic efficiency of the implementation effort will be assessed following the HAS 2020 recommendations (25). A Cost-Utility Analysis (CUA) expressed as a cost per Quality Adjusted Life Year (QALY) will be performed from a collective perspective and with a time horizon of 12 months. The CUA will consider the direct costs of care from randomization to M12. Hospital and city care consumption data related to the management and its consequences will be collected in both arms via the Health Insurance database (SNDS). The data collected will include: medications, medical consultations, hospitalizations if applicable, and emergency room visits. A budgetary impact analysis from the point of view of the Health Insurance will be carried out following the CUA. It will be based on different scenarios of 5-year diffusion levels of the joint intervention.

Fidelity

The proportion of pairs completing the study, the proportion of patients who actually made appointments with the pharmacist, the number, duration and frequency of MI, and the rate of reporting made by the pharmacist to the GP will be measured through a logbook.

Effectiveness

The effectiveness will be assessed by the cessation or reduction of BZDR use at 12 months from inclusion. It will be described as the proportion of patients no longer being dispensed BZDR at 10 months after inclusion, with the last two months (10 to 12 months) not counted to account for possible residual BZDR use, or having decreased their average Daily Drug Dose (DDD) dispensing by 50%. The decrease will be calculated by comparing the average DDD dispense over the last 3 months of patient follow-up to the dispense observed during the 3 months prior to inclusion.

Aim 2: patient reported outcomes

Secondary outcomes will aim to evaluate improvement in patients reported outcomes, and use of other substances. Patients' quality of life (measured by EQ5D-5L), anxiety disorders (GAD-7), quality of sleep (ISI), time to first hospitalization after inclusion (SNDS), occurrence of falls, dependence on BZDR (ECAB), autonomy (IADL) and use of other substances will be assessed.

A stratified analysis by type of BZDR (hypnotic or anxiolytic) will be carried out on each of the outcomes to determine the impact of the indication on the implementation elements.

Sample size and power

The calculation of the number of subjects needed is based on the effectiveness outcome, on the basis of the following assumptions: risk α equal to 5%, statistical power equal to 80, 5% deprescribing proportion in control group based on current trend, a proportion of at least 15% in the intervention group, an intraclass correlation coefficient of 0.05 (26) and a number of 20 GP-CP pairs per arm. The number of patients to be recruited will be 400 (200 per arm), based on the inclusion of 10 patients per GP-CP pair, with 20 GC-CP pairs per arm during the 12 months of inclusion (27). To reach target sample size, various networks will be involved in recruitment: primary care research network, professional associations, regional unions of practitioners, university training masters.

Statistical analysis

Variables measured at inclusion will be described according to the randomization group for all included patients. Quantitative variables will be described using the mean, standard deviation, quartiles and range. Qualitative variables will be described using the numbers and proportions for each modality.

In order to measure the impact of the intervention in real life, the analysis will focus on the intention-to-treat population: all patients

included will be kept in the analysis sample according to their randomization group, regardless of protocol deviations.

For the effectiveness endpoint, a mixed logistic model will be built to study the proportion of deprescribing between MI condition (intervention) and usual care condition (control), and concomitantly accounting for the cluster effect associated with our design (28). For secondary analysis, the impact of the intervention on quality of life, anxiety disorders, sleep quality, dependence and autonomy will be estimated by comparing the EQ-5D-5L, GAD-7, ISI, ECAB, and IADL scores between the two groups using mixed models. As advocated by the literature (29), models will be adjusted on baseline covariates that are prognostic of the outcome, balanced or not at baseline, including *a minima* the following: age, sex, number of past attempts, suspected addiction. The impact of the intervention on hospitalizations and deprescribing failures will be estimated from hospitalizations (number of hospitalizations) and failures (number of discontinuations and then resumption).

Discussion

The objective of this trial is to assess the added value of a primary care collaboration between GPs and CPs in order to implement inappropriate BZDR deprescribing in older adults. In various countries, legislative and regulatory developments have led to an expansion of the scope of practice of pharmacists for the substitution or discontinuation of certain medications, including BZDR (30). The patient-centered intervention developed in this study aims to reinforce known levers and overcome barriers to stopping inappropriate medications.

Wei et al., in a 2022 meta-review, reported that improving interprofessional collaboration requires organizational, teams, and individuals' combined efforts but that when effective collaborations occur, all stakeholders can benefit – organizations, professionals, and patients. Our study is grounded in a concrete way on existing collaborations. It strengthens the bond between physicians and pharmacists who work together on a daily basis. This pragmatism is a major implementation tool when setting up studies in primary care.

The use of MI techniques have demonstrated their effectiveness in various studies (31, 32) and allows us to hypothesize that this intervention will be beneficial to a patient who is initially reluctant to stop or reduce his or her consumption of BZDR. Indeed, the literature suggests that MI is a powerful tool for BZDR deprescribing, as it is popular with healthcare professionals (33) and has been shown to be effective with other drugs such as opioids (34). A recently published review (35) described that different interventions had a positive impact as soon as they were based on patient empowerment (36–38). MI, for this purpose, is based on taking into account the ambivalence a patient may have about taking action. This ambivalence is well described: patients are aware of the benefits of stopping their BZDR (perception of long-term side effects, burden of treatment, desire for natural sleep), but face inner barriers that block initiation or persistence of cessation (fear of withdrawal effects or return of pathology) (39). Perceived self-efficacy, which may be due to a previous failure to quit, or a lack of knowledge about how to cut down, may also come into play (40). All of these factors provide fertile ground for the implementation of MI in the deprescription of BZDRs in our study. The expected results are a decrease in BZDR consumption for patients in the intervention arm compared to the control group. In addition, this study could show an improvement in cognitive functions (41–43), an improvement in the quality of life of patients (32, 44, 45) and an economic benefit of the deprescribing intervention. Training pharmacists in MI through a specific two-day hands-on training should improve the adoption of the intervention by health professionals. Moreover, as this technique can also be used on other occasions (smoking cessation, therapeutic adherence, etc.), we believe that it is a lever for the involvement of pharmacists in the trial and for the development of a more effective approach. In addition, accompanying CPs during the first interviews should be important levers for the implementation of the MI.

Patient empowerment is a key mechanism for increasing responsibility for shared decision-making with health care providers (46). It is an effective strategy when it comes to deprescribing (47) combined with behavior change strategies and progressive de-escalation. Patient empowerment, in which patients strengthen their ability to effectively care for themselves, has been shown to be a powerful transformative process (31), and giving them educational material may promote deprescribing conversations (48). Combined with direct education, these methods have been shown to be effective in reducing inappropriate use of BZDR in the older adults (49). This tripartite approach for pharmacists, physicians and patients aims to achieve a synergistic impact.

Strengths

Strengths of the study include its pragmatic design that will allow the observed process to reflect real-world practice as accurately as possible. This pragmatic approach involves intervention at the group level, rather than the individual level, and as such cluster randomizations are the most common (50). Furthermore, this cluster-randomized design is considered the most appropriate for conducting deprescribing trials (51). To our knowledge, this is the first deprescribing trial in France involving interprofessional collaboration of GPs and pharmacists in primary care. Multiple implementation outcomes will allow us to assess how this intervention can be scaled up beyond the clinical trial. Indeed, the qualitative study will allow us to explore the appropriateness of the program by assessing the experiences and representations of the pairs and patients concerning deprescribing. This part will highlight the obstacles and levers to intervention. Finally, an objective assessment of BZDR discontinuation rates from the National Health Insurance database will increase the internal validity of the study.

Limits

Despite these strengths, our trial has several limitations. Firstly, neither the patients nor the GP-CP pairs will be blinded due to the pragmatic design of the trial (52). However, the statisticians and the clinical research officer will be blinded to reduce the risk of confirmation, monitoring and evaluation bias. Secondly, it is likely that the pairs agreeing to participate in the study will be health professionals already convinced by the deprescribing approach, which is why this study is randomized and controlled. In addition, although pharmacists will be trained in MI by a certified organization, some

may be more or less comfortable than others and the implementation of the intervention may depend on the operator of the training. This will be measured by the fidelity of the study to the protocol. Finally, a limitation of this study is that the evaluation of a multifaceted intervention prevents the determination of the specific component(s) responsible for the observed outcomes or failures at the conclusion of the study.

Conclusion

This study will provide evidence on the effectiveness of a joint GP-CP intervention to aid benzodiazepine deprescribing. If so, this strategy and intervention could be implemented more widely and also for other potentially inappropriate drugs in older people.

Ethics statement

Ethics committee (CPP Nord Ouest 1) reviewed and approved the study protocol on December 1st, 2022 (22.03226.000131).

Author contributions

J-FH and J-PF designed and piloted the study. PN co-piloted the study and wrote the first draft of the manuscript. HL is the team's expert in qualitative evaluation. CV-V contributed to the methodology, in particular the outcomes issues. PC contributed to the selection of methods, analysis plan, and preparation of manuscript. All authors have read and approved the submitted version and have agreed to be personally accountable for their own contribution.

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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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Visceral adipose tissue and osteoarthritis, a two-sample Mendelian randomized study

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Background: The relationship between visceral adipose tissue and osteoarthritis is not clear. The purpose of our study was to explore the relationship between visceral adipose tissue and osteoarthritis.

Methods: We used a two-sample Mendelian randomization method to select single-nucleotide polymorphisms (SNPs) significantly associated with visceral adipose tissue as instrumental variables to explore the relationship between visceral adipose tissue and all osteoarthritis, hand osteoarthritis, hip osteoarthritis, knee osteoarthritis, and spine osteoarthritis. The reliability of the results was tested using sensitivity analysis.

Results: Our findings indicated that visceral adipose tissue was associated with all osteoarthritis, hip osteoarthritis, knee osteoarthritis, and spine osteoarthritis (all osteoarthritis: OR = 1.399, 95% CI: 1.335–1.467, p = 7.95e-44; hip osteoarthritis: OR = 1.399, 95% CI: 1.284–1.524, p = 1.41e-14; knee osteoarthritis: OR = 1.794, 95% CI: 1.662–1.937, p = 1.33e-50; and spine osteoarthritis: OR = 1.445, 95% CI: 1.314–1.589, p = 2.89e-14). Sensitivity analysis demonstrated the reliability of these results.

Conclusion: Our study suggests that genetically predicted visceral adipose tissue is associated with osteoarthritis. Reducing the accumulation of visceral adipose tissue could potentially have an impact on the incidence of osteoarthritis.

KEYWORDS

obesity, visceral adipose tissue, osteoarthritis, Mendelian randomization, two-sample MR

1 Introduction

Osteoarthritis (OA) is a chronic degenerative disease characterized by cartilage degeneration, subchondral bone changes, and synovitis, primarily affecting the hip, knee, hand, and other joints (1). It has a high global prevalence (2) and ranks fifth among all causes of disability worldwide, posing a significant threat to human health (3). Treating OA includes early pain management and end-stage joint replacement, but the high cost of treatment imposes a significant burden on society and individuals (4). Although the

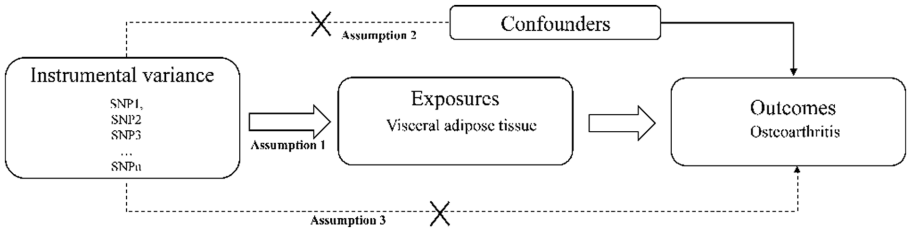

FIGURE 1
Basic assumptions for Mendelian randomization.

mechanism and risk factors of OA are not fully understood, it is generally believed to be closely related to age, obesity, and other factors (5).

Obesity has been shown to be closely associated with the pathogenesis of various diseases (6–8). In these studies, obesity is often assessed using human indicators such as BMI, waist-to-hip ratio, waist circumference, and hip circumference. However, due to the heterogeneity of obesity, there are considerable individual differences in body fat distribution and metabolic characteristics, even among individuals with the same body mass index (BMI) (9). Thus, BMI or other general obesity measurement methods may not accurately assess metabolic status and body fat distribution. Visceral adipose tissue, which is considered a marker of ectopic fat deposition and hormonal environmental disorders, is more metabolically active and potentially reflects the natural metabolic abnormalities of obesity (10). It refers to the adipose tissue accumulated in the peritoneal cavity between the organs and the trunk and is a significant component of total body adipose tissue (11). Increased visceral adipose tissue, also known as central obesity, is an important manifestation of obesity. While previous studies have reported a genetic causal relationship between BMI and knee and hip OA (12), there is limited research on the relationship between visceral adipose tissue and OA, and the precise association between them remains unclear (13).

Mendelian randomization is an analytical method that utilizes genetic variation as an instrumental variable to investigate the causal relationship between exposure and outcomes based on the random distribution of genetic variations during conception (14). This method can largely mitigate the influence of reverse causality and confounding factors in observational studies (15), making it increasingly utilized in clinical studies. The purpose of this study is to explore the relationship between visceral adipose tissue and OA using a two-sample Mendelian randomization research method, aiming to provide insights for managing OA.

2 Method and design

2.1 Research design

In this study, a two-sample Mendelian randomization analysis was used to select SNPs significantly associated with visceral adipose tissue as instrumental variables to explore the relationship between visceral adipose tissue and all OA, hand OA, hip OA, knee OA, and spine OA. Mendelian randomized research design must meet three assumptions: (1) Instrumental variables are related to exposure factors. (2) Instrumental variables are not related to confounding factors. (3) Instrumental variables can only affect outcomes through exposure factors (16) Figure 1.

2.2 Data sources

Visceral adipose tissue-related data were obtained from a recent large-scale summary of GWAS by Karlsson et al. (17) which included 325,153 white British subjects. The study consisted of two cohorts and used estimates by dual-energy X-ray absorptiometry (DXA) to create predictive models. Through screening, we selected the single-nucleotide polymorphism (SNP) that was significantly correlated with VAT ($p < 5 \times 10^{-8}$) at the whole-gene level. After removing the linkage imbalance and palindrome sequence, the *F*-value of each SNP was calculated, and SNPs with an F-value >10 were selected as tool variables. In addition, we removed SNPs associated with confounding factors (apolipoprotein B, low-density lipoprotein, smoking, and osteoporosis) and outcomes through the online website PhenoScanner.[1]

Data related to OA were obtained from the latest GWAS data (18) of the Osteoarthritis Genetics (GO) Consortium, which included 826,690 samples from 177,517 OA patients. The number of OA cases in the hand, spine, hip, and knee joints was 20,901, 28,372, 36,445, and 62,497, respectively, all of which were European population samples. The basic information included in the data sources is presented in Table 1.

2.3 Statistical analysis

The main effect analysis in this study was the inverse variance weighting (IVW) of random effects, which combined the Wald ratio of results for each SNP and conducted a meta-analysis. In addition, MR-Egger regression and a weighted median estimator (WME) were used to supplement the IVW method. Outliers were screened using the MR PRESSO method. If any outliers were found, they were excluded, and MR analysis was performed again. The reliability of the results was tested using sensitivity analysis methods such as Cochran's Q, MR-Egger intercept analysis, and funnel plot. Cochran's Q statistics were used to test for heterogeneity. A *p*-value of >0.05 indicates no

1 http://www.phenoscanner.medschl.cam.ac.uk

TABLE 1 Data sources related to exposure and outcome.

Exposure or outcome	Participants (Ncase/ Control case)	Descent	Source	Pubmed ID
Exposure				
Visceral adipose tissue	325,153	European	https://www.ebi.ac.uk	31501611
Outcome				
All osteoarthritis	17,7,517/649,173	European	https://www.genetics-osteoarthritis.com	34822786
Hand osteoarthritis	20,901/282,881	European	-	34822786
Hip osteoarthritis	36,445/316,943	European	-	34822786
Knee osteoarthritis	62,497/333,557	European	-	34822786
Spine osteoarthritis	28,372/305,578	European	-	34822786

significant heterogeneity in the analysis. To evaluate the bias for gene pleiotropy using MR-Egger intercept analysis, the closer the regression intercept to 0, the less likely the gene pleiotropy would be. We also generated power values for each MR analysis using an online MR power calculation tool[2] (19).

All analyses in this study were performed on R 4.2.1 and the MR PERESSO and TwosampleMR packages. After Bonferroni correction, a p-value of <0.01 (0.05/5) was considered significant.

3 Results

3.1 Instrumental variables

After screening, 218 SNPs associated with visceral adipose tissue were identified, explaining approximately 3.38% of the genetic variation. The F-values of the included SNPs were > 10, excluding the possibility of weak instrumental variables. The details of the included SNP are shown in the Supplementary material.

3.2 MR results

The results of the MR analyses are presented in Figure 2. Our results showed that genetically predicted visceral adipose tissue was associated with all OA (OR = 1.399, 95% CI: 1.335–1.467, p = 7.95e-44), which was also directionally consistent and significantly validated in the MR Egger, WME, and MR PRESSO methods. In addition, visceral adipose tissue is also associated with hip OA, knee OA, and spinal OA (hip OA: OR = 1.399, 95% CI: 1.284–1.524, p = 1.41e-14; knee OA: OR = 1.794, 95% CI: 1.662–1.937, p = 1.33e-50; and spine OA: OR = 1.445, 95% CI: 1.314–1.589, p = 2.89e-14), indicating that the visceral adipose tissue is closely associated with OA at multiple sites. The scatter plot of the MR analysis of the visceral adipose tissue and OA can be seen in Figure 3.

The results of sensitivity analyses are presented in Table 2, and in sensitivity analyses, the MR Egger intercept test was used to find potential horizontal pleiotropy. No horizontal pleiotropy was found with each MR analysis. The results of Cochran's Q-test showed extensive heterogeneity. Because we used random effects IVW as the primary outcome, the heterogeneity was acceptable (20). In addition, no significant bias was observed in the funnel plots of each MR analysis (Figure 4).

4 Discussion

Our study has demonstrated a relationship between visceral adipose tissue and OA. Specifically, for every unit increase in visceral adipose tissue, the risk of developing all OA increases by 40%. Moreover, the risk of hip OA increases by 40%, knee OA increases by 79%, and spine OA increases by 45%. These findings may provide new insights into the connection between OA and obesity.

The association between obesity and OA has been extensively explored in previous studies. Reyes et al.'s cohort study highlighted the association between BMI and OA (21). Similarly, Yuan et al.'s Mendelian randomization analysis indicated that elevated BMI increases the risk of hip OA (22). Another study comprehensively evaluated various measures of obesity, such as waist-to-hip ratio, waist circumference, hip circumference, and body fat content, and their effects on knee and hip OA. This study revealed that different measures of obesity have varying impacts on OA (23). However, these studies did not specifically focus on the influence of visceral adipose tissue on OA. Therefore, our study contributes additional evidence to elucidate the relationship between visceral adipose tissue and OA. To the best of our knowledge, this is the first Mendelian randomized study investigating the connection between visceral adipose tissue and OA.

Prior research has suggested that the accumulation of visceral adipose tissue may be more detrimental than adipose tissue in other body locations (24). In a study by Erdal Belen et al., the thickness of epicardial fat in knee OA patients was found to be greater than that in the control group, and this thickness was associated with the severity of knee OA (25). Furthermore, Eric et al. demonstrated that patients with knee OA exhibited excessive fat accumulation in the central region (26). Although there is no direct evidence linking visceral adipose tissue to OA, Li et al. demonstrated an association between visceral adipose tissue and joint pain (27). Additionally, Visser et al.'s epidemiological study (28) on the Dutch population revealed an association between hand OA and visceral adipose tissue, corroborating our findings.

2 https://shiny.cnsgenomics.com/mRnd/

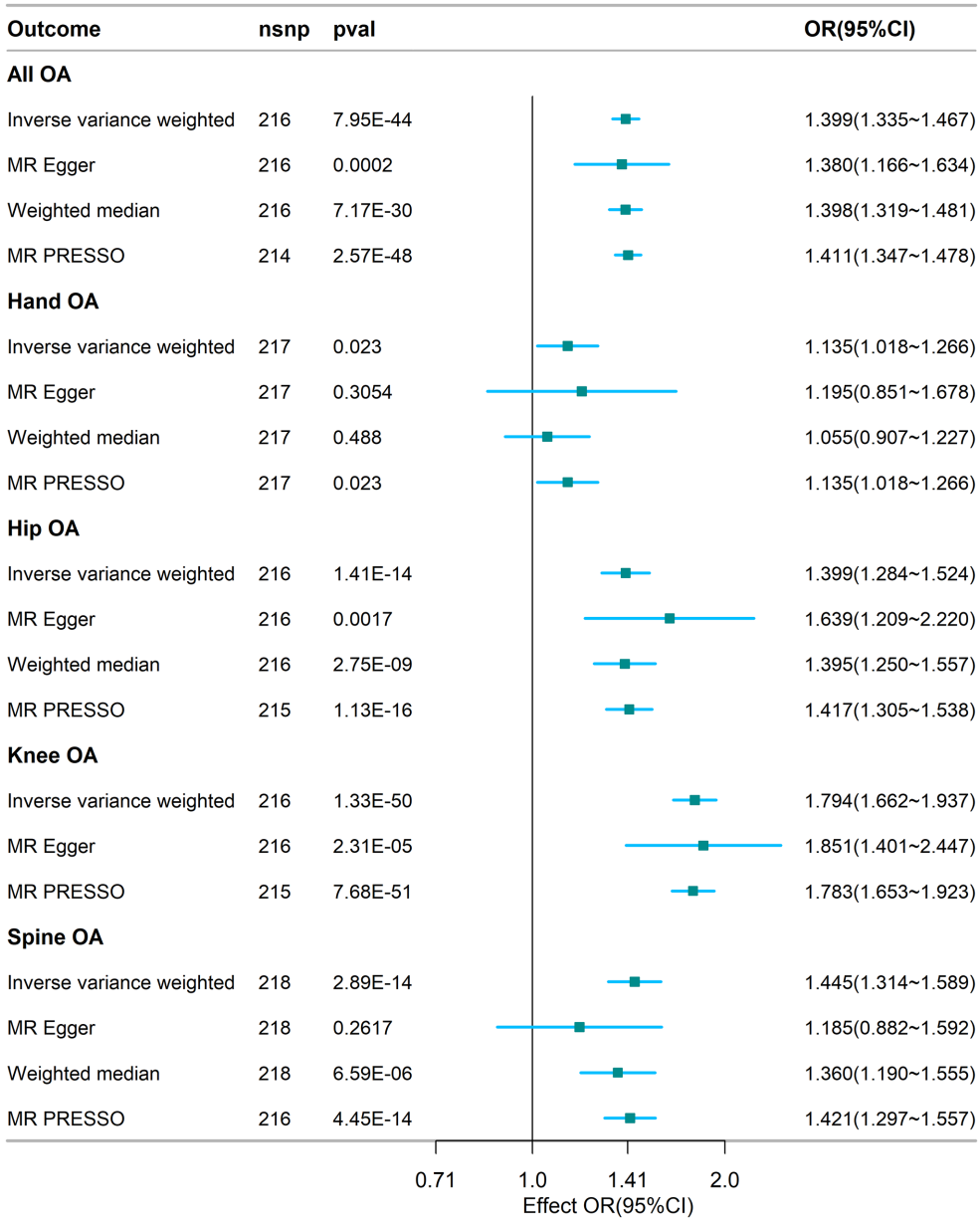

FIGURE 2
Association between visceral adipose tissue and osteoarthritis based on different methods. OA, osteoarthritis; SNP, single nucleotide polymorphism; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; nsnp, number of snp.

The link between visceral adipose tissue and OA may be influenced by multiple mechanisms. OA, being a degenerative disease, is believed to be associated with inflammatory processes (29). As the primary fat reservoir in the human body, the visceral adipose tissue is thought to secrete various adipokines, including interleukin-6 (IL-6) and tumor necrosis factor (TNF). These adipokines are believed to play a role in the pathogenesis of OA (30, 31). Interleukin 6 is believed to facilitate cartilage degradation in post-traumatic OA by promoting an increase in MMP-13 and aggrecanase expression. Additionally, its effects are influenced by gender (32). In their study, Xue et al. demonstrated that tumor necrosis factor enables the upregulation of mRNA for a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4), which plays a key role in the pathogenesis of OA by promoting cartilage breakdown in humans (33). Furthermore, leptin, an inflammatory adipose factor, has been shown to affect distal joints. It can enhance collagen degradation and regulate the production of metalloproteinases, thus promoting chondrocyte degradation (34, 35). On the other hand, adiponectin may have a protective effect against OA progression (36), but the accumulation of visceral adipose tissue may inhibit adiponectin transcription, thus enhancing its pro-inflammatory effect (37).

Observational studies are bound to be influenced by confounding factors. However, we have minimized the impact of reverse causality and confounding factors as much as possible by using Mendelian randomization methods. This method provides evidence for the

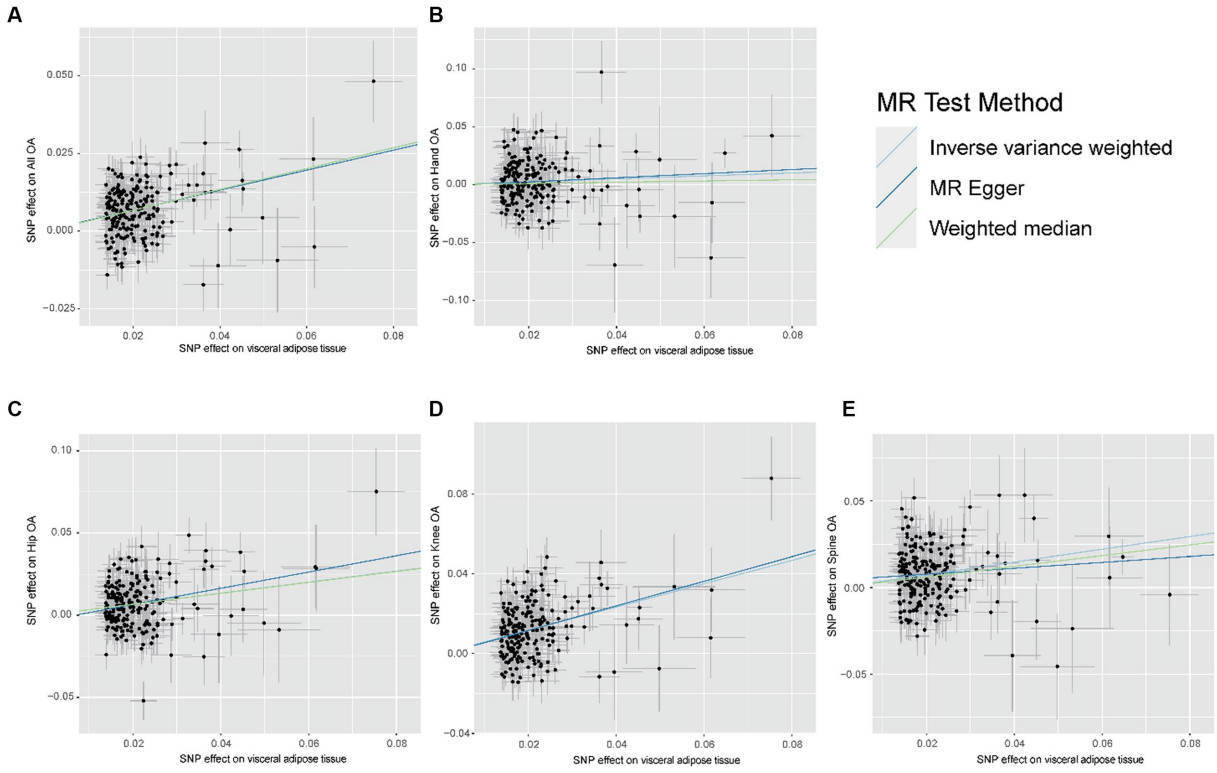

FIGURE 3
Scatter plot of the relationship between visceral adipose tissue and OA. **(A)** Scatter plot of the relationship between visceral adipose tissue and All OA. **(B)** Scatter plot of the relationship between visceral adipose tissue and Hand OA. **(C)** Scatter plot of the relationship between visceral adipose tissue and Hip OA. **(D)** Scatter plot of the relationship between visceral adipose tissue and Knee OA. **(E)** Scatter plot of the relationship between visceral adipose tissue and Spine OA; OA, osteoarthritis.

TABLE 2 **Sensitivity analysis results and power value of the correlation between visceral adipose tissue and osteoarthritis.**

	p for pleiotropy	Cochrane's Q	*p* for Cochrane's Q	Power
All osteoarthritis	0.870	382.2652	9.32E-12	100%
Hand osteoarthritis	0.755	316.6116	9.55E-06	93%
Hip osteoarthritis	0.246	309.1645	2.20E-05	100%
Knee osteoarthritis	0.659	412.9010	9.11E-15	100%
Spine osteoarthritis	0.309	326.1286	1.48E-06	100%

connection between visceral adipose tissue and OA at different anatomical sites. This association has also been verified through sensitivity analysis. Nonetheless, our study has certain limitations. First, due to the constraints of the original GWAS data source, our research primarily encompasses the European population, and we have not explored similar associations in other populations. Second, although we did not identify the presence of level pleiotropy in our study, there was significant heterogeneity among SNPs, and we did not undertake further data filtering to reduce heterogeneity. Third, the original data did not provide age stratification, which prevented us from conducting stratified data analysis to assess the impact of age. Fourth, the proportion of genetic variation explained by visceral adipose tissue remains relatively small. Additionally, our MR analysis may reflect the effect of lifelong exposure to high visceral adipose tissue on OA, yet the risk of OA at a specific time may be influenced differently. Finally, the susceptibility of visceral adipose tissue to OA may be influenced by maternal effects. Intrauterine exposure or maternal behavior, influenced by the maternal genetic background, may contribute to the association between offspring genotype and the risk of OA (38).

5 Conclusion

Above all, our study showed that genetically predicted visceral adipose tissue is associated with OA, which also reveals the adverse effects of obesity on human health at the genetic level. Controlling central obesity through intervention is of positive significance for the prevention of OA. However, further large-scale longitudinal studies or randomized controlled trials are needed to further investigate the profound relationship between visceral adipose tissue and the increased risk of OA.

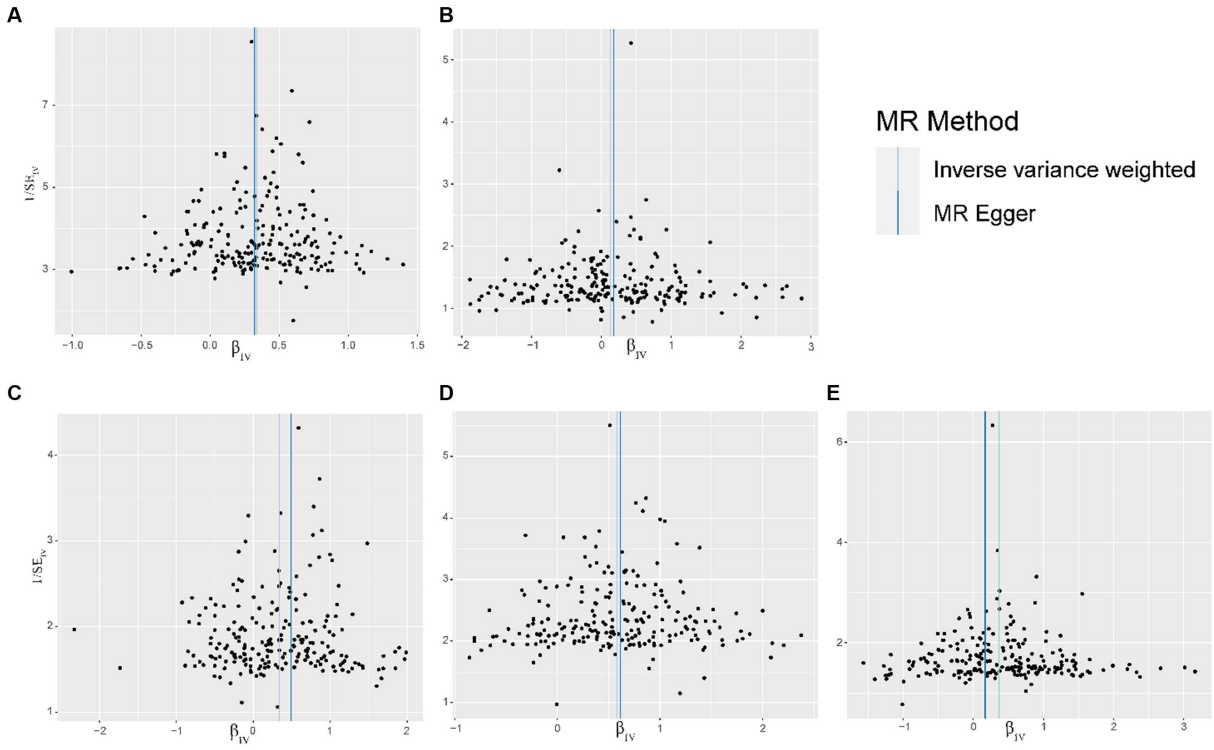

FIGURE 4
Funnel plot of the relationship between visceral adipose tissue and OA. **(A)** Funnel plot of the relationship between visceral adipose tissue and All OA. **(B)** Funnel plot of the relationship between visceral adipose tissue and Hand OA. **(C)** Funnel plot of the relationship between visceral adipose tissue and Hip OA. **(D)** Funnel plot of the relationship between visceral adipose tissue and Knee OA. **(E)** Funnel plot of the relationship between visceral adipose tissue and Spine OA; OA, osteoarthritis.

Data availability statement

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

Author contributions

YZ: Writing – original draft, Data curation, Methodology, Supervision, Writing – review & editing. YW: Writing – review & editing, Conceptualization, Investigation, Writing – original draft. JX: Data curation, Writing – review & editing. ZW: Methodology, Writing – review & editing. WZ: Supervision, Writing – review & editing. CZ: Funding acquisition, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1324449/full#supplementary-material

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A retrospective analysis of the prevalence and impact of associated comorbidities on fibromyalgia outcomes in a tertiary care center

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Background: This retrospective study was designed to analyze the prevalence and impact of associated comorbidities on fibromyalgia (FM) outcomes (functionality, pain, depression levels) for patients who participated in an intensive multicomponent clinical program in a tertiary care center.

Methods: Participants included a sample of 411 patients diagnosed with FM at a large tertiary medical center using the 2016 ACR criteria. Patients completed an intensive 2-day cognitive behavioral treatment (CBT) program, filled out the Fibromyalgia Impact Questionnaire Revised (FIQR), the Center for Epidemiologic Studies Depression Scale (CES-D), the Pain Catastrophizing Scale (PCS), and were followed for 6 months after treatment completion. *T*-tests were performed to analyze differences between the presence or absence of select comorbidities for the three outcomes at follow-up. Statistically significant comorbidities ($p < 0.05$) were used as predictors in multivariable logistic regression models.

Results: The FM associated comorbidities in this cohort that had significant impact on the measured outcome domains after treatment program completed were Obesity (FIQR $p = 0.024$), Hypothyroidism (CES-D $p = 0.023$, PCS $p = 0.035$), Gastroesophageal reflux disease GERD (PCS $p < 0.001$), Osteoarthritis (CES-D $p = 0.047$). Interestingly, Headache, the most frequent FM associated comorbidity in this cohort (33.6%), did not have a significant impact on the outcome domains at follow-up. Obesity (18.2%) was the only FM associated comorbidity significantly impacting all three outcome domains at follow-up.

Conclusion: The present study suggests that addressing obesity may significantly impact outcomes in FM patients.

KEYWORDS

fibromyalgia FM, comorbidities, outcome domains, multimorbidities, treatment

Introduction

Fibromyalgia (FM) affects approximately 10 million people in the US alone with estimates as high as 8% of the population world-wide (1, 2). The prevalence rate of FM in the general population is estimated to be 2–4% (3). It is a chronic pain syndrome with features that includes widespread musculoskeletal pain, extreme fatigue, sleep disturbance, and cognitive complaints (4–7). FM can result in significant incapacity with 35% of patients with FM in the United States on government disability assistance (8). Patients with FM struggle with depression with numerous studies documenting a high prevalence of depression in this population (9). Further, pain catastrophizing has been linked to important outcomes in chronic pain patients such as higher opioid use, longer hospital stay and increased likelihood of being on disability (10). FM is associated with other medical and/or psychiatry conditions that affect its clinical presentation, and result in complications that require specific treatments, and may potentially impact outcome (11).

FM is considered a complex condition that affects the way that the brain processes pain signal, leading to high sensitivity and discomfort. Along with pain, individual with FM experience sleep disturbances, cognitive difficulties (sometimes refer to as a "fibro fog"), mood disorders. The most widely used criteria for diagnosing FM is the 2016 American College of Rheumatology (ACR) criteria. According to this criteria, widespread pain, tender trigger points,

and the updated comprehensive evaluation symptoms and their impact on a person quality of life are the main elements to make a FM diagnosis currently (3, 5, 6, 12).

Sex and age can play a role in the prevalence, symptoms, and management of FM, though individual experiences can vary. FM is more commonly diagnosed in women than in men. Studies suggest that women have a higher likelihood of developing FM (70–90%). FM can affect individuals of all ages, but it is more commonly diagnosed in middle aged adults (30–50-year-old) (1, 2).

FM patients experience a higher rate of comorbid conditions, specifically rheumatologic and psychiatric conditions as compared with the general population (13–15), that have included coronary artery disease, myocardial infarction (MI), hypertension, stroke (16–18), diabetes mellitus, and irritable bowel syndrome (13, 19). In one study involving a large sample of community-dwelling adults with FM, over 50% were found to have seven or more chronic conditions (20). Most scientific studies that have examined comorbidity in FM has focused on clinical presentation, pain management, and medications (21–24). FM has been associated with various comorbid entities including medical and psychiatric disorders. During the last few decades, the prevalence of chronic illnesses has risen due to multiple factors including but not limited to better understanding of the diseases, increased longevity, improved access to health care, electronic medical record, patient online services, etc. (25, 26). Comorbidities may lead to a delay in the diagnosis of FM, may be mistaken as poor control of the primary disease, may cause leading to incorrect treatment decisions, and may also increase Morbi and mortality in these patients (23, 27).

The aim of this study is to determine the prevalence of comorbidities in a cohort of FM patients (25, 28, 29) who attended a 2-day cognitive behavioral treatment program, and examine the impact of each comorbidity on specific outcomes of level of psychological distress/depression, functional status, and cognitive strategies that specifically impact pain and its management.

Methods

Participants and procedure

Participants were recruited from a large tertiary medical center's Fibromyalgia Treatment Program. Inclusion criteria for the study included a diagnosis with FM using the 2016 ACR criteria (5) and informed consent to participate in the study. No exclusion criteria were used for the study. The Fibromyalgia Treatment Program is an intensive 2-day cognitive behavioral treatment program. Participants completed follow up surveys approximately 6-months following treatment to assess outcomes. The study was approved by the Mayo Clinic Institutional Review Board (Protocol ID: 19–000495). Baseline data including study measures and demographic information were collected before the patients started the 2-day program. Post-intervention data were collected with mailed surveys at post-treatment. If patients did not respond to the mailed survey a reminder letter was sent out.

Measures

Comorbidities

Presence of a comorbidity was defined as any diagnosis from a patient's medical history. Individual comorbidities were grouped into twelve broader categories with patients belonging to a particular category if they had any diagnosed conditions from medical history or current visit (29, 30). Multi-morbidities were defined as low (2 or less), and high (3 or more) comorbidity-associated medical diagnosis documented at any time (medical history/current visit) (26, 31).

The Fibromyalgia Impact Questionnaire-Revised (FIQR) measures functional status and is the most widely used measure of functional impairment in FM patients. Three domains are evaluated with this measure and include function, overall impact, and symptoms. The scale includes twenty-one items that are scored from 0–10 with higher scores reflecting greater functional impairment. Severe functional impairment is indicated by scores of 60 or above. The psychometric properties of this scale have been researched (12).

The Center for Epidemiologic Studies of depression Scale (CES-D) is a 20-item scale that assesses the presence and severity of depressive symptoms (32). Scores range from 0 to 6-with higher scores reflecting a higher degree of depressive symptomatology. The clinical threshold for depression is a score of 16 on this measure. The psychometric properties of the CES-D are well researched (33).

The Pain Catastrophizing Scale (PCS) is a self-report questionnaire designed to measure the tendency of individuals to catastrophize or magnify the significance of pain they experience. It assesses the degree to which a person experiences some negative thoughts and emotions

Abbreviations: CES-D Score, Center for Epidemiologic Studies Depression Scale; FIQR Score, Fibromyalgia Impact Questionnaire-Revised; PCS Score, Pain Catastrophizing Scale; IBS, Irritable bowel syndrome; GERD, Gastroesophageal reflux; RA, Rheumatoid arthritis.

related to pain, such as rumination, magnification, and helplessness. These 3 subscales help researchers and healthcare professionals better understand and evaluate the psychological impact of pain on individuals (34–36).

Treatment program

The Fibromyalgia Treatment Program is a 16-h, cognitive behavioral based, group program that addresses education and evidence-based strategies to decrease central sensitization. Strategies addressed include relaxation training, use of moderation, pacing, exercise, cognitive skills, sleep hygiene, stress management, social support, and the use of pharmacological options to improve symptoms and functioning (37). The effectiveness of this intervention has been described elsewhere (38).

Statistical analysis

Cohort characteristics, comorbidities, and outcomes were summarized with frequency (percentage) for categorical variables and with mean, standard deviation, and range for continuous variables. Twelve individual conditions selected based on prevalence as well as twelve grouped comorbidities were further used in outcome analysis. *T*-tests were performed to analyze differences between presence or absence of individual comorbidities as well as grouped comorbidities for the three outcomes (FIQR, CES-D, PCS at follow-up). Additionally, we compared patients with 2 or less vs. 3 or more comorbidities for each outcome. The comorbidities that were statistically significant comorbidities ($p < 0.05$) in our univariate analyses were selected for inclusion into our multivariable logistic regression models as predictors; all the comorbidities were evaluated under this criterium for each outcome independently. The multivariable logistic regression models were adjusted for patient's age and sex, where odds ratios (ORs) and 95% confidence intervals (Cis) were estimated; binary outcomes were defined as severe functioning (FIQR >60), severe depression (CES-D ≥ 20), and severe pain catastrophizing (PCS ≥ 30). Analyses were conducted using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

The effect of baseline measures of pain, depression, and function was not considered in the regression modeling. The main aim of this study was to look at associations of comorbidities with our outcomes at follow-up. Another study we published using the same cohort discussed the treatment effectiveness between our baseline and follow-up outcome scores (38).

Results

Participants included 411 patients diagnosed with fibromyalgia at a large tertiary medical center using the 2016 ACR criteria (5). The sample completed an intensive 2-day cognitive behavioral treatment program and were followed after treatment to assess treatment effectiveness. Follow up data was received 4–8 months after treatment with an average for the sample of 6-month follow-up.

In our cohort, women represent 90.3%, and the age mean was 54.7 years for the overall sample (411) with a standard deviation SD of 13.9 years (Table 1). As seen in Figure 1, 1,000 patients were assessed for eligibility from the Fibromyalgia Treatment Program. From them, zero patients were excluded due to ineligibility and all consented to participate. All 1,000 patients completed baseline data collection. Of them, 511 patients were lost to follow up as they did not complete mailed surveys at 6-months post-intervention. A subset of patients ($n = 78$) were excluded due to inability to locate sufficient medical chart review information. In the present analysis, 411 patients were included.

The results, as contained in Table 1, revealed the following comorbidities: headaches (33.6%), osteoarthritis (23.4%), hypertension (23.1%), insomnia (22.4%), obesity (18.2%), low back pain (18%), obstructive sleep apnea (OSA) (16.5%), irritable bowel syndrome (IBS) (14.8%), abdominal pain (10%), hypothyroidism (7.1%), rheumatoid arthritis (RA) (5.8%), and gastroesophageal reflux (GERD) (4.1%).

Comparisons between patients with vs. patients without a certain comorbidity for the three outcomes are summarized in Table 2. Obesity negatively impacted functioning at follow-up with obese patients having, on average, a poorer functioning score than non-obese patients (mean: 51.0 vs. 45.1, $p = 0.024$). Patients with hypothyroidism, however, were more likely to have lower depression (mean: 18.2 vs. 21.6, $p = 0.023$) and pain catastrophizing (mean: 12.1 vs. 16.0, $p = 0.035$) scores at follow-up than patients without hypothyroidism. Similarity, patients with osteoarthritis had a lower depression score (mean: 19.6 vs. 21.9, $p = 0.047$) and patients with gastroesophageal reflux (GERD) had a lower pain catastrophizing score (mean: 12.1 vs. 16.0, $p = 0.023$) six months after the treatment program. Although not statistically significant, abdominal pain, headache, irritable bowel syndrome, and rheumatoid arthritis negatively impacted all three outcomes at follow-up (Table 2).

In Table 3, we examined logistic regressions for significant comorbidities and binary treatment outcomes. In our multivariate analysis, obesity was the only statistically significant predictor of FIQR score greater than 60 after adjusting for patient's age and sex, showing that obese patients were twice more likely to have poorer functional status after completing the treatment program (OR = 1.77, 95% CI: 1.04–2.98, $p = 0.033$).

Adjusting logistic regression models for age and sex is important for several reasons: confounding variables can distort the observed associations, population characteristics are fundamental demographic variables that reflect important differences in the population, and standardization allows for more meaningful comparisons and reduces the potential impact of demographic differences on the observed associations (3, 6, 8, 39).

Table 4 compares differences between grouped comorbidities for these three outcomes at follow-up. Patients in the psychiatry and gynecology groups tended to have higher depression scores (mean: 22.6 vs. 20.1, $p = 0.008$; 25.2 vs. 21.1, $p = 0.022$, respectively). Also, patients in the psychiatry group experienced higher pain catastrophizing score (mean: 17.1 vs. 14.4, $p = 0.035$).

Comparison was done with those having 2 or fewer comorbidities vs. 3 or more comorbidities to see if the outcome measures were negatively impacted by the number of comorbidities (possibly

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TABLE 1 Summary of cohort characteristics.

Characteristic	Overall (*N* = 411)
Age at survey (years)	
Mean (SD)	54.7 (13.9)
Range	22.5–85.6
Gender	
Female	371 (90.3%)
Male	40 (9.7%)
Race	
White	372 (90.5%)
Black or African American	16 (3.9%)
Other	23 (5.6%)
Ethnicity	
Hispanic or Latino	34 (8.3%)
Not Hispanic or Latino	368 (89.8%)
Other	8 (2.0%)
Marital Status	
Married/Domestic partnership	300 (73.2%)
Single/Divorced/Widowed	110 (26.8%)
Duration of symptoms	
Less than 1 year	20 (4.9%)
1–2 years	81 (19.7%)
3–5 years	109 (26.5%)
Greater than 5 years	201 (48.9%)
Time since diagnosis (months)	
Mean (SD)	48.1 (79.6)
Range	0.0–480.0
Abdominal pain	41 (10.0%)
Headache	138 (33.6%)
Hypertension	95 (23.1%)
IBS	61 (14.8%)
Insomnia	92 (22.4%)
Low back pain	74 (18.0%)
Osteoarthritis	96 (23.4%)
Obesity	75 (18.2%)
OSA	68 (16.5%)
RA	24 (5.8%)
GERD	17 (4.1%)
Hypothyroidism	29 (7.1%)
Multi-morbidities	
2 or less	276 (67.2%)
3 or more	135 (32.8%)
Admission FIQR	
Mean (SD)	59.1 (18.1)
Range	0.0–94.7
Admission CES-D	
Mean (SD)	25.3 (9.8)
Range	0.0–52.0
Admission PCS	
Mean (SD)	22.8 (12.3)
Range	0.0–52.0
Follow-up FIQR	
Mean (SD)	46.2 (21.3)
Range	0.0–98.0
Follow-up CES-D	
Mean (SD)	21.4 (9.8)
Range	0.0–56.0
Follow-up PCS	
Mean (SD)	15.7 (12.7)
Range	0.0–52.0
Met severe threshold for functional impairment (FIQR >60)	117 (28.5%)
Met clinical threshold for depression (CESD ≥ 20)	235 (57.2%)
Met severe threshold for pain catastrophizing (PCS ≥ 30)	67 (16.3%)

IBS, Irritable Bowel Syndrome; OSA, Obstructive Sleep Apnea; RA, Rheumatoid Arthritis; GERD, Gastroesophageal Reflux Disease; FIQR, Fibromyalgia Impact Questionnaire Revised; CES-D, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale.

indicative of worse health which could be confounding or contributing factors to dysfunction, depression, and pain catastrophizing) in addition to the condition of FM. In our cohort, 32.8% of patients had 3 or more comorbidities while 67.2% had 2 or less (Table 1). When we analyzed impact of multi-morbidities on outcomes, we found no statistically significant differences between the two groups in functioning, depression or pain catastrophizing scores (Table 5).

Discussion

The present study assessed the prevalence and impact of comorbidities on treatment effectiveness in FM patients. We examined comorbidities and treatment outcomes (functional impairment, pain catastrophizing, and depression) using several statistical techniques. The data revealed that in our sample, similar to other published studies with FM populations, the most common comorbid conditions were identified: headaches, hypertension, osteoarthritis, and insomnia. Unlike other published studies with higher rates, Rheumatoid arthritis was only identified in 5.8% of our sample (12, 21–37).

Treatment outcomes were then compared for FM patients with and without each comorbidity. This analysis indicated that FM patients with obesity had significantly poorer treatment outcomes in functional impairment. Other comorbidities, including Osteoarthritis, GERD, and Hypothyroidism appeared to impact

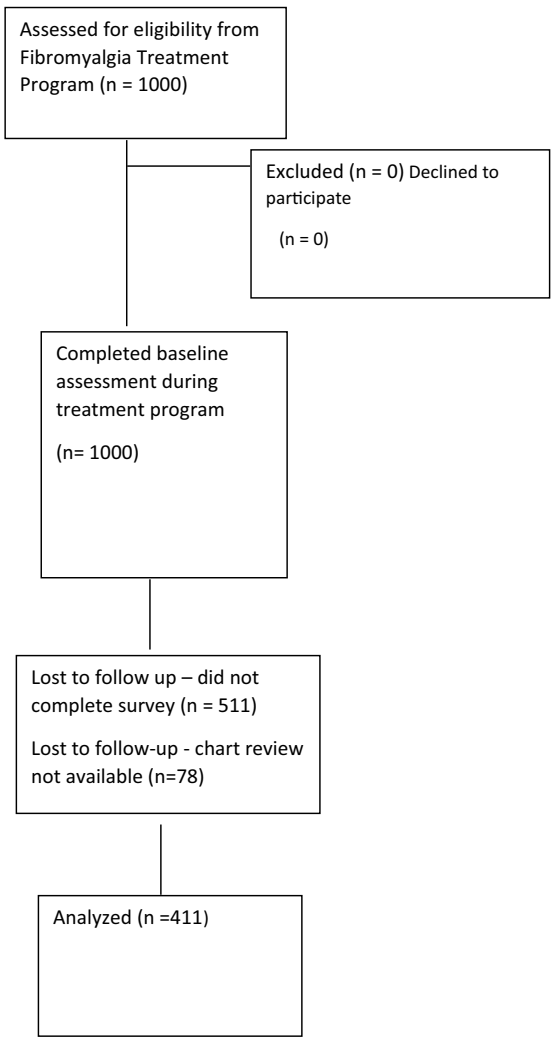

FIGURE 1
Participant flow chart.

treatment outcomes in a positive direction. These positive findings may be artificial, as the comorbidity occurred in a very small subset of patients (e.g., Osteoarthritis $n = 96$; GERD $n = 17$; Hypothyroidism $n = 29$).

Taking into account age and sex, Odds Ratios (ORs) were analyzed for Obesity, Osteoarthritis, and Hypothyroidism. These comorbidities were selected based on their significance in the previous analysis (40, 41). ORs were calculated to predict dichotomous treatment outcomes (FIQR >60 = significantly impaired; CES-D > 20 = clinically significant depression; PCS > 30 = clinically significant pain catastrophizing). Of these OR's, only Obesity indicated a significantly increased risk of functional impairment (OR = 1.77). Put differently, FM patients with Obesity had a 77% higher risk of being significantly impaired at 6-months follow-up, compared to FM patients without Obesity. Obesity adversely affected functioning in our sample at follow-up and needs further investigation. Obesity may impact ability to exercise leading to a deconditioned state that further intensifies FM symptoms (Table 3). A previous systematic review and meta-analysis showed that obesity may impact FM in several ways in addition to potentially limiting

TABLE 2 Impact of select comorbidities on outcomes at follow-up.

Comorbidity type/Outcome	No comorbidity	Comorbidity	*p*-value
Abdominal pain	N = 370	N = 41	
FIQR			0.148
Mean (SD)	45.6 (21.2)	51.0 (22.3)	
Range	0.0–98.0	18.0–96.8	
CES-D			0.169
Mean (SD)	21.1 (9.5)	23.8 (12.0)	
Range	0.0–47.0	4.0–56.0	
PCS			0.496
Mean (SD)	15.6 (12.6)	17.0 (12.9)	
Range	0.0–52.0	0.0–50.0	
Headache	N = 273	N = 138	
FIQR			0.116
Mean (SD)	45.0 (21.4)	48.5 (21.2)	
Range	4.0–98.0	0.0–96.8	
CES-D			0.072
Mean (SD)	20.8 (9.6)	22.6 (10.1)	
Range	0.0–47.0	0.0–56.0	
PCS			0.054
Mean (SD)	14.9 (12.7)	17.4 (12.4)	
Range	0.0–52.0	0.0–50.0	
Hypertension	N = 316	N = 95	
FIQR			0.211
Mean (SD)	45.4 (21.3)	48.6 (21.3)	
Range	0.0–98.0	4.3–92.0	
CES-D			0.989
Mean (SD)	21.4 (9.9)	21.4 (9.5)	
Range	0.0–56.0	2.0–44.0	
PCS			0.477
Mean (SD)	15.5 (12.7)	16.5 (12.5)	
Range	0.0–52.0	0.0–46.0	
IBS	N = 350	N = 61	
FIQR			0.604
Mean (SD)	45.9 (21.2)	47.5 (22.2)	
Range	0.0–96.8	10.7–98.0	
CES-D			0.180
Mean (SD)	21.1 (9.5)	23.1 (11.2)	
Range	0.0–56.0	0.0–45.0	
PCS			0.182
Mean (SD)	15.3 (12.4)	17.9 (14.1)	
Range	0.0–52.0	0.0–50.0	
Insomnia	N = 319	N = 92	
FIQR			0.236
Mean (SD)	46.8 (21.0)	43.7 (22.4)	
Range	4.0–98.0	0.0–88.3	

(Continued)

TABLE 2 (Continued)

Comorbidity type/Outcome	No comorbidity	Comorbidity	*p*-value
CES-D			0.855
Mean (SD)	21.3 (9.5)	21.6 (10.8)	
Range	0.0–56.0	0.0–45.0	
PCS			0.990
Mean (SD)	15.7 (12.8)	15.7 (12.3)	
Range	0.0–52.0	0.0–43.0	
Low back pain	N = 337	N = 74	
FIQR			0.494
Mean (SD)	45.8 (21.2)	47.7 (21.9)	
Range	2.0–98.0	0.0–88.7	
CES-D			0.102
Mean (SD)	21.8 (9.8)	19.7 (9.8)	
Range	0.0–56.0	0.0–42.0	
PCS			0.132
Mean (SD)	16.1 (12.9)	13.8 (11.7)	
Range	0.0–52.0	0.0–46.0	
Osteoarthritis	N = 315	N = 96	
Follow-up FIQR			0.528
Mean (SD)	46.5 (21.5)	45.0 (20.8)	
Range	0.0–96.8	4.0–98.0	
Follow-up CES-D			0.047**
Mean (SD)	21.9 (9.6)	19.6 (10.2)	
Range	0.0–56.0	0.0–45.0	
Follow-up PCS			0.424
Mean (SD)	16.0 (12.7)	14.8 (12.7)	
Range	0.0–52.0	0.0–50.0	
Obesity	N = 336	N = 75	
FIQR			0.024**
Mean (SD)	45.1 (21.4)	51.0 (20.3)	
Range	0.0–98.0	8.5–81.8	
CES-D			0.092
Mean (SD)	21.0 (9.9)	23.0 (9.1)	
Range	0.0–56.0	2.0–47.0	
PCS			0.371
Mean (SD)	15.5 (12.8)	16.9 (12.2)	
Range	0.0–52.0	0.0–46.0	
OSA	N = 343	N = 68	
FIQR			0.913
Mean (SD)	46.1 (21.2)	46.4 (22.1)	
Range	0.0–98.0	5.0–88.8	
CES-D			0.611
Mean (SD)	21.5 (9.4)	20.8 (11.5)	
Range	0.0–56.0	0.0–43.0	
PCS			0.921

(Continued)

TABLE 2 (Continued)

Comorbidity type/Outcome	No comorbidity	Comorbidity	*p*-value
Mean (SD)	15.7 (12.3)	15.9 (14.6)	
Range	0.0–50.0	0.0–52.0	
RA	N = 387	N = 24	
FIQR			0.188
Mean (SD)	45.8 (21.4)	51.7 (20.6)	
Range	0.0–98.0	7.7–84.8	
CES-D			0.218
Mean (SD)	21.3 (9.8)	23.7 (9.0)	
Range	0.0–56.0	8.0–40.0	
PCS			0.101
Mean (SD)	15.4 (12.5)	20.6 (14.7)	
Range	0.0–52.0	0.0–50.0	
GERD	N = 394	N = 17	
FIQR			0.050**
Mean (SD)	46.6 (21.2)	35.1 (22.1)	
Range	2.0–98.0	0.0–70.2	
CES-D			0.286
Mean (SD)	21.5 (9.7)	18.3 (11.9)	
Range	0.0–56.0	0.0–44.0	
PCS			< 0.001
Mean (SD)	16.0 (12.8)	8.6 (7.0)	
Range	0.0–52.0	0.0–22.0	
Hypothyroidism	N = 382	N = 29	
FIQR			0.527
Mean (SD)	46.3 (21.4)	43.8 (20.2)	
Range	0.0–98.0	4.3–81.3	
CES-D			0.023*
Mean (SD)	21.6 (9.9)	18.2 (7.4)	
Range	0.0–56.0	5.0–33.0	
PCS			0.035*
Mean (SD)	16.0 (12.9)	12.1 (9.0)	
Range	0.0–52.0	0.0–40.0	

p-values result from two-sided *t*-test. ** $p < 0.05$; * $p < 0.01$. FIQR, Fibromyalgia Impact Questionnaire Revised; CES-D, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale.

exercise or activity level which included level of pain, number of tender trigger points used in previous diagnostic criteria, level of disability, degree of fatigue, and sleep disturbance as well as quality of life (42).

We then grouped comorbidities into different specialty domains (e.g., Rheumatological, Psychiatry, Pain). These analyses revealed Psychiatric comorbidities yielded associations with increased depression and pain catastrophizing scores at follow-up. As these outcomes are expected to correlate with psychological functioning, this finding is expected. The prevalence of psychiatric disorders found in our study was 48.2% which is significantly higher than a

TABLE 3 Comparison between patients with vs. without select comorbidities by outcomes at follow-up.

	OR (95% CI)	*p*-value
FIQR (>60)		
Obesity	1.77 (1.04, 2.98)	**0.033***
CES-D (≥20)		
Osteoarthritis	0.79 (0.49, 1.28)	0.33
Hypothyroidism	0.48 (0.21, 1.04)	0.067
PCS (≥30)		
Hypothyroidism	0.36 (0.06, 1.27)	0.18

p-values result from multivariate logistic regression models. All the models were adjusted for age and sex. ** $p < 0.05$; *$p < 0.01$. OR, odds ratio; CI, confidence interval; FIQR, Fibromyalgia Impact Questionnaire Revised; CES-D, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale.

previous report where only 25.3% were found to have a psychiatric disorder (27). However, Kleycamp et al. (43) completed a systematic overview of psychiatric and chronic pain comorbidities among patients diagnosed with FM and noted the most prevalent comorbidity was depression that was found in over 50% of patients similar to our findings. Depression (38) is a significant comorbidity associated with FM and prevalence was consistent with results of another cross-sectional studies (44) In addition, Gynecological comorbidities were associated with worse depressive symptoms at follow-up. Gynecological comorbidities were less frequently observed in this study sample ($n = 21$). This finding is consistent with other studies with depression and Gynecological conditions.

Finally, we examined the impact of multimorbidities on treatment outcomes. Data revealed that the Fibromyalgia Treatment Program was equally efficacious for patients with 2 or less comorbidities as 3 or more comorbidities. To clarify the possible confusion between what constitutes a FM symptom versus an associated comorbidity, we based this not only in terms of the scientific society criteria, but also in the consideration that pain syndrome is not exclusive of FM, it is one of its main characteristics. Abdominal pain, headache could be part of the FM diagnosis, however there are other areas to be considered such as overlapping chronic pain syndromes that make them sometimes independent conditions (19–23). We included abdominal pain, headache since they were documented in the electronic medical record prior to the diagnosis of FM, and specific treatments and follow ups were given previously.

Insomnia and sleep disorder are related but have distinct differences. FM symptoms could include sleep disturbance; however, this is a broader term that encompasses various conditions that disrupt normal sleep pattern. Sleep disorders can include insomnia, as well as other conditions like obstructive sleep apnea (OSA), narcolepsy, restless leg syndrome, and parasomnias. Each sleep disorder has his own specific characteristics diagnostic criteria (42, 44, 45). We have included insomnia as an associated comorbidity in this study since prior to the diagnosis of FM, and documented in medical history, it was a diagnosis (22.38%), not a FM symptom and a specific treatment and follow ups were offered in some of the cohort patients.

Limitations of this study include the setting of a tertiary medical care clinic that results in patients with a higher degree of symptom severity and potentially comorbidity. Additionally, conducting multiple comparisons for hypothesis-generation purposes increases

TABLE 4 Impact of select grouped comorbidities on outcomes at follow-up.

Comorbidity type/Outcome	No comorbidity	Comorbidity	*P*-value
Rheumatological	N = 14	N = 395	
FIQR			0.112
Mean (SD)	36.3 (22.2)	46.5 (21.3)	
Range	10.3–84.8	0.0–98.0	
CES-D			0.078
Mean (SD)	16.7 (9.2)	21.5 (9.8)	
Range	0.0–31.0	0.0–56.0	
PCS			0.077
Mean (SD)	11.1 (8.9)	15.8 (12.8)	
Range	0.0–33.0	0.0–52.0	
Psychiatry	N = 212	N = 197	
FIQR			0.600
Mean (SD)	45.6 (21.1)	46.7 (21.7)	
Range	4.0–98.0	0.0–96.8	
CES-D			0.008*
Mean (SD)	20.1 (9.1)	22.6 (10.3)	
Range	0.0–44.0	0.0–56.0	
PCS			0.035**
Mean (SD)	14.4 (12.0)	17.1 (13.3)	
Range	0.0–50.0	0.0–52.0	
Pain	N = 232	N = 177	
FIQR			0.702
Mean (SD)	45.8 (22.2)	46.6 (20.4)	
Range	2.0–98.0	0.0–92.0	
CES-D			0.737
Mean (SD)	21.2 (9.8)	21.5 (9.7)	
Range	0.0–56.0	0.0–44.0	
PCS			0.602
Mean (SD)	15.4 (12.8)	16.1 (12.6)	
Range	0.0–52.0	0.0–50.0	
Neurological	N = 249	N = 160	
FIQR			0.478
Mean (SD)	45.6 (21.5)	47.1 (21.3)	
Range	4.0–98.0	0.0–96.8	
CES-D			0.405
Mean (SD)	21.0 (9.6)	21.8 (10.1)	
Range	0.0–47.0	0.0–56.0	
PCS			0.551
Mean (SD)	15.4 (13.0)	16.1 (12.3)	
Range	0.0–52.0	0.0–50.0	
Endocrinological	N = 281	N = 128	
FIQR			0.662
Mean (SD)	45.9 (21.8)	46.8 (20.6)	

(Continued)

TABLE 4 (Continued)

Comorbidity type/Outcome	No comorbidity	Comorbidity	*P*-value
Range	0.0–98.0	4.3–87.0	
CES-D			0.518
Mean (SD)	21.1 (10.0)	21.8 (9.3)	
Range	0.0–56.0	0.0–47.0	
PCS			0.413
Mean (SD)	16.0 (13.1)	15.0 (11.7)	
Range	0.0–52.0	0.0–46.0	
Cardiovascular	N = 292	N = 117	
FIQR			0.320
Mean (SD)	45.5 (21.3)	47.8 (21.6)	
Range	0.0–98.0	4.3–92.0	
CES-D			0.715
Mean (SD)	21.2 (9.9)	21.6 (9.6)	
Range	0.0–56.0	2.0–44.0	
PCS			0.455
Mean (SD)	15.4 (12.7)	16.4 (12.8)	
Range	0.0–52.0	0.0–46.0	
Pulmonary	N = 308	N = 101	
FIQR score			0.485
Mean (SD)	45.7 (21.5)	47.4 (21.0)	
Range	0.0–98.0	5.0–88.8	
CES-D			0.597
Mean (SD)	21.5 (9.5)	20.9 (10.5)	
Range	0.0–56.0	0.0–43.0	
PCS			0.718
Mean (SD)	15.5 (12.4)	16.1 (13.7)	
Range	0.0–50.0	0.0–52.0	
Sleep	N = 309	N = 100	
FIQR			0.108
Mean (SD)	47.2 (21.0)	43.1 (22.3)	
Range	4.0–98.0	0.0–88.3	
CES-D			0.954
Mean (SD)	21.3 (9.5)	21.3 (10.7)	
Range	0.0–56.0	0.0–45.0	
PCS			0.646
Mean (SD)	15.8 (12.9)	15.2 (12.1)	
Range	0.0–52.0	0.0–43.0	
Gastrointestinal	N = 310	N = 99	
FIQR			0.564
Mean (SD)	45.8 (20.9)	47.3 (22.8)	
Range	2.0–88.8	0.0–98.0	
CES-D			0.438
Mean (SD)	21.1 (9.1)	22.1 (11.7)	
Range	0.0–47.0	0.0–56.0	

(Continued)

TABLE 4 (Continued)

Comorbidity type/Outcome	No comorbidity	Comorbidity	*P*-value
PCS			0.262
Mean (SD)	15.3 (12.4)	17.0 (13.6)	
Range	0.0–52.0	0.0–50.0	
Muscle-skeletal	N = 313	N = 96	
FIQR			0.810
Mean (SD)	46.0 (21.3)	46.6 (21.9)	
Range	2.0–96.8	0.0–98.0	
CES-D			0.064
Mean (SD)	21.8 (9.7)	19.7 (9.9)	
Range	0.0–56.0	0.0–44.0	
PCS			0.116
Mean (SD)	16.2 (13.0)	14.0 (11.6)	
Range	0.0–52.0	0.0–50.0	
Gynecology	N = 388	N = 21	
FIQR			0.290
Mean (SD)	45.9 (21.2)	51.7 (24.0)	
Range	0.0–98.0	4.3–93.5	
CES-D			0.022*
Mean (SD)	21.1 (9.9)	25.2 (7.3)	
Range	0.0–56.0	10.0–37.0	
PCS			0.087
Mean (SD)	15.5 (12.7)	19.9 (11.0)	
Range	0.0–52.0	0.0–39.0	
Nephrology	N = 394	N = 15	
FIQR			0.058
Mean (SD)	45.8 (21.3)	56.8 (20.4)	
Range	0.0–98.0	18.0–86.3	
CES-D			0.294
Mean (SD)	21.2 (9.8)	23.6 (8.2)	
Range	0.0–56.0	10.0–39.0	
PCS			0.541
Mean (SD)	15.6 (12.6)	18.1 (15.1)	
Range	0.0–52.0	4.0–48.0	

p-values result from two-sided *t*-test. ** $p < 0.01$; * $p < 0.05$. FIQR, Fibromyalgia Impact Questionnaire Revised; CES-D, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale.

the risk of false positive results. This possibility should be considered when interpreting the findings. Moreover, correction procedures for multiple comparisons were not applied in our study, potentially influencing the significance of certain findings. Future research should address this limitation by employing appropriate correction methods. Further replication studies are needed to validate the significant finding related to obesity and establish the reliability and generalizability of our results.

One of the major limitations of this study is that the comorbidities were collected from medical records and relied on a

TABLE 5 Impact of multi-morbidities on outcomes at follow-up.

	2 or less (*N* = 276)	3 or more (*N* = 135)	*P*-value
FIQR			0.486
Mean (SD)	45.6 (21.1)	47.2 (21.9)	
Range	2.0–98.0	0.0–92.0	
CES-D			0.993
Mean (SD)	21.4 (9.4)	21.4 (10.6)	
Range	0.0–56.0	0.0–45.0	
PCS			0.669
Mean (SD)	15.5 (12.6)	16.1 (12.9)	
Range	0.0–52.0	0.0–48.0	

p-values result from two-sided *t*-test. $^{**}p < 0.01$;$^{*}p < 0.05$. FIQR, Fibromyalgia Impact Questionnaire Revised; CES-D, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale.

condition having been diagnosed/documented in the patient notes to be considered a comorbidity The process of collecting data from the electronic medical record was done through an electronic search and by hand in order to ensure accuracy of the data. However, these methods used retrospectively may have underestimated the occurrence of comorbid health conditions. Future studies may be able to collect this information from health care providers prospectively to improve this aspect of the data. Given the limited sample size specific to our tertiary care setting, it is unclear whether it is the obesity or a combination of other less statistically significant comorbidities in association with the obesity that negatively impacted these outcome measures along with the FM. The study assessed the prevalence of comorbidities in our FM patients, but further evaluation needs to be done regarding the generalizability of our results. Further, in our population of FM patients, headaches, osteoarthritis, and hypertension were the most common comorbidities and although cannot be directly linked to gender or age, they are common concerns in middle-aged women (90% of our FM population). Lastly, the limited sample size may impact the percentage of FM patients with concomitant rheumatoid arthritis compared to other studies.

The most important clinical implication of this study is that obesity, which is a modifiable comorbidity, had a significant influence on treatment outcomes. In other words, treatment of obesity in tandem with treatment of FM may yield improved patient outcomes compared to treatment of FM alone for patients with comorbid obesity.

Conclusion

.Our data suggests that specific comorbidities may need to be addressed more aggressively by primary and specialty physicians to improve outcomes in FM. In particular, obesity was found to negatively impact the success of an intense cognitive behavioral treatment program and needs further investigation. This finding has important implications in the treatment of FM as obesity has been linked to many other modifiable comorbid conditions. Healthcare providers who take care of these patients should keep in mind the potential impact of associated comorbidities on outcomes and address and modify them if possible.

Data availability statement

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

Ethics statement

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

Author contributions

FR: Conceptualization, Writing – original draft, Writing – review & editing, Methodology, Project administration. BM: Conceptualization, Writing – original draft, Writing – review & editing. MA: Conceptualization, Methodology, Writing – review & editing. DH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. MW: Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. BW: Conceptualization, Methodology, Writing – review & editing. AA: Conceptualization, Methodology, Writing – review & editing. AP: Conceptualization, Methodology, Writing – review & editing. DK: Conceptualization, Methodology, Writing – review & editing. BB: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Online pain neuroscience education and graded exposure to movement in breast cancer survivors: protocol of a randomized controlled trial

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Introduction: Cancer-related chronic pain is an important sequelae that damages the quality of life of breast cancer survivors. Pain neuroscience education and graded exposure to movement are therapeutic tools that have been shown to be effective in the management of chronic pain in other populations. However, there are no previous studies that combine them after breast cancer.

Objective: To evaluate the effectiveness of an online physiotherapy focused-person program which combines pain neuroscience education and graded exposure to movement for quality of life improvement in breast cancer survivors.

Methodology: This protocol is a randomized controlled trial with a sample size of 40 breast cancer survivors with pain in the last 6 months. Participants will be allocated to the experimental or control group using a fixed size block randomization method. The evaluator and statistician will be blinded to participant allocation. Participants in the experimental group will receive a 12-week intervention based on pain neuroscience education and therapeutic yoga as a graded exposure to movement exercise; participants in the control group will continue with their usual cancer-related symptoms care. Both groups will receive an education booklet. The main outcome will be quality of life, measured by the Functional Assessment of Cancer Therapy – Breast (FACT–B+4); secondary, four outcomes related to pain experience (catastrophising, self-efficacy, kinesiophobia and fear-avoidance behaviors) will be also assessed. All variables will be assessed by two blinded evaluators at four timepoints. A mixed-model analyses of variance ANOVA (2 × 4) will be used to study the effects of the treatment on the dependent variables. All statistical tests will be performed considering a confidence interval of 95%. SPSS program will be used for the data analysis.

Discussion: This research is expected to contribute to breast cancer rehabilitation field. The proposed intervention is also expected to improve self-care skills related to chronic pain and to empower women regarding the management of their symptoms and quality of life.

Clinical trial registration: https://clinicaltrials.gov/, NCT04965909.

KEYWORDS

breast neoplasms, quality of life, pain neuroscience education, exercise therapy, yoga

1 Introduction

Currently, chronic pain is one of the sequalae with the highest incidence in breast cancer survivors, seriously impacting their quality of life and making it difficult for them to reintegrate into society and their workplace (1–3). According to a biopsychosocial perspective (4), the chronification of pain must be understood as a complex and multifactorial process involving biological, psychological, emotional and social factors (5).

Together with the advances in the understanding of chronic pain, several therapeutic approaches have emerged. Among them, interventions based on pain neuroscience education (PNE) and graded exposure to movement (GEM) have reported important benefits for different chronic pain conditions (6–17). PNE is defined as a therapeutic tool implemented by a healthcare professional aimed at the empowerment of people related to their pain process management (18–21), while GEM applies movement following the "Twin Peaks" metaphor proposed by Butler (22) to get more functionality associated with less painful experiences. In this clinical trial therapeutic yoga will be applied as a graded movement intervention in conjunction with techniques of movement representation (GEM-Y). Therapeutic yoga has demonstrated to be an effective exercise for the improvement of quality of life in adults with cancer (23), for addressing other adverse effects on breast cancer survivors (24), and to manage symptoms in other chronic painpopulations (14, 15). In addition, yoga is a body–mind exercise that allows us to follow biopsychosocial approach (5) and to adjust easily the intensity of exercise to each individual context. PNE has been scarcely investigated in breast cancer survivors (25, 26), and for our knowledge the combination of PNE with GEM-Y has never been studied in this population. As breast cancer prevalence and survivorship rate is growing exponentially in transitioned countries, but also cancer-related symptoms (27), it would be helpful to investigate biopsychosocial interventions aiming to improve quality of life in this population.

Thus, the purpose of this clinical trial will be to evaluate if an intervention combining PNE and GEM-Y is more effective than usual care for quality of life and chronic pain improvements in breast cancer survivors.

2 Methodology

2.1 Study design

A randomized controlled clinical trial will be carried out according to the Consolidated Standards of Reporting Trials (CONSORT) Statement (28). The Template for Intervention, Description and Replication Checklist (TIDieR) (29) will be used as a guide to provide transparency and make the intervention replicable. Also, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) was followed to develop this protocol. The protocol of this study has been registered on clinicaltrials.org with the registry number: NCT04965909.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) Women aged between 18 and 65 years; (2) diagnosis of stage 0–III breast cancer; (3) primary treatment (surgery, radiotherapy and chemotherapy) completed at least 3 months ago but may still be receiving hormone therapy; (4) pain related to primary treatment in the last 6 months; (5) access to the Internet and an electronic device that allows the use of the applications used in this study and skills for their use or assistance from a close person who has them; (6) ability to communicate fluently verbally and in writing in the language of the research team (Spanish); and (7) approval to participate in the study by the coordinator of the health team that assisted during the course of cancer and its treatment.

Exclusion criteria: (1) another previous type of cancer or breast cancer recurrence in a period of less than 1 year; (2) medical diagnosis of a neurological or autoimmune disease that limits or prevents exercise; (3) some type of pathology that is associated with a contraindication to physical exercise; and (4) the diagnosis of serious psychiatric or neurologic disorders that do not allow the participant to follow orders.

2.3 Sampling method and sample's size calculation

For sampling, non-probabilistic convenience and snowball methods will be used. The sample size was calculated based on the change in FACT-B score between the treatment and control groups at week 12. According to a previous study (30), it is estimated that patients in the intervention group would have a difference in FACT-B score of 10.11 points or more compared to the control group (F-value = 4.86). This difference is above the minimal important difference reported for this measure (7–8 points) (31) and results in an expected partial Eta2 effect size of 0.049. Considering 2 groups, 4 measurements, a type I risk or α 0.05, type II risk or β 0.20 (study power of 80%) and an estimated dropout rate of 15%, a total of 40 participants (20 per group) are needed to be enrolled. Sample size was calculated using the G*Power software, version 3.1.9.7 (Heinrich-Heine University, Düsseldorf, Germany). Figure 1 shows the flow chart of the study.

2.4 Subjects' recruitment

The sample for this study will be recruited through the dissemination of the project using social networks and with the collaboration of three Spanish breast cancer survivor support associations (Amama Sevilla, AGAMAMA and ASAMMA). Participation in the study will be voluntary. All participants will be facilitated by written informed consent that must be signed to be part of the clinical trial.

2.5 Group assignment and masking

This study will have two groups (experimental and control). For assignment, a random method will be carried out using an online tool called 'random allocation software' (2.0 version). A stratified allocation will be applied according to the women's age (≤45 years old or >45 years old). On each of the strata, a randomization will be carried out by blocks of constant size. The assignment sequence will be hidden from the evaluator and the study subjects through an automated assignment system. The preparation of the sequence, the inclusion of the individuals in each group and the assignment of the treatments will be carried out by different members of the research team. On the

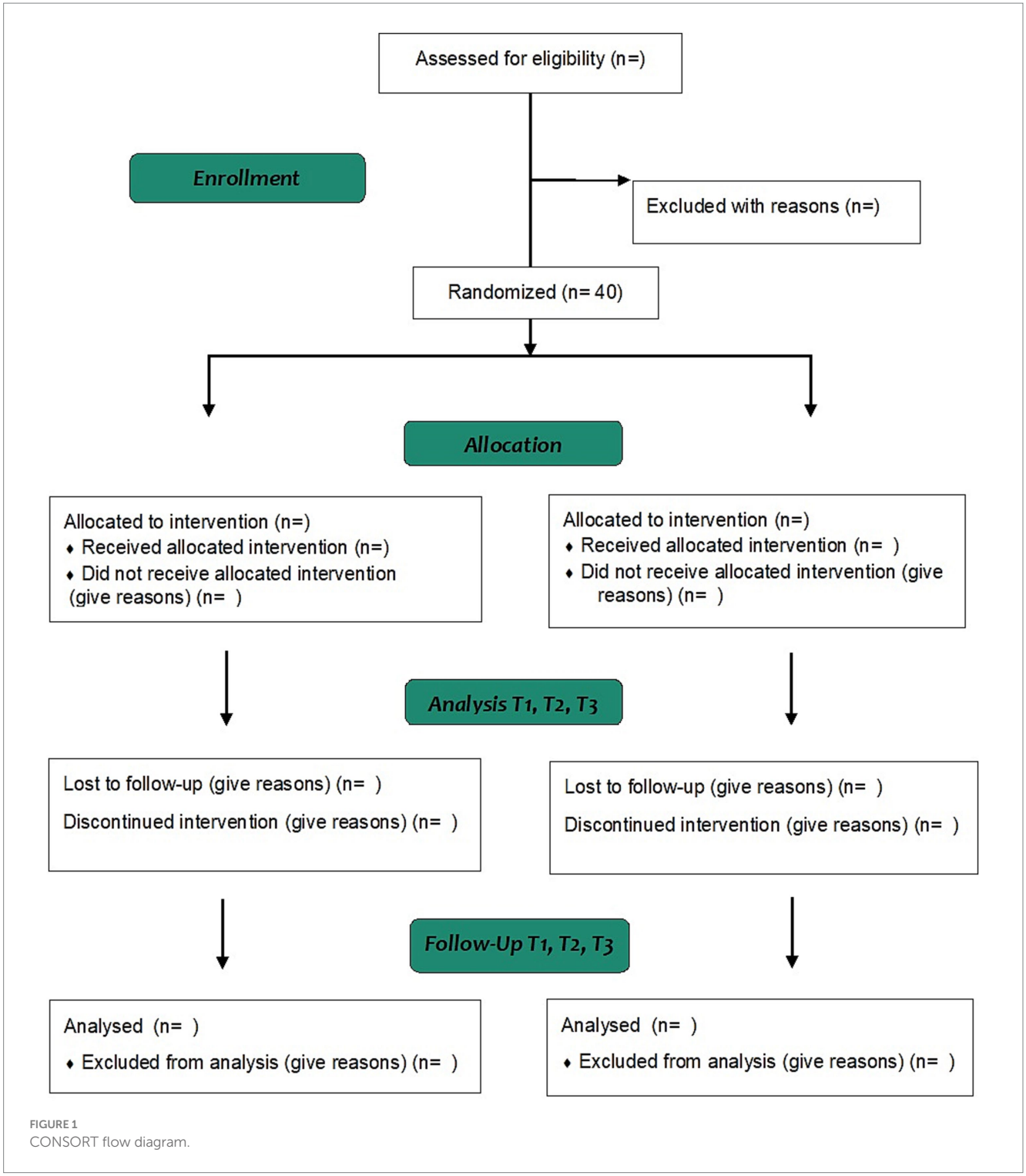

FIGURE 1
CONSORT flow diagram.

other hand, the evaluator and statistician will be blinded. Nonetheless, the therapist and subject will not be able to be blinded because of the type of intervention.

2.6 Outcomes and data collection

The main outcome of this trial is quality of life related to health, measured by the Functional Assessment of Cancer Therapy – Breast (FACT–B+4) (32); five secondary outcomes related to chronic pain experiences will be also measured: intensity of pain, catastrophising level, pain self-efficacy, kinesiophobia, and fear-avoidance behaviors.

2.6.1 The Functional Assessment of Cancer Therapy – Breast+4

The Functional Assessment of Cancer Therapy – Breast (FACT–B+4) (32) is a 41-item instrument designed to measure six domains of quality of life in patients with breast cancer: physical (PWB), social

(SWB), emotional (EWB) and functional (FWB), breast cancer subscale (BCS) and lymphedema subscale (ARM). The overall score of the FACT–B+4 ranges from 0 to 148 points (obtained from the sum of the PWB, SWB, FWB and BCS). The score of the PWB, SWB, EWB and FWB ranges between 0 and 28 points, the score of BCS between 0 and 40 points and the score of ARM between 0 and 20 points. In all of them, a higher score translates to a better quality of life. The alpha coefficient (internal consistency) and test–retest reliability for the FACT–B+4 overall score was high (alpha = 0.87; intraclass correlation coefficient: 0.986). This measure has been widely used in breast cancer population previously (33).

2.6.2 Brief Pain Inventory – Short Form

The Modified Brief Pain Inventory – Short Form (BPI–SF) (34) is a 9-item instrument designed to measure pain intensity and pain interference with the daily activities, which has been previously assessed in breast cancer population for this purpose (25, 26). The questionnaire has two subareas, one related to pain intensity, whose score ranges from 0 to 50, with a higher score being an indication of greater intensity; and another related to the interference of pain in activities of daily living, whose score ranges from 0 to 70, with a higher score being indicative of a greater impact on daily life. The internal consistency and the test–retest reliability between dimensions were good (0.87 and 0.89) and low to moderate (0.53 and 0.77), respectively.

2.6.3 Pain Catastrophizing Scale

Pain Catastrophizing Scale (PCS) (35) is one of the most widely used instruments to assess the degree of catastrophizing of pain as a result of various pathologies or diseases, including breast cancer population (25, 36). The scale consists of 3 subscales (rumination, magnification and helplessness), whose items will be valued from 0 (nothing) to 4 (all the time) to obtain a total score that ranges from 0 to 52. A higher score translates into a higher level of catastrophizing. The scale has adequate internal consistency (Cronbach's alpha = 0.79), test–retest reliability (intraclass correlation coefficient = 0.84) and sensitivity to change (effect size ≥2).

2.6.4 Pain Self-Efficacy Questionnaire

The Pain Self-Efficacy Questionnaire (PSEQ) (37) is a 22-item instrument designed to measure self-efficacy level related to pain. Each item is scored from 0 to 10. Here, 0 is equal to 'I think I am totally incapable' and 10 is equal to 'I think I am totally capable'. The total score ranges from 0 to 220. A higher score on the questionnaire corresponds to a higher level of self-efficacy. The internal consistency and test–retest reliability between dimensions were 0.91 and 0.75, respectively. This measure has been previously used in cancer survivors with pain (38, 39).

2.6.5 Tampa Scale for Kinesiophobia-11

Tampa Scale for Kinesiophobia (TSK-11) (40) is one of the most commonly used to evaluate kinesiophobia in patients with pain, including breast cancer population (36). It is composed of two factors (avoidance of activity and harm) with a total of 11 items that are valued from 1 (totally disagree) to 4 (totally agree). The total score obtained ranges from 11 to 44. More punctuation shows a higher kinesiophobia level. The internal consistency (Cronbach's alpha = 0.79) found for this scale is good.

2.6.6 Fear Avoidance Components Scale Questionnaire – Spanish Version

The Fear Avoidance Components Scale Questionnaire – Spanish Version (FACS – SP) (41) is a questionnaire that allows us to evaluate a patient's fear of pain and consequent avoidance of physical activity due to fear. The questionnaire consists of 20 items in which a patient rates his agreement with each statement on a 6-point Likert scale. Where 0 = completely disagree and 6 = completely agree. There is a maximum score of 100. A higher score indicates more strongly held fear-avoidance beliefs. Five severity levels are available for clinical interpretation: subclinical (0–20), mild (21–40), moderate (41–60), severe (61–80) and extreme (81–100). It has been previously used in breast cancer population (42).

All outcomes will be assessed at four different timepoints: before intervention (T0), after four-week PNE (T1), after 12-week complete intervention PNE + GEM-Y (T2) and after 3-month of follow-up (T3) (Figure 2). The outcomes will be assessed using the aforementioned validated scales or questionnaires that women will complete by themselves. Moreover, extra information related to their pain context will be collected by two trained evaluators in an online meeting. All data will be collected on a standardized sheet. It will be encrypted and only members of the research team will have access.

2.7 Description of the intervention in the experimental and control group

An online focused-person therapeutic program, a more up-to-day modality for this type interventions (43), that combines PNE and GEM-Y will be implemented in the experimental group. The sessions will be applied in groups of 10–15 participants, with 3 months being the duration of the entire program. The program will have two parts: the first will involve 8 sessions of PNE during the first month (2 sessions each week, 1 h/session), while the second will involve the use of 16 sessions of GEM-Y during the following 2 months (2 sessions each week, 1 h/session). Figure 3 shows an overview of the experimental intervention.

PNE sessions are divided into two content blocks: Block 1. *Knowing my painful process* and Block 2. *Pain self-management.* The Block 1 is divided into three sessions with the following educational topics: sessions (1–3) the concept of pain, acute pain and chronic pain, respectively; session (4) the concept of self-management in relation to pain and healthy habits; sessions (5–8) sleep, stress, diet and exercise habits in relation to chronic pain, respectively. A brief theoretical introduction to the GEM will be also given in the last session. A more detailed description of the content of all PNE sessions and the educational strategies to be followed is presented in the Supplementary material. Figure 4 shows an overview of the PNE programme.

GEM-Y sessions will be organised into four phases: theoretical content of the session, 'pranayama' or breathing exercises, 'dhyana' or guided meditation, and 'asanas' or postures and movements. Moreover, each session will focus on a different part of the body. In this way, yoga is used as a method of therapeutic exercise together with movement representation techniques (44, 45). The program will be delivered by a trained therapist following the principles of progression, gradualness and individualisation proposed by "Twin Peaks" metaphor (22). Thus, at the beginning of the sessions each

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation			Close-out	
TIMEPOINT	$-t_1$	0	T_0	T_1	T_2	T_3	t_x
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
Allocation		X					
INTERVENTIONS:							
PNE intervention			X	X	X		
Intervention offered to control group							X
ASSESSMENTS:							
Baseline variables: age, BMI, time since diagnostic, type of treatments received			X				
Outcome variables: Quality of life, pain intensity, pain catastrophising, self-efficacy, kinesiophobia and fear-avoidance behaviours			X	X	X	X	
Adherence rate						X	

FIGURE 2
SPIRIT schedule.

participant must identify their pain baseline in order to apply an optimal dose of exercise (principle of individualisation). Instructions are given to the participants so that they can always adapt the level of effort to their needs and their progression (more functionality with less associated pain). With regard to the principles of progression and gradualness, since each participant will have a different starting point at the beginning of the programme and will move to their own level, the rate of progression of each participant must also be different. The

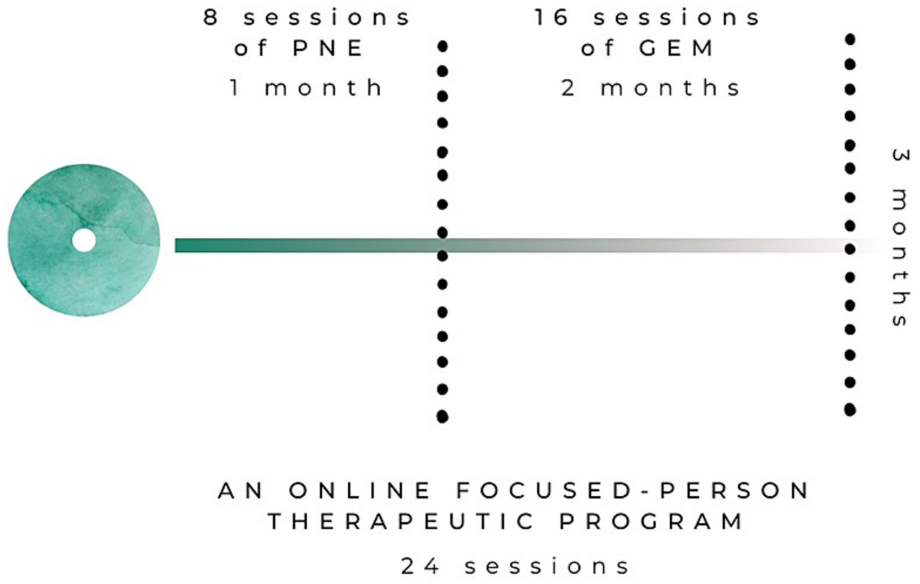

FIGURE 3
Overview of the experimental intervention.

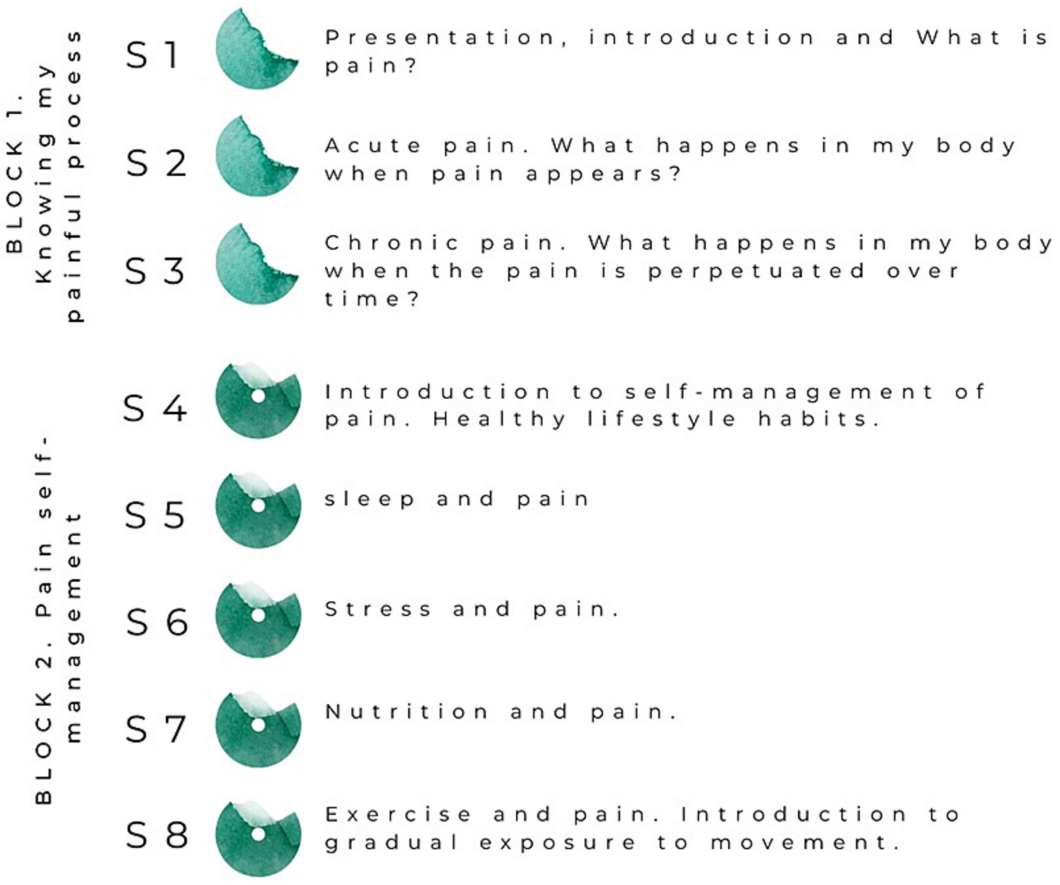

FIGURE 4
Overview of the PNE sessions.

intensity of the proposed exercises will be progressively adapted to the needs of the group by varying the following parameters: complexity of the 'asanas', volume of work (number of exercise blocks and repetitions), control of the relationship work time - rest time ratio. To identify the needs and progress of the group we will use the feedback collected from the participants at the end of each session, and the weekly pain diaries. A more detailed description of the GEM-Y sessions can be found in the Supplementary material.

The whole intervention will be implemented online using the videoconference platform of the University of Seville. Furthermore, WhatsApp and e-mail will be used during the study to give information, provide material or answer queries. Participants' attendance will be recorded, along with the reasons for non-attendance.

Participants in the control group will only receive traditional biomedical information (26, 36), i.e., explanations of perceived pain based on tissue issues, and general oncological recommendations for analgesia. They will not receive any additional educational or movement-based intervention during the study period. They will be offered the content of the program after the follow-up period for ethical reasons. An online educational booklet will be provide to both groups.

2.8 Method for data analysis

The statistical processing of the data will be conducted with the PASW Advanced Statistics, version 26.0 (IBM Corp, New York, NY, United States). Intention-to-treat principles will be considered for all analyses. The normal distribution of the variables will be assessed with the Shapiro–Wilk test. Descriptive data will be reported as mean (standard deviation), median (interquartile range Q_3–Q_1) or in percentages. Baseline homogeneity will be tested with Chi-square or Fisher's exact tests; student's t test or Mann–Whitney *U*-test.

In those variables in which the 4 measurements are adjusted to normality in both groups, a mixed-model analyses of variance ANOVA (2 × 4) will be used to differences in the outcomes after intervention, with group (PNE + GEM-Y or control) as a between-subject factor and time (the different measurements performed) as a within-subject factor. The hypothesis of interest will be the interaction group by time with an *a priori* alpha level of 0.05. Partial eta squared (η2) will be calculated to estimate the effect size. If any of the measurements do not adjust to normality, we will use the Friedman ANOVA test and the effect size will be calculated as Rosenthal's r with the formula: $r = Z/\sqrt{N}$. All statistical tests will be performed considering a confidence interval of 95%.

2.9 Ethical considerations

This protocol has the approval of the Andalusian Research Ethics Committee (CEI) of the Virgen Macarena - Virgen del Rocío University Hospitals, Sevilla, Spain (protocol code: 2170-N-20; date of approval: 14th June 2021). This clinical trial will follow the recommendations of the Declaration of Helsinki (46) and Spanish legal regulation regarding clinical research in humans (Law 14/2007 on Biomedical Research) (47).

Participants will be verbally informed in a clear and precise way of all aspects of the study. Written information, informed consent and revocation sheet will be given to all participants. Informed consent will be signed before randomization process. All data will be managed in accordance with Spanish Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights (48).

3 Reflexive discussion

The current trial aims to determine if the application of an online programme combining PNE with GEM-Y presents higher efficacy than no intervention in improving quality of life and chronic pain in breast cancer survivors. Preliminary evidence has showed that PNE may reduce pain intensity and pain catastrophizing in cancer survivors with persistent pain, but no effect on quality of life was observed (49). Particularly for breast cancer, previous findings about the effect of PNE are controversial. Cramer et al. (24) evaluated the effect of perioperative PNE on pain chronification 1 year after surgery and reported that PNE was more beneficial than general biomedical information for this purpose. In contrast, Manfuku et al. (25) concluded that perioperative PNE had not significant effect on pain-related disability or pain intensity 18 months after surgery.

Yoga has been showed to be an effective exercise modality for improving overall quality of life in people with cancer (50). In breast cancer in particular, the majority of studies to date support this benefit (24, 51–53), but no effects have been reported in other cases (54, 55). The effects of yoga on cancer-related pain have been scarcely investigated, with controversial findings for pain severity reduction in breast cancer population (51, 56).

Although the evidence for PNE in breast cancer is still limited, we consider it is possible that the combination of this intervention with yoga may benefit the quality of life and chronic pain experience of breast cancer survivors. To our knowledge, this type of programme has not been previously tested and fits with future directions for pain management in cancer survivors (57). Thus, this clinical trial is an innovative proposal that could have significant benefits for women's health and their resources for coping with chronic pain. In addition, women and health policies could benefit from a reduction in medication use and socio-economic savings. In addition, the results of this trial will be disseminated in peer-reviewed journals and at international conferences, and shared with participants and other people with cancer.

Finally, some limitations need to be discussed. First, the follow-up period could be considered short as most of the educational interventions in this population consider longer periods; however, when educational interventions are presented in an online modality, it is common to consider this time period (43). Secondly, the proposed snowball sampling method could limit the generalisability of our results, as well as the representativeness of the subjects analyzed.

Ethics statement

The studies involving humans were approved by Andalusian Research Ethics Committee (CEI) of the Virgen Macarena - Virgen del Rocío University Hospitals, Sevilla, Spain (protocol code: 2170-N-20; date of approval: 14th June 2021). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PM-M: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MC-H: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. CG-M: Writing – original draft, Writing – review & editing. MM-F: Writing – original draft, Writing – review & editing. JJ-R: Conceptualization, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1355964/full#supplementary-material

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The effectiveness and safety of lifestyle medicine and integrative therapies in inflammatory arthritis: an umbrella review using a hierarchical evidence gathering approach

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Objective: An umbrella review was conducted to provide a comprehensive evaluation of the evidence on lifestyle medicine and integrative therapies for inflammatory arthritis.

Methods: Five electronic databases were searched for umbrella reviews, meta-analyses, and systematic reviews of randomised controlled trials on acupuncture, diet, exercise, herbal medicine, nutrient supplements, and mind–body therapies for rheumatoid arthritis, spondyloarthritis, and gout published from January 2012 to December 2022. The primary outcomes were functional status and quality of life. Quality assessment was performed using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2) tool, and the certainty of evidence for our primary outcomes was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach where possible.

Results: We included 52 reviews. Exercise was beneficial for functional status in both rheumatoid arthritis and spondyloarthritis, with moderate certainty of evidence. Chinese herbal medicine in combination with disease-modifying anti-rheumatic drugs may improve functional status in rheumatoid arthritis (very low certainty evidence). Acupuncture may improve functional status in rheumatoid arthritis and pain in both rheumatoid arthritis and gout; however, the evidence is of very low certainty. Evidence for other therapies was not clinically significant; however, it suggests possible benefits from quercetin and polyunsaturated fatty acids. Yoga may result in a moderate improvement in functional status when used as an adjunct to medication; however, the certainty of evidence is very low. Diet interventions offered inconsistent improvements to functional status in rheumatoid arthritis, spondyloarthritis, and gout with low to very low certainty.

Conclusion: Exercise should be prescribed for people with rheumatoid arthritis and spondyloarthritis. More research is needed to confirm or refute evidence for Chinese herbal medicine, acupuncture, yoga, and anti-inflammatory diets.

KEYWORDS

rheumatoid arthritis, ankylosing spondylitis, gout, complementary therapies, exercise, diet

1 Introduction

Arthritis is a broad term for a group of diseases that cause pain and swelling in joints and connective tissues and encompass approximately 100 conditions (1). Arthritis is estimated to affect 53.2 million adults in the United States, with one in five people living with a diagnosis of arthritis (1). The most prevalent forms of arthritis include osteoarthritis, characterised by cartilage deterioration with a loss of joint space, and inflammatory arthritides (IA) such as rheumatoid arthritis (RA), spondyloarthritis, and gout (2). Although the pathogenesis of this latter group is diverse, IA have a chronic and progressive natural history that, if uncontrolled, may lead to irreversible joint damage (3).

The potential impact of IA on the quality of life is significant. People with RA and ankylosing spondylitis are more likely to experience persistent ongoing symptoms such as chronic pain and fatigue, as well as functional disability from progressive joint damage, resulting in substantial deficits to both physical and mental health when compared with the general population (4). Permanent work disability occurs in over a third of people (37%) with RA, and this impact is evident globally (5). The onset of disability may be rapid, with up to 20–30% of work disability occurring within the first 5 years of symptom onset (6).

The aim of treatment in IA is to relieve pain and stiffness and target the underlying disease process to restore function and prevent progressive joint damage (7). Pharmacological management is a mainstay of treatment with the use of disease-modifying anti-rheumatic drugs (DMARDs) to control disease activity. In RA and spondyloarthritis, this finding may involve conventional synthetic DMARDs such as methotrexate, as well as more novel biological and targeted synthetic drugs (8, 9). In chronic gout, pharmacotherapy with the use of urate-lowering therapy is strongly recommended for those with frequent flares, subcutaneous tophi, or radiographic evidence of joint damage (10).

There is currently an increased inclusion of lifestyle interventions such as dietary changes and exercise in clinical guidelines. Exercise is recognised as an essential part of disease management in spondylarthritis (8) and is strongly recommended in RA (9), although there is less certainty for other lifestyle recommendations in RA and gout (9, 10).

However, many people with IA also report using complementary and integrative therapies. While an estimated 47% of people with RA use complementary therapies worldwide, only 30% of patients report this use to their physician (11). For people with ankylosing spondylitis, the prevalence of integrative therapy usage is reported to be over 40% (12). The prevalence of integrative therapy usage in gout may be less than that in other rheumatic diseases at 23.9%, although the available research is limited (13).

Complementary medicine describes healthcare approaches not traditionally considered part of conventional medical care or originating outside of usual Western practice (14). Complementary medicine refers to a diverse range of practices and therapies, including acupuncture, mind–body therapies, and herbal medicines (14, 15). Integrative medicine describes the coordinated and multimodal use of conventional health approaches and complementary therapies to promote the overall wellbeing. This review will use the term "integrative therapies" to refer to these non-mainstream approaches (16).

The prevalence of integrative therapy utilisation may reflect patient-reported priorities for care in arthritis, which include the control of physical symptoms and the achievement of normalcy, self-efficacy, and general wellbeing (17). In Australia, users of integrative medicine tend to be well engaged with conventional health services and highly educated, but with multiple or chronic diseases causing a lower than average quality of life (15, 18). A scoping review elucidated the use of natural products in individuals with RA and reported that decreased pain intensity, improvement of sleep, alleviation of symptoms, health promotion, reduced swelling, reduced fatigue, and improved activity level were some of the criteria used by individuals with RA to assess whether a natural product was effective and were reasons for the use of integrative therapies (11). Integrative therapies may offer patients additional means of achieving their desired health outcomes.

However, common concerns about integrative therapy use reported by medical practitioners include: a lack of comfort in answering questions about integrative therapies, and a lack of high-quality experimental evidence regarding their efficacy and safety (14).

The available high-level evidence for integrative therapies in the specific population of IA is limited. To the best of our knowledge, an umbrella review focussing on integrative therapies for chronic IA has not yet been conducted. Clinical guidelines from national rheumatology associations are limited. The American College of Rheumatology (ACR) recently published a guideline on exercise, diet, and integrative therapies in RA, the first to our knowledge; however, the scope is limited to RA alone and does not include herbal therapies (19).

Given the prevalence of integrative therapy utilisation and the scarcity of high-level evidence in the population of IA, additional research is necessary to facilitate an informed discussion between patients and practitioners. The aim of this umbrella review is to identify and synthesise existing evidence from umbrella reviews, meta-analyses and systematic reviews of randomised control trials (RCTs) in order to systematically evaluate the effectiveness and safety of lifestyle medicine and integrative therapies in the management of chronic IA.

2 Methods

An umbrella review, also known as an overview of reviews, is a systematic approach for the identification of multiple systematic reviews on a related topic for the purpose of collating results for pre-identified outcomes. It may be used to describe the current body of systematic review evidence or adapt existing evidence towards a new clinical question (20).

2.1 Protocol registration

Our study was designed and reported in accordance with the PRIOR reporting guidelines (21). A protocol was developed a priori and registered on Open Science Framework (https://osf.io/5y39u/) on 7th February 2024.

2.2 Search strategy

A comprehensive search strategy was developed by a team of clinician-researchers, including a rheumatologist and general practitioner, with assistance from a university librarian. One author (JL) conducted a systematic search of five electronic databases (Ovid

TABLE 1 Inclusion criteria—eligibility criteria.

Population	All adults (≥18) with a diagnosis according to established clinical criteria of chronic inflammatory arthritis, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout. The following were excluded: • Studies enrolling participants <18 years (where age limitations were not specified, the included studies were evaluated to see if age characteristics were extracted and reviews that did not report age characteristics or did not provide separate data analysis for paediatric and adult populations) were excluded. • Studies that evaluated acute arthritis (e.g., septic arthritis, acute gout flare treatment) or mechanical disease (e.g., osteoarthritis) were excluded. • Studies on participants without joint involvement as the primary manifestation of disease, such as those that enrolled patients with psoriasis or cutaneous lupus without specifying arthritis, were excluded.
Interventions	Adjunctive or stand-alone treatment with any type of acupuncture, Chinese herbal medicine, mind–body medicines, nutraceuticals, dietary interventions, massage and/or exercise therapy, or a combination of these with any duration and frequency.
Comparisons	Control can be any comparative control.
Outcomes	Primary outcomes: • Functional status and health-related or general quality of life (including instruments like health assessment questionnaire/HAQ and variants, Patient-Reported Outcome Measurement Information System/PROMIS, medical outcomes study/MOS item short score). Secondary outcomes: • Pain (e.g., numerical rating, visual analogue, joint pain index, Lysholm scores, and Western Ontario and McMaster Universities Arthritis Index). • Clinical assessments of disease activity or clinical response (e.g., disease activity score-28/DAS28, tender joint count/TJC, swollen joint count/SJC, duration of morning stiffness/DMS, and ACR20), inflammatory biomarkers (e.g., C-reactive protein/CRP, erythrocyte sedimentation rate/ESR, and serum uric acid/sUA), and symptom control. • Safety and tolerability data including side effects, adverse reactions, adverse events, and attrition. Any studies whose primary outcomes are listed above were included. Studies whose primary outcomes were not listed above (e.g., depressive or anxious symptoms, fatigue) were excluded.
Study design	All umbrella reviews, meta-analyses, and systematic reviews of data from randomised controlled trials (RCTs) meet the following criteria: • Published within the last 10 years. • Clear inclusion criteria. • Describes a systematic search and data extraction procedure. • Reports relevant quality assessment of included studies, e.g., Risk of Bias for randomised controlled trials in a systematic review/meta-analysis, and A MeaSurement Tool to Assess systematic Reviews (AMSTAR)/Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) or similar validated instrument for systematic reviews in an umbrella review. • English language. Reviews that included non-randomised trial designs were included only if a separate analysis of data from randomised trials was available. Published conference abstracts and clinical guidelines were included if they included an umbrella or systematic review that fulfilled the above criteria.

MEDLINE, PsycINFO, Embase, CINAHL, and Cochrane) up to 16 September 2022. The search was updated on 31 December 2022. A full copy of the search strategy is available in the Supplementary material.

Two of the four authors (JL, CP, CE, and SD) independently assessed the title and abstracts of the identified studies using our selection criteria below. Two of the four authors (JL, SD, CP, and CE) then independently assessed full-text articles. Any disagreements were resolved either by consensus or by discussion with a third author.

2.3 Selection criteria

The inclusion criteria for this study were designed using the Population, Intervention, Comparator, Outcome, Study Design (PICOS) model and are summarised in Table 1.

2.4 Data collection and analysis

2.4.1 Hierarchal evidence gathering

Due to the broad scope of the research question and resource limitations, it was not feasible to gather data from all studies. We have previously developed a systematic approach towards data gathering, favouring the top tiers of evidence (22). One author (JL) reviewed the extracted data to identify the most recent and highest tier of evidence available using the following hierarchy in order: (1) umbrella reviews; (2) network meta-analyses; (3) meta-analysis of double-blind randomised control trials (RCTs); (4) meta-analysis of RCTs; and (5) systematic reviews. The selection was verified by a second author (CE).

Where there were multiple high-tier reviews available using the same PICO criteria, the study with the most recent search date was chosen. Where an older umbrella review or network meta-analysis covered the same topic as newer meta-analyses, the latest meta-analysis was used to update the results of the prior review. If there was doubt regarding the overlap of evidence, underlying references were compared, and a citation matrix was produced. If the overlap was high or greater (>15%) as described in Pieper 2014, the review with the most recent search end date was retained (23, 24). Where there was a partial overlap between included studies, only the most recent data for a specific intervention-control comparison were extracted.In this way we aimed to avoid overlap and present the most recent data from the highest tier of evidence for each individual comparison of intervention versus comparator in specific patient groups and for specific outcomes.

2.4.2 Data extraction

One review author (JL) extracted relevant information from the included studies, including study design, population, intervention and comparator details, and outcome information. Ten percent of the included studies were extracted in duplicate and verified by a second author (CE) to ensure consistency. Outcomes were extracted as weighted or standardised mean differences with confidence intervals for continuous outcomes, risk ratios or odds ratios for dichotomous outcomes, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (25) quality rating was extracted for primary outcomes where available.

2.4.3 Quality assessment of included reviews

Included studies were assessed using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2) tool (26). This was done in duplicate and independently in pairs by JL, CP, CE, VR, AM, JLiu, and AO, with disagreements resolved by discussion and a third reviewer (CE, AO, and JL) arbitrating if necessary. An overall rating of study quality from "critically low" to "high" was given based on the number of critical and non-critical domains met by the included reviews, as described in Shea et al. (26). To the best of our knowledge, there is no validated tool to assess the methodological quality of umbrella reviews, and these were therefore not assessed for quality.

2.4.4 Certainty of evidence

The GRADE approach (25) was used to assess and report the certainty of evidence. Due to resource limitations, only functional status was assessed. Where functional status was not available, a GRADE assessment was conducted for composite measures of disease activity or clinical response. If the study authors conducted a GRADE assessment for these outcomes, then functional status was extracted directly.

Otherwise, GRADE assessments were conducted independently in duplicate pairs (JLiu, CE, AO, CP, and SA). Disagreements were resolved by discussion with a third reviewer (CE and JLiu), arbitrating if necessary. Not all studies reported enough information to conduct a GRADE assessment or reported a relevant outcome.

3 Results

3.1 Search results

Figure 1 presents the search results, study selection, and inclusion process in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. After duplicates were removed, we screened 1,674 studies and excluded 1,401 at the title and abstract stage. A total of 82 studies were eligible to be included. Of the 82, 30 studies were subsequently excluded after the hierarchical evidence synthesis screening, leaving 52 studies in our review. A full list of the excluded studies with reasons is provided in Supplementary Table S1.

3.2 Study characteristics

Of the 52 included reviews, 38 enrolled participants had rheumatoid arthritis, 12 had spondyloarthritis, and 6 had gout. These 52 reviews include three (27–29) which included both RA and spondyloarthritis patient cohorts and one (30) which included RA and gout patient cohorts. Overall, 5 umbrella reviews, 3 network meta-analyses, 39 meta-analyses, and 5 systematic reviews were included. A broad overview of study information is presented below, with full characteristics of the included studies in Supplementary Table S2.

We found five studies on acupuncture and moxibustion, including one network meta-analysis (31) and four meta-analyses (32–35), covering several acupuncture and related therapies both alone and together with pharmacotherapy. There were three studies on diet interventions, including two meta-analyses (10, 36) and one systematic review (10, 37), encompassing Mediterranean, low-inflammatory, hypocaloric, and a range of other diets, most commonly compared with the usual diet. There were 14 studies evaluating exercise interventions, including three umbrella reviews, (38–40) nine meta-analyses, (27, 41–48), and two systematic reviews (49, 50) covering a range of exercise subtypes and programmes compared with both alternative treatments (active controls) and no physical activity (inactive controls).

There were 17 studies on Chinese herbal medicines, both as monotherapy and combination therapy with conventional pharmacotherapy, including 1 umbrella review, (51) 2 network meta-analyses, (52, 53), and 14 meta-analyses, (54–67). *Tripterygium wilfordii* Hook F extract was the intervention in seven studies, with nine other studies reviewing the glucosides of paeony, specific Chinese herbal decoctions and pills, and pooled analyses of Chinese herbal medicines. Non-Chinese herbal medicines were reviewed in five studies: one umbrella review (28), two meta-analyses, (10, 30) and two systematic reviews (10, 68, 69) covering spices and plant extracts primarily against placebo.

We found nine studies on nutrient supplements, including one umbrella review, (28) seven meta-analyses, (10, 29, 70–74), and one systematic review (10, 37). These evaluated omega fatty acids/fish oils, vitamins, probiotics, and other supplements against a variety of comparators, including placebo, medication, and other nutrient supplements. Mind–body therapies, including yoga, Tai Chi, and mindfulness programmes, were reviewed in three studies, all of which are meta-analyses (75–77).

3.3 Quality assessment

The methodological quality of the included reviews was mostly critically low or low (Table 2). Common critical flaws included not providing a list of excluded studies with reasons (item 7) or evidence of a protocol (item 2). A complete list of AMSTAR-2 findings is provided in Supplementary Table S3.

3.4 Findings: integrative therapies for rheumatoid arthritis

We included 38 reviews on integrative therapies for rheumatoid arthritis, covering acupuncture, diet interventions, exercise, Chinese and other herbal medicines, nutrient supplements, and mind–body

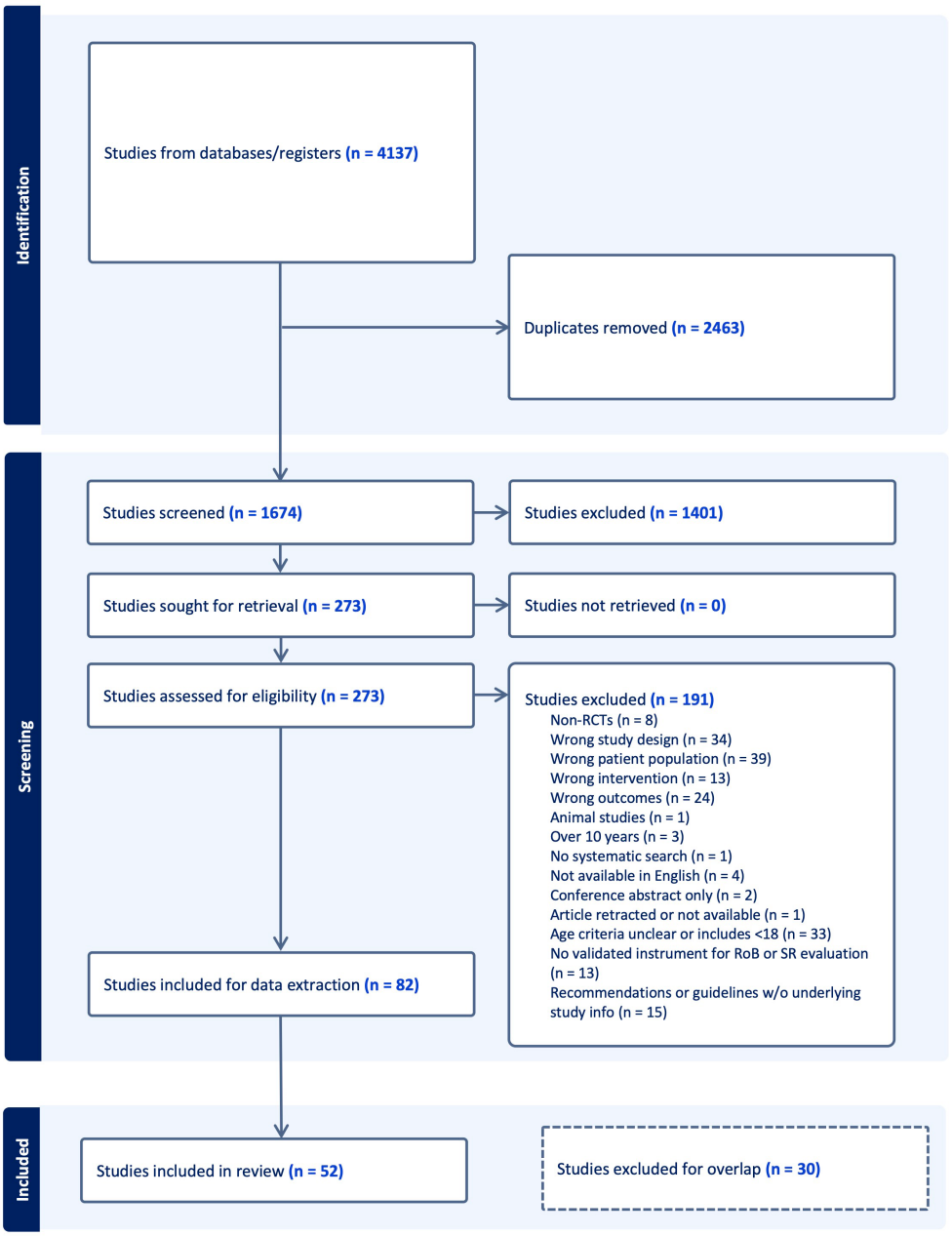

FIGURE 1
PRISMA flow diagram.

interventions. A full summary of the findings is provided in Supplementary Table S4.

3.4.1 Acupuncture and related techniques for rheumatoid arthritis

We included four reviews on acupuncture and moxibustion (one NMA and three MAs) (31–33, 35). Needle or laser acupuncture resulted in a clinically non significant improvement in functional status compared to sham or oral medication (32) but there was no additional improvement when combined with Western medicine (33). There may be no clinical improvement in disease activity with moxibustion in combination with a DMARD compared with DMARD alone but the evidence is very uncertain. Electroacupuncture was the only other subtype of acupuncture that improved disease activity in combination with a DMARD; however, these findings were based on a single trial (31).

Laser or needle acupuncture improved pain, quality of life, and biomarkers against a pooled control of sham or oral medications (32). When combined with Western medicine, needle acupuncture improved biomarkers, joint counts, and pain, and a number of other acupuncture subtypes improved biomarkers (33). Moxibustion had a mixed clinical response, improving ACR50 (American College of Rheumatology response criteria) but not ACR70 (35).

These reviews reported a limited number of adverse effects (AE). Minor skin irritation and swelling were the most common AE in the

TABLE 2 AMSTAR-2 assessment of included studies*

Author	Critical flaws	Outcome	Author	Critical flaws	Outcome
Bjork (27)	—	Moderate	Ortolan (50)	7, 15	Critically low
Byrnes (49)	2, 7	Critically low	Pecourneau (43)	2, 7, 13, 15	Critically low
Daily (54)	7	Low	Philippou (69)	7, 15	Critically low
Feng (55)	7	Low	Regnaux (44)	15	Low
Fitzgerald (10)	2, 7	Critically low	Schonenberger (36)	7	Low
Geng (56)	—	Moderate	Sieczkowska (45)	7, 11, 15	Critically low
Gkiouras (70)	7	Low	Sigaux (74)	7	Low
Guan (71)	2, 7	Critically low	Sobue (46)	2, 7, 11, 13	Critically low
Han (57)	2, 7	Critically low	Sun (35)	2, 7, 11	Critically low
Jo (59)	7	Low	Wan (31)	7, 13	Critically low
Kou (72)	2, 7, 13, 15	Critically low	Wang (53)	7, 13	Critically low
Letarouilly (68)	2, 7	Critically low	Wang (63)	2, 7, 15	Critically low
Li (58)	7,	Low	Wang (62)	7, 13	Critically low
Li (52)	7, 13	Critically low	Williams (47)	2	Low
Li (32)	2, 7, 15	Critically low	Xu (64)	7	Low
Liang (42)	2, 7, 11	Critically low	Ye (76)	2	Low
Liang (41)	9, 15	Critically low	Ye (48)	7, 15	Critically low
Liu (60)	2, 7, 13, 15	Critically low	Zeng (29)	2, 15	Critically low
Luo (61)	7	Low	Zeng (30)	15	Low
Lu (34)	2, 7, 13	Critically low	Zhang (65)	2, 7	Critically low
Lu (33)	7, 11, 13	Critically low	Zheng (66)	2, 7, 13	Critically low
Mudano (75)	11	Low	Zhou (67)	2, 7, 13, 15	Critically low
Nguyen (73)	2, 7, 9, 13, 15	Critically low	Zhou (77)	2, 13, 15	Critically low
Ortolan (37)	2, 7, 15	Critically low			

*Umbrella reviews not assessed.

acupuncture group, as were gastrointestinal disturbances in the DMARD group.

3.4.2 Diet interventions for rheumatoid arthritis

One MA reported on diet interventions. Pooled analysis with data from various anti-inflammatory diets (Mediterranean, vegetarian, vegan and ketogenic diets) suggest there may be improved functional status in comparison to an omnivorous diet which approached clinical significance (36), however the evidence is very uncertain. Anti-inflammatory diets also improved pain and SJC in the same pooled analysis; however, no improvements were reported for TJC, ESR, or CRP (36). Detailed information on AEs was not reported.

3.4.3 Exercise for rheumatoid arthritis

There were six reviews on exercise interventions (one umbrella review and five meta-analyses). An umbrella review reported that a pooled analysis of exercise types, including aerobic, strength, aquatic, and combined aerobic/strength exercise, improved functional status, but either strength training or aquatic exercise independently did not (40). A meta-analysis conducted in 2022 reported that aerobic exercise may result in a clinically significant improvement in functional status compared to control, but the evidence is very uncertain (48). Another meta-analysis reported that physical activity and exercise were more effective for activity performance than inactive controls (no treatment, usual care) but not more effective than active controls involving alternative physical activity or treatment (27).

Overall, both aerobic and a pooled exercise group were effective for reducing pain; however, an improvement in biomarkers was only found for strength training (40, 48). Exercise did not demonstrate efficacy for modifying disease activity, irrespective of intervention type (40, 45, 46). Two reviews reported on safety, with no adverse events occurring in the intervention groups (47, 48).

3.4.4 Chinese herbal medicine for rheumatoid arthritis

There were 14 studies on Chinese herbal medicines, including two reviews on various Chinese herbal medicines as a pooled group (57, 59), seven on *Tripterygium willfordii* Hook F extract (TwHF[1]) (also known as *leigongteng* or thundergod vine) (51, 53, 56, 60, 63, 64, 66), and five on other specific medicines (52, 54, 55, 61, 62).

1 In traditional Chinese medicine, TwHF is an important extract widely used for various autoimmune-mediated inflammatory diseases, with increasing interest in its anti-inflammatory and immunosuppressive pharmacological characteristics.

Chinese herbal medicines combined with DMARDs may improve functional status compared with DMARDs alone but the evidence is very uncertain (57). However, as monotherapy, they may not improve functional status compared to conventional pharmacotherapy (59). Chinese herbal medications, either as monotherapy or in combination with DMARDs, improved pain, joint counts, and biomarkers compared to pharmacotherapy alone (57, 59). Both comparisons were also associated with a reduced incidence of AEs.

Monotherapy with TwHF extract showed an improved clinical response (ACR20) when compared with most DMARDs except cyclosporine A (53). Additionally, a combination of TwHF with methotrexate also showed improved disease activity when compared with placebo or other medications (56). With regard to other outcomes, TwHF, either as a monotherapy or a combination therapy with various DMARDs, demonstrated benefit for biomarkers, disease activity, and pain across most comparisons, although the impact on joint counts was mixed (51, 56, 60, 63, 66). When compared with DMARDs, monotherapy with TwHF resulted in fewer AEs (63). However, no significant difference in AEs was found when TwHF monotherapy was compared with placebo or when combined with DMARDs (63, 64, 66).

A network meta-analysis compared four different compounds (*Bai Ju GuiZhi Decoction*/BHGZD, *Dang Gui Nian Tong Decoction*/DGNTD, *Si-Miao Pill*/SMP, and *Xuan Bi Decoction*/XBD) in combination with DMARDs against DMARDs alone and found that all four formulations reduced biomarkers. However, only XBD was superior to DMARDs for disease activity, although this was based on a single trial, and only BHGZD improved clinical response (ACR20). The highest reporting of AEs was in the groups receiving DMARDs, while the lowest was in the groups receiving SMP and DGNTD (52).

The combination of modified *Si-Miao Pill* and Western medicine reduced disease activity and biomarkers with fewer AEs in comparison with conventional pharmacotherapy (62). *GuiZhi-ShaoYao-ZhiMu Decoction*/GSZD, either as monotherapy or a combination therapy, resulted in improved joint counts and ESR as compared to conventional medication (54). Furthermore, a combination of GSZD and methotrexate also showed improved joint counts and biomarkers with fewer AEs when compared with placebo or other medications (55). Glucosides of peony in combination with a DMARD were reported by the review authors to have improved functional status based on one trial however we note a discrepancy where HAQ score was higher in the intervention group suggesting deterioration of functional status. Glucosides of paeony improved clinical response (ACR20/50/70), disease activity, and pain with a reduced incidence of AEs in the intervention group; however, we also note the discrepancy with pain outcomes, where pain scores were reported to be higher in the intervention group, but review authors noted this as an improvement (61).

3.4.5 Other herbal medicines for rheumatoid arthritis

We found four studies reviewing other non-Chinese herbal medicines (one umbrella review (28), one meta-analysis (30), and two systematic reviews (68, 69)). A systematic review reported that several spices, including garlic, ginger, cinnamon, and saffron, demonstrated mixed improvements in disease activity, pain, and biomarkers; however, these improvements were from single, small trials, albeit all double-blind placebo-controlled, and assessed as a low risk of bias (68). A meta-analysis reported that curcumin may result in clinically non-significant improvement in disease activity, biomarkers and joint counts, but the evidence is very uncertain. There was no difference between groups for AEs (30). One systematic review reported that evening primrose oil decreased disease activity and pain; however, this evidence is observed from two single trials (69).

An umbrella review reported no benefit in functional status, pain, disease activity, or quality of life with pomegranate, *aloe vera*, or rose hip powder. A single RCT reported improvements in disease activity, joint count, and ESR with a combined intervention of ginger, curcumin, and black pepper (28). The overall certainty of evidence for other herbal medicines for RA ranged from very low to low, with many outcomes only supported by single, small RCTs.

3.4.6 Nutrient supplements for rheumatoid arthritis

Nutrient supplements were reported by seven studies (one umbrella review (28) and six meta-analyses (29, 70–74)). Probiotics did not result in any change in disease activity, joint counts, or ESR, and no serious AEs were reported (29). Vitamin K and folic acid compared to placebo were of no benefit for functional status or disease activity (73). Vitamin D improved disease activity but not pain, with mixed improvements in biomarkers and index counts (71). There was no difference between Vitamin E and pooled controls for pain (73), although a subsequent MA reported benefits for disease activity and joint counts, with a mixed impact on biomarkers (72).

In one MA, omega-3 fatty acids (FAs) had no benefit for disease activity, pain, TJC, SJC, or biomarkers (70). Conversely, another MA found omega-3 and omega-6 FAs may improve functional status, joint counts, pain, disease activity and ESR, but the evidence is very uncertain. Greater effects were observed in higher doses (>2 g/day) and after a 3 months duration (74).

An umbrella review on a heterogenous range of nutrient supplements found that quercetin may be beneficial for functional status though this is limited by very low certainty evidence, potassium improved disease activity, pain, joint counts and biomarkers, and one trial reported that mussel extracts improved disease activity (28). Antioxidants may improve functional status and pain, but not other outcomes. The additional interventions in the review showed no significant effects.

3.4.7 Mind–body interventions for rheumatoid arthritis

We found three meta-analyses evaluating mind-body interventions (75–77). Yoga may improve functional status when used as an adjunct to conventional medication and when compared alone against any non-yoga intervention although not as stand-alone therapy against usual care (76). However these findings are limited by very uncertain evidence. Mindfulness-based interventions may result in a non-clinically significant reduction in disease activity in comparison with routine nursing but the evidence is very uncertain (77). Tai Chi, compared with no exercise or other types of exercise, did not benefit functional status (75).

With regard to pain, yoga resulted in a small reduction in disease activity, however, no significant differences (clinically or statistically)

were found for the other mind–body therapies. One study reported withdrawals due to AEs and found no significant differences between groups (75).

3.5 Integrative therapies for spondyloarthritis

We included 12 reviews on exercise, diet interventions, and nutrients for spondyloarthritis (see Supplementary Table S5). We did not find any systematic review evidence on acupuncture or herbal medicines for spondyloarthritis.

3.5.1 Exercise for spondyloarthritis

A total of 9 studies reported on exercise, including overall exercise and exercise subtypes against active and inactive controls (two umbrella reviews (38, 39), five meta-analyses (27, 41–44), and two systematic reviews (49, 50)). Overall, exercise resulted in clinically non-significant improvements in functional status measured using the Bath Ankylosing Spondylitis Functional Index/BASFI when compared to no intervention (44) and usual care (44) while there may also be clinically non-significant improvements compared to pooled controls but the evidence is very uncertain (43). There was no effect on activity performance when compared to active controls (e.g., other exercise programmes, home exercises, and medications) (27).

Home-based exercise may result in a clinically nonsignificant improvement in BASFI when compared with other exercise types and medical therapy but the evidence is very uncertain (42). There is high certainty of evidence for the benefit of combined aerobic and strength exercise compared to any control for functional status in axial spondyloarthritis and moderate certainty evidence for the benefit of strength exercise on functional status (38). However, no benefit was found for aerobic exercise alone or aquatic exercise (38), and there is very limited evidence of benefit for Pilates (49).

General exercise programmes and most exercise subtypes (home-based, land-based, aquatic, aerobic, aerobic/strength, strength) improved pain and disease activity when compared to no intervention, usual care, or a pooled control (27, 38, 39, 42–44, 50). However, exercise combined with anti-TNF agents did not improve disease activity compared with medication alone (41). Only one meta-analysis reported on AEs, finding a single AE in the intervention group with none in the control group (two trials, $n = 110$) (44).

3.5.2 Diet for spondyloarthritis

One systematic review provided limited information on diet interventions. A hypocaloric diet showed improved disease activity in participants with psoriatic arthritis who had not improved on traditional DMARDs. The frequency of achieving minimal disease activity was correlated with increasing weight loss (37).

3.5.3 Nutrient supplements for spondyloarthritis

Three studies were reported on nutrient supplements (one umbrella review (28), one meta-analysis (29), and one systematic review (37)). A combination of selenium, coenzyme Q10, and vitamin E may improve disease activity in psoriatic arthritis, but the evidence is very uncertain (28). Marine omega-3 fatty acids did not show benefit for functional status, pain, inflammatory markers, or TJC in psoriatic arthritis, while there is low certainty evidence for an improvement in SJC (28).

Alpha-linoleic acid, linoleic acid, and polyunsaturated fatty acid supplementation did not reduce disease activity in ankylosing spondylitis, but the evidence is very uncertain (28). Probiotics compared to a pooled control group in ankylosing spondylitis did not significantly affect functional status (BASFI) or disease activity (BASDAI, TJC, and SJC) or show any differences in AEs (29). High-dose fatty acids (4.55 g) were found to significantly improve disease activity (BASDAI) in ankylosing spondylitis compared to lower doses (1.95 g), although this was based on a single trial (37).

3.6 Integrative therapies for gout

We found six reviews on acupuncture, diet, Chinese herbal medicines, other herbal medicines, and nutrient supplements for gout (see Supplementary Table S6). We did not find any reviews on exercise or mind–body therapies.

3.6.1 Acupuncture for gout

Acupuncture, including manual and electroacupuncture, may result in greater serum uric acid reduction as compared to Western medicine but the evidence is very uncertain (34). Additionally, clinically significant benefits were found for pain reduction and mixed effects for inflammatory biomarkers. Fewer AEs were reported in the intervention group.

3.6.2 Diet for gout

There was very low certainty of evidence from a single trial reported in Fitzgerald 2020 that a 6 months purine-limited diet had no effect on serum uric acid or the rate of gout flares (10). The level of dairy protein intake showed no effect on sUA or gout flares (10).

3.6.3 Chinese herbal medicines for gout

Three studies reviewed Chinese herbal medicines, both as a group and *Guizhi-Shaoyao-Zhimu Decoction*/GSZD individually. Chinese herbal medicines as a pooled analysis of either monotherapy or in combination with Western medicines may improve sUA and CRP, but not pain (58). There was very low certainty of evidence that Chinese herbal medicine decoctions may reduce serum uric acid compared to Western medicine in another meta-analysis. The relative risk of AE was reported to be lower in the intervention group (67).The duration of treatment/follow-up was not reported in either meta-analysis.

The GSZD herbal formula may improve sUA both alone and as combined therapy when compared to conventional pharmacotherapy, but the evidence is very uncertain. The GSZD formula, whether as monotherapy or a combination therapy, improved biomarkers (ESR, CRP) and reduced the risk of AE in the intervention group (65). Gout flares were not reported in these reviews.

3.6.4 Other herbal medicines for gout

We found two meta-analyses (10, 30) on other herbal medicines. Based on a single trial, curcumin was not found to be effective in reducing sUA when compared with placebo (30). Similarly, cherry extract also showed no efficacy for reducing sUA or the incidence of gout flares based on one small trial (10).

3.6.5 Nutrient supplements for gout

A meta-analysis conducted to inform the 2020 American College of Rheumatology Guideline for the management of gout reported that Vitamin C resulted in a clinically insignificant sUA reduction compared with starting or increasing allopurinol with no effect on gout flares (based on a single trial) (10).

4 Discussion

To the best of our knowledge, this is the first umbrella review to evaluate the evidence on a comprehensive range of lifestyle medicine interventions and integrative therapies for spondyloarthritis and gout. We provide additional evidence on herbal medicines for RA, complementing the 2022 ACR guidelines (19).

For RA, exercise interventions (particularly aerobic exercise) and Chinese herbal medicine in combination with DMARDs resulted in clinically significant improvements in functional status. The evidence evaluating anti-inflammatory diets (e.g., Mediterranean) approached clinical significance (36). There was very low certainty and conflicting evidence on the benefits of various acupuncture modalities, and the results were largely but not clinically significant, except for pain. Evidence for other therapies was very limited and mostly negative or not clinically significant, although the available evidence suggests possible benefits from quercetin and omega-3 and omega-6 fatty acids (28, 74). Yoga resulted in moderate improvements in functional status when used as an adjunct to medication; however, the certainty of evidence was very low (76). Our findings broadly align with recommendations from the ACR guidelines, which offer conditional support for acupuncture, mind–body therapies, and a Mediterranean diet. At present, the ACR conditionally recommends against all supplementation (19).

We found very low to moderate certainty evidence of the benefit of exercise in RA, particularly for functional status, with more limited improvement in inflammatory biomarkers or disease activity. This effect estimate was greater in combined aerobic and strength exercise, with weaker evidence for other subtypes (40, 48). There was moderate certainty that exercise was beneficial against inactive controls (no exercise/usual care) but not active controls (other exercise or treatment). This finding may suggest that the type of exercise is less important than maintaining regular exercise for the improvement of functional status (27). ACR offers a strong recommendation for consistent engagement in exercise to improve the functional status (19), which is consistent with the findings in our review.

Chinese herbal medicines, particularly TwHF, are widely used in China to treat RA (78). TwHF may have a clinically significant benefit for functional status when used as an adjunct to DMARDs, but the certainty of evidence is very low (57). Individual remedies that demonstrated benefit for clinical response (ACR criteria) and disease activity include TwHF extract and glucosides of paeony but with low to very low certainty. A network pharmacology analysis suggests that five main compounds are involved in the mechanism of action of Chinese herbal medicines: quercetin, stigmasterol, sitosterol, kaempferol, and beta-sitosterol. These compound act to mediate inflammatory markers and may have immunomodulatory effects (52). However, reports of hepatic and renal impairment with the ingestion of TwHF have led to warnings issued by the State Food and Drug Administration in China and by the Medicines and Healthcare Products Regulation Agency in the United Kingdom (79). TwHF may result in gastrointestinal, reproductive, dermatologic, haematologic, and cardiovascular AEs (80). A clinical practice guideline on the use of TwHF for RA recommends monitoring of toxicity during administration due to the risk of adverse effects (81). However, a network meta-analysis did not find evidence of an increase in AEs when TwHF monotherapy was compared to DMARDs (53). Evidence on the safety of other Chinese herbal medicines is somewhat limited, as 33% of RCTs in one meta-analysis did not report on AEs. The AEs reported were abnormal liver and renal function tests and gastrointestinal reactions (53). The lowest reporting of AEs was with *Si-Miao Pill* and *Dang Gui Nian Tong Decoction*, whereas the highest reporting was DMARDs alone or *Xuan Bi Decoction* + DMARDs (52). Consideration must also be given to challenges relevant to Chinese herbal medicine use, which include variable quality control and regulation of herbs and a lack of accreditation standards for Chinese medicine practitioners in most countries outside of China. Limited information on dosing regimens and pharmacological assessments of drug levels for herbal medicines add further challenges to the interpretation of the data (82).

In spondyloarthritis, exercise compared to both inactive and pooled controls (usual care, physical therapy, and education) showed very low to moderate certainty of evidence for benefit (43, 44). There was moderate to high certainty of evidence that combined aerobic and strength exercises, or strength exercises alone, have a moderate effect size (SMD $\geq$ 0.5) on functional status (38). Our study findings are consistent with the European Alliance of Associations for Rheumatology (EULAR) guidelines that encourage regular exercise and recommend combined aerobic and strength exercises to improve functional status (83). However, at present, the evidence is very uncertain about the benefits of other interventions such as diet and nutrient supplements.

Acupuncture may be of benefit for pain reduction in gout (34); however, we are uncertain about the benefits of other interventions, including herbs and nutrient supplements. While we report findings from three reviews (58, 65, 67) on Chinese herbal medicines, there were few clinical outcomes (such as flare prevention) reported; hence, we are uncertain about the benefits of Chinese herbal medicines for the management of gout.

Although most of our findings are very uncertain due to the limitations of the available evidence, many of our studied interventions are relatively low risk and may provide additional benefits to people with inflammatory arthritis. While reporting of AEs was somewhat limited, the available evidence on acupuncture, mind–body therapies, curcumin, and probiotics suggests that there were no serious AEs in the intervention groups, and in fact, reduced AEs in the intervention group were commonly reported. These interventions are often widely available and used, particularly in China, where traditional Chinese medicine (acupuncture and Chinese herbal medicine) is well integrated with Western or mainstream medicine and is used by three-quarters of the population nationwide for the management of multimorbidity and chronic disease (84). There is a need for improved reporting of adverse events from RCTs in order to inform shared decision-making incorporating scientific evidence, clinical expertise, and patient values and preferences.

The strength of our review is its focussed selection of the most recent, hierarchical, and highest-level evidence available. The broad scope of our research question allowed us to identify links between integrative therapies across different pathologies and add to existing guidelines. We used validated tools and processes, such as AMSTAR-2

and GRADE, to assess study quality and confidence in effect estimates. Given the relative lack of existing overviews of integrative therapies in IA, our review provides a more comprehensive summary through a hierarchical evidence-gathering approach.

However, this approach is not without limitation. Only more recent studies were included, which may have resulted in the exclusion of older, yet high-quality reviews. Despite our efforts to minimize overlap, it may be possible that some primary research has been duplicated among the included reviews. Our study selection was limited to reviews of RCTs, which avoids bias arising from non-randomised designs, although it may result in a less comprehensive overview. Despite this limitation, the purpose of our review was to focus on high-level evidence in order to translate this evidence into recommendations for clinical practice. The study design also does not allow for a direct comparison of different interventions. Furthermore, due to resource limitations, we performed a GRADE assessment for our primary outcomes of functional status and quality of life only and cannot comment on the certainty of evidence for other outcomes.

There is a need for further rigorous RCTs and primary research to increase confidence in effect estimates. Many findings were downgraded for a serious risk of bias in underlying studies, inconsistent findings, and small study sizes, resulting in consistently low certainty of evidence. In addition, utilisation of standardised outcome measures, preferentially the use of validated patient-reported outcome measures in addition to biomarkers, would increase reliability and allow for more robust evaluations of efficacy, particularly in herbal medicine interventions. At present, the available evidence evaluating integrative interventions for IA is the most comprehensive for RA. Little to no high-level evidence was found for acupuncture, diet, mind–body, and herbal interventions in spondyloarthritis. Similarly, evaluations of diet, exercise, and mind–body therapies in gout are sparse, indicating a considerable need for further research in these areas. Future reviews should ensure their methodology aligns with established reporting guidelines and, in particular, provide a list of excluded studies with a rationale and evidence of a protocol.

5 Conclusion

There is consistent, moderate-quality evidence that exercise is beneficial for functional status in RA and spondyloarthritis. The low to very low overall quality and certainty of evidence for most diet interventions, nutrient supplements, herbal medicines, mind-body therapies and acupuncture across the IA literature precludes our ability to determine benefit. There is a pressing need for further high-quality research on integrative therapies for IA, particularly in spondyloarthritis and gout, to improve the quality of life, reduce symptom burden, and prevent disability.

Author contributions

JoL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. JiL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. AO: Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. CP: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SB-D: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. AM: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. VR: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SA: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. BN: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. CE: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

CE declares that she is the Jacka Foundation Senior Research Fellow, practicing GP and acupuncturist, Chair of the RACGP Integrative Medicine Specific Interest Network (voluntary role), Program Lead of an academic integrative healthcare centre (no financial interest), past GP Advisory Board member for Blackmores Research Institute, has received industry funding from nutraceutical and acupuncture device companies to conduct clinical trials, and has received honoraria and had travel expenses covered for presenting at complementary medicine events. As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies, and industry. Sponsors and donors provide untied and tied funding for work to advance the vision and mission of the Institute. AM declares that she is a naturopathic practitioner at a clinic in Sydney, Australia. She is the recipient of a scholarship from the Jacka Foundation of Natural Therapies for her PhD.

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1357914/full#supplementary-material

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Assessing multidisciplinary follow-up pattern efficiency and cost in follow-up care for patients in cervical spondylosis surgery: a non-randomized controlled study

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Background: The use of multidisciplinary treatment programs in out-of-hospital healthcare is a new area of research. Little is known about the benefits of this method in the management of discharged patients undergoing cervical spondylosis surgery.

Objective: This study aimed to explore the effect of a contracted-based, multidisciplinary follow-up plan in patients after cervical spondylosis surgery.

Methods: This non-blinded non-randomized controlled study was conducted with 88 patients (44 in the intervention group, 44 in the control group). The clinical outcomes, including Neck Disability Index (NDI), pain score (VAS), Self-Efficacy for Managing Chronic Disease 6-item Scale (SECD-6), and 12-Item Short-Form Health Survey (SF-12) score were assessed at the time of discharge, 24–72 h, 1 month, and 3 months post-discharge. The complications, patient satisfaction, and economic indicators were assessed at the final follow-up (3 months).

Results: Patients who received contracted follow-up showed greater improvement in neck dysfunction at 24–72 h, 1 month, and 3 months after discharge compared to those who received routine follow-up ($p < 0.001$). At 1 month after discharge, the intervention group exhibited better self-efficacy ($p = 0.001$) and quality of life ($p < 0.001$) than the control group, and these improvements lasted for 3 months. The intervention group reported lower pain scores at 24–72 h and 1 month ($p = 0.008$; $p = 0.026$) compared to the control group. The incidence of complications was significantly lower in the intervention group (11.4%) compared to the control group (40.9%). The total satisfaction score was significant difference between the two groups ($p < 0.001$). Additionally, the intervention group had lower direct medical costs ($p < 0.001$), direct non-medical costs ($p = 0.035$), and total costs ($p = 0.04$) compared to the control group. However, there was no statistically significant difference in indirect costs between the two groups ($p = 0.59$).

Conclusion: A multidisciplinary contract follow-up plan has significant advantages regarding neck disability, self-efficacy, quality of life, postoperative complications, patient satisfaction, and direct costs compared with routine follow-up.

KEYWORDS

multidisciplinary team, cervical spondylosis surgery, contracted follow-up pattern, cost, continuity of care

Introduction

Cervical degenerative disc disease is a common condition that can cause myelopathy and radiculopathy. It has been reported that 3.8–17.6% of the population experience pain in the neck (1). These symptoms can significantly impact a patient's work and quality of life. A report from the England provides the first cost-estimate to their society, an annual cost of £681.6 million per year (2). Non-surgical methods are typically used to manage pain and neurological symptoms in the cervical spine. However, if these treatments are unsuccessful, surgical interventions may be considered (3–5). Enhanced recovery after surgery (ERAS) is an interdisciplinary, multimodal approach aimed at improving postoperative outcomes. This approach employs evidence-based protocols in the care of surgical patients (6). Evidence regarding the use of ERAS protocols in spine surgery suggests that they have the potential to expedite recovery, minimize postoperative pain, and reduce hospital stay duration (7, 8). Despite the benefits of ERAS protocols, the short duration of hospitalization often prevents healthcare staff from adequately addressing patients' questions about their postoperative condition. Studies have shown that patients undergoing cervical spondylosis surgery may experience complications such as heterotopic ossification, facet joint changes, adjacent segment degeneration, dysphagia, superficial wound infections, and others (4, 5). Furthermore, patients require professional nursing services and guidance after being discharged from the hospital. This is crucial for the effective and safe implementation of postoperative rehabilitation programs, including setting functional goals, traditional exercise therapy, and cognitive-behavioral strategies following cervical surgery (9).

Continuing care after discharge from the hospital is crucial for improving function and disability in patients who have undergone cervical spondylosis surgery. Multidisciplinary treatment programs that focus on biopsychosocial rehabilitation have shown promise in addressing both physical and mental health problems in patients with neck pain, and similar components may apply to the spine surgery population (10, 11). Implementing a family physician-contracted service can enhance the continuity and coordination of care, reduce inappropriate use of specialty services, and improve overall population health (12, 13). Many countries and regions, including England, Cuba, Australia, the United States, and Canada, have already implemented a family doctor system (14, 15). In China, previous studies have shown that the family doctor system has positive effects on improving health outcomes, such as lower hospitalization rates, reduced visits to the emergency department, and higher patient satisfaction levels among those with chronic diseases (16, 17). However, there are still many problems to be solved, such as family physician shortages, inadequate contract service rates, and the absence of supporting policies. Currently, the follow-up management of patients with cervical spondylosis is often carried out by a single healthcare professional, and most of the existing plans only focus on patients' functional exercises, lacking comprehensive attention to their multidimensional health needs, such as psychological well-being, nutrition, pain management, and medication (18, 19). The evaluation of follow-up methods is often limited to a single outcome measure, without considering the cost-effectiveness of the follow-up plan.

Our study utilizes the continuity of care model proposed by Sarah et al. (20). According to this model, there are overlapping and hierarchical relationships among three dimensions of continuity of care: patient-provider relationship, communication, and collaboration. The model offers a framework for designing follow-up plans, aiming to prevent fragmented care and promote care continuity. The multidisciplinary follow-up pattern primarily consists of five components: Management of the multidisciplinary team, objectives, and content, settings, follow-up pathways, and patient experience. Our study, for the first time in China, introduced contract-based multidisciplinary team collaboration in the follow-up of patients after cervical spine surgery. Based on the continuity of care model, multidisciplinary teams provided effective guidance and interventions to patients in each dimension, aiming to enhance care continuity and assess its impact on patient care practices and outcomes.

This study aimed to investigate the short-to medium-term effects of a contracted-based, multidisciplinary follow-up pattern on patients who have undergone surgery for cervical spondylosis. The study specifically focused on comparing the effects of a multidisciplinary follow-up pattern with regular follow-up in terms of neck disability, pain, self-efficacy, health-related quality of life, complications, patient satisfaction, and economic indicators.

Methods

This study was designed as a prospective, non-randomized controlled study with 3 months follow-up. The study adhered to the principles of the Helsinki Declaration (21) and the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) (22) statement regarding transparent reporting. Blinding was not applicable in this study. All patient data were used strictly for research purposes, and patient privacy was rigorously protected. Written informed consent was obtained from all patients or their guardians.

Ethics approval

The study was approved by the Ethics Committee of West China Hospital, Sichuan University (No. 971; ref: 2021).

Sample size calculation

Sample size calculation was performed using PASS 15 software with a two-sided significance level of $\alpha = 0.05$ and statistical power of $\beta = 0.2$. Based on preliminary study results, the Neck Disability Index (NDI) was selected as the primary outcome measure with a standard

deviation of 2 and a margin of error of 1.4. The sample size was estimated, and $n1 = n2 = 35$ was obtained. Considering a dropout rate of 20%, we estimated that a total of approximately 88 patients would be required (44 per group).

Participants

A total of 88 patients diagnosed with confirmed cervical spondylosis were assigned to undergo cervical spondylosis surgery. The patients were discharged between June 2, 2021, and July 7, 2022. Inclusion criteria for the study were: (1) age ≥ 18 years; (2) eligibility for cervical spondylosis surgery; and (3) ability to provide informed consent, communicate effectively, and understand/read Chinese language. All discharged patients were required to meet uniform discharge criteria based on standard clinical care.

Patients with a history of previous cervical spine surgery, diagnosed dementia, blindness, or deafness, cervical malformation or significant instability, a history of severe cervical trauma, pregnancy, rheumatoid arthritis, malignancy, active infection, or other systemic diseases, as well as patients who are not recommended for follow-up, and those who faced difficulty in attending in-person visits for diagnostics or treatment or declined to participate, were excluded from the study.

Study design

This study utilized convenience sampling as the sampling method. Patient recruitment was conducted prior to hospital admission. The head of the medical team explained the purpose and process of the program to patients who were about to undergo cervical spine surgery and invited them to participate in the study. Patients who agreed to participate were required to sign an informed consent form, confirming their voluntary participation in the research. Since the terms of the multidisciplinary follow-up contract needed to be personally confirmed and signed by the patients, blinding was not applicable in this study. Patients were non-randomly separated into two groups based on whether they signed a multidisciplinary team follow-up contract: patients who signed the contract were placed in the intervention group, while those who did not sign were placed in the control group. The sequential enrollment process started with the first eligible patient who signed the informed consent and continued until the last patient completed the 3-month follow-up study.

Procedures

The study period was from June 2, 2021, when the first patient was enrolled, to July 7, 2022, when the last patient completed the follow-up. The study was conducted at the spinal surgery ward of West China Hospital, Sichuan University.

Intervention group

This study utilized the continuity of care model proposed by Sarah et al. (20). The model suggests that there are overlapping and hierarchical relationships among the three dimensions of continuity of care: patient-provider relationship, communication, and collaboration. The theoretical dimensions mentioned involve the three types of continuity as identified by Haggerty et al. (23): relational continuity, informational continuity, and coordination continuity. Additionally, continuity is only required when there are changes in time and settings, which serves as the foundation for these three types of continuity. Our multidisciplinary follow-up pattern primarily consists of five components: Management of the multidisciplinary team, objectives, and content, settings, follow-up pathways, and patient experience. According to the TIDier checklist, we provided a detailed description of the intervention measures for the multidisciplinary follow-up pattern (Supplementary material 1).

Control group

Patients in the control group received standard preoperative and postoperative nursing care following the established protocols for cervical spondylosis upon their admission to the hospital. One day before discharge, the responsible nurse and medical team leader provide the patient with pre-discharge health education, including postoperative skin and wound management, common discomfort symptoms after surgery, discharge instructions, postoperative rehabilitation exercise plan for cervical spondylosis, methods and duration of wearing a cervical collar, guidance on pain medication, hospital health consultation hotline, outpatient follow-up, and reexamination schedule, methods for appointment and registration, as well as distribution of postoperative health education materials. After discharge, the patient needs to make an appointment for postoperative follow-up visits for cervical spondylosis, at 1 month, 3 months, 6 months, and 1 year after the surgery. During the postoperative outpatient follow-up visits, the patient's appointed physician will assess their health condition, provide medical advice based on the patient's health needs, and offer corresponding health guidance.

Data collection

The assessor (follow-up nurse), who had completed relevant professional courses, filled out a follow-up questionnaire. The assessor is aware of the distribution of patients in both groups. To ensure survey quality, a second researcher was invited to assist in the removal of invalid questionnaires. The primary outcome measure was neck pain-related disability, assessed using the NDI (0–100). Secondary outcome measures included the Visual Analog Scale (VAS), Self-Efficacy for Managing Chronic Disease 6-item Scale (SECD-6), and Study 12-Item Short-Form Health Survey (SF-12), which were used to assess neck pain, self-efficacy, and health-related quality of life. Additional measures included complications, patient satisfaction, and economic indicators. Patient characteristics, such as age, gender, marital status, qualifications, occupation, telephone number, length of stay, employment status, number of people living together, family income, body mass index (BMI), number of previous hospitalizations, admission patterns, cervical spondylosis classification, number of surgical segments, American Society of Anesthesiologists (ASA) physical status classification of I, II, or III, and convenience of medical

treatment, were obtained from medical records and patient responses at baseline (the day of discharge). The NDI, VAS, SECD-6, and SF-12 were collected on the day of discharge, 24–72 h, 1 month, and 3 months after discharge. Patient satisfaction, complications, and economic indicators were recorded at 3 months after discharge. Data on the day of discharge for both groups of patients were collected in the ward. Data for the intervention group after discharge were collected through the Cervical Spondylosis Surgery Follow-up Platform, while data for the control group after discharge were collected either in the outpatient department or through telephone follow-up.

The NDI (24) is a 10-item questionnaire that measures the impact of neck symptoms on functional activities, with each item scored from 0 to 5, a higher score indicates a higher disability. The NDI covers pain, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. The NDI had acceptable responsiveness and construct validity to assess self-perceived disability (25).

The VAS (26) is a 100 mm horizontal line used to measure neck pain. The left end of the scale represents "no pain" and the right end represents the "most severe pain imaginable." Patients mark the location that best represents their pain intensity based on their own condition and degree of pain.

Six items were included in the SECD-6 (27) to help assess how confident patients are in doing certain activities. The scale ranges from 1 (not at all confident) to 10 (totally confident). The score for the scale is the mean of the 6 items, and high scores indicate high self-efficacy.

The SF-12 (28), a measure of Health-related Quality of Life, is a shortened version of the SF-36 with 12 items, covering eight dimensions–general health (GH), physical functioning (PF), role-physical (RP), bodily pain (BP), vitality, social functioning (SF), role-emotional (RE), and mental health (MH). The eight dimensions can be consolidated into two summary scores using scoring algorithms, a physical component score (PCS) and a mental component score (MCS), ranging from 0 to 100, with higher scores representing a better health-related quality of life.

The follow-up satisfaction questionnaire consists of 10 items, covering satisfaction with the follow-up staff, health education, rehabilitation guidance, medical services, outpatient consultation, appointment registration process, auxiliary examination process, physical health, mental health, and costs related to cervical spondylosis after discharge. Responses are graded from 1 (not at all satisfied) to 5 (very satisfied), with higher scores representing higher satisfaction.

Economic indicators encompass direct medical costs, direct non-medical costs, indirect costs, and total costs. The estimation of direct medical costs and direct non-medical costs is conducted using the micro-costing method (29). These cost data are derived from hospital systems and patient interviews. Direct medical costs consist of post-discharge registration fees, medication expenses, treatment fees, examination fees, costs related to the treatment of complications, and other medical expenditures directly associated with the disease. Direct non-medical costs comprise transportation and accommodation expenses incurred by patients during medical visits. Total transportation costs are calculated based on patients' reported round-trip transportation expenses and the number of visits made after discharge. Accommodation costs are estimated based on patients' self-reported expenditures. Indirect costs pertain to income loss following cervical spine surgery and are estimated based on the patient's lost work time post-discharge, converted into costs using daily wages as a basis. For employed individuals or those with fixed monthly incomes, indirect costs are represented by the total hours or days of productivity lost (seeking care and productivity time lost) multiplied by the average hourly or daily earnings. Total costs encompass both direct and indirect costs.

Statistical analysis

Descriptive statistics, mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQ) for non-normally distributed continuous variables, and absolute numbers and percentages for categorical variables were calculated to summarize the data. Since the data included repeated measurements and did not follow a normal distribution, we used Generalized Estimating Equations (GEE) to examine the effects of interventions on disability, pain intensity, self-efficacy, and health-related quality of life. In our analysis, we considered the intervention group (contract follow-up vs. routine follow-up), visit number (as a categorical variable), and the interaction between the intervention group and visit number as independent variables. We used robust standard errors and specified an exchangeable working correlation structure. We utilized all available time-point data. Differences between medians and their 95% confidence intervals were calculated using the Hodges-Lehmann estimator. For normally distributed categorical variables, we performed chi-square tests. For cases suitable for Fisher's exact test, we used Fisher's exact test. For normally distributed continuous variables, we conducted independent samples *t*-tests. For non-normally distributed continuous variables and ordered ordinal data, we used Mann–Whitney U tests. Results were considered significant at a 5% level of significance ($p < 0.05$). Data analysis was performed using licensed STATA 16 software, and graphs were generated using licensed GraphPad Prism 9.0.

Results

The study commenced in June 2021, and the final follow-up was concluded in July 2022. A comprehensive three-month follow-up was conducted for all patients. Out of the initial pool of eligible patients, consisting of 91 individuals, only 44 agreed to participate in the intervention group, while 47 agreed to be part of the control group. Three patients from the control group withdrew from the study due to concerns regarding adherence to the protocol, as well as personal or other study-related issues. Ultimately, the study included a total of 88 patients who had undergone cervical spondylosis surgery, divided equally between the intervention and control groups, with 44 participants in each (Figure 1). The baseline characteristics of these 88 participants are presented in Table 1. Notably, there were no statistically significant differences observed between the two groups at baseline for all the variables that were examined, as anticipated.

Primary outcome

The comparison between groups revealed a significant difference in the NDI scores after discharge, specifically at 24 to 72 h, 1 month, and 3 months ($p < 0.001$), with the intervention group scoring notably

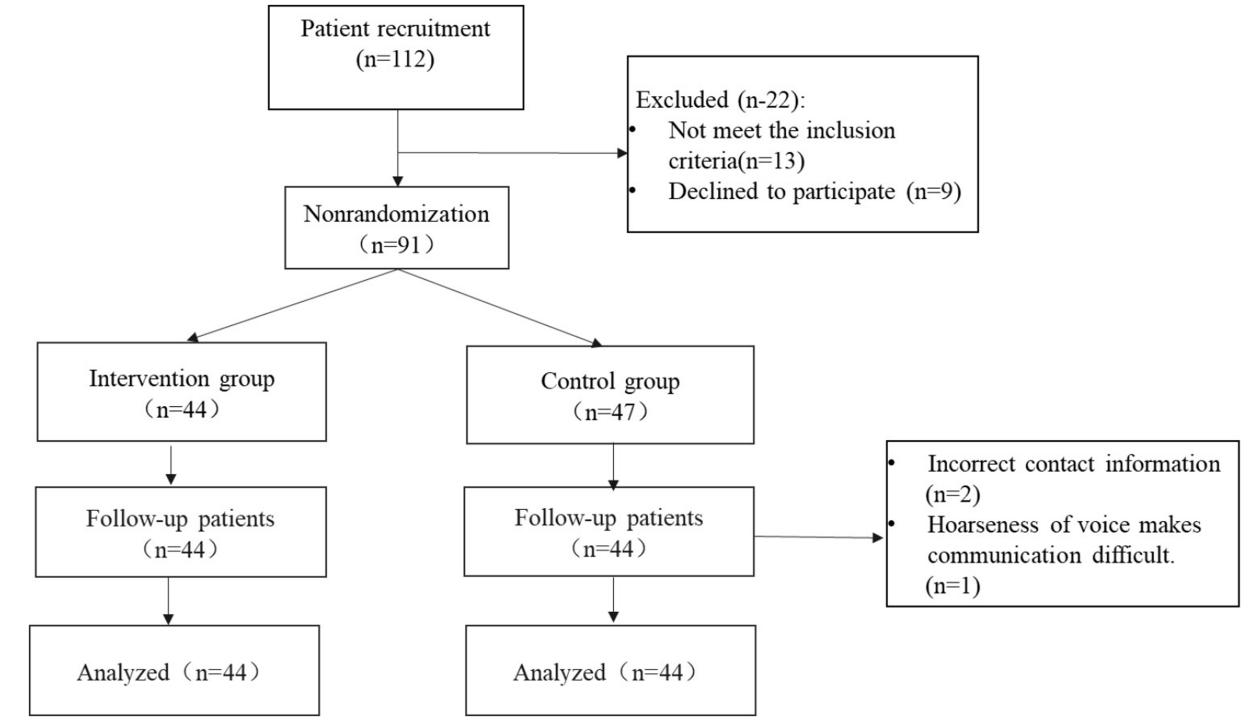

FIGURE 1
Study schematic panel.

lower than the control group. In addition, the intervention group exhibited sustained improvement in NDI scores at 24 to 72 h, 1 month, and 3 months after discharge according to within-group comparisons. However, there was no statistically significant difference in NDI scores among the control group during the first 24 to 72 h after discharge compared to initial baseline (Figure 2; Table 2).

Secondary outcome

In this study, we observed that patients in intervention group had significant improvements in various secondary outcome measures, including SECD-6, VAS, PCS, and MCS, at the 1-month mark ($p < 0.05$, Table 2). Furthermore, at the 3-month mark, the intervention group exhibited a greater increase in SECD-6, PCS, and MCS scores compared to the control group, demonstrating statistical significance ($p < 0.001$). However, no significant differences were observed between the two groups within the 24-to-72-h period. Additionally, the VAS scores showed a statistically significant difference between the two groups at both the 24–72 h and 1-month time points ($p < 0.05$).

Patient satisfaction

The findings demonstrate that the intervention group (mean 42.52, SD 8.2) is significantly more effective in meeting the needs of patients compared to control group (mean 41.56, SD 7.34) ($p < 0.001$, Table 3). Moreover, when assessing various aspects of the follow-up satisfaction questionnaire, patients in the intervention group consistently expressed significantly higher levels of satisfaction ($p < 0.001$, Table 3).

Complications

During the study, a total of 11.4% of patients in the intervention group experienced complications, while 40.9% were in the control group ($p < 0.01$; Supplementary Table S1). Importantly, it is worth noting that no patients discontinued the study due to complications. When patients experience complications, they have been duly reported to the ethics committee. These complications are recognized as being caused by the patient's underlying condition, rather than the intervention measures.

Post-discharge costs

The findings of this study revealed significant differences in direct medical costs between the intervention group and the control group. The median direct medical cost in the intervention group was 1821.2 yuan, whereas it was 2421.7 yuan in the control group ($p < 0.001$; Supplementary Table S2; Figure 2). Furthermore, notable distinctions were observed in the median direct non-medical costs. The intervention group had a median direct non-medical cost of 110 yuan, whereas the control group had a median cost of 270 yuan ($p = 0.035$). Regarding indirect costs, no significant differences were found between the intervention group (median cost of RMB 4750) and the control group (median cost of RMB 5000) ($p = 0.59$). Moreover, the

TABLE 1 Baseline characteristics of patients.

Variables		Intervention group (*N* = 44)	Control group (*N* = 44)	*p*-value
Age Mean (SD)		51.64 (8.99)	52.43 (10.86)	0.7
Gender (female): number (%)		21 (47.7)	29 (65.9)	0.09
BMI (kg/m^2): Mean (SD)		24.22 (2.62)	24.33 (2.94)	0.85
ASA:number (%)	Grade I	0 (0)	0 (0)	0.52
	Grade II	22 (50)	19 (43.2)	
	Grade III	22 (50)	25 (56.8)	
Surgical segments: number (%)	Single	18 (40.9)	13 (29.5)	0.27
	Multiple	26 (56.8)	31 (70.5)	
Length of stay Mean (SD)		5.41 (2.46)	5.94 (2.69)	0.2
Employment status: number (%)	Retired	13 (29.5)	16 (36.4)	0.49
	Working	31 (70.5)	28 (63.6)	
People living together: number (%)	Alone	0 (0)	2 (4.5)	0.49
	Gregarious	44 (100)	42 (95.5)	
Family income (per month)	<5,000	1 (2.3)	4 (9.1)	0.24
	5,001–10,000	14 (31.8)	17 (38.6)	
	>10,000	29 (65.9)	23 (52.3)	
Previous hospitalization Mean (SD)		24 (54.4)	28 (63.6)	0.39
Admission patterns: number (%)	Emergency	0 (0)	1 (2.3)	1
	Outpatient	44 (100)	43 (97.7)	
Cervical spondylosis classification: Mean (SD)	Radiculopathy	40 (90.9)	34 (77.3)	0.15
	Myelopathy	4 (9.1)	10 (22.7)	
Baseline NDI Mean (SD)		8.80 (6.71)	10.16 (7.60)	0.375
Baseline VAS Mean (SD)		2.01 (0.94)	2.15 (1.66)	0.627
Baseline SECD Mean (SD)		7.37 (1.09)	7.11 (1.34)	0.307
Baseline PCS M (IQR)		31.46 (13.13)	31.25 (18.75)	0.683
Baseline MCS M (IQR)		37.14 (23.24)	37.40 (9.92)	0.967

BMI, Body Mass Index; ASA, American Society of Anesthesiologists Physical Status Classification; SD, Standard Deviation; NDI, Neck Disability Index; VAS, visual analog scale; SCED-6, Self-Efficacy for Managing Chronic Disease 6-item Scale; SF-12, Study 12-Item Short-Form Health Survey; PHS, physical health score; MHS, physical health score.

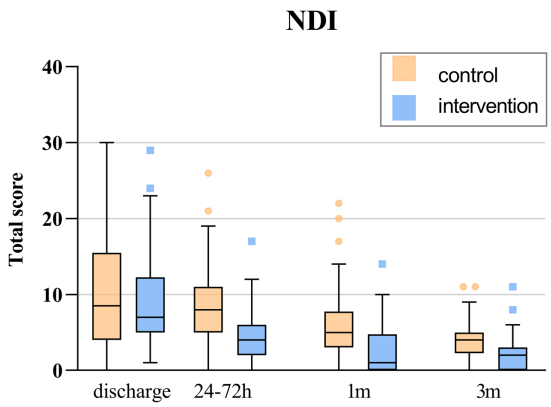

FIGURE 2
The total score of NDI over time. The box indicates P_{25} and P_{75}. The horizontal line in the box represents the median of the NDI score. The error line represents the upper and lower limits of Tukey formula. Points outside the error line represent values for individual patients outside this range.

total cost of the intervention was significantly lower in the intervention group (7621.2 yuan) compared to the control group (8725.2 yuan) ($p = 0.04$) (Figure 3).

Discussion

The main finding of this study indicates significant improvements in neck disability, self-efficacy, quality of life, post-operative complications among patients who received contract-based follow-up, compared to routine follow-up. Contract-based follow-up demonstrated higher levels of patient satisfaction and lower total costs after discharge.

Postoperative outcomes such as pulmonary, postoperative hematoma, and dysphagia have been demonstrated as complications of cervical spine surgery, and can also cause poorer patient prognosis after surgery (30). Complications of cervical spine surgery can arise after discharge. Without professional guidance, it can be very dangerous. Continuing care extends hospital care into daily life and maintains a connection between individual patients and the care team,

TABLE 2 Summary of outcomes.

Parameter	Invention group M (IQR)[a]	Control group M (IQR)[a]	Between-group differences (95%CI)[b]	*p*- value[c]
NDI				
24–72 h	4 (4)***	8 (6)	-4 (−6, −2)	<0.001
1 m	1 (4.75)***	5 (4.75)**	-3 (−5, −2)	<0.001
3 m	2 (3)***	4 (2.75)***	-2 (−3, −1)	<0.001
VAS				
24–72 h	1 (1)***	1.55 (2.15)	−0.5 (−1, 0)	0.008
1 m	0.5 (1.2)***	1 (2)**	−0.3 (−1, 0)	0.026
3 m	0 (1)***	0 (1.38)***	0 (0, 0)	0.899
SECD-6				
24–72 h	8.75 (1.42)***	7.92 (2.08)***	0.67 (0.17, 1.33)	0.071
1 m	8.84 (1.67)***	8.5 (2.05)**	0.34 (0, 0.84)	0.001
3 m	9.17 (1.01)***	8.17 (1.96)**	1.17 (0.83, 1.67)	<0.001
PCS				
24–72 h	37.5 (18.75)***	37.5 (23.44)**	0 (0, 6.25)	0.362
1 m	87.5 (37.50)***	40.63 (42.19)***	31.25 (12.50, 50)	<0.001
3 m	81.25 (35.94)***	55.63 (56.25)***	25 (6.25, 31.25)	<0.001
MCS				
24–72 h	19.74 (47.37)	10.53 (10.53)	8.16 (3.95, 19.74)	0.949
1 m	98.68 (36.18)***	20.39 (76.71)*	35.53 (5.26, 60.53)	0.001
3 m	94.74 (23.68)***	60.53 (78.95)***	25 (5.26, 46.05)	<0.001

NDI, Neck Disability Index; VAS, visual analog scale; SCED-6, Self-Efficacy for Managing Chronic Disease 6-item Scale; SF-12, Study 12-Item Short-Form Health Survey; PCS, physical component score; MCS, mental component score.

[a]*, **, and *** indicated within-group differences at the $p < 0.05$, 0.01, and 0.001 values, respectively. For within-group comparisons, all comparisons were made relative to the scores at discharge.

[b]The median difference and 95% confidence interval (CI) for between-group comparisons were calculated using the Hodges-Lehmann estimator.

[c]Indicated the value of *p* for between-group comparisons.

with the primary goal of actively involving patients in their recovery process (31). In our study, we introduced a pioneering model of contracted continuous follow-up, utilizing a multidisciplinary team. Various medical experts from different disciplines fully utilize their professional skills to achieve complementary backgrounds and multiple layers of safety. This approach addressed the specific self-care needs of post-discharge patients, improving their quality of life and adherence to medical recommendations. Personalized services were provided under the contracted continuous follow-up model tailored to each patient's requirements.

Compared to the control group, the intervention group showed potential improvements in neck dysfunction and pain, which may be attributed to the professional rehabilitation provided by doctors and better compliance from patients. Previous evidence suggests that proper exercise methods can contribute to reducing neck pain and disability in patients with cervical spondylosis (32). Some studies suggest that structured postoperative physical therapy may bring benefits to patients undergoing surgical treatment for cervical disc disease, compared to standard care methods (33, 34). Regular exercise may promote pain relief by reducing NMDA receptors phosphorylation and decreasing serotonin transporter expression (35). However, it has been shown by Wibault et al. (19) that the potential for further improvement in NDI and VAS scores through postoperative physical therapy may be limited, as these measures reflect immediate postoperative outcomes. Interestingly, our study also revealed no statistically significant difference in VAS scores between the two groups at 3 months after discharge. This lack of significance may be due to over 75% of patients having the lowest possible VAS score (0), indicating a floor effect. Consequently, there might be some debate surrounding the responsiveness of VAS as a tool for detecting pain changes during the postoperative period of cervical spondylosis. Therefore, it is essential to extend the follow-up period in future studies to observe the long-term effects of the contractual follow-up model on outcomes such as NDI and VAS.

Patients in the intervention group showed a higher sense of self-efficacy than the control group at 1 and 3 months after discharge. However, no significant difference was observed between the two groups within the first 24–72 h post-discharge, possibly due to the short-term nature of the intervention measures. The study highlights the importance of a multidisciplinary follow-up team that provides specialized pain neuroscience education, functional exercises, and psychological counseling to improve patients' self-efficacy. Previous studies have demonstrated that comprehensive treatment including pain neuroscience education and functional exercises can help alleviate pain and disability in patients and enhance their self-efficacy (36). According to social cognitive theory, self-efficacy is critical to

TABLE 3 Patient follow-up satisfaction.

Variables	Intervention group/Mean (SD)	Control group/ Mean (SD)	Fisher	*p*-value
Satisfaction with follow-up staff	4.2 (0.90)	4.2 (0.76)	38.05	<0.001
Satisfaction with health education	4.16 (0.86)	4.18 (0.84)	34.87	<0.001
Satisfaction with rehabilitation guidance	4.23 (0.91)	4.2 (0.85)	33.63	<0.001
Satisfaction with medical services	4.3 (0.79)	4.43 (0.7)	48.71	<0.001
Satisfaction with outpatient consultation	4.25 (0.86)	4.18 (1.02)	49.57	<0.001
Satisfaction with registration	4.18 (0.99)	3.75 (0.94)	32.83	<0.001
Satisfaction with the auxiliary examination	4.2 (0.95)	3.98 (0.9)	29.4	<0.001
Satisfaction with physical health	4.27 (0.85)	4.32 (0.88)	31.7	<0.001
Satisfaction with mental health	4.36 (0.92)	4.16 (0.94)	35.32	<0.001
Satisfaction with the medical costs after discharge	4.36 (0.87)	4.16 (0.96)	32.29	<0.001
Patient overall satisfaction	42.52 (8.2)	41.56 (7.34)	43.46	<0.001

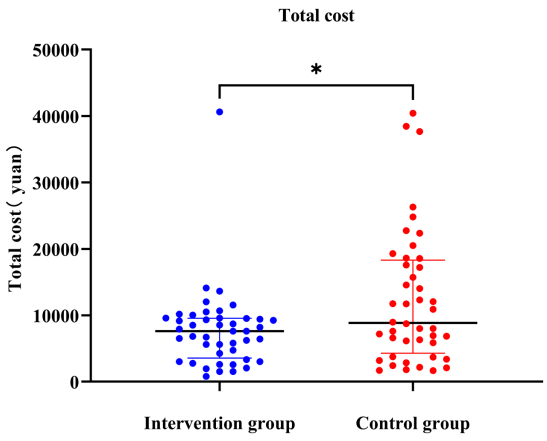

FIGURE 3
The total cost over time. *indicated within-group differences at the $p < 0.05$.

behavioral change, as individuals who believe in their thoughtful and deliberate actions are more likely to implement action plans. Higher self-efficacy can also reduce patient anxiety and self-doubt (37). Future studies should investigate more effective self-efficacy intervention methods that can be applied during post-discharge follow-up to improve patients' self-efficacy and facilitate their recovery. In the first and third months after discharge, the intervention group showed significantly better quality of life compared to the control group. This may be attributed to the targeted intervention provided by a multidisciplinary team, such as psychologists and specialized nurses. Studies have demonstrated that tools like SF-36 and SF-12 can effectively assess patients' quality of life (38). It is worth noting that a considerable proportion of cervical spine disease patients also suffer from psychological disorders. It has been reported that more than 30% of cervical spine disease patients have depression or anxiety (39). Previous research indicates that higher SF-MCS scores before surgery are associated with better post-operative quality of life, improved psychological well-being, and higher patient satisfaction (40). Therefore, timely psychological interventions before surgery are crucial. Looking ahead, expanding the scope of contracted follow-up services to include the pre-surgery stage can achieve continuous management throughout the entire process for cervical spine surgery patients, promoting their preoperative recovery.

Our study demonstrates that contracted follow-up management can reduce the incidence of complications at 3 months after cervical surgery. Early postoperative dysphagia and neurological complications were the most common complications in both groups. This may be attributed to the comprehensive care and specialized guidance provided by a multidisciplinary team, which effectively mitigated the risk of developing complications. Previous studies have reported a wide range of dysphagia incidence following cervical spine surgery, ranging from 17.5 to 71% (41). However, the exact causes of postoperative dysphagia in this context remain unclear. Factors such as the type of surgery, including multilevel procedures (particularly involving C4-5 and C5-6), age, smoking status, operative duration, and body mass index, have been identified as closely associated with the occurrence of early dysphagia (42, 43). Consequently, future research may benefit from conducting subgroup analyses to further elucidate the effects of contracted follow-up management, with a focus on specific surgical segments and operative duration. Our study indicated that the implementation of a contracted follow-up program, carried out by a multidisciplinary team, can greatly enhance patient satisfaction following cervical spine surgery. In this study, we established a dedicated postoperative follow-up management center designed specifically for cervical spine diseases. This center offers a range of services including online consultations, free appointments, physical examinations, test result interpretations, imaging analyses, and even convenient expert outpatient services available during the night. Additionally, the utilization of an intelligent electronic follow-up platform assists in the seamless and continuous storage of patients' health information. In recent years, the practice of prehabilitation has started gaining traction within the field of orthopedics. However, there remains a lack of consensus regarding its ability to expedite patient recovery (44, 45). In the future, standard nursing procedures for preoperative rehabilitation should be explored for patients undergoing cervical spine surgery.

The intervention group of patients showed lower total costs, direct medical costs, and direct non-medical costs compared to the control group. Complications following cervical spine surgery can have a negative impact on postoperative patient outcomes (30). Postoperative

complications related to cervical spine conditions can still occur after discharge, posing risks to patients and increasing healthcare expenses without professional guidance. A multidisciplinary team provides personalized services to patients when necessary, such as in-hospital referrals and emergency admissions, ensuring patient safety and reducing the occurrence of complications outside the hospital while also lowering healthcare costs. However, our study showed no significant difference in indirect costs between the two groups, which may be attributed to the relatively short study duration and potential recall bias in obtaining indirect cost data through patient interviews. Further research is required to investigate the long-term effectiveness and economic benefits of implementing a contracted follow-up model in spinal surgery.

Limitation

There are several limitations associated with this non-randomized control study design. Firstly, due to the requirement of voluntary patient consent in contractual terms, a randomized study design and blinding was not feasible. Non-randomized controlled designs may suffer from selection bias, raising doubts about the reliability and validity of study findings. To mitigate potential biases arising from non-randomization, this study rigorously enforced inclusion criteria for participants and ensured that both groups of patients originated from the same medical group. The lack of blinding may cause researchers to exhibit heightened concern for the patients, potentially impacting the objectivity of the observed outcomes. Secondly, our follow-up period was relatively short, lasting only 3 months after discharge. A short follow-up time may result in insufficient assessment of patients' post-discharge conditions and intervention effects. Future studies should incorporate long-term follow-ups to ascertain the long-lasting benefits of multidisciplinary contractual continuing care. Thirdly, this study was conducted at a single center, and the findings exclusively reflect the performance of that specific center. To enhance external validity, future research endeavors could encompass various geographical regions and diverse tiers of hospitals. Finally, our study protocol has not been previously published, which may have an impact on the credibility and transparency of the study. However, we have included a detailed research protocol (Supplementary material 1) in this study to facilitate reproducibility by other researchers.

Conclusion

Compared with the routine follow-up plan, the multidisciplinary contracted follow-up plan demonstrates significant benefits for postoperative cervical dysfunction, self-efficacy, quality of life, complications, patient satisfaction, and direct costs in patients undergoing cervical spine surgery.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data that support the outcomes of this paper are available from NN, upon reasonable request. Requests to access these datasets should be directed to NN, ningninggk@163.com.

Ethics statement

The studies involving humans were approved by Ethics Committee of West China Hospital, Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZF: Writing – original draft, Data curation. YX: Writing – review & editing, Methodology, Investigation. LP: Writing – review & editing, Supervision, Formal analysis. MG: Supervision, Software, Writing – review & editing. JC: Writing – original draft, Project administration, Data curation. NN: Writing – review & editing, Resources, Conceptualization.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1354483/full#supplementary-material

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Impact of ankylosing spondylitis on foot health and quality of life: an observational case–control study

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Background: Ankylosing spondylitis (AS) is a chronic, inflammatory, and autoimmune disease. This condition primarily affects the axial skeleton and presents direct foot involvement, such as Achilles enthesitis or plantar fascia involvement.

Objective: This study aimed to investigate the impact of foot health on the quality of life of individuals with AS compared to a control group without AS.

Materials and methods: A sample of 112 subjects was recruited, with a mean age of 46.80 ± 10.49 years, divided into two groups: 56 individuals with AS (cases) and 56 individuals without AS (controls). Demographic data were collected, and the scores obtained in the Foot Health Status Questionnaire domains were recorded.

Results: Of the participants, 27.79% ($N = 30$) were men and 73.21% ($N = 82$) were women. The mean age in the group was 46.80 ± 10.49. Significant differences ($p < 0.05$) were found in the domains of foot function, foot pain, footwear, overall foot health, general health-related physical activity, and social capacity between the AS group and the control group.

Conclusion: Individuals with AS exhibited a decreased quality of life, as indicated by their Foot Health Status Questionnaire scores.

KEYWORDS

ankylosing spondylitis, foot deformities, foot diseases, quality of life, foot

1 Introduction

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis, is a chronic, inflammatory, and autoimmune disease classified within the group of spondyloarthritis (1–3). This group of diseases shares clinical characteristics including involvement of the axial skeleton (sacroiliitis and ankylosed spine), peripheral manifestations (enthesitis, dactylitis, and lower limb arthritis), and extra-articular features (uveitis, psoriasis, bowel disease, kidney, lung, heart, skin, and bone) (4, 5).

The prevalence of AS varies worldwide, ranging from 0.1 to 1.4%; however, there is a lack of sufficient prevalence studies (6, 7). In 2013, Dean et al. concluded that significant prevalence differences existed across all continents, with higher rates in Europe and Asia and a sex ratio of 3.4:1 (male:female) (6). The influence of this condition is also noticeable across multiple dimensions of workforce engagement, spanning from a heightened reliance on support in paid employment to workforce disengagement. Additionally, individuals with AS, along with society at large, incur significant healthcare costs related to medications and healthcare service providers (8–10).

However, there are no studies assessing foot-related quality of life in AS individuals, making this study valuable in emphasizing the importance of foot evaluation.

Such issues can exert repercussions on both occupational and personal activities, akin to patterns observed within the broader populace where foot health complications are pervasive (ranging from 71 to 93%). These complications stem from multifaceted origins and hold the potential to prognosticate a decline in self-reliance, increased susceptibility, heightened vulnerability, compromised quality of life, and overall wellbeing (11–13).

AS typically starts with insidious lower back pain and morning stiffness. Its main symptoms are divided between joint-related (lower back stiffness, sacroiliitis, etc.) and extra-articular (uveitis, upper lobe lung fibrosis, etc.) manifestations. Enthesitis is common, often causing local pain. It predominantly occurs in the lower extremities, especially affecting the Achilles tendon insertions and plantar fascia (2, 14). Slouma et al. concluded that heel enthesis ultrasound lesions are frequent in spondyloarthropathies.

Given the previously unmet need for comprehensive and ongoing podiatric care in patients with AS, it is crucial to include foot-related pathologies, postural anomalies, and key comorbidities in the development of treatment plans and preventive measures. This approach aims to enhance the overall quality of life and wellbeing of individuals living with AS.

To date, the impact of foot health and quality of life on AS individuals has not been studied. In this study, we used the Foot Health Status Questionnaire (FHSQ) to analyze both foot-specific factors (pain, function, and footwear) and overall wellbeing factors (general health, physical activity, social capacity, and vigor).

This investigation aims to investigate the impact of foot health on the quality of life of individuals with AS compared to a control group without AS.

2 Materials and methods

2.1 Sample design

A descriptive observational case–control study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (15).

A consecutive non-random sampling method was used to recruit a total of 112 participants, 56 with AS (cases group) and 56 healthy individuals (control group). AS participants were recruited from patient associations in Córdoba and Sevilla, while control group participants were recruited from the podiatry departments of the medical specialty centers Policlínica Alhaurín Torre Salud and Policlínica Lacibis.

Both cases and controls were informed in advance about their participation in a study on foot health and quality of life. All participants provided informed consent and agreed to take part in the study.

The inclusion criteria comprised being over 18 years old, having the ability to walk, and having signed informed consent. Exclusion criteria included having undergone lower limb surgeries and not being in full mental capacity.

2.2 Sample size calculation

To determine the required sample size for our case–control study, we used version 4.2 of the EpiData software, developed by the Health Department of the Xunta de Galicia, Spain, in collaboration with the Pan American Health Organization (PAHO-WHO) and Universidad CES, Colombia. The calculation was based on parameters including a 95% confidence level, a statistical power of 80%, an expected odds ratio of 2.0, and presumed exposure rates of 50% in case participants and 33.333% in control participants. This led to the identification of a necessary sample of 112 individuals, evenly divided between 56 cases and 56 controls.

2.3 Procedure

A sole investigator conducted all the measurements. Participant height, weight, and BMI were collected at the beginning of the interview and were used to match the participants from the case group with the control group. Subsequently, subjects completed the self-reported FHSQ, acknowledged as a validated instrument (16, 17).

The assessment of health-related quality of life, encompassing both general and specific foot aspects, was carried out using the validated Spanish version 1.03 (18) of the FHSQ. This questionnaire consists of three primary sections. The initial section, comprising 13 items, is divided into four specific domains evaluating foot health-related quality of life, encompassing dimensions such as foot health, foot pain, footwear, and overall foot health. This section has demonstrated high content, criterion, and construct validity (Cronbach's $\alpha = 0.89–0.95$), as well as noteworthy test–retest reliability (intraclass correlation coefficient of 0.74–0.92) (16). Furthermore, it has been established as the most suitable measure for evaluating health-related quality of life in populations experiencing foot pain (19).

The second section focuses on four domains relating quality of life to general health, covering physical activity, overall health, social capacity, and vigor. This section largely constitutes an adaptation of the Medical Outcomes Study 36-Item Short-Form Health Survey (20).

The third section encompasses descriptive data regarding socioeconomic status, comorbidities, satisfaction, and clinical history. Each questionnaire item uses an ordinal Likert scale with multiple response options, from which participants select the most appropriate

answer. Through software analysis, scores ranging from 0 to 100 are generated for each domain, with 0 representing the worst possible outcome in foot health-related quality of life and 100 indicating the best result (18).

2.4 Ethical considerations

This research received approval from the Ethics Committee for Experimentation at the University of Málaga (Málaga, Spain) with the code 122-2022-H. The entire study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki (21).

2.5 Statistical analysis

Sociodemographic data, including age, height, weight, and BMI, along with independent variables, were analyzed. These data were presented as mean and standard deviation (SD), as well as the minimum and maximum range. To assess data normality, the Kolmogorov–Smirnov test was applied, with p-values of >0.05 indicating normal distribution. However, all study variables yielded results of $p < 0.05$, indicating a non-normal distribution. Consequently, the Mann–Whitney U-test was utilized to ascertain statistically significant differences between groups. Additionally, a 95% confidence level was established for the obtained results.

All statistical analyses were conducted using SPSS v27.0.1.0 (IBM Corporation, Armonk, NY, United States).

3 Results

3.1 Descriptive data

The study encompassed a sample of 112 individuals of both genders (56 with AS and 56 healthy). Of these, 26.8% ($n = 30$) were men and 73.2% ($n = 82$) were women. The mean age of the entire sample was 57.78 years (SD: 12.78), ranging from 24 to 88 years. Table 1 illustrates that the demographic and descriptive data of the study participants did not display significant differences ($p > 0.01$). Furthermore, the study observed that the average duration of illness among individuals with AS was 12.63 years.

3.2 Comparison of patients with and without AS

All domains exhibited a normal distribution ($p < 0.05$). The results of comparing the scores obtained for different FHSQ domains are presented in Table 2. Statistically significant differences ($p < 0.05$) were observed between the case and control groups across all specific foot domains (foot pain, foot function, foot health, and footwear), as well as within most general domains (overall health, physical activity, and social capacity). Therefore, the results indicate that the AS population presents lower quality of life concerning foot health and overall wellbeing compared to the matched healthy population. The vitality domain is the only one showing no significant differences between the groups.

4 Discussion

The aim of this study was to investigate the impact of foot health on the quality of life of individuals with AS compared to a control group without AS.

Upon evaluating the results of our study, a non-significant difference was found in the vigor domain levels between the AS group and the control group, which aligns with findings from other studies conducted in chronic diseases (22–24). However, significant differences ($p < 0.05$) were observed in the remaining domains, including foot pain, foot function, footwear, overall foot health, overall health, physical activity, and social capacity. These results are consistent with findings from other studies that assessed foot health-related quality of life using the FHSQ tool, such as a study conducted in multiple sclerosis patients (25) and fibromyalgia patients (26), both chronic conditions and degenerative conditions affecting the musculoskeletal system, such as AS. Therefore, it would be worthwhile to conduct further research to correlate these findings with the duration of AS diagnosis or to explore differences between men and women with the disease, as suggested by another study (27).

Several studies have indicated that AS has a direct impact on the foot (28–31), For instance, Koka et al. analyzed the impact of AS on the foot and found a significantly higher foot function index in individuals with AS, concluding that the foot and ankle are frequently affected in AS individuals (28). Sahli et al. assessed foot impact in spondyloarthritis patients, considering symptoms, deformity type and frequency, localization, and radiological changes, finding that 52% of

TABLE 1 Sociodemographic and descriptive data (Spain, 2023).

Descriptive data	Total ($n = 112$)		AS ($n = 56$)		Control ($n = 56$)		p-value
	Mean (SD)		Mean (SD)		Mean (SD)		
Age (years)	46.8 ± 10.5 (24–70)		47.0 ± 11.2 (24–70)		46.6 ± 9.8 (28–68)		0.683†
Weight (kg)	70.2 ± 14.7 (44–115)		71.2 ± 16.6 (44–115)		69.2 ± 12.7 (52–102)		0.751†
Height (m)	1.7 ± 0.1 (1.5–1.9)		1.7 ± 0.1 (1.5–1.9)		1.7 ± 0.8 (1.5–1.9)		0.816†
BMI (Kg/m^2)	25.3 ± 4.9 (17.0–44.4)		25.8 ± 5.1 (17.0–44.4)		25 ± 4.2 (19.3–39.8)		0.520†
Sex M/F (%)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)	
	30(26.8%)	82(73.2%)	15(26.8%)	41(73.2%)	15(26.8%)	41(73.2%)	1‡

BMI, body mass index; M, male. F, female. In all analyses, a p-value of < 0.05 (with a 95% confidence interval) was considered statistically significant.
†U de Mann–Whitney U-test was applied. ‡Frequencies (percentages) and chi-square (X^2) test were utilized.

TABLE 2 Comparisons of foot health status questionnaire scores (Spain, 2023).

FSHQ domains	Total ($n = 112$)	AS ($n = 56$)	Control ($n = 56$)	p-value
Foot pain	65.0 ± 27.8 (0–100)	51.9 ± 29.0 (0–100)	78.2 ± 19.2	**<0.001**†
Foot function	68.9 ± 30.9 (0–100)	54.5 ± 32.1 (0–100)	83.3 ± 21.7 (0–100)	**<0.001**†
Footwear	43.9 ± 33.1 (0–100)	34.5 ± 33.1 (0–100)	53.3 ± 30.7 (0–100)	**0.002**†
General foot health	51.1 ± 31.3 (0–100)	35.8 ± 27.6 (0–100)	66.3 ± 27.3 (0–100)	**<0.001**†
General health	55.4 ± 29.6 (0–100)	35.8 ± 21.6 (0–100)	75 ± 22.9 (0–100)	**<0.001**†
Physical activity	68.7 ± 27.8 (0–100)	50.1 ± 23.3 (0–100)	87.4 ± 17.5 (0–100)	**<0.001**†
Social capacity	64.2 ± 33.5 (0–100)	46.2 ± 32.3 (0–100)	82.1 ± 23.8 (0–100)	**<0.001**†
Vigor	54.1 ± 23.7 (6.25–100)	54.7 ± 24.9 (6.25–100)	53.6 ± 22.6 (6.25–100)	0.963†

FHSQ, Foot Health Status Questionnaire. †U de Mann–Whitney U-test was applied. In all analyses, a p-value of < 0.05 (with a 95% confidence interval) was considered statistically significant (bold).

patients showed foot involvement (31). Previous studies have also examined how gait is significantly altered in patients with AS (32, 33), and further research has suggested that these gait parameters might predict physical function in axial spondyloarthritis patients (34).

Considering both direct effects, such as Achilles tendon involvement, and indirect effects, such as gait changes induced by AS at the foot level, which significantly increase pain (32, 33, 35–37).

Previously, it was found that individuals with AS experienced peripheral joint involvement and severe disability, leading to a reduced quality of life (38). A recent study concluded that the quality of life in AS patients was poor and correlated with high disease activity (39). Quality of life in AS patients has been studied by various authors, and the consensus is that it is inferior to the general population, particularly in the dimensions of physical health, mental health, and social role (40). Moreover, certain authors advocate that AS treatments should be oriented toward enhancing patients' quality of life (41).

In addition, the present study had some limitations. First, identifying the presence of comorbidities in the control group would be beneficial to strengthen the study and may help identify factors where this association does not exist, as well as the mechanisms involved. Second, the absence of blinding the evaluator to participant group assignments, and third, the geographical origin of participants, stemming from two distinct locales (Córdoba and Seville).

Finally, future research would benefit from larger sample sizes, investigation among different cultures, ethnicities, and living locations, and a random sampling approach to enhance the generalizability of findings.

5 Conclusion

This investigation provides further evidence that individuals with AS exhibit a decreased quality of life, as indicated by the FHSQ scores. Consequently, regular checks of the foot are crucial to improving overall foot health status and the wellbeing of individuals affected by AS.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee for Experimentation at the University of Málaga (Málaga, Spain) with the code 122-2022-H. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AC-R: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. LA-G: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. ML-l: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. JG-S: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. RB-d-B-V: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. MS-G: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. AM-L: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. DL-L: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. AJ-C: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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The effectiveness of video-based exercise training program for people with intellectual disability: a multicenter study

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Objective: To examine the effectiveness of a specially designed video-based exercise program in promoting physical and balance performance in people with intellectual disability.
Methods: This study was a multicenter controlled trial. Participants with intellectual disability were divided into exercise group and control group by cluster sampling. The participants in the exercise group received 1 h exercise training sessions twice a week for 8 weeks, and the controls continued their usual care without exercise training. The exercises were specially designed to match the physical ability level of the participants classified as high and low, and a third group called "special" was designed for those wheelchair-bound persons with limited mobility. Elements of light-tempo music and animation were introduced in the videos to motivate the participants. Recording the exercises in video format makes it easier for the class instructors and participants to perform the exercises together, and ensure consistency across different exercise groups conducted in different centers. Each participant underwent the pre- and post-intervention assessment including 30-s chair stand repetitions, five-time chair stand duration, 4-m comfortable walk time, standing static balance level, 6-min walk test, and short physical performance battery score. These variables were compared within each group at pre- and post-intervention stages, and they were also compared between the two groups.
Results: A total of 180 participants were enrolled in 16 subcenters, including 160 participants in the exercise group and 20 participants in the control group. After 8 weeks of exercise training, there were significant improvements in their physical performance including 30-s chair stand repetitions and five-time chair stand duration, 4-m comfortable walk time and also 6-min walk test, within the exercise group (all $P < 0.05$). Approximately 39% of the participants in the exercise group also showed significant improvement in standing static balance level. No significant differences were found when compared with the control group participants who did not have any regular exercise participation.
Conclusion: A specially designed video-based exercise program has demonstrated some positive effects on physical and balance performance after 8 weeks of training among adults with intellectual disability.

KEYWORDS

exercise, intellectual disability, multicenter study, physical performance, balance

1 Introduction

People with intellectual disability (ID) exhibit many physical impairments that affect their daily functions. It has been reported that they have consistently lower levels of physical fitness and balance performance compared with the age-matched healthy population (1, 2). People with ID often adopt a sedentary lifestyle and lack motivation to exercise, resulting in obesity, poor fitness, and secondary health problems (3). The prevalence of multimorbidity in adults with intellectual disabilities is 98.7%, including visual impairment, obesity, epilepsy, constipation, and gait disorders (4). In particular for those aged 40 years and above, aging in people with ID is associated with low physical fitness and high prevalence of chronic diseases (5).

Falls are highly prevalent in people with ID causing severe injuries such as bone fractures (6). Physical deficit significantly contributes to health problems of people with ID by reducing their ability or motivation to participate in physical activity (7). Their inactive lifestyles may further lower their physical capacities and function, which also affect balance resulting in a vicious cycle. A meta-analysis has shown that exercise can significantly improve both static and dynamic balance in people with ID (8).

While there have been some studies in the research literature on the effects of exercise training among people with ID, the evidence is limited and varied. It is indeed a challenge to motivate people with ID to exercise on a regular basis, hence there is a need to make exercise entertaining and interesting to encourage their participation. It is also important to incorporate different components such as cardiovascular, strength training, flexibility, coordination, and balance in the same training program. Multi-component exercise training can improve functional independence, muscle strength, and balance of people with ID and promote better quality of life (9).

When designing exercises for people with ID, it is important to keep the movements and instructions simple and straightforward. Using music and animation to produce exercise videos can be effective in motivating the clients to engage in the exercises actively. Rhythmic movements with music were shown to improve the attention and concentration of students with intellectual disability (10). Using a light-tempo music helps to make the exercises more fun and motivate the participants to follow. These elements provide sensory cues that will stimulate the sensorimotor system of the participants and may help to facilitate their movements and coordination. This may have a positive benefit on their ability to perform physical movements in their daily lives. These sensory cues also serve to improve the attention focus of the participants. By repeating the same video clips, the participants also become more familiar with the exercises. Developing an exercise program with input from different healthcare professionals such as physiotherapists, occupational therapists, and healthcare workers can generate creative ideas that can address the specific needs of the people with ID.

The objective of the present study is to develop a special video-based exercise program with added elements of music and animation that may benefit those individuals with ID at high and low fitness levels. The aim is to enhance their active lifestyle and improve their overall fitness and health conditions. It is hoped that such a training program can be adopted in different community-based organizations that look after people with intellectual disabilities.

2 Materials and methods

2.1 Study design

This was a multicenter controlled trial to evaluate the effectiveness of an exercise program for people with intellectual disabilities.

This study was approved by the Research Ethics Committee of the Tung Wah College, Hong Kong, China. Each participant and their caregiver were informed of the purpose and procedures of the study and signed the consent before the study began.

2.2 Participants

The organizations that provided care for people with ID were invited to participate in this project. The person-in-charge of the center was responsible for identifying individuals who were suitable to join the training program. People over 15 years of age diagnosed with intellectual disabilities were recruited. The participants were invited to join in the group training and they were expected to be able to follow simple instructions in the group activities. Participants who had contraindications to exercise that might influence the response to exercise or with the inability to communicate were excluded. All participants and/or their caregivers were screened by the Physical Activity Readiness Questionnaire (PAR-Q) for their health conditions to ensure they were suitable to participate in exercise training and to determine a starting level for exercise training. The PAR-Q questionnaire contained questions about cardiovascular (heart) condition, chest pain, hypertension, chronic disease, or serious musculoskeletal disorder that would affect the ability to participate in the exercise training. Those with any of these conditions identified were excluded from the study. The residents of the invited centers who passed the PAR-Q screening and had signed the consent form were included in the study. For those who could not sign, consent was obtained from their family members via the social worker of the center.

The participants were divided into the exercise group and control group by cluster sampling. A total of 160 participants from 16 subcenters among five non-governmental organizations completed the video-based exercise program. In addition, 20 participants with intellectual disabilities were recruited as control. The participants of the control group continued with their daily living activities while receiving usual care from their centers with no exercises classes.

2.3 Intervention

A video-based exercise program with a series of short duration and moderate intensity exercise sessions with progression over

8 weeks was designed for people with ID to improve their body composition and physical performance. The video comprised rhythmic movements with light-tempo music and animation. The classes were held in the daycare center or hostels, providing a safe and enclosed exercise environment. Participants in groups of 10–15 with 2–3 caregivers/staff participated in each exercise class. Each session lasted for 1 h and comprised the following: (i) 10 min warm up and stretching; (ii) 15 min cardio fitness training exercises; (iii) 10 min muscle strength training; (iv) 10 min balance and coordination training; (v) 10 min fun activities; and (vi) 5 min cool down and stretching. Each participant received training sessions twice a week for 8 weeks. Five video clips were produced with two video clips for the low-level group (LLG) and two videos for the high-level groups (HLG). One video clip was specially made for those who may be more severely disabled with visual or hearing impairments and be wheelchair-bound [labeled as the special-level group (SLG)] Exercise variety included individual exercises, exercise with partners, chair exercise, towel exercise, Ball Fun, and Steps with beats. Registered physiotherapists and physiotherapy students were present at training sessions to supervise the participants and caregivers.

2.4 Outcome measures

Physical performance was measured as a primary outcome. Body composition including waist circumference and body mass index (BMI) were measured as secondary outcomes. Assessments were conducted at baseline and at the end of the exercise training. Physical performance was measured by a number of standardized tests that were commonly used in previous research on people with ID (1, 11–14) and are described as follows:

2.4.1 Thirty-second chair stand

The 30-s chair stand repetitions were used to assess participants' lower limb strength and endurance (13). This test measures the maximum number of times a participant can rise to a full standing position from the seated position in a 30-s period. A standardized unarmed chair was used. The participants were instructed to sit with back straight and feet approximately shoulder-width apart and placed on the floor. Their arms were crossed at the wrists and held against the chest for as long as possible. The maximum number of repetitions achieved was recorded.

2.4.2 Five-time chair stand

The five-time chair stand duration test involves standing up fully from a sitting position and sitting down five times as quickly as possible without pushing off (1). The amount of time a participant took to stand up five times in a row from a seated position on a standard chair with arms folded across the chest was recorded.

2.4.3 Four-meters comfortable walk time

Walking speed was assessed by the 4-m comfortable walk time (1). A 4 m distance was measured and the starting and ending points were marked on the floor. Participants were instructed to walk at their usual pace from a standing position that was normal and comfortable for them until they crossed the finish line. Time was recorded from the first foot movement to the stop timing when the participant's foot made contact with the floor at the end of the walking course.

2.4.4 Six-min walk test

The 6-min walk test was used to assess mobility and submaximal exercise performance. The participants were instructed to walk to and fro on a 10-me walkway on level ground as far as possible. The distance covered by each participant was measured and recorded (12).

2.4.5 Standing static balance level

The standing static balance level was assessed in four increasingly challenging positions (1): (1) feet together (side-by-side stand), (2) instep of foot advanced to toe of other foot (semi-tandem stand), (3) foot in front of other foot (tandem stand), and (4) single-leg stand. Stage success was graded when a participant was able to maintain the position for 10 s, with less than 10 s indicating stage failure. Improvement was demonstrated by completion of more test stages (0–4) at post-intervention testing.

2.4.6 Short physical performance battery score

The short physical performance battery (SPPB) score is a composite score calculated based on the five-time chair stand duration test (for lower extremity strength), 4-m comfortable walk time (for gait speed), and standing static balance level (for standing balance) (1, 14). The performance in each of the three tests was assigned a categorical score ranging from 0 (unable to complete the test) to 4 (highest level of performance) using standardized scoring. The total score ranging between 0 and 12 was calculated.

2.5 Body composition

The participants in the exercise group were evaluated in terms of their body mass index (BMI) and waist girth before and after the exercise training. These were also compared with those in the control group at the same time intervals.

2.6 Data analysis

Data analyses were conducted using SPSS Statistics 29.0 (IBM, Armonk, NY, USA). Baseline characteristics of the two groups were compared using independent t-test for continuous variables and Chi-square tests for the categorical variables. Differences between groups before and after exercise were evaluated using repeated measures ANOVA. Analyses of covariance (ANCOVA) with

baseline as the covariate were used to examine the difference in means between the exercise group and control group on SPPB and the 6-min walk test. Data were analyzed on an "intention-to-treat" basis, with patients being analyzed in the group to which they were assigned. All statistical tests were performed at the level of significance of $P < 0.05$.

3 Results

3.1 Participants' characteristics

In this study, a total of 180 participants with intellectual disabilities (160 in exercise group and 20 in control group) were recruited from 16 subcenters from five non-governmental organizations. The demographic characteristics of the participants are provided in Table 1. The participants in this study can be generally of middle age with the mean age being in the mid-40s for the two groups. The mean age in the control group was somewhat higher (49.20 ± 10.91), but their body size measures were largely similar to the exercise group. In terms of their baseline measures in the physical performance tests, there were no significant differences between groups. These results suggest that the unbalanced group sizes did not significantly affect the comparisons of their outcome measures.

3.2 Physical test performance

The outcomes of the physical tests are presented in Table 2 to compare the baseline and post-intervention measures within group and between groups.

3.2.1 Thirty-second chair stand

On average, from baseline to after exercise training, there was significant improvement in the 30-s chair stand test (from 9.63 ± 3.19 to 10.33 ± 3.23 repetitions, $P = 0.001$) in the exercise group. The control group also showed slight decrease, but the change was not statistically significant ($P = 0.083$). However, no significant difference was found between groups at post-intervention assessment ($P = 0.388$).

TABLE 1 Demographic and clinical characteristics of study participants.

	Exercise group ($n = 160$)	Control group ($n = 20$)	*P*-value
Age (years)[b]	44.59 ± 11.79	49.20 ± 10.91	0.098
Gender (n)	Male 95	Male 18	0.006[a]*
	Female 66	Female 2	
Level of intellectual disabilities (n)	Mild 41	Mild 6	0.909[a]
	Moderate 108	Moderate 13	
	Severe 10	Severe 1	
Tested positive in COVID-19 (n)	123	20	0.015[a]*
Weight (kg)[b]	58.47 ± 9.65	60.33 ± 12.85	0.436
Height (m)[b]	1.59 ± 0.11	1.61 ± 0.09	0.319
Waist girth (cm)[b]	84.55 ± 9.05	81.99 ± 12.18	0.299
Body mass index (kg/m^2)[b]	23.27 ± 3.44	23.40 ± 5.00	0.930

[a]Chi square.
[b]Data expressed as mean ± SD.
*$P < 0.05$.

TABLE 2 Physical performance before and after exercises among participants with intellectual disabilities.

		Exercise group	Control group	Between-group *P*-value
30-s chair stand (reps)	Baseline	9.63 ± 3.19	8.90 ± 2.47	0.333
	Post	10.33 ± 3.23	9.65 ± 2.86	0.388
	Within-group *P*-value	0.001*	0.083	
	Overall within-group effects $P = 0.014$; Overall between-groups effect $P = 0.310$; Group-time interaction $P = 0.937$.*			
Five-times chair stand (s)	Baseline	15.47 ± 8.19	16.13 ± 8.19	0.882
	Post-intervention	14.20 ± 6.93	16.23 ± 12.25	0.463
	Within-group *P*-value	0.013*	0.939	
	Overall within-group effect $P = 0.415$; Overall between-group effect $P = 0.443$; Group-time interaction $P = 0.341$.			
4-m comfortable gait speed (s)	Baseline	4.87 ± 2.47	4.88 ± 1.39	0.910
	Post-intervention	4.53 ± 2.05	4.36 ± 1.28	0.731
	Within-group *P*-value	0.008*	0.006*	
	Overall within-group effect $P = 0.015$; Overall between-group effect $P = 0.870$; Group-time interaction $P = 0.615$.*			
6-min walk test (m)	Baseline	312.35 ± 0.00[a]	312.35 ± 0.00[a]	1.000
	Post-intervention	339.84 ± 5.04[a]	324.45 ± 13.83[a]	0.299
	Within-group *P*-value	<0.001[b]*	0.657[b]	
	Overall within-group effect $P = 0.001$; Overall between-group effect $P = 0.299$; Group-time interaction $P = 0.299$. Covariates are evaluated as 6-min walk test (m) = 312.35.*			
SPPB score	Baseline	8.83 ± 0.00[a]	8.83 ± 0.00[a]	1.000
	Post-intervention	9.42 ± 0.13[a]	9.98 ± 0.36[a]	0.286
	Within-group *P*-value	<0.001[b]*	0.003[b]*	
	Overall within-group effect $P < 0.001$; Overall between-group effect $P = 0.286$; Group-time interaction $P = 0.286$. Covariates are evaluated as SPPB = 8.83.*			

[a]Data expressed as adjusted mean ± SEM.
[b]Adjusted for multiple comparisons by Bonferroni correction.
*$P < 0.05$.

3.2.2 Five-time chair stand

The five-time chair stand test showed a decrease from 15.47 ± 8.19 to 14.20 ± 6.93 s at post-exercise in the exercise group, and this change was statistically significant ($P = 0.013$). No statistical difference was found within the control group ($P = 0.939$) or between two groups at post-intervention assessment ($P = 0.463$).

3.2.3 Four-meters comfortable walk time

Significant improvement in the 4-m comfortable gait speed (from 4.87 ± 2.48 to 4.53 ± 2.05 s, $P = 0.008$, vs. 4.88 ± 1.39 to 4.36 ± 1.28 s, $P = 0.006$) were seen in both the exercise group and the control group, respectively. Yet, there were no statistical differences between the groups ($P = 0.731$).

TABLE 3 Frequency table on 10-s static balance test before and after the exercise program among participants with intellectual disabilities.

			10-s Static balance test (level)—post				Total
			Side-by-side stand	Semi-tandem stand	Tandem stand	Single-leg stand	
Exercise group	10-s static balance test (level)—Baseline	Side-by-side stand	11	9	11	1	32
		Semi-tandem stand	2	12	14	5	33
		Tandem stand	0	7	26	14	47
		Single-leg stand	0	0	4	24	28
	Total		13	28	55	44	140
Control group	10-s static balance test (level)—Baseline	Side-by-side stand	0	0	0	0	0
		Semi-tandem stand	0	0	0	0	0
		Tandem stand	0	0	11	4	15
		Single-leg stand	0	0	3	1	4
	Total		0	0	14	5	19

3.2.4 Six-minute walk test

The 6-min walk test improved from 312.35 ± 0.00 to 339.84 ± 5.04 m in the exercise group and this is a significant change ($P < 0.001$). No statistical difference was found within the control group ($P = 0.657$) or between the two groups at post-intervention assessment ($P = 0.299$).

3.2.5 Static standing balance level

Approximately 26% of the participants showed significant improvement in the 10-s static balance test at post-intervention while 52% remained the same (Chi-square $P < 0.001$) (Table 3). However, the participants in the control group did not show any changes in balance performance after the study period (Chi-square $P = 0.926$).

3.2.6 Short physical performance battery score

Significant improvement in the SPPB score (from 8.83 ± 0.00 to 9.42 ± 0.13, $P < 0.001$, vs. 8.83 ± 0.00 to 9.98 ± 0.36, $P = 0.003$) was seen in both the exercise group and control group, respectively. The between-group differences were not statistically significant at post-intervention assessment ($P = 0.286$).

3.3 Body composition

There was a significant decrease in waist girth in the exercise group after the exercise program (from 84.55 ± 9.05 to 83.72 ± 8.59 cm, $P = 0.015$), whereas there was no statistical change in waist girth in the control group (group × time interaction $P = 0.002$) (Table 4). Body mass index remained stable for both the exercise group and control group, before and after the exercise program.

4 Discussion

It is well known that people with ID have impaired fitness levels due to their sedentary lifestyle and lack of exercise (1, 15). The purpose of this clinical trial is to design a special exercise program that can cater to the different physical abilities of people with ID, and also integrate the elements of music and animation to enhance the compliance of the participants. Training the frontline staff in the residential centers and using the video clips to standardize the exercise training program also helps to ensure that the program is run in a consistent manner across the different centers. Particularly, the exercises were adapted to the different mobility levels of the participants, so it was easier for the participants in the same group to perform the movements required. The results of the present project have demonstrated the effectiveness of such a video-based exercise program that has significantly improved participants' physical and balance performance.

The significant improvements in the 30-s chair stand and five-time chair stand imply that the participants have gained more muscle strength in their lower limbs, so they can perform better in these tasks. This is also consistent with the faster walking speed in the 4-m gait speed test and the distance walked in the 6-min walking test. The participants have gained more endurance in

TABLE 4 Body composition before and after the exercises among participants with intellectual disabilities.

		Exercise group ($n = 160$)	Control group ($n = 20$)	Between-group P-value
Waist girth (cm)	Baseline	84.55 ± 9.05	81.99 ± 12.18	0.299
	Post-intervention	83.72 ± 8.59	84.25 ± 12.18	0.851
	Within-group P-value	*0.015	0.066	
	Overall within-group effect $P = 0.152$; Overall between-group effect $P = 0.637$; Group-time interaction $P = 0.002$.*			
Body mass index (kg/m^2)	Baseline	23.27 ± 3.44	23.40 ± 5.00	0.930
	Post-intervention	23.38 ± 9.36	23.22 ± 4.42	0.880
	Within-group P-value	0.469	0.792	
	Overall within-group effect $P = 0.872$; Overall between-group effect $P = 0.985$; Group-time interaction $P = 0.539$.			

*$P < 0.05$.

their walking ability. In a similar trend, their balance performance has also improved as they could perform the various components in the balance testing more successfully. The reduction in waist girth was a good indicator of the exercise effects on improving body composition. Although there was no significant improvement in the body mass index, this may show a more apparent change if the exercise program was continued for longer periods.

The positive results in the present project are generally in agreement with the results reported in past research studies demonstrating the benefits of exercise training on the physical performance or "skill-related fitness" of people with intellectual disability, but there may not be demonstrable benefits in terms of cardiovascular fitness outcomes or body composition measures (9).

Several past studies have reported the benefits of conventional exercise training in terms of aerobic training in improving the cardiovascular fitness and brachial systolic blood pressure in people with intellectual or developmental disabilities (16–18). However, the outcomes were varied and not conclusive. Jo et al. (19) conducted the exercise training for 12 weeks on adults with ID, with only 10 subjects in the exercise group and 10 subjects in the control group. The program included aerobic exercises with background music and conventional strength training with Theraband for 90 min each session, twice a week. Their results did not show significant improvement in muscle mass, strength, and cardiovascular fitness outcomes but significant improvement in muscle endurance (sit-up) (19). A recent study by Melo et al. (16) compared the effects of gym-based vs. home-based multi-component aerobic training regimes on cardiorespiratory fitness on 17 adult participants with ID. Home-based exercise training was most relevant for the COVID pandemic and this was shown to be useful on maintaining central arterial stiffness and central blood pressure, but the overall benefits on cardiovascular fitness were to a lesser extent compared with gym-based training (16). Our current study with the video-based exercise program can be applied both in-person or online, which offers a flexibility to the service units and participants. Our findings are also consistent with these past studies, demonstrating more apparent benefits in skill-related fitness rather than cardiovascular fitness.

Besides aerobic and resistance training, balance training has also been an important component in exercise training for people with ID. In the systematic review by Maiano et al. (8) that evaluated the effects of exercise on balance performance in young people with ID, it was reported that static and dynamic balance performance was significantly better in the exercise intervention group as compared with the control group. The research studies were included from 1991 to 2017 and the majority of the studies involve balance and strengthening exercises in the traditional approach. There were also large variations in the exercise types including creative dance, Tai Chi, Swiss ball, and rope skipping (8). Our present results also showed positive benefits on balance performance in the participants after 8 weeks of a multi-component exercise program.

Indeed, the problem of low physical activity in adults with intellectual disability is a well-recognized problem internationally (15). Particularly, in the current worldwide trend of improved care and standard of living, this group of people is facing the problem of aging. Previous studies reported that older adults with ID had even lower levels of physical activity compared with the normal population of similar age (20, 21). In our present study with the mean age of 40+ years in the exercise group, it was also found that they had lower levels of fitness, which may also be partly due to their experience of COVID-19 in the few months before the exercise program. It is hoped that participating in the exercise program would motivate them to continue with increased physical activity levels in the future.

In the recent research, there has been increasing work to try different types of exercise interventions including gamification and virtual reality technology to attract the people with ID to be more physically active (22). Future studies of randomized controlled experimental design and follow-up assessment are needed to examine the long-term effect and compliance of video-based exercise programs. In conclusion, participation in the exercise program is a key strategy for improving physical and balance performance and could potentially improve the quality of life for people with ID.

4.1 Study limitations

The present exercise training program was run for 8 weeks' period, which has been fixed arbitrarily as there were large variations in previous research studies with training durations ranging from 6 to 28 weeks. The 8-week intervention program has produced significant improvement in some physical performance measures in the exercise group. However, there were no significant between-group differences in the outcome measures, which may be due to the small and unbalanced sample sizes. To produce more effective and long-lasting improvement in cardiovascular fitness and body composition, it would be good to have these training programs adopted as regular activities in the various centers.

Our present study did not have any long-term follow-up after the exercise training was completed and this would be another limitation of the study. It would be useful to re-assess the participants in 3–6 months' time after the exercise training was completed, to see whether they would continue to exercise, and whether they continued to improve in their fitness and physical performance.

5 Conclusion

A specifically designed exercise training program of 60 min, incorporating music and animation captured in short video clips of 15 min have produced positive outcomes in terms of skill-related fitness and balance performance within the exercise group among adults with intellectual disability. A larger-scale study is required in the future to confirm the effectiveness of such a training program with balanced group sizes between the intervention and control groups.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Tung Wah College Human Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RK: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. GS: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing, Supervision. EH: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. AW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing, Supervision. LW: Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. GH: Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. RL: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. EW: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing, Investigation. AK: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. DC: Formal Analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia

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Background: Medication regimen complexity (MRC) is suspected to hinder medication adherence in patients with multiple illnesses. Despite this, the specific impact on Ethiopian patients with multimorbidity is unclear. This study assessed MRC and its impact on medication adherence in patients with multimorbidity.

Methods: A hospital-based cross-sectional study was conducted on patients with multimorbidity who had been followed at the University of Gondar Comprehensive and Specialized Hospital (UoGCSH), Ethiopia, from May to July 2021. Medication complexity was measured using the validated Medication Regimen Complexity Index (MRCI) tool, and the Adherence in Chronic Diseases Scale (ACDS) was used to measure medication adherence. Pearson's chi-square test was used to examine associations between MRCI levels and medication adherence. Ordinal logistic regression analysis was used to determine the impact of MRC and other associated variables on medication adherence. Statistical significance was determined using the adjusted odds ratio (AOR) at p-value <0.05 and its 95% confidence range.

Results: Out of 422 eligible patients, 416 (98.6%) were included in the study. The majority of participants (57.2%) were classified as having a high MRCI score with a mean (±SD) score of 9.7 (±3.4). Nearly half of the patients (49.3%) had low medication adherence. Patients with medium (AOR = 0.43, 95% CI: 0.04, 0.72) and higher (AOR = 0.31, 95% CI: 0.07, 0.79) MRCI levels had lower odds of medication adherence. In addition, monthly income (AOR = 4.59, 95% CI: 2.14, 9.83), follow-up durations (AOR = 2.31, 95% CI: 1.09, 4.86), number of medications (AOR = 0.63, 95% CI: 0.41, 0.97), and Charlson comorbidity index (CCI) (AOR = 0.36, 95% CI: 0.16, 0.83) were significantly associated with medication adherence.

Conclusion: Medication regimen complexity in patients with multimorbidity was found to be high and negatively impacted the levels of medication adherence. Healthcare providers and other stakeholders should seek interventions aimed at simplifying drug regimen complexity and improving adherence.

KEYWORDS

medication regimen complexity, multimorbidity, medication adherence, chronic diseases, Ethiopia

Introduction

Patients with multiple chronic conditions could potentially have a complicated medication regimen that alters the level of medication adherence. Multimorbidity has been defined as the presence of two or more chronic conditions in one individual (1, 2). It affects 23–33% of adults, with the prevalence further rising to 75% or higher at the age of 70 (2–4). This trend will amplify as life expectancies rise and idviduals with 65 years of age or older are expected to live with more than four chronic conditions by 2035 (5). Patients with multimorbidity are associated with increased healthcare and social services utilization (6), increased healthcare costs (7), poorer clinical outcomes (8), and increased disability and mortality (3).

Patients with chronic diseases are usually taking medications for long-term management, and the benefits of medications in preventing or slowing the progression of the adverse consequences of these diseases are indisputable (9). However, patients with multimorbidity require complex clinical care, including treatment with multiple medications (polypharmacy) (10–12). Although medication adherence is a significant aspect of clinical practice and research, only around 50% of chronically ill individuals adhere to their medications even in developed countries, according to WHO data, and nonadherence was much higher in low- and middle-income countries (13). Guidelines also emphasize that medication adherence is the cornerstone for managing and preventing long-term complications in multimorbidity patients (14). However, poor medication adherence remains a barrier to effective treatment outcomes, particularly in the management of chronic conditions (15, 16). Non-adherence or failing to adhere to the prescribed instructions with prescribed medication regimens contributes to treatment failure, hospitalization risk, increased medical expense, and morbidity and mortality risks in patients on long-term therapeutic plans (16–18).

Different studies have documented that low adherence to medications is multifactorial and multidimensional and related to patients, physicians, and healthcare systems (11, 12). A study conducted on Ethiopian diabetes patients with comorbidity showed that the source of medication cost, monthly income, number of medications, and medical conditions were significantly correlated with the level of medication adherence (15). Other studies also revealed that personal beliefs, sociodemographic characteristics, medication regimen complexity, clinical characteristics, and the number of medical conditions are factors that influence medication adherence in patients with chronic diseases (19–21).

The complexity of medication regimens could significantly impact patients' medication adherence, particularly in patients with multimorbidity who have been taking long-termtherapy (22, 23). The presence of high-complexity therapies is related to recent changes in the epidemiological profile and the wide availability of drugs on the market, as pharmacotherapy is the main therapeutic strategy to cure and control diseases (24). The complexity of the medication regimen is a term used to describe multiple characteristics of the drug regimen of a patient, beyond just the number of medications. This includes factors such as the number of doses per day, the number of units per dose, forms of dosage, and additional guidelines (25). MRCs are more likely to be error-prone and impact patient safety and quality of life (26). The complexity of a person's medication regimen depends on the characteristics of the pharmacotherapy, such as the number of drugs consumed, their pharmaceutical forms, schedules, and doses, and additional instructions given by the physician (27). MRC is commonly involved in patients with long-term medication therapeutic needs, in particular (28–30). Studies have shown a negative association between increased MRC and nonadherence to prescribed medication regimens (28, 31–35).

There is an increasing number of patients with multimorbidity in Ethiopia, and most patients with chronic diseases have at least one comorbid chronic condition with a high number of prescribed medications (36–39). This could be attributed to the increasing complexity of medication regimens, which in turn impacts patients' medication adherence. The burden could be significant particularly in the Ethiopian population with most of the patients having a lower level of health literacy (40, 41) and a higher level of misunderstanding of dosage regimen instructions (42). A part of this study also demonstrated that patients with higher regimen complexity scores had a lower quality of life (43). Despite some studies have shown that increasing of MRCI score negatively affects medication adherence only in patients with specific diseases, such as asthma (28) and diabetes (32), there is a paucity of evidence that showed the levels of MRC and its impact on medication adherence in patients with multimorbidity. As a result, assessing the extent of MRC and its impact on medication adherence in these high-risk patients is crucial to designing tailored interventions to maximize the treatment outcomes of patients living with multimorbidity. Therefore, this study assessed MRC and its impact on the levels of medication adherence in patients with multimorbidity having chronic follow-up at the University of Gondar Comprehensive and Specialized Hospital (UoGCSH), Ethiopia. In addition, this study also examined the association between other independent variables and medication adherence in patients with multimorbidity.

Method and materials

Study design, setting, and period

An institutional-based cross-sectional study was conducted on patients with multimorbidity who had chronic follow-ups at the University of Gondar Comprehensive Specialized Hospital (UoGCSH) from May 1 to July 30, 2021. The hospital is one of the largest teaching hospitals in the country and has served more than 9 million population in the catchment area.

Study participants and eligibility criteria

The study population consisted of patients with multimorbidity who visited the UoGCSH chronic ambulatory clinic during the study period and fulfilled the inclusion criteria. To be included in the study, participants should be adults (18 years and older), have been diagnosed with at least two or more chronic conditions, and have been treated and followed up on for at least 3 months in the study area. Patients who had a serious mental illness and were unable to cooperate

Abbreviations: ACDS, Adherence of Chronic Disease Scale; CCI, Charlson Comorbidity Index; MRC, Medication Regimen Complexity; MRCI, Medication Regimen Complexity Index; UoGCSH, University of Gondar Comprehensive Specialized Hospital.

with the interview and sought emergency medical attention, those with incomplete medical records, and pregnant women because of special ethical requirements as a special population were excluded from the study.

Sample size determination and sampling techniques

The sample size was determined by using a single population proportion formula:

$$n = Z^2 p(1-p)/w^2$$

Where: n, the sample size required; w, the marginal error of 5% ($w = 0.05$); Z, the degree of accuracy required at a 95% level of significance ($Z = 1.96$); and $p = 50\%$ (0.5) is the level of regimen complexity. This is because no study was done previously in the study area. Finally, considering 10% of possible non-respondents, the final sample size was 422.

The study participants were selected using systematic random sampling techniques from eligible study populations. The projected number of patients with multimorbidity at two-month follow-up was 2,340, so $K = 52$ *45/422 = 5.5, approximately = 6. Initially, the first study participant was selected using simple random sampling as the starting point. Then, subsequently, participants were included in the study using this sampling interval, every six patients, through the coding of their medical records until sufficient samples were maintained.

Operational definition of terms

Chronic diseases

In this study, as defined by the U.S. National Centre for Health Statistics (US-NCHS), a chronic disease lasts for a year or longer and is permanent. It results in residual disability, is caused by an irreversible pathological alteration, necessitates specialized training for the patient during rehabilitation, or the patient may need a prolonged period of care, supervision, or observation (44). The primary diagnosis of the patients was categorized according to the International Classification of Diseases (ICD) tenth edition code. It includes chronic endocrine diseases like diabetes and thyroid disorders; chronic circulatory diseases, including hypertension and heart failure; chronic respiratory diseases like asthma and COPD; chronic gastrointestinal diseases including, pancreatitis and liver diseases; and chronic musculoskeletal disorders, including rheumatoid diseases.

Charlson comorbidity index (CCI)

In this study, it indicates a severity of a combined comorbidities in patietns with multimorbidity. Three classes were established for the severity of comorbidity based on the CCI score: mild (CCI scores 1–2), moderate (CCI scores 3–4), and severe (CCI scores ≥5) (45).

Multimorbidity

It implies the presence of at least two chronic diseases in one individual at the same time (2).

Medication adherence

Defined as patients taking their medications as prescribed. The level of medication adherence was measured based on the Adherence in Chronic Diseases Scale (ACDS) and categorized as low adherence if a total score is <21 points; a total score of 21–26 points, medium adherence; and high adherence if a total score > 26 points (46).

Medication regimen complexity (MRC)

It indicates the patient's drug regimen, beyond just the number of medications, which includes the dosage forms, frequency, and instructions for each medication administered (47).

Medication regimen complexity index (MRCI)

In this study, the MRCI was defined as the overall patient-level MRCI, including both prescription and OTC medications (48).

Polypharmacy

Defined as, when greater than or equal to 5 drugs are prescribed for the patient (39). Polypharmacy did not incorporate the dosage forms, frequency, and instructions for each medications administered.

Data collection instruments and procedures

A semi-structured data collection instrument was used to gather the data. The instrument was developed by reviewing previous similar studies with some modifications, focusing on the nature of the study population (32, 33). The data were collected through patient interviews, a review of the patients' medical records, and direct observation. Certain variables were collected through firsthand observation, particularly focusing on the instructions provided for each medication during administration. We directly requested and observed clients as they demonstrated the administration process for special drug formulations that necessitate specific attention and instructions, such as aerosols, eye drops, and suspensions.

The patients' medical records, including prescription and non-prescription medications, were carefully reviewed and observed. The instrument consisted of three sections. The first section consisted of participants' sociodemographic and clinical characteristics. In our study, we collected data on patients' medical history, including their diagnosis, through patient medical record reviews. We ensured that the diagnoses were made by qualified healthcare professionals, such as physicians and specialists, and were recorded in the patients' medical records. For each disease included in our study, healthcare professionals used standard diagnostic criteria, as established by local, national and international guidelines.

The second section of the instrument consisted of the types of medications used by the patients, and it was used to measure MRC, the MRCI instrument, which included medications' dosage forms, dosage frequency, and additional instructions. The last section of the data collection instrument consisted of the Adherence in Chronic Diseases Scale (ACDS), a 7-question questionnaire used to measure and categorize the level of medication adherence of the study participants.

As the different diseases vary in terms of their impact on health, each medical condition should objectively be weighed to measure the comorbidity burden using the Charlson Comorbidity Index. The Charlson comorbidity index (CCI) is currently the most commonly used comorbidity assessment tool. It consists of three parts: disease assessment, severity assessment, and scoring. It contains 18 scoring

items which including's warfarin from the drug class. Additional chronic diseases such as cancer, diabetes mellitus, heart attacks, and various other medical conditions were also assessed and scored.

Outcome measures

This study has two primary outcomes. To measure the levels of MRC in patients with multimorbidity and to examine the association between MRC and levels of medication adherence. Additionally, the study explored factors beyond MRC that influence medication adherence in patients with multimorbidity as a secondary outcome.

The level of MRC was measured by the MRCI instrument, a 65-item validated tool that considers the number of medications, dosage form, dosage frequency, and extra directions (e.g., break/crush the tablet, take at a specified time, and relation to food/liquid). The instrument consists of three sections related to the route of drug administration (section A), dosing frequency (section B), and additional directions (section C). The sum of these sections (A + B + C) contributes to the patient-level MRCI. The MRCI score was categorized into low (≤4), moderate (5–8), or high (>8) levels of MRCI (32, 48). Patient-level MRCI was calculated using the Microsoft Access 2013 electronic data capture tool.

Medication adherence was assessed using the Adherence in Chronic Diseases Scale (ACDS), a 7-question questionnaire. Questions 1–5 addressed the patient's medication behavior, while 6–7 assessed the doctor-patient relationship. Each item received 0–4 points, with total scores ranging from 0 (minimum adherence) to 28 (maximum adherence). Scores were categorized as high (>26), medium (21–26), or low (<21) (46).

The association between the level of MRCI and medication adherence levels was examined using Pearson's chi-square test, and further analyzed by ordinal logistic regression to show the impact of MRC on medication adherence.

Data quality conrtol

Initially, the questionnaire was pre-tested on 21 patients (5%) before the actual data collection and avoided in the final analysis to check clarity, ease of understanding, and cleanliness. The reliability (internal consistency) of the questionnaires was assessed by independent expert personnel in the area. In addition, the Cronbach's alpha value of the medication regimen complexity measurement tool ($\alpha = 0.87$) and the adherence level measurement tool ($\alpha = 0.845$) were examined and found to be in acceptable ranges. After some modifications to its appropriateness and suitability, actual data collection was followed. Data collectors (two pharmacists and two bachelor nurses) were recruited voluntarily based on their educational level and possible familiarity with medical and health research. They were trained intensively by the principal investigator on the contents of the questionnaire, data collection methods, and ethical concerns. The filled-out questionnaire was checked daily for completeness, clarity, cleanliness, uniformity, and understandability.

Data management and analysis

Collected data were sorted, cleaned, coded, and entered into Epi-data version 4.6.02 and then exported to SPSS version 26 for analysis. Descriptive statistics like frequencies, means, and percentages were used to summarize categorical and continuous variables. Pearson's chi-square test was used to assess the association between MRCI levels and medication adherence. Associations of MRC and other associated variables with the level of medication adherence were examined using ordinal logistic regression, given the ordinal nature of the medication adherence levels (low, moderate, and high). The proportional odds (PO) assumption was checked using a likelihood ratio test (p-value <0.05) to ensure model suitability. Variables with p-values ≤0.25 in the bivariable analysis were included in the multivariable proportional odds model. Adjusted odds ratios (AOR) with 95% CI and p-values <0.05 were considered statistically significant.

Ethical considerations

The proposal was reviewed and approved by the ethical review committee of the Department of Clinical Pharmacy, and the study was ethically approved by the ethical review board of the University of Gondar, with a reference number of UOG-Sop/129/2021. Permission to conduct the study was obtained from the UoGCSH. All individuals enrolled in the study were provided with a written document containing details about the study prior to data collection. For participants who were unable to read or write, the interviewer read out the information sheet and assisted them in providing their signature, typically through a thumbprint. They were also advised to withdraw at any time if they did not want to take part in it. Confidentiality was ensured by making all information anonymous. The data collection procedure was carried out based on the Helsinki Declaration.

Results

Sociodemographic and clinical characteristics

Out of a total of 422 participants, 416 (96.8%) participated in the study. The mean (±SD) age was 56.1 (±13.8) (range: 18 to 92) years. Around two-thirds (64.2%, 267) of them were females. Most of the participants (65.9%, 274) had health insurance to cover their medical expenses. Among the study participants, more than half (57.7%, 240) had a diagnosis and had been taking treatments for less than 5 years. More than half of the patients (52.7%, 215) had two chronic conditions. Most of the patients were diagnosed with diseases of the circulatory system (93.5%, 388) (Table 1).

Medication regimen complexity and medication adherence

The total number of medications used for the management of studied patients were 1980. Commonly prescribed drug classes were cardiovascular drugs (32.6%, 645) followed by endocrine drugs (18.2%, 360). Almost half of the patients (46.4%) had been taking ≥5 drugs, with a mean (±SD) medication count per patient of 4.8 (±2.3). The MRCI score ranged from 2 to 20, with an average score of 9.7 (±3.4). Almost half of patients (49.3%) had low medication adherence

(Table 2). The majority of patients (57.2%, 237) with a 95% CI (52.4, 61.8) were found to have a high complexity score (Figure 1).

Association between MRCI and medication adherence level

Pearson's chi-square test of association was used to identify a statistically significant association between MRCI and level of adherence, and the results revealed that patients with a higher MRCI had lower medication adherence ($p = 0.003$) (Table 3).

Factors associated with medication adherence

The multivariable ordinal logistic regression analysis showed that partcipants' income level, duration of follow-up, severity of CCI, number of medications, and MRCI levels were significantly associated with medication adherence. The odds of having higher medication adherence in individuals with a monthly income of >5,000 were increased by 4.6 times (AOR = 4.59, 95% CI: 2.14, 9.83) compared with those who had a monthly income level of <1,500 Ethiopian birr. Simultaneously, the odds of medication adherence were higher in patients who had >10 years of follow-up duration compared with patients who had <5 years of follow-up duration (AOR = 2.31, 95% CI: 1.10, 4.87). On the other hand, the odds of medication adherence among individuals who had severe CCI decreased by 64% (AOR = 0.36, 95% CI: 0.15, 0.83) compared with those patients with mild CCI. Patients who were on polypharmacy (≥5 medications) were also found to have lower odds of medication adherence compared with those who received <5 medications (AOR = 0.63, 95% CI: 0.41, 0.97). More importantly, patients with a medium (AOR = 0.43, 95% CI: 0.04, 0.72) and a high (AOR = 0.31, 95% CI: 0.07, 0.79) MRCI level were found to have decreased odds of medication adherence compared to patients with a low level of MRCI levels (Table 4).

Discussion

To the best of the investigators' knowledge, this is the first study that assessed MRC and its association with medication adherence that accounts for the complexity of medication in patients with multimorbidity in Ethiopia. In the current study, MRCI scores were stratified by low, medium, and high regimen complexity. The majority of participants had a high MRCI score. The finding showed a significant association: patients with higher MRCI levels were more likely to have lower odds of high medication adherence. In addition to MRC, monthly income, duration of follow-up, number of medications, and CCI levels were significantly associated with medication adherence in patients with multimorbidity.

Consistent with earlier studies, a current study also showed that most patients were found to have a higher MRCI score with a higher medication count (49, 50). This might be because patients with multimorbidity could have prescriptions for multiple medications, which is responsible for the complexity of their regimens. The complexity of pharmacotherapy is composed of multiple features of the prescribed regimen, including the number of different drugs in the

TABLE 1 Sociodemographic and clinical characteristics of study participants attending chronic care follow-up at UoGCSH, Ethiopia, 2021 ($N = 416$).

Variable	Category	Frequency (%)	Mean (±SD)
Sex	Male	149 (35.9)	
	Female	267 (64.2)	
Age	18–29	14 (3.4)	56.1 (±13.8)
	30–39	27 (6.5)	
	40–49	85 (30.4)	
	50–64	159 (38.2)	
	>+65	131 (31.5)	
Marital status	Single	22 (5.3)	
	Married	317 (76.2)	
	Divorced	54 (13)	
	Widowed	23 (5.5)	
Religion	Orthodox	347 (83.4)	
	Protestant	10 (2.4)	
	Muslim	58 (13.9)	
	Catholic	1 (0.2)	
Educational status	No formal education	117 (28.1)	
	Primary education	134 (32.2)	
	Secondary	87 (20.9)	
	College and above	78 (18.8)	
Occupation	Farmer	63 (15.1)	
	Employed	93 (22.4)	
	Merchant	70 (16.8)	
	Housewife	166 (39.9)	
	Retired	24 (5.8)	
Monthly income in Ehiopian birr (ETB)	<1,500 ETB	128 (30.8)	4765.4 (±1105.3)
	1,500–2,999 ETB	154 (37)	
	3,000–5,000 ETB	80 (19.2)	
	>5000ETB	54 (13)	
Alcohol consumption	Yes	107 (25.7)	
	No	309 (74.3)	
Cigarette smoking	Yes	9 (2.2)	
	No	407 (97.8)	
Residence	Rural	143 (34.4)	
	Urban	273 (65.6)	
Herbal drug use	Yes	62 (14.9)	
	No	354 (85.1)	
Physical exercise	Yes	53 (12.7)	
	No	363 (87.3)	
Source of medication fee	Health insurance	274 (65.9)	

(Continued)

TABLE 1 (Continued)

Variable	Category	Frequency (%)	Mean (±SD)
	Out of pocket	142 (34.1)	
Medication administration	Self (autonomous)	259 (62.3)	
	Relatives (required assistance)	157 (37.7)	
Duration of diagnosis in years	< 5	240 (57.7)	4.7 (±3.1)
	5–10	148 (35.6)	
	>10	28 (6.7)	
Duration of treatment in years	< 5	240 (57.7)	4.8 (±2.7)
	5–10	153 (56.8)	
	>10	28 (6.7)	
Previous hospitalization	No	149 (35.8)	
	Yes	267 (64.2)	
Number of drugs per patient	<5	223 (53.6)	4.8 (±2.3)
	≥5	193 (46.4)	
Number of Multimorbidity	2	215 (51.7)	2.6 (±1.7)
	3	158 (38)	
	≥ 4	43 (10.3)	
Charlson comorbidity index (CCI)	Mild	328 (78.8)	
	Moderate	56 (13.5)	
	Severe	32 (7.7)	
*Primary diagnosis of study participants	Disease of the Circulatory system	388 (93.4)	
	Disease of the endocrine system	220 (53.0)	
	Disease of respiratory system	57 (13.7)	
	Disease of the renal system	27 (6.5)	
	Disease of the gastrointestinal system	21 (5)	
	Disease of hematology system	17 (4.1)	
	Disease of the central nerve system	16 (3.8)	
	Disease of the musculoskeletal system	12 (2.9)	
	Others	24 (5.9)	

* one patient could have diseases of different systems, Others, diseases of the eye and adnexa, diseases of the skin and subcutaneous tissue, neoplasms, mental and behavioral disorders, nutritional and electrolyte disorders.

TABLE 2 Distribution of medications used by patients, medication complexity score, and level of medication adherence.

Variables	Category	Frequency (%)	Mean (±SD)
Class of medications ($N = 1980$)	Cardiovascular drugs	645 (32.6)	
	Endocrine drugs	360 (18.2)	
	Respiratory drugs	265 (13.4)	
	Analgesic and anti-pyretic	196 (9.9)	
	Gastrointestinal drugs	173 (8.7)	
	Hematology Drugs	132 (6.7)	
	Centeral nerve system drugs	84 (4.2)	
	Others	125 (6.3)	
Medication count per patient ($N = 416$)	< 5	223 (53.4)	4.8 (±2.3)
	≥5	193 (46.6)	
Avrage MRCI score	-		9.7 (±3.4)
Level of medication adherence ($N = 416$)	Low adherence	205 (49.3)	
	Moderate adherence	125 (30)	
	High adherence	86 (21)	

Others, Chemotherapy (antibiotic), musculoskeletal drugs, vitamin and mineral drugs.

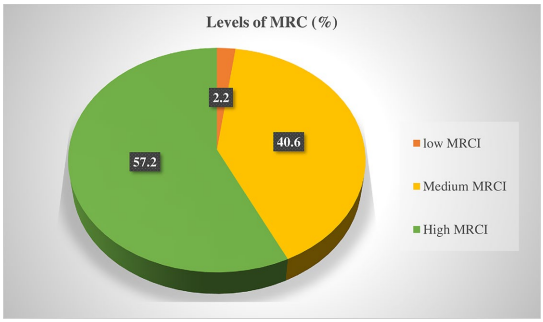

FIGURE 1
Level of MRC in patients with multimorbidity at the UoGCSH, 2021.

treatment, the number of doses of each drug per day, the number of per-dose dosage units, the total number of doses per day, and drug interactions with food (51). In contrast, the MRCI score in the current finding was higher in the previous study done in Brazil (52). This discrepancy may be due to the use of different cut-off points, the treatment approach of clinicians in line with guidelines, and the difference in the sociodemographics of patients. As compared with previous studies conducted on Ethiopian patients with specific diseases such as asthma (28) and diabetes (32), a higher proportion of patients were found to have a higher MRCI score in the current study. This might be because of the current study conducted on patients with multimorbidity who could have additional prescribed medications because of multiple medical conditions. As a result, a higher level of MRC in patients with multimorbidity may suggest that physicians need to be vigilant to minimize the complexity of medications in such risky patients by applying the deprescription of inappropriate medications and simplification of regimens (53). Identified strategies that were used to reduce the complexity of medication regimens should be considered, like, fixed-dose combination (FDC), once-daily dosing, and a combination of more than one approach. Educating and empowering patients to understand the treatment regimen and its

TABLE 3 Association of MRCI and levels of medication adherence using Pearsno's chi-square test in patients with multimorbidity at the UoGCSH.

Level of medication adherence (*n*, %)						*p*-value
		Low	Moderate	High	Total	
MRCI levels	Low	4 (1)	2 (0.5)	3 (0.7)	9 (2.2)	0.003
	Medium	73 (17.5)	46 (11.1)	50 (12.0)	169 (40.6)	
	High	128 (30.1)	77 (18.5)	33 (7.9)	238 (57.2)	

TABLE 4 Assocaition between independent variables and medication adherence in patients with multimorbidity at the UoGCSH.

Variables		COR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
Gender	Male	1		1	0.097
	Female	1.79 (1.22, 2.63)	0.003	1.45 (0.93, 2.25)	
Level of education	No formal education	1		1	
	Primary education	1.26 (0.74, 2.14)	0.391	0.85 (0.45, 1.59)	0.641
	Secondary	1.44 (0.87, 2.57)	0.22	1.1 (0.60, 2.12)	0.715
	College and above	1.05 (0.615, 1.841)	0.843	1.02 (0.43, 2.74)	0.183
Residence	Urban	1		1	0.355
	Rural	0.67 (0.45, 0.98)	0.04	0.80 (0.50, 1.27)	
Monthly Income level	<1,500	1		1	
	1,500–2,999	2.38 (1.667, 6.0720)	0.045	1.71 (0.63, 6.77)	0.135
	3,000–5,000	2.25 (0.87, 4.56)	0.065	1.56 (0.43, 5.76)	0.321
	>5,000	3.5 (1.86, 6.67)	<0.001	4.59 (2.14, 9.83)	0.011*
Alcohol history	No	1		1	0.346
	Yes	0.64 (0.42, 0.98)	0.042	0.79 (0.4, 1.27)	
Traditional medicine use	No	1		1	0.417
	Yes	0.67 (0.39, 1.15)	0.144	0.79 (0.45, 1.39)	
Cost of healthcare service	Health insurance	1		1	0.277
	Out of pocket	0.73 (0.4, 1.06)	0.101	0.7 (0.511, 1.21)	
Managing medicine	Autonomous	1		1	0.142
	Required assistance	0.61 (0.41, 0.89)	0.010	0.73 (0.48, 1.12)	
Duration of follow-up in years	< 5	1		1	
	5–10	1.07 (0.73, 1.59)	0.707	1.11 (0.729, 1.70)	0.613
	>10	1.83 (0.95, 3.55)	0.078	2.31 (1.0, 4.86)	0.027*
Leve of CCI	Mild	1		1	
	Moderate	0.81 (0.47, 1.40)	0.453	0.88 (0.49, 1.56)	0.679
	Severe	0.37 (0.17, 0.80)	0.012	0.36 (0.15, 0.82)	0.016*
Number of medications	< 5	1	0.021	1	0.036*
	≥ 5	0.48 (0.33, 0.7)		0.63 (0.41, 0.97)	
MRCI levels	Low	1		1	
	Medium	0.39 (0.02, 0.85)		0.43 (0.04, 0.72)	0.015*
	High	0.30 (0.06, 0.82)		0.31 (0.07, 0.79)	0.001*

CCI, Charlson comorbidity index; * statistically significant at $p < 0.05$.

benefits should be considered. More over Work diligently with patients and families to secure an accurate list of medications, Reorganize the medication list,look for inappropriate and incorrect prescriptions, and use caution when deprescribing medications.

Patients with multimorbidity with complex medication regimens are expected to adhere to their medications to be effective in their treatment outcome. However, in this study, the findings revealed that a significant number of participants had low levels of adherence to their medications. Similarly, earlier studies done in the United Arab Emirate (54), Saudi Arabia (55), and South India (56) showed that a significant number of study subjects had a level of low medication adherence. A study done on Ethiopian diabetes patients with

comorbidity also showed significantly low medication adherence (15). The findings may implicate that patients with multimorbidity need strict follow-up and support to adhere to their prescribed medications. However, the findings varied with the study done in Spain (57), which revealed that a significant proportion of the study participants were in the range of high levels of medication adherence. This variation potentially might be due to differences in patients' medication knowledge and perceptions about medication complexity and fear of side effects. The current study was conducted on patients with low levels of medication and health literacy compared with the earlier study. High medication costs in patients with polypharmacy might also be a potential reason for low medication adherence. In addition to this attributed differences in the study setting, methods used to measure medication adherence, and physicians' and pharmacists' approach to their patients could bring differences in patients' attitudes toward their medication.

Although MRC and medication adherence are different outcome measures, it is believed that MRC has been associated with low medication adherence. Consistent with earlier studies conducted on Ethiopian patients with asthma (28) and diabetes (32), the current study also disclosed that patients with a higher level of MRC were found to have significantly lower levels of medication adherence. This is also in line with other studies conducted worldwide (22, 23, 49, 50, 54). This could be because patients with multimorbidity are potentially treated with polypharmacy, which can be the reason for the increased MRC burden, and in turn, it could result in poor medication adherence. An increasing number of patients with multimorbidity means that more and more patients are faced with complex medication regimens. As a result, patients with multimorbidity who have been treated with polypharmacy should be assessed for medication adherence levels. The findings may suggest that as patients with multimorbidity are at high risk of having high MRCI and low levels of medication adherence, due to the presence of multiple chronic comorbidities and polypharmacy for long durations, close follow-up of these patients could be warranted.

The present study has identified the association of participants' sociodemographic and clinical variables with the level of medication adherence beyond the complexity of medication regimens. Consistently with previous studies (22, 23, 58), the current study showed that monthly income, duration of diseases, CCI levels, and number of medications were found to have a significant association with the level of medication adherence. The associated factors identified in this study were also largely consistent with findings from previous large-scale territory-wide study using patient health records in the Chinese population (59) and Italian (60). The findings may implicate that most of the independent factors that affect medication adherence in patients with multiple chronic diseases are similar and need interventions to enhance the treatment outcome of patients. On the other hand, participants' age, level of education, and social drug use were also associated with the level of medication adherence in previous studies (55, 61–63). The difference could be due to variability in the study participants, adherence measurement tools used, healthcare systems and policies, and knowledge, skill, and patient care approaches of healthcare professionals. In addition, we need to consider that heterogeneity of factors related to diseases may affect the patient's medication-taking behavior. For example, the treatment approach of clinicians and patients' lifestyles, medication-related knowledge, and perceptions may have a pivotal impact on variability.

Consistently with earlier studies (15, 64–66), the current study showed that patients with a lower monthly income were found to have lower odds of high medication adherence. This could be because patients with low economic status and household income have the potential to withdraw medications because of affordability issues. This problem might be severe in chronic illnesses and patients with comorbidities because of increased medication costs for treating additional conditions. Particularly in Ethiopian settings, most patients are of low socioeconomic status (67, 68). On the contrary, most patients with chronic diseases have comorbid conditions and receive multiple medications (36–39). Thus, patients with a lower income will have a lower level of medication adherence because most multimorbidity patients may be unable to afford treatment costs for multiple medications. Therefore, the findings may suggest that healthcare practitioners and prescribers should devise strategies to acknowledge patients' socioeconomic situation and facilitate effective and transparent communication regarding the pricing of prescribed medications. Patients may also benefit from engaging in Ethiopian community-based health insurance (CBHI) programs (69), which may help individuals by providing optimum pre-paid coverage costs and protecting them from catastrophic expenditures.

In this study, patients treated with several medications (polypharmacy) and a higher Charlson commorbidy index (CCI) were found to be lower odds of medication adherence. The finding is in line with previous studies (22, 23, 32, 49, 50). The association might be because patients with polypharmacy and a higher number of comorbidities may have poor medication adherence due to the complexity of medication regimens, potential adverse effects related to potential drug–drug interactions, and the affordability issue of multiple medications. The loss of medication administration time may also be caused by taking more medications. Healthcare professionals, especially prescribers, should thus concentrate on honing the art of writing prescriptions for the least amount of pharmaceuticals possible while taking into account the requirement for medication treatment for patients with multimorbidity. To manage potential and existing comorbidities, patients also need to be extremely watchful and driven to take all of their prescribed medications.

In addition, the possible reason associated with low level of adherence was due to those with multiple medical conditions might encounter difficulties to complying with their daily medication-taking schedule, probably due to poorer bodily function and the higher possibility of polypharmacy, referrals or adverse drug events. The CCI score highlights the severity of chronic disease and chronicity which affects self-managing to take medications. Moreover, CCI indicated the severity of the disease status, which results difficulty of taking medications regularly and autonomously.

In general, the current study finds that patients with multimorbidity have a high prevalence of MRC, which affects medication adherence negatively. The numerous barriers to the effective use of medications in resource-limited settings include poor communication between the patient and physician, inappropriate knowledge gaps on medications, fears of adverse events, long-term therapy, polypharmacy, and cost and access barriers (70). These barriers could have a significant impact, particularly on patients with multimorbidity receiving complex medication regimens. Therefore, the identification of specific barriers for each patient and the design of appropriate prevention strategies are indispensable to mitigating medication adherence.

Strengths and limitations of the study

Considering the burden of patients with multimorbidity, the present study has highlighted the level of MRCI and medication adherence, which has a significant implication for further study. However, there are some limitations to the present study that need to be considered. First, it is a cross-sectional study design, whereby claims about the directionality of the causal relationship between the dependent and independent variables cannot be verified. Secondly, MRCI was calculated using only what was captured in the patient's medical chart. As a result, any medications or instructions not recorded were missed. Another limitation was that the extent of generalizability may be limited since it was a single-center study. The authors would like to welcome further studies with prospective follow-up, including a relatively larger population in multicenter settings.

Implication and contribution to the field

This study provides crucial data from an understudied region, Ethiopia, like many African countries, faces a growing burden of multimorbidity but has limited research on medication adherence and regimen complexity. This article contributes valuable data from this region, informing healthcare strategies and interventions. Investigates a key factor in multimorbidity management that medication regimen complexity is a significant barrier to adherence in multimorbid patients, leading to poorer health outcomes. This study sheds light on the specific challenges faced by Ethiopian patients and the impact on adherence. The findings also inform intervention development by identifying factors associated with low adherence (e.g., high regimen complexity), the study helps tailor interventions to the specific needs of Ethiopian patients with multimorbidity. This could include simplified regimens, medication reminders, or educational programs. It can also raise awareness of patient burden by highlights the challenges faced by multimorbid patients in managing complex medication regimens, urging healthcare professionals to consider patient perspectives and advocate for patient-centered care. The also study opens doors for further research on effective interventions to improve adherence in Ethiopian patients with multimorbidity. This could involve testing different strategies and evaluating their impact on clinical outcomes.

Overall, the article makes a valuable contribution to the field of medicine by providing data and insights on medication adherence in a previously understudied population. This can inform healthcare practices, intervention development, and further research, ultimately improving health outcomes for multimorbid patients in Ethiopia.

Conclusion

Medication regimen complexity was highly prevalent in patients with multimorbidity and had a significant impact on medication adherence. In addition, patients with low income, a shorter duration of treatment, and those with polypharmacy and a high CCI should strictly follow and require intervention to maximize their medication adherence to enhance treatment outcomes and reduce healthcare costs in patients with multimorbidity. Physicians and healthcare providers could be engaged in strategies to simplify and minimize MRC in patients with multimorbidity.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethical Review Committee of the Department of Clinical Pharmacy and the study was ethically approved by the Ethical Review Board of the University of Gondar, with a reference number of UOG-Sop/129/2021. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. AS: Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BG: Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Does the nurse-led case management benefit rheumatoid arthritis patients in reducing distressing symptoms and C-reactive protein: a 2-year follow-up study in Taiwan

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Background: Rheumatoid arthritis (RA) is a chronic disease and may worsen over time. Today, nurse-led case management (NLCM) has been recommended to improve clinical outcomes for chronic disease patients, yet little is known regarding its impact on pain, fatigue, and C-reactive protein (CRP) among RA patients. We aimed to explore this issue among such groups via a two-group pre- and post-test approach.

Methods: All subjects were recruited from one hospital in Taiwan from January 2017 to June 2018 and assigned to either a 6-month NLCM program in addition to usual care or to a control group that received usual care only. All of them were followed for 2 years. Outcomes of interests were compared at four time points: baseline, the third day after NLCM completion, and at 6 and 24 months after NLCM. Effects between them were tested using the generalized estimating equations (GEE) model after adjusting for differences at baseline.

Results: A total of 50 patients in the NLCM group and 46 in the control group were recruited for data analysis. Results from the GEE model indicated that integrating NLCM into conventional care benefited patients in decreasing levels of pain and fatigue, as well as CRP value. These improvements were still observed for 2 years after NLCM.

Conclusion: NLCM was shown to be helpful in lowering pain, fatigue, and CRP, which implies that NLCM may be a reference in the provision of tailored care for those affected by rheumatism.

KEYWORDS

fatigue, generalized estimating equations, C-reactive protein, nurse-led case management, pain, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA), an autoimmune disease with systemic inflammation, can cause a wide range of uncomfortable symptoms, from mild joint stiffness to severe functional disability. According to the National Health Interview Survey in 2011–2013, arthritis/rheumatism was one of the top three leading causes of long-term disability in the United States, causing a tremendous socioeconomic burden (1). A nationwide estimation in the United States showed that annual direct medical costs of newly diagnosed RA were $20,919 per patient on average, which nearly tripled that of those without RA ($7,197) (2).

Beyond joint pathology, RA may place people at a higher risk of developing other extra-articular manifestations due to systemic inflammation, such as cardiovascular disease, pulmonary disease, or cancer (3, 4), thereby leading to a higher mortality rate than the general population (5). In such a case, *a priori* study that followed patients with inflammatory arthritis had found that C-reactive protein (CRP), a commonly used marker of systemic inflammation in RA (6), was an independent predictor of mortality from cardiovascular diseases among this group (7). Thus, in view of the irreversible nature of RA, some specific distressing side effects, such as fatigue and pain, maybe the prevalent symptoms associated with this illness. It has been estimated that one in every two RA patients may experience persistently high levels of fatigue or pain (8, 9). Making matters worse, fatigue not only increased the length of hospitalization by 83% (10) but also caused a conspicuous increase in the likelihood of mortality (11). Therefore, actively implementing a disease management program to minimize the distressing symptoms and inflammation status driven by RA is of paramount importance.

Case management is a widely used care model for patients with chronic diseases who require consistent management over prolonged periods. Specifically, case management represents "a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote quality, cost-effective outcomes" (12, 13). In this model, a specialized nurse often takes on the primary coordination, management, and continuity of care for a specific episode of treatment or intervention (14). Accordingly, the European League Against Rheumatism has put out a call on the integration of case management into routine care to meet quality-of-life needs and to assist with the management of RA symptoms (15). Recently, the use of nurse-led case management (NLCM) for RA patients has attracted a lot of attention, but there is a lack of consensus regarding its impacts. Several studies addressed that the NLCM group experienced remarkable increases in self-efficacy ability and disease activity scores, which were measured by a 28-joint scale (DAS 28) (16–20). Another study also showed that NLCM minimized the RA patients' daily disability assessed by the Health Assessment Questionnaire-Disability Index (21). However, some investigations failed to reveal a significant association between NLCM and DAS 28 scores among RA patients (18, 22–24). The controversy over the effectiveness of NLCM may be related to the neglect of the cluster-specific baseline adjustments and the potential auto-correlations within subjects across time in the priori research, thus prejudicing the findings.

Furthermore, as of now, most of the relevant assessments of NLCM were performed in Western populations (8, 19, 21, 22, 24). The direct application of the results to Chinese populations may be premature because of the intrinsic differences in lifestyle and environmental features between Chinese and Western populations. A noteworthy feature of the priori evidence is that there is a lack of knowledge of the long-term NLCM effects among RA patients, especially in changes of pain, fatigue, and inflammatory symptomatology. To fill the gap, we carried out a study that followed RA participants until a 2-year period following completion of the NLCM program to compare the changes over time in both their subjective symptoms and inflammation status. Such documentation could provide an empirically robust ground for healthcare policymakers to initiate more appropriate care processes for individuals with RA.

Methods

Design and participants

First, this non-randomized follow-up study enrolled RA participants from a rheumatological clinic of the target hospital in Taiwan from January 2017 to June 2018, and all patients were followed for 2 years. To be eligible, the subjects were required to have a diagnosis of RA by rheumatologists, utilizing the classification criteria published by the 2010 American College of Rheumatology and the European League Against Rheumatism (EULAR) (25, 26), and aged 20 years or older at the time of recruitment. Those unable to reliably express their opinions or sign a written consent were excluded. Additionally, we marked all questionnaires with an encryption code instead of any personal identifiers. The required sample size in this study was determined based on previous research, where the effect size was set at 0.33, which concentrated on the fatigue change between the two groups (22), and the power was set to 80% at a significant level at 0.05. Hence, at least 92 participants were required for reliable statistical calculation using PASS 14.0 software (NCSS, Kaysville, UT, USA).

Before participating in the present research, all enrollees received detailed written and verbal information about the aims and protocol of the present study and signed informed consent. Participants were free to withdraw from the study at any time without any penalty. The current study protocol has been approved by the Institutional Review Board and the ethics committee of the target hospital (No. B11004003).

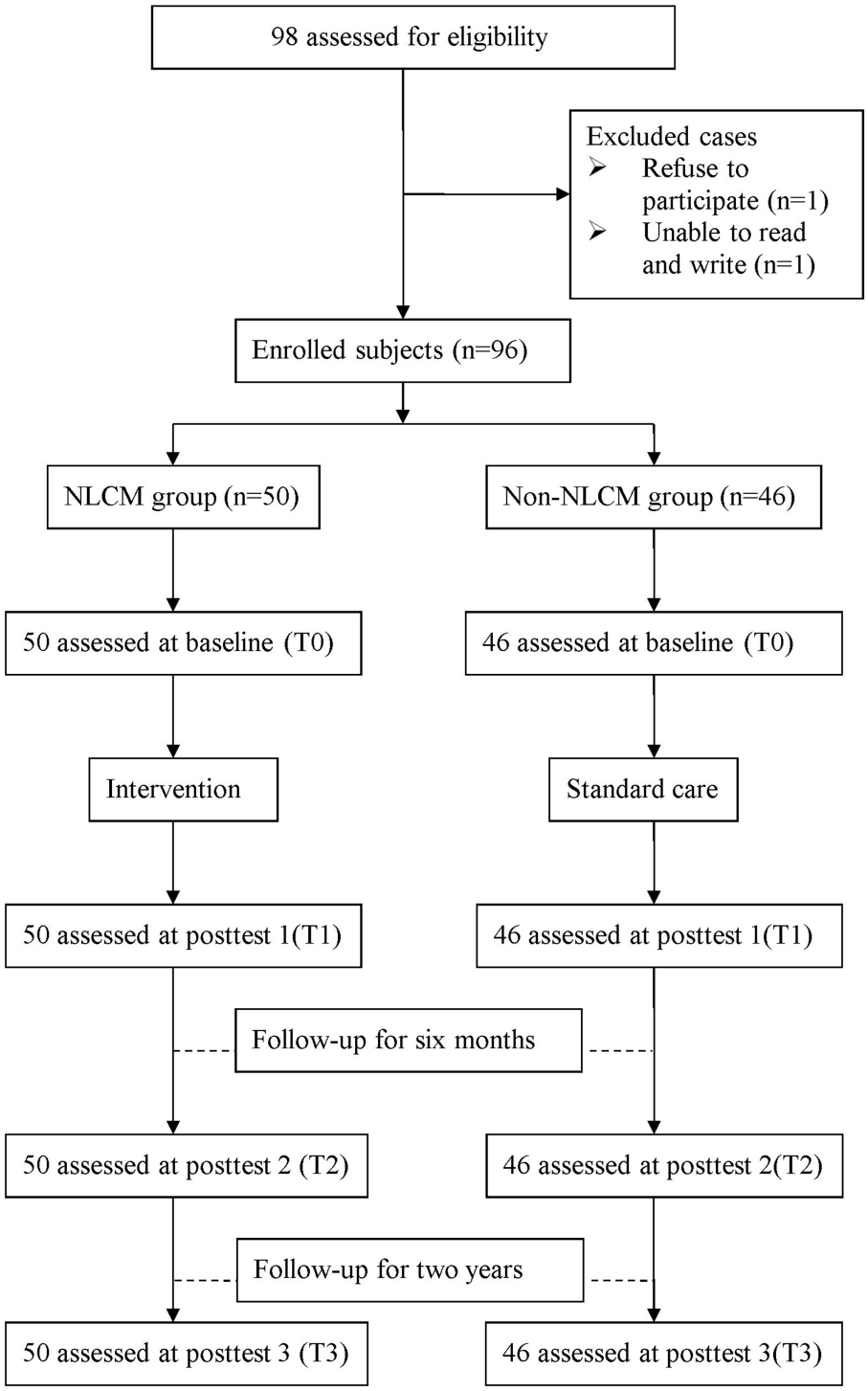

FIGURE 1
Participant recruitment flowchart.

The enrollees were informed that all personal information would be kept confidential.

Procedure

A flowchart of the participant recruitment is displayed in Figure 1. Before the study commenced, all participants were instructed to complete a form that included information on socioeconomic status, prescription medications, and self-health management behaviors. In addition, the information on the outcome indicators was assessed at four time points: baseline (T0), 3 days after completion of NLCM (T1), 6 months after NLCM completion (T2), and 24 months after completion of NLCM (T3). One independent interviewer, who was blinded to the study group assignment, took responsibility for obtaining informed consent and administering all measures during

the study timeframe. To minimize the dropout rate, all enrollees were telephoned and reminded to return to the hospital for the completion of assessments as scheduled.

Intervention

Patients with RA seeking care in the target hospital were referred to the following process. First, they were informed of their right to opt to receive either conventional care or conventional care plus NLCM. Those joining the conventional care would receive health education lasting for 15 min per medical visit from ward nurses as scheduled, consisting of consultation in terms of disease symptoms, related treatments, and the doctor's orders. In this study, they would be deemed the non-NLCM group.

By contrast, those enrolling in the NLCM group would receive the consecutive intervention programs that were developed by an extensive review of the literature and discussions with experts. The NLCM consisted of three key components: (1) a series of RA-related education sessions, including disease etiology, complications, and self-care management; (2) instructions on the individual exercise program, containing explanations and demonstrations of the various steps; and (3) monthly telephone follow-up evaluation to identify difficulties faced by the participants, monitor their daily practice, and answer any questions. The first two components were delivered through one-to-one health education sessions lasting for approximately 50 min each, once a month for 6 consecutive months. An educational booklet on the relevant issues discussed was also given to each participant as a guide. Additionally, they were instructed to report time spent on and frequency of exercise per week using the electronic diary provided at a freeware instant-communications app LINE. As a whole, we used an interactive learning environment to allow enrollees to discuss the impact of illness, the treatment received, and changes in self-image and relationships with friends and family. All involved strategies were systematically planned and modified on the basis of the individualized therapeutic regimen offered to the patient. The nursing case manager offered consultation with patient's family and other healthcare providers of the medical team as needed.

Collectively, the NLCM in the target hospital integrated a multi-component intervention comprised of health education and professional advice, referring patients to other healthcare team members, discussing a daily life plan, making medical appointments, and conducting telephone follow-up provided by the trained registered nurse. This NLCM program was conducted in one rheumatology health education room and delivered by one specific nurse case manager who had more than 10 years of experience in nursing care for RA patients and possessed the NLCM certification.

Outcome indicators

In this study, we collected three primary outcome indicators, including fatigue, pain, and CRP. These outcome indicators were measured before and after the initiation of intervention, all of which were obtained from patient's medical records.

In the target hospital, levels of fatigue and pain were both determined via the self-reported Visual Analog Scale (VAS), which has been extensively used and validated across the rheumatic disease spectrum (27, 28). VAS is used to assess the intensity and frequency of subjective pain experienced by the patient on an 11-point numerical scale, ranging from 0 to 10, where higher scores reflect a more severe degree of fatigue or pain experienced (28, 29). The reliability and validity of VAS measures have been previously confirmed (30). The VAS was demonstrated to possess acceptable psychometric properties, with a concurrent validity of 0.90 and an intraclass correlation coefficient of 0.94 (31). In this study, the Cronbach's alpha scores for pain and fatigue were 0.85 and 0.89, respectively. Apart from these two subjective symptoms, we used CRP as the major marker of inflammation status. CRP is a protein produced by the liver and is a commonly used marker of systemic inflammation for autoimmune diseases (6).

Covariates

The demographic variables herein included age, sex, marital status, educational level, job status, household status, and lifestyle factors (smoking and exercise habits). Patients who answered "currently" or "yes/past" to the question on smoking were classified as smokers. Patients who exercised 3 or more days per week were classified as having regular exercise. Disease characteristics included comorbidities (diabetes mellitus, hypertension, heart disease, or stroke), body mass index, DAS 28, duration of RA, and use of conventional disease-modifying anti-rheumatic drugs (DMARDs) and biological agents. The latter indicator comprised adalimumab, etanercept, infliximab, rituximab, and tocilizumab. The last two indicators were defined as using the relevant drugs for more than 3 months following disease onset.

Evaluation of data

The descriptive statistics, including the mean, standard deviation (SD), and percentage, were used to describe the distributions. We then compared the distributions of demographic and disease characteristics between the two groups using the t-test and χ^2 test as applicable. Additionally, intergroup differences before and after the intervention for each of the outcomes were tested using the generalized estimating equations (GEE) model, a statistical procedure that extends the capabilities of generalized linear models (GLM) for analyzing longitudinal data or other clustered response data (32). Each GEE model produces estimates of the time effect (baseline as the reference category), intervention effect (control group as the reference category), and effect of the interaction term between intervention and time after covariate adjustment (33). The effect of the intervention, as it varies over time, can, then, be confirmed, provided that the interaction term was pronounced. Covariates, where the difference reached statistical significance at baseline, were identified as the control variables in the GEE model. Robust standard errors were selected to calculate the significance of parameter estimates, and the autoregressive first-order working correlation matrix was utilized to adjust for the time effect (33). All analyses were conducted using SPSS 22.0 (Chicago, IL, USA), and all statistical tests were performed at the two-tailed significance level of 0.05.

TABLE 1 Demographic and clinical data by two groups.

Variable	All participants ($N = 96$)		NLCM group ($n = 50$)		Non-NLCM group ($n = 46$)		p
	N	%	N	%	N	%	
Sex (female)	79	82.3	38	76.0	41	89.1	0.09
Marital status (married)	81	84.4	44	88.0	37	80.4	0.31
Educational level (≥ 9th grade)	54	56.2	27	54.0	27	58.7	0.64
Household status (Cohabitating)	89	92.7	46	92.0	43	93.5	0.78
Monthly income (≤ 30,000 NTD)	52	54.2	27	54.0	25	54.3	0.97
Regular exercise	34	35.4	24	48.0	18	39.1	0.15
Cigarette smoking	14	14.6	9	18.0	5	10.9	0.32
Conventional DMARDs	79	82.3	42	84.0	37	80.4	0.65
Biological agents use	34	35.0	18	36.0	16	34.8	0.90
Comorbidities	68	71.0	34	68.0	34	73.9	0.52
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	53.80	10.5	56.66	10.4	50.74	10.8	0.01
Disease duration†	5.1	4.3	3.7	3.5	6.6	4.5	0.01
Body mass index (Kg/m^2)	23.7	3.8	23.2	3.4	24.2	4.1	0.21
DAS 28†	4.5	1.6	5.0	1.4	3.9	1.5	<0.01
C-reactive protein	1.5	1.2	1.9	1.1	1.0	1.3	0.06
Pain†	5.7	2.4	6.9	2.8	4.4	2.5	<0.01
Fatigue†	5.2	3.3	6.3	2.9	4.0	3.3	<0.01

†Data were expressed as mean ± standard deviation.
NLCM, nurse-led case management; DAS 28, disease activity score measured by a 28 joint-scale; NTD, New Taiwan Dollar.

Results

Baseline characteristics

Demographic and clinical characteristics of the study sample are given in Table 1. During the study period, a total of 96 RA patients were recruited, consisting of 50 in the NLCM group and 46 in the non-NLCM group. None of the participants dropped out or were lost to follow-up. The mean (SD) age was 56.6 (10.3) years in the NLCM group and 50.7 (10.8) years in the control group, respectively. Most participants were women and had comorbidities at the time of the study, and 35% of them had been treated with at least one biological agent. Demographic and clinical characteristics between them were comparable at the baseline, except for age and the duration of RA. Compared with the non-NLCM group, subjects in the NLCM group were found to experience higher scores of DAS 28, pain, and fatigue at baseline (all $p \leq 0.01$).

Comparison of effect of NLCM versus conventional care

After taking into consideration the significant variables at baseline (displayed in Table 1), the multivariate analysis using the GEE procedure indicated that a baseline difference occurred regarding fatigue score between the NLCM and the non-NLCM groups ($p = 0.03$) (Table 2). Fatigue scores at T1, T2, and T3 were similar to those measured at T0, implying that a maturation effect might not have arisen. Following consideration of baseline differences in fatigue, age, DAS 28, and disease duration by GEE procedure, the reduction slope of fatigue scores was still larger in the NLCM group than in the non-NLCM group, irrespective of elapsed time (Figure 2).

As to pain, the GEE model indicated a difference at T1 and T3, which implied that a maturation effect might occur regardless of the use of intervention employed. After adjustment for age, DAS 28, disease duration, inherent pain level, and maturation effects, we found that NLCM was helpful in reducing pain for RA patients during the study timeframe as compared with the control group, yielding statistical differences of $\beta = -1.29$ (T1), $\beta = -1.49$ (T2), and $\beta = -1.99$ (T3) (Table 2). The change in pain levels between the two groups is displayed in Figure 3.

Regarding CRP, maturation effects were detected at T2 and T3 since CRP levels measured at both T2 and T3 were greater than those measured at T0 (both $p < 0.05$, Table 2). Additionally, the baseline inflammatory status was similar for the two groups ($p = 0.25$, Table 2). After adjusting for the initial differences in age, DAS 28, disease duration, and maturation effects, the mean value of CRP in the NLCM group was found to be lower than in the non-NLCM group at both T1 ($\beta = -0.66$; $p = 0.04$), T2 ($\beta = -0.94$; $p = 0.01$), and T3 ($\beta = -0.72$; $p = 0.03$) (Table 2). These benefits were still detected for 2 years after the NLCM program (Figure 4).

Furthermore, to minimize the baseline imbalances in this comparative study, we carried out one sensitivity analysis where each selected NLCM case was randomly matched to one control without NLCM use via the propensity score matching (34). The

TABLE 2 Regression coefficients associated with nurse-led case management (NLCM) on patients with rheumatoid arthritis were obtained by generalized estimating equation model ($n = 96$).

Variables	Fatigue		CRP		Pain	
	β	p	β	p	β	p
Intercept	3.33	<0.01	0.67	0.01	2.56	0.41
NLCM vs. non-NLCM	2.43	0.03	−0.05	0.25	1.54	0.01
Time						
T1 vs. T0	−0.36	0.46	0.98	0.06	−0.66	0.01
T2 vs. T0	−0.59	0.10	1.08	<0.01	−1.05	0.16
T3 vs. T0	−0.22	0.71	0.45	0.02	−1.40	<0.01
Interaction term						
Interaction of T1 × NLCM	−1.32	0.04	−0.66	0.04	−1.29	0.03
Interaction of T2 × NLCM	−1.42	0.02	−0.94	0.01	−1.49	0.02
Interaction of T3 × NLCM	−1.76	<0.01	−0.72	0.03	−1.99	0.01
DAS 28	0.65	<0.01	0.63	0.01	0.90	0.01
Disease duration (year)	−0.04	0.12	−0.03	0.25	−0.02	0.54
Age (year)	−0.02	0.23	0.02	<0.01	0.01	0.56

T0, prior to NLCM inception; T1, the 3th day after NLCM commencement; T2, 6 months after NLCM completion; T3, 2 years after the completion of NCLM. Interaction of T1 × NLCM, difference between NLCM and control group in change from T0 to T1. Interaction of T2 × NLCM, difference between NLCM and control group in change from T0 to T2. Interaction of T3 × NLCM, difference between NLCM and control group in change from T0 to T3. CRP, C-reactive protein; DAS 28, disease activity score measured by a 28-joint scale.

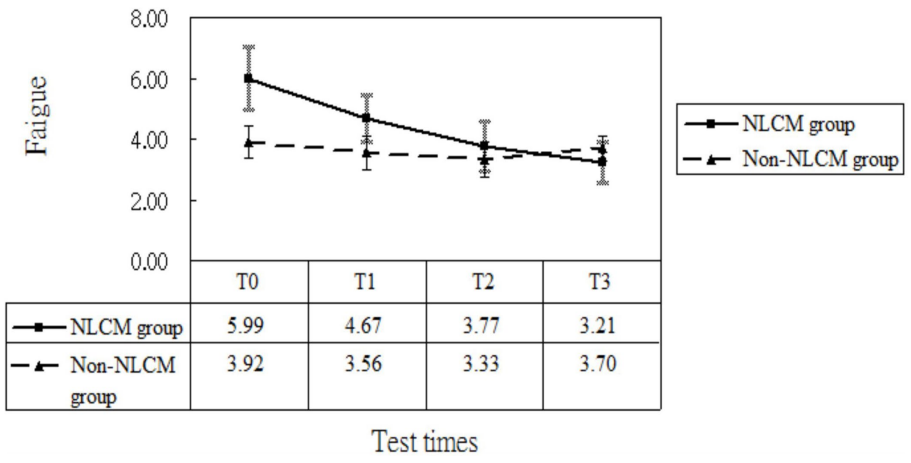

FIGURE 2
Fatigue scores of patients in the NLCM and the control groups.

propensity score was calculated using logistic regression derived from patients' demographics and baseline comorbidities at enrollment. Thereafter, a total of 26 NLCM users and 26 control users were included after propensity score matching and no conspicuous differences were found between the two groups, indicating the matched intervention and comparison groups were comparable in terms of baseline characteristics. The reanalysis based on the GEE procedure indicated that NLCM was still significantly related to reductions in levels of pain (T1 = −2.54, p < 0.01; T2 = −2.20, p = 0.03; T3 = −1.92, p = 0.04), fatigue (T1 = −1.27, p = 0.02; T2 = −1.31, p = 0.01; T3 = −1.25, p < 0.01), and CRP (T1 = −0.36, p = 0.03; T2 = −0.51, p = 0.01; T3 = -0.31, p = 0.02), among the enrollees.

Discussion

While the effects of NLCM have been recognized, few studies have directly examined this association in persons with RA, especially the long-term effects of NLCM on the reduction of fatigue, pain, and intrinsic inflammation. The GEE model used in this study provided further control of participants' attributes at baseline and temporal maturation effect, enabling us to evaluate the effects of NLCM more precisely. As compared to the participants in the non-NLCM group, we discovered that levels of fatigue, pain, and CRP decreased more in the NLCM group, which implied that the implementation of the 6-month NLCM program into routine care may indeed bring benefits for RA patients. The

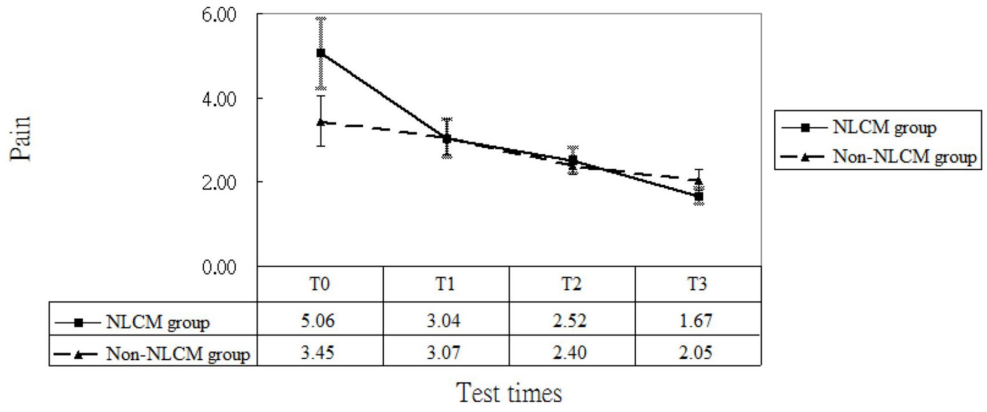

FIGURE 3
Pain levels of patients in the NLCM and the control groups.

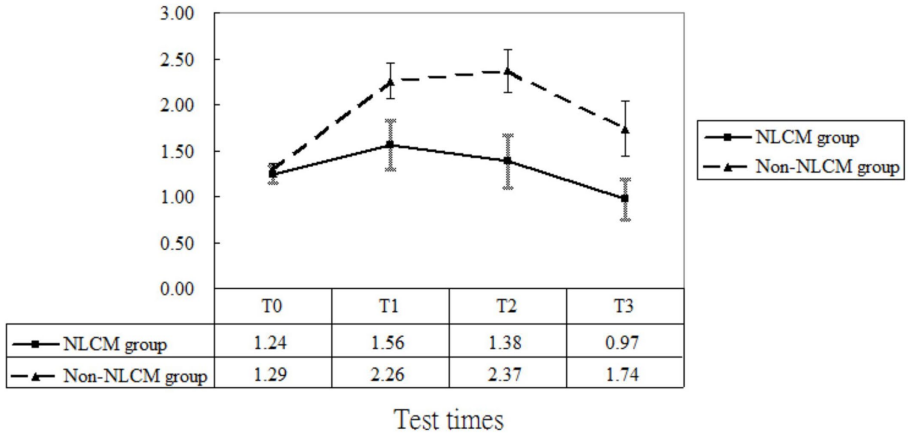

FIGURE 4
C-reactive protein levels of patients in the NLCM and the control groups.

beneficial impacts herein were consistent with earlier reports (17, 18, 24, 35).

Notably, the findings of our study further supported that the beneficial effects could be maintained for 2 years after the completion of NLCM. We inferred that the implementation by a nursing case manager in the form of one-on-one consultation/education and regular follow-up were the keys. It has been suggested that continuing education activities contributed to better clinical manifestation in chronic disease patients (13). Unlike the traditional care approach from one direction, a highly interactive approach and colored images utilized in the NLCM might be more beneficial in engaging patients in the health information they are learning and assisting them in making appropriate plans for disease management, thereby increasing their at-home self-care skills to diminish the disturbances caused by the RA symptoms. In addition, regular follow-ups may ensure the long-term compliance of the patients. Including fitting physical activity, a key component of NLCM used in this study, may account for the beneficial effect reported herein. A growing body of research findings has indicated that reasonable intermediate exercise loads may decrease leptin levels in serum, which is a well-known adipocytokine that can elevate mRNA and protein expression of inflammatory precursor substances, such as tumor necrosis factor-α (TNF-α) (36). An animal study reported a positive correlation between levels of leptin and interleukin-6 (IL-6) (37). Moreover, the secretions of IL-6 and TNF-α played a role in the development of fatigue in both autoimmune and non-autoimmune diseases via neuroinflammation and neuroprogressive changes (38, 39). Altogether, we propose that early inclusion of a fitting exercise program to the routine pharmacological therapy, as well as prolonging its use, may serve to psychologically benefit RA patients.

The findings of the present study revealed a difference in CRP levels between the NLCM and non-NLCM groups. Since no relevant studies were found to examine the long-term impact of NLCM on CRP in these patients, a direct comparison with earlier studies is impossible. We speculated that direct participation in NLCM programs insensibly contributes to increased socialization and individual self-efficacy, which in turn may assist patients in mitigating the physical and emotional burden of the illness. The concept of self-efficacy has been proven to significantly influence behavior changes that buffer the potential negative effects of various diseases. For example, a recent cross-sectional study by Hladek and colleagues found an association between coping-associated self-efficacy and low

serum IL-6 and TNF-α in senior adults (40). These physiologic mediators are known to play indispensable roles in synthesizing and secreting CRP (41). Despite this preliminary evidence, the underlying mechanism of how NLCM alleviates CRP is not well understood, which implies that future large-scale studies to verify the effect of NLCM against inflammatory responses reported herein should be undertaken.

GEE, an extension of the GLM procedure, could model a known function of the marginal expectation of the dependent variable as a linear function of explanatory variables. On top of that, this study was the first to investigate the relation between NLCM and changes in pain, fatigue, and systemic inflammation in RA patients through a long-term follow-up perspective, enabling authors to cautiously shed light on NLCM impacts. Notwithstanding the foregoing issues, this study may be affected by some limitations. First, the sampled participants were selected from a single hospital in Taiwan and accordingly, the generalization of study results may be limited. Second, the subjective scale was used to measure pain or fatigue, so further studies employing more objective measures of psychological change are warranted. Third, the experimental group in this study comprised patients who agreed to take part in the program. Thus, willingness to participate might bias the results of this study. To address this issue, we set objective criteria to balance the baseline differences between the two groups through the evaluation of demographic and disease characteristics, as shown in Table 1. Furthermore, we capitalized on the GEE model to control for possible baseline differences between the two groups (if any) and further consider potential maturation effects. Additionally, the initial descriptive analysis suggested that NLCM users indeed exhibited poorer manifestations than did non-NLCM users, yet they displayed substantial reductions in pain, fatigue, and CRP than did the non-users, implying that the present findings are likely to underestimate, rather than overestimate, the effects of NLCM. Taken together, we concluded that baseline differences between the two groups, in all likelihood, did not distort the present findings. Fourth, even though we used the GEE model to control for baseline differences between the two groups, the application of an observational design herein may still be affected by potential confounders that were not included in the models (33). We conducted a sensitivity analysis by utilizing the propensity score with one-to-one matching to reduce the imbalance of the characteristics between the two groups (34). The reanalysis based on the GEE procedure indicated that NLCM was still related to reductions in levels of pain, fatigue, and CRP, suggesting that the baseline imbalance did not appreciably impact the relationship reported herein. To lend further credence to the present findings, future prospective randomized trials are needed to overcome the experimental weaknesses of this study via employing psychometrically sound measurements, which would allow for more efficient approaches to disease management of RA.

Conclusion

On the whole, this study supported the idea that adding the NLCM to conventional care can ameliorate the distressing symptoms and systemic inflammation of RA patients. Findings demonstrated that participants in the NLCM group experienced lower levels of pain, fatigue, and CRP after the intervention than their control counterparts. Notably, we observed that these beneficial effects were maintained for 2 years after the completion of NCLM. The findings of this study may be a reference in facilitating the implementation of the NLCM program among patients with newly diagnosed RA for long-term survival benefits. Due to the potential drawbacks regarding recruitment strategy and data collection, the effects of NLCM still must be further elucidated via well-designed, long-term randomized controlled trials.

Data availability statement

Data are available upon reasonable request. The data used and/or analyzed during the current study are available from the corresponding authors only on academic research request.

Ethics statement

The studies involving humans were approved by Institutional Review Board and the Ethics Committee of Buddhist Dalin Tzu Chi Hospital No. B11004003. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

W-CC: Formal analysis, Investigation, Validation, Writing – review & editing, Writing – original draft. HL: Methodology, Writing – review & editing. H-LH: Data curation, Investigation, Writing – original draft. H-HL: Conceptualization, Investigation, Validation, Writing – original draft. M-CLu: Data curation, Project administration, Writing – original draft. M-CLi: Conceptualization, Investigation, Writing – original draft. W-JC: Formal analysis, Funding acquisition, Project administration, Validation, Writing – original draft. T-YT: Conceptualization, Formal analysis, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Co-creation in healthcare and research to improve service delivery for young people with chronic pain

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Introduction: The process of co-creation can enable more effective, agile and integrated healthcare solutions achieving outcomes that effectively translate to healthcare delivery. Collaborative knowledge generation is particularly important in fields such as pediatric chronic pain where there is a complex interplay between biological, social, environmental, emotional, familial and school factors. The co-creation initiative described here was designed to amplify the voices of youth with chronic pain and their families and a variety of key stakeholders and generate novel approaches to the management of chronic pediatric pain in the setting of the South Australian Pediatric Chronic Pain Service.

Methods: Stakeholders who were identified as influential in this ecosystem were allocated to 6 groups. A skilled facilitator co-prepared and delivered the workshop, engaging participants in three structured activities. Firstly, the challenges to service delivery were outlined, followed by the groups discussing what is currently working. The second activity involved lateral thinking without restrictions on time, resources or system to generate solutions to the key challenges presented. Finally, stakeholders were asked to agree on a generated solution from Activity 2 and build a case for actionable implementation of this solution. Data were summarised by the workshop facilitator and reflexive thematic analysis was used for coding and generating themes.

Results: From Activity 1, six themes collectively demonstrated that stakeholders valued many of the existing strengths of the service delivery, but some areas such as pain education was undervalued. Activity 2 generated solutions from high-level ideas to more day-to- day management strategies. Each of six groups generated unique solutions to an identified challenge for Activity 3.

Discussion: Engaging a wide variety of stakeholders in collaborative knowledge generation successfully provided the South Australian Pediatric Chronic Pain

Service with a variety of novel, scalable solution across the healthcare continuum. Equally important is that this initiative helped to raise awareness about the complex issues faced in pediatric chronic pain care and helped to establish new partnerships that have led to enhanced service delivery.

KEYWORDS

pediatric, chronic pain, multidisciplinary, co-creation, collaborative knowledge

1 Introduction

The process of co-creation can enable more effective, agile and integrated healthcare solutions achieving outcomes that effectively translate to healthcare delivery (1, 2). Co-creation supports the optimization of person-centered care through purposeful engagement at all levels of the healthcare and wellness system using facilitated processes and enriched experiences to co-design new services (1, 3). This includes collaborative knowledge generation with consumers, clinicians, academics, government, and policy makers to share insights that align research with consumer needs and service development with improved outcomes.

Collaborative knowledge generation is particularly important in fields such as pediatric chronic pain where there is a complex interplay between biological (4, 5), social (6), environmental (7), emotional (8, 9), familial (10, 11) and school factors (12). Chronic pain is defined as persistent or recurring pain of any cause lasting longer than 3 months (13, 14), and is a common problem in pediatrics with a recent systematic review representing data from 73 countries, placing overall population prevalence at 20.8% (15). Pediatric chronic pain places a considerable financial burden on society. Although not well defined, the total annual costs to society per adolescent with moderate to severe chronic pain in the US was estimated between $7,000 and $12,000 US (16, 17). Data from the Population Health Survey in 2018 (18) can be extrapolated to suggest that 72,000 children are managing chronic pain in South Australia, at a conservative cost of AUD$684 million to society annually (19).

The Pediatric Chronic Pain Service (PCPS) opened in South Australia in March 2018. The service is located in the Women's and Children's Hospital, Adelaide, and is the only publicly available service for youth with chronic pain in the state of South Australia. At the 2021 census the total population of South Australia was approximately 1.8 million people and of that number 23% (402,293) of people were between the ages of 0–19 years. The majority of the population live in Adelaide (80%), and 20% in lower density country towns or on farming properties at a distance from Adelaide. Nine percent of households are in regions of relative socio-economic disadvantage (20, 21). Ethnically, South Australians identify as English, Scottish or Irish (54%), Australian (32.5%), German (7.6%), Indian (2.5%) and Aboriginal or Torres Strait Islanders (2.4%) (20).

The PCPS is a multidisciplinary service that delivers a biopsychosocial model of assessment and management of chronic pain (22–26). Youth who attend the service are predominately female (71%), have an average age 13 years, and the most common reasons for referral are abdominal pain (23%), back pain (21%) or daily headache (12%). Thirteen percent of youth report taking daily opioids on presentation. The service team collaborates with young people (aged 0–18 years) with chronic pain, and their families and carers, including wider community outreach into schools if appropriate, to assess physical, psychological, medical and sociocultural factors that contribute to the pain experience. The aim is to provide a combination of targeted and coordinated multidisciplinary interventions inclusive of physical, cognitive behavioral, and medical therapies in the sociocultural context of the youth and family (27–29). This multidisciplinary model of care is the gold standard of care in the complex landscape of young people with chronic pain and meets the guidelines of the World Health Organization (19, 30, 31). Yet, the requirement for service delivery to be of high value, sensitive to the needs of culturally and linguistically diverse community and efficient is challenging because at the time of the workshop, and despite its mandate to service the state, the service was only funded to a total 1.7 full time equivalent positions spread between administration, medical and allied health staff. The co-creation workshop was focused on generating innovative ways this tertiary level of care could deliver effective care more efficiently and with broader reach.

With complexity of care, high prevalence rates and high healthcare costs, pediatric chronic pain is a formidable healthcare problem requiring thoughtful solutions that can work within the constraints of a state-funded healthcare system while optimizing care for patients and carers. The co-creation initiative described here was designed to amplify the voices of youth with chronic pain and their families and a variety of key stakeholders and generate novel approaches to the management of chronic pediatric pain within the context of the Pediatric Chronic Pain Service (PCPS) offered by the Women's and Children's Hospital, Adelaide, South Australia.

2 Materials and methods

To generate ideas about how to deliver evidence-based and efficient care equitably across a large catchment area, the South Australia PCPS in conjunction with the Robinson Research Institute (The University of Adelaide) facilitated a co-creation workshop. International, national, and local stakeholders were invited to attend (see Table 1 for a breakdown of invited stakeholders) and consent to use the de-identified data was obtained at sign-in. Ethics approval to use the data was received from the Women's and Children's Health Network Human Research Ethics Committee 2020/HRE01639.

TABLE 1 The numbers of those in invited to and those who participated in the co-creation workshop by sex and role.

Stakeholders invited by role	Gender		Number invited	Number attended	Percent yield
	F	M			
Acute care nurse	2		2	0	0%
Advocacy representative	1	1	2	1	50%
Anesthetist		2	2	0	0%
Business analyst		1	1	1	100%
Educator	2		2	0	0%
General practitioner	1		1	1	100%
Medical consultant (palliative care/pain/physician)	5	1	6	3	50%
Medical director		2	2	0	0%
Medical registrar	1		1	1	100%
Neonatologist		1	1	0	0%
Parent/carer of youth with chronic pain	3		3	3	100%
Pediatrician	1	2	3	0	0%
Pharmacist	2	1	3	2	67%
Physical therapist	5		5	3	60%
Policy maker	2	1	3	3	100%
Psychologist	9		9	5	55%
Researcher - clinical	2		2	2	100%
Researcher – academic	3	4	7	6	86%
Rural primary health care network	1		1	0	0%
Youth with chronic pain	3		3	3	100%
Total			59	34	

2.1 Participants

Fifty-nine stakeholders from diverse fields were identified as influential in this ecosystem and invited to the workshop with the aim of attracting a minimum of 20 participants.

2.2 Description of the initiative

Attendees were pre-allocated to 6 stakeholder groups of approximately 6–8 people per group with a purposive mix of different stakeholders and experiences. To address the possibility of power imbalances that might arise from mixing professionals with lived experience participants (particularly youth) we did three things: 1. We employed a skilled facilitator (Dr. Seanna Davidson)[1] to co-prepare and deliver the workshop explicitly engendering the values of respect, equality and inclusiveness throughout the process. 2. We talked with the youth and parents/carers ahead of the session to let them know what to expect and to let them ask questions. 3. We were purposeful in the allocation of stakeholders to tables, and assigned a buddy at the table to each youth/parent dyad. Each group engaged in three structured activities, facilitated by Dr. Davidson. The workshop was not recorded.

2.3 Data synthesis

The workshop facilitator undertook the first synthesis of the data, creating a summary of the generated information. For the first activity we used reflexive theme analysis approach following the example of Braun and Clark (32). NF, CB and TS adopted a constructionist and predominately inductive approach to coding and generating themes.

2.3.1 Activity 1: What works and identifying systems-level challenges

This activity began with a presentation from the PCPS Service Lead that included a brief history about the PCPS service, its current model of multidisciplinary care, patient demographics, service provision, and resources. The PCPS Service Lead also provided a detailed description of seven key challenges that impede service delivery in the PCPS, highlighting how each challenge directly impacts patient care. Challenges included:

1 https://www.the-systems-school.org/about

1. Insufficient staffing: The PCPS could only support 1 day of new clinic assessments per month and waitlists were 12 months long.
2. Clinical complexity: Young (0–18 years) people with chronic pain and their families require a co-ordinated, flexible and dynamic multidisciplinary approach to care that requires time and resources above ordinary outpatient clinics.
3. Limited accessibility: Indigenous and people who live in rural areas could not access PCPS services easily.
4. Lack of prevalence data: It is very difficult to determine the prevalence of young people with chronic pain (due to variable study populations, heterogenous pain issues, and the absence of centralized data collection across primary and tertiary services), and as such the state-wide unmet need in this area of pediatrics has not been clearly identified.
5. Minimal education for allied health professionals: Pediatric patients with chronic pain often have comprehensive care plans, but most community providers do not have the skills needed to implement these plans, making it difficult to refer patients into the community.
6. Researchers and providers are in silos: The lack of connectivity between clinicians and researchers impedes opportunities to innovate and improve care.
7. Disjointed advocacy: Chronic pain is a widely reported symptoms across illness, injury, and disease populations resulting in disjointed advocacy for better care across a range of clinical settings and policy groups.

Following this presentation, stakeholder groups were first prompted to discuss the key strengths of the service and create a list of "What is working." Ideas generated were written onto sticky notes and placed on butcher's paper and each idea represented a unit of analysis. They were then asked to consider how the seven key challenges impacted the current practices in the PCPS from a clinical and resource perspective.

This discussion was followed by a presentation from Associate Professor Rachael Coakley from the Boston Children's Hospital who spoke about the widely implemented Comfort Ability® Program (CAP) (33). Briefly, CAP is a structured, cognitive-behavioral based workshop offered to adolescents with chronic pain and their carers which may be run over a day or virtually over several weeks. The program has demonstrated outcomes of enhanced pain self-efficacy and functional ability for adolescents and changes in parental beliefs about the ability of their adolescents to manage pain (33) and also may reduce associated maladaptive carer practices that are known to delay recovery (34). Notably, CAP was designed for knowledge and clinical service mobilization with the intent of broadly supporting resource-challenged pain services (such as the PCPS) through shared clinical innovations and a network of providers.

After the presentation, each group was given the opportunity to discuss CAP, considering specifically how adoption of a clinical innovation like CAP could enhance the mission of PCPS and increase access to multidisciplinary chronic pain care in South Australia. Additionally, groups were asked to discuss which of the seven key challenges CAP would help to address.

2.3.2 Activity 2: Linking challenges to solutions

In a second activity the same stakeholder groups were asked to "think outside the box" and without restrictions on time, resources or system, generate solutions to the seven key challenges set out by the PCPS. The goal was to elicit a range of perspectives and approaches for solving the complex challenges faced by the PCPS. Given the diversity of stakeholders, solutions represented a variety of high-level ideas (i.e., changes in government policy) as well as more day-to-day management strategies (i.e., changing the frequency of clinic schedules). These ideas were generated collaboratively and recorded by group. Each idea represented a unit of analysis. We determined the importance of the challenges (which ones need addressing first) by the percentage of responses provided for each challenge.

2.3.3 Activity 3: Refining the South Australian model

In the third activity, each stakeholder group was asked to agree on a generated solution that best fit with the vision of the program, "*an interdisciplinary service that offers a coordinated, evidence-based, therapeutic intervention for the effective treatment of persistent pain*" and that was achievable, given the significant challenges faced by the PCPS. Once this solution was selected, they were asked to build a case for actionable implementation of this solution by responding to the following four questions:

1. What challenge is this solution addressing?
2. What is the action/change that is needed for this solution?
3. How might this solution be made feasible for PCPS?
4. What impact would this solution have if implemented?

The workshop concluded with each stakeholder group presenting their actionable solutions to the broader group and discussing imperative next steps to support the growth and development of the PCPS. Stakeholders were united in their recognition of the current strength of the PCPS service as well as the need for immediate clinical expansion and long-term solutions for sustainability.

3 Results

In total 34 stakeholders attended the workshop (see Table 1), a clear indication of the strong interest in improving pediatric pain care in South Australia.

Qualitative data and feedback was generated collaboratively, collected during this workshop, and collated. Data management procedures and outcomes are described by each activity below. The full data set can be accessed:

3.1 Activity 1: What works and identifying systems-level challenges

Each stakeholder's response to the question "what is working?" was considered a unit of analysis. On average, each stakeholder provided three responses and in total 175 responses were collected. Three authors independently reviewed the data and used an

inductive approach to classify responses into themes, agreeing on a total of six themes. The number of responses per theme and an example of the responses can be seen in Table 2.

The six themes collectively demonstrate that stakeholders valued many of the strengths of existing practices of PCPS and have a working knowledge of the complex treatment and management of pediatric chronic pain. The first two themes (i.e., importance of multidisciplinary model of care and community and collaborative care) reflected the key strengths of the service, providing best practice care according to guidelines for clinical management of chronic pain in children from the World Health Organization (19). These guidelines encourage treatment of chronic pain from a biopsychosocial and interdisciplinary model. As pediatric chronic pain not only impacts the child, but also the social fabric of the child's life, it is imperative that any approaches align with family, school, leisure time and economic considerations [World Health Organization (19), p. 15–16].

However, there were also places where stakeholders may have undervalued the strengths of essential components of the PCPS. For example, only 17% of stakeholders placed value on pain education for patients and providers. This may in part be due to the lack of pain education in undergraduate medical and allied health programs (35, 36) and in part because many stakeholders have not previously been exposed to this essential area of training in pediatric practice. The final three themes presented opportunities to build strength in the areas of data support, funding, research and use of technology.

3.2 Activity 2: Linking challenges to solutions

Data evaluation for Activity 2 similarly included categorization of stakeholder responses. In this activity stakeholder groups identified solutions for specific PCPS challenges. Ninety responses were received and data were categorized by the challenge they address (see Table 3). Given the diversity of stakeholders, solutions represented a variety of high-level ideas (i.e., lobby for changes in University healthcare education) as well as more day-to-day management strategies (i.e., use readily available resources). Unique responses accounted for many of the solutions, showing the strength of bringing together such a diverse group. The top three challenges for the service were 1. Insufficient staffing, 2. Clinical complexity, 3. Minimal pain education for all healthcare professionals.

3.3 Activity 3: Refining the South Australian model

Data for Activity 3 included a brief written summary of ideas to refine the PCPS model of care in South Australia (SA). This involved stakeholder groups selecting a key problem, proposing solutions, and identifying and actionable steps for implementation which have been integrated into the solutions linked to challenges in Activity 2 (see Table 3). In total there were six groups of stakeholders and each group generated unique solutions to an identified challenge. Additionally, this activity generated vibrant discussion within and across stakeholder groups. The identified challenges set forth by each group established that stakeholders had a clear understanding of the complexity of the issues faced by the PCPS. The proposed solutions were well aligned with the challenges and again reflected the unique perspectives of the heterogenous stakeholder groups and provided suggestions for directions for the service to pursue in the future.

4 Discussion

Engaging a wide variety of stakeholders in a collaborative problem-solving workshop such as this successfully provided the PCPS with a variety of novel ideas and solutions across the healthcare continuum. Equally as important, this initiative helped to raise awareness about the complex issues faced in pediatric chronic pain care and helped to establish new partnerships that have led to enhanced service delivery. Stakeholders promoted systems level change in medical education, government policy, hospital administration, community, and allied health professional networks. Moreover, suggested improvements in the South Australian model targeted physicians, psychologists, educators and consumers. All stakeholder groups acknowledged the need for comprehensive improvements in pediatric chronic pain care, but also thought realistically about attainable and sustainable solutions for the PCPS and South Australia.

While some stakeholders presented longer-term systems level changes (e.g., implementation of new public healthcare policies), many also identified short-term practical solutions that may help to improve service delivery (e.g., provider webinar to enhance referral pipelines). Most participants within this co-creation workshop concluded that many of the day-to-day clinical challenges faced by the PCPS reflected a need to optimize state-wide management of pediatric chronic pain. This can occur through a variety of state-based initiatives such as increasing quality pain education for health professionals, linking hospital and community services, and enhancing network connections between clinicians, researchers, and consumers.

Encouragingly, stakeholders were energized by this activity and many expressed interests in further engagement with PCPS and improving South Australian pediatric pain care more broadly. Given that comprehensive change requires a network of engaged stakeholders beyond this co-creation workshop, the relationship building that occurred within the context of this co-creation workshop was a highly valued outcome. Importantly, while the PCPS faces formidable challenges, this workshop also served to highlight the many areas in which they are succeeding in their endeavor to provide high-quality, comprehensive pain care to patients and their carers.

Co-creation in healthcare has been applied in the therapeutic situation when co-creation amongst stakeholders is used to successfully focus healthcare professionals on generating meaningful outcomes for the patient (37). Co-created therapeutic decision making goes beyond shared decision making in the clinical setting to include all healthcare and non-healthcare environments that are important to the patient such as social media environments, environments in which patients find pleasure and relationships between family, peers and friends in the decision

TABLE 2 Responses to "What is working [within the service]?" organized into six themes and presented by the number of responses by participant per theme.

Themes	Percent response (n)	Description of activities within the themes
Multidisciplinary model of care	32% (56)	• Investment in allied health • Active approaches • Patient and family centered treatment • Skilled use of language, presenting choices, deep listening and validation • Bring patients together to hear from each other, decrease isolation and increase support • Marrying the concept of child development stages to treatment choices
Collaborative care/advocacy	31% (54)	• Widespread community support and awareness • Clear and accessible pathways and links between primary and tertiary care, acute and chronic pain teams, child to adult care • Supporting partnership with family doctors • University, industry and consumer partnerships • Lobby to put pediatric chronic pain on the government radar
Multi-level whole of community pain education strategies	17% (29)	• Involve the whole family in pain education • Upskill peer supporters/mentors • Generate a bank of success stories for sharing • Use stories and metaphors to explain chronic pain and the mind-body connection • Shared language of pain and consistent messaging about pain • Talking about pain in the medical community
Data support and funding	9% (16)	• Data collection to support service development • National data collection initiative can be used to benchmark service • Collecting and sharing data to identify patterns • Factor in sustainability • National and international collaborations to secure funding • Use data to lobby for funding and underpin grant success
Research/clinical science	8% (14)	• Value the importance of evaluating new initiatives/strategies • Youth with chronic pain and their parents/carers integrated into research • Opioids don't have a role in chronic pain • Evidence based interventions tailored to condition • National and international collaborations to integrate clinical care and research • Links with Universities to translate research into education and practice • Evaluated tools, manuals and workbooks that are iterative • Provide a variety of evidence-based ideas for service development
Use of technology and telehealth	3% (6)	• Telehealth—improve rural and equitable access • Virtual reality • APPs such as period tracking apps, day management apps and pain apps

The higher the number of responses, the stronger the theme is perceived to be working within the service.

making process. The patient is at the center of care and also takes care of themselves along a continuum of interactivity with all stakeholders. Practically, co-created decision making aims to improve the patient's wellbeing by including the patient as an active participant in the process. Co-design has also been used to refine the "GETLiving" program for youth with chronic pain (38). Three co-design meetings with youth with chronic pain and three parallel meetings with parents/carers were run to prioritize 12 ideas for program improvement that had been generated by earlier interviews. Within and between group consensus was used to rank the ideas by importance, providing the organizers of the program with a clear understanding of what key elements of the program were most helpful to participants.

Since the conclusion of this workshop, the PCPS has taken steps toward implementing changes that were first discussed within this workshop. For example, the cognitive behavioral workshop, CAP, has been successfully implemented and is running three times a year. CAP facilitates knowledge about the underlying contributions and impacts of chronic pain in young people and their families and carers and promotes vocabulary to talk about pain, shared experiences, and perspective taking. Consumer feedback from this implementation has been very positive and the PCPS are finalizing the outcomes of a research study that has evaluated the feasibility and acceptability of adapting the workshop to Australian needs. This initiative aligns with the stakeholder's concern around improved pain education, scalable interventions, and access to care at the community level. Additionally, research engagement and collaborations between researchers and clinicians connected to the CAP network has continued to develop. Indeed, the PCPS has been instrumental in supporting the instantiation of the CAP workshop in Western Australian where it is run both face to face and online and in Queensland.

Quality assurance data from this workshop and stakeholder investment has also helped to support the PCPS in increasing their staffing levels. Increased and stable funding has enabled the service to build up a dedicated multidisciplinary team over three days each week with a view to increasing to five days a week in mid-2024. The service is now permanently established and consistently able to respond to patient referrals within timeframes recommended by the guidelines of the WHO for the management of chronic pain in children (19).

TABLE 3 Linking challenges to solutions and actionable steps.

PCPS key challenges	Percent responses (n)	Sample stakeholder solutions and actionable steps
1. Insufficient staffing	21% (19)	• Develop relationships with universities to take students on clinical placement • Upskill the parent/carer with pain management strategies • Include disciplines currently under-utilized such as pharmacy and the families' General Practitioner • Use readily available internet resources for chronic pain and other published material to enhance communication and learning • Establish group programs
2. Clinical complexity	17% (16)	• Develop a shared language around pain • Move the focus of treatment toward promoting comfort and function and away from medication • Focus efforts on improving communication between healthcare professionals, families and school and social supports embedded in the interdisciplinary approach
3. Limited accessibility	13% (12)	• Enhance online opportunities for education through credible resources already available (e.g., online telehealth consultations and group programs or chats) • Conduct outreach via school programs for pain • Contact universities to determine whether there are existing outreach programs for rural communities where pain could be an "add-on" to current care models
4. Lack of prevalence data	8% (8)	• Use other countries such as Canada and the United States of America as a blueprint for service development of a state-wide pain clinic • Share information regarding prevalence more broadly • Create an advisory board to assist with the more complex decisions around meeting system needs • Develop a prevalence study to guide service development
5. Minimal pain education for all health professionals	17% (15)	• Lobby for improvements in university level pain education • Provide outreach education and develop an intervention that extends into the community • Build capacity amongst patients/peer mentors and practitioners • Incorporate pain education for all healthcare practitioners into Hospital Grand rounds and inhouse education • Coordinate access to community allied healthcare providers through GP care planning • Collaborate with education committees in tertiary healthcare institutions to develop a common understanding and capacity to manage chronic pain
6. Researchers and providers are in silos	10% (9)	• Foster research within the service by embedding student led research • Build a research translation culture by disseminating relevant research to service providers • Enhance efforts to move evidence-based care models into practice
7. Disjointed advocacy	12% (11)	• Learn how to advocate, develop patient advocates, and lobby for chronic pain in children to be recognized at the state policy level • Use service data collection to support the development of the service and promote early intervention • Use client and community engagement to promote advocacy • Establish a closed moderated private social media group for children and young adults with chronic pain to share their journey with peers.

Within the Women's and Children's Hospital (WCH) the PCPS has also increased communication and knowledge about pediatric pain. For example, they fostered a joint understanding with the Emergency Department by sharing resources and approaches to pain flares (hypnotherapy, pain education), presented to the wider WCH community at the weekly Grand Round and been in regular communication with the Director of Consumer and Community Engagement, presenting the mission of the PCPS to consumer and community advisory groups and using the feedback from these groups for the development of education resources, research priorities and resources. The PCPS has invited leading clinicians from the pelvic pain treatment service, cancer care service and rheumatology to observe the CAP workshop and encouraged shared care between these services.

Additionally, a culture of student led research has been embedded within the PCPS, fostering closer links with University faculties and enabling clinical outcomes to inform service improvement. Further, collaborations with national researchers and stakeholders have won funding to improve the model of care by codesign, strengthening stakeholder engagement with the service and raising the profile of pediatric chronic pain within central government bodies. The PCPS has become a site for clinical innovation, collaborating with other national and international pain services to trial a custom developed, pain specific virtual reality program to augment interventions targeting pain and pain rehabilitation in pediatric populations.

4.1 Strengths and limitations

Competing demands prevented 25 invitees from attending the workshop, but we recruited more than our desired sample size of 20 people (34 attended) from a diverse range of stakeholders. A limitation of our process was that we were not funded for a consensus meeting with participants and were unable to check whether the themes that we generated resonated with them. Finally, strong engagement with current healthcare systems is needed to promote long term sustainability and scale out of the solutions and the success of this will depend on healthcare system funding priorities.

5 Conclusion

The South Australian PCPS led a co-creation workshop to bring together key stakeholders including clinicians, researchers, administrators, policy makers, patients, and carers. The primary goal was to educate participants about the strengths and challenges faced by the newly launched PCPS and to generate innovative ideas and solutions to support pediatric chronic pain care in South Australia. Most workshop participants valued existing services for youth with chronic pain. However, there was also widespread recognition that systems-level challenges impede the quality and availability of care.

Since the completion of this stakeholder workshop, PCPS has grown significantly, successfully addressing issues in all seven key challenge areas identified by the service. Specifically, they have improved referral pipelines, increased state funding and full time equivalents (FTE's), engaged in community education, enhanced advocacy, built new partnerships within and outside WCH, implemented additional evidence-based practices, improved access to care, worked in collaboration with consumers (patients and carers), and developed several collaborative research initiatives with universities across Australia and internationally. It is strongly believed that this co-creation workshop helped to spur this change by generating novel ideas, providing data for PCPS leadership, and establishing new allies who could help to champion growth.

Ongoing challenges include developing safe and regularly convened communities for young people with chronic pain, no matter their linguistic or cultural diversity, to discuss their situations with peers, building healthcare professional capacity to manage chronic pain in young people beyond the PCPS team, and developing models of care coordinated across primary and tertiary centers. To meet these challenges the PCPS will continue to engage a wide variety of stakeholders in a solutions-focused approach to improving pediatric chronic pain care in South Australia.

Data availability statement

The datasets presented in this study can be found at https://doi.org/10.6084/m9.figshare.25800499.v1.

Ethics statement

The studies involving humans were approved by the Women's and Children's Health Network Human Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin (for youth 16 and under) and written informed assent (from youth 16 and under) was also provided.

Author contributions

CB: Conceptualization, Data curation, Funding acquisition, Methodology, Visualization, Writing – original draft, Writing – review & editing. TS: Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. NF: Data curation, Writing – original draft, Writing – review & editing, Funding acquisition. RC: Conceptualization, Data curation, Writing – review & editing, Funding acquisition.

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Conflict of interest

TS, NF, and CB were employees of the Pediatric Chronic Pain Service at the Women's and Children's Hospital. RC is the founder and director of the Comfort Ability® Program, a clinical intervention licensed by Boston Children's Hospital. Proceeds from the license partially fund her research lab; there was no commercial involvement. CB had received speaker fees for lectures on pain and rehabilitation and received support from ReturnToWorkSA and Kaiser Permanente Southern California.

Publisher's note

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