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Effects of exercise-based interventions on inflammatory markers in patients with fibromyalgia: A systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of the present review was (1) to determine the effects of exercise based-interventions (EBIs) on pro-inflammatory and anti-inflammatory biomarkers in patients with fibromyalgia (FM), and (2) to determine the most effective type (acute or maintained) and modality (aerobic, resistance, etc.).
Methods: A systematic search was conducted in various electronic databases to identify all the relevant studies: Medline (PubMed), PEDro, EBSCO and Google Scholar. Clinical trials assessing the effects of EBIs in patients with FM were selected. Methodological quality was evaluated by two independent investigators using the Cochrane Risk of Bias Tool. Qualitative analysis was based on the classification of the results into levels of evidence according to GRADE.
Results: Eleven studies were included. The meta-analysis showed a statistically significant decrease in proinflammatory biomarkers by EBIs with a large clinical effect in 19 comparisons (SMD: 1.74; 95 % CI: 0.85–2.62; $p < 0.05$), especially for IL8. The certainty of the evidence was low. The meta-analysis showed no statistically significant increase in anti-inflammatory biomarkers (IL10) by EBIs in 6 comparisons and very low certainty of evidence. Evidence was found for acute and maintained effects of exercise, with aerobic and aquatic exercise modalities showing better improvements than resistance exercise.
Conclusions: EBIs are effective in inducing an immunomodulatory response in FM, characterized by decreased pro-inflammatory signaling. However, there was no evidence of an increase in anti-inflammatory biomarkers. These results should be interpreted with caution due to low certainty of evidence.

Introduction

Fibromyalgia (FM) is a rheumatologic syndrome with widespread pain being the most characteristic symptom [1]. FM has a prevalence of around 2 % of the population, mainly affecting women [2,3]. The disturbances in pain processing (i.e., allodynia and hyperalgesia) are common among patients with FM [4,5] and could be partially explained by findings compatible with a central sensitization process [6,7].

Central sensitization has been defined as a neuroinflammatory process that affects the nervous system [8]. In this process, the activation of inflammatory cells, such as macrophages, and the release of pro-inflammatory molecules, such as cytokines, chemokines, and other mediators occurs [9]. The interactions of pro-inflammatory markers with specific nociceptors or spinal cord neurons lead to a biological process that modifies the excitability, conductivity, and transmissibility of pain-processing pathways, leading to pain-processing disturbances [10]. Among the pro-inflammatory molecules, cytokines are one of the most important, especially interleukins (IL). Cytokines can be divided into pro-inflammatory (e.g., IL-1, IL-6, and TNF-α) and anti-inflammatory (e.g., IL-4, IL-10 and TGF-β) types.

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Previous research supports the hypothesis that pain may be related to inflammation, given the involvement of inflammatory cytokines [11]. Two groups of cytokines, chemokines (cytokines involved in chemotactic functions) and ILs (cytokines involved in lymphocyte-to-lymphocyte signalling) play a central role as mediators of neuro-inflammation associated with chronic pain [12]. Recent research has shown that cytokine levels are imbalanced in FM patients, with increased levels of pro-inflammatory cytokines such as TNF-α, IL-1RA, IL-6, and IL-8 [13–15]. Disease severity was also significantly correlated with serum IL-8 and IL-6 levels compared to healthy individuals [16]. In particular, IL-8 is more strongly correlated with sleep disturbance and pain [17].

Exercise based-interventions (EBIs) are considered the first-line non-pharmacologic intervention for FM patients [18,19]. EBIs can induce metabolic, biomechanical, neurophysiological, and psychosocial adaptations that have relevant clinical effects on patients suffering from pain [20–22]. An umbrella review published in 2020 pooled the effects of EBIs and found positive effects on clinical variables related to the treatment of FM patients (i.e. pain intensity, disability, or quality of life) [23]. However, the mechanisms of action to explain these beneficial effects are not fully understood. One of how EBIs can have these positive effects is through an anti-inflammatory effect. The immune system can be influenced via exercise through the release of specific signaling molecules, called exerkines, secreted by several tissues throughout the body [24]. Furthermore, the acute and chronic exercise-induced effects differ in healthy individuals after chronic exercise as compared to healthy untrained individuals, it appears that factors related to exercise intensity or modality may influence its anti-inflammatory effects [25]. However, the abnormalities present in FM patients do not currently allow us to determine the effect of EBIs on the immune system. Therefore, the aim of the present review was [1] to determine the effects of exercise based-interventions (EBIs) on pro-inflammatory and anti-inflammatory biomarkers in patients with FM, and [2] to determine the most effective type (acute or maintained) and modality (aerobic, resistance, etc.).

Methods

Design

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines [26]. Systematic review protocol was pre-registered in PROSPERO (CRD42022378111).

Search strategy

A systematic search was conducted in various electronic databases to identify all the relevant studies: Medline (PubMed), PEDro, EBSCO and Google Scholar. The search strategy combined Medical Subject Headings (MeSH) and non-MeSH terms, adding a Boolean operator (OR and/or AND) to combine them. The comprehensive search strategy is presented in **Supplementary File 1** and was adapted for each database. No language restriction was used with the purpose to analyse all the literature on this topic. The last search was run on 1st February 2023. Two researchers made the research independently using the same methodology (ASS & LSM), a third researcher solved disagreements in consensus (JC). In addition, the reference sections of original studies were manually screened. We employed the Mendeley citation management software (Mendeley desktop v1.17.4, Elsevier, New York, New York) and hand checked the results to remove duplicates [27].

Inclusion criteria

We use the Population, Intervention, Comparison, Outcomes, Time and Study design (PICOTS) as a framework to formulate eligibility criteria [28].

Population

Participants older than 18 years and included patients with FM. Patients should have been diagnosed with FM by their attending physicians (e.g., rheumatologists, specialists in internal medicine, general practitioners, etc.) in any health care setting according to American College of Rheumatology (ACR) criteria. The patients' gender was irrelevant.

Intervention

Intervention of interest was EBIs, as planned and structured physical activity [26]. All types of EBIs (e.g., aerobic, resistance, flexibility, aquatic) were allowed. There was no restriction on the duration of the intervention (acute or maintained).

Comparison

Comparison groups were pre-intervention measures, since the aim of this study is to compare the effects of exercise in FM patients (within-group change).

Outcomes

The measures used to assess the results and effects of EBI were one or more of the following outcomes: pro-inflammatory cytokines (e.g., TNF-α, IL-1β, etc.), anti-inflammatory cytokines (e.g., IL-4, IL-10, etc.) other stress and inflammatory markers levels (e.g., IGF-1, cortisol, etc.).

Time

We did not apply any time restriction in term of training duration or outcome measures. The timeframe in which the outcomes were assessed could be immediately after treatment (post-intervention) and after the end of the treatment (follow-up).

Study design

Only randomized controlled trials (RCTs) were included.

Selection criteria and data extraction

The two phases of study selection (title/abstract screening and full-text evaluation) were conducted by two independent reviewers (ASS and LSM). First, they assessed the relevance of the studies regarding the study questions and aims, based on information from the title, abstract, and keywords of each study. If there was no consensus or the abstracts did not contain sufficient information, the full text was reviewed. In the second phase of the analysis, the full text was used to assess whether the studies met all the inclusion criteria. Disagreements between the two independent reviewers were resolved by a consensus process moderated by a third reviewer (JC). Data described in the results were extracted by means of a structured protocol that ensured that the most relevant information was obtained from each study. Data were extracted from the included studies, in a standardized form, including: First author, year of publication, diagnosis, number of participants, gender, age, outcomes, type of intervention, type of control groups, results and time-points.

Risk of bias assessment

Risk of bias was evaluated using the "Cochrane Risk of Bias Tool for Randomized Controlled Trials 2″ which contains seven domains: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases [29]. Each item was rated as high risk of bias (+ sign), low risk of bias (- sign) and unclear risk of bias (? Sign).

Two independent reviewers (LSM and ASS) assessed the risk of bias and methodological quality independently using the same methodology, and any disagreement was resolved by a third reviewer in consensus (JC). The inter-rater reliability was determined using the kappa

coefficient (κ) and percentage (%) agreement scores to assess reliability prior to any consensus and estimated the inter-rater reliability using κ: [1] $\kappa > 0.7$ indicated a high level of agreement between the reviewers; [2] $\kappa = 0.5$–0.7 indicated a moderate level of agreement; and [3] $\kappa < 0.5$ indicated a low level of agreement.

Methodological quality

The methodological quality of the included studies was assessed independently by two reviewers (LSM, RNC) using the PEDro scale. Disagreements were resolved by a third reviewer (JC). This scale consists of 11 check items (yes or no) and studies are scored out of a total of 10 (item 1 is not included in the calculation). Studies with a score above 6 points were considered to be of good methodological quality, studies with a score of 4–6 points were considered to be of fair methodological quality and studies with a score of 0–3 points were considered to be of poor methodological quality [30].

Certainty of evidence

The certainty of evidence was based on classifying the results into levels of evidence according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), which is based on 5 domains: study design, imprecision, indirectness, inconsistency and publication bias [31].

The evidence was categorized accordingly into the following 4 levels accordingly: (a) *High quality*. Further research is very unlikely to change our confidence in the effect estimate. All 5 domains are also met: (b) *Moderate quality*. Further research is likely to have an important impact on our confidence in the estimate of effect and might change the estimate of effect. One of the 5 domains is not met: (c) *Low quality*. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Two of the 5 domains are not met; and (d) *Very low quality*. Any estimate of effect is very uncertain. Three of the 5 domains are not met.

Data synthesis and analysis

The statistical analysis was conducted using *RStudio* software (RStudio, PBC, Boston, MA) according to the guide from Harrer et al. [32] To compare the outcomes reported by the studies, we calculated the standardized mean difference (SMD) over time and the corresponding 95 % confidence interval (CI) for the continuous variables. The statistical significance of the pooled SMD was examined as Hedges' g to account for a possible overestimation of the true population effect size in the small studies [33]. The estimated SMDs were interpreted as described by Hopkins et al. [34], i.e., we considered that an SMD of 4.0 represented an extremely large clinical effect, 2.0–4.0 represented a very large effect, 1.2–2.0 represented a large effect, 0.6–1.2 represented a moderate effect, 0.2–0.6 represented a small effect, and 0.0–0.2 represented a trivial effect.

We used the same inclusion criteria for the systematic review and the meta-analysis and included 3 additional criteria: 1) In the results, there was detailed information regarding the comparative statistical data of the exposure factors, therapeutic interventions, and treatment responses; [2] the intervention was compared within group (pre and post intervention in patients with FM); and [3] data on the analysed variables were represented in at least 3 studies. Since we pooled different treatments, we could not assume that there was a unique true effect. Therefore, we anticipated between-study heterogeneity and used a random-effects model to pool effect sizes. In order the calculate the heterogeneity variance τ^2, we used the Restricted Maximum Likelihood Estimator as recommended for continuous outcomes [35,36].

We estimated the degree of heterogeneity among the studies using Cochran's Q statistic test (a p-value <0.05 was considered significant), the inconsistency index (I^2) and the prediction interval (PI) based on the between-study variance τ^2 [34]. The Cochran's Q test allows us to assess the presence of between-study heterogeneity [37]. Despite its common use to assess heterogeneity, the I^2 index only represent the percentage of variability in the effect sizes not caused by sampling error [38]. To detect publication bias, we performed a visual evaluation of the Doi plot, seeking asymmetry. We also performed a quantitative measure of the Luis Furuya-Kanamori (LFK) index, which has been shown to be more sensitive than the Egger test in detecting publication bias in a meta-analysis of a small numbers of studies [39]. An LFK index within ±1 represents no asymmetry, exceeding ±1 but within ±2 represents minor asymmetry, and exceeding ±2 involves major asymmetry.

Results

The study search strategy is shown in the form of a flowchart (Fig. 1). 11 articles that met the inclusion criteria were selected. The characteristics for which data were extracted (study design, demographic characteristics, intervention, control, outcomes, main results, and conclusions) are presented in Table 1.

Study population characteristics

The total number of participants was 817, and the age of the participants ranged from 25 to 57 years old, 11 studies selected only women. All FM patients were diagnosed according to ACR criteria. Ten studies compared patients with FM and healthy subjects as control group, one study compared patients with FM and patients with chronic fatigue syndrome [40].

Study intervention characteristics

Regarding the intervention protocol, EBIs was detailed in Table 1. Two studies were performed using arm-leg cycle ergometer [40,41], 2 studies using stationary bicycle [42,43] 1 study using treadmill [44], 1 study using Nordic walking [45], other using a protocol of resisted exercises [46] and 4 studies using aquatic fitness programs [41,47–49]. The intensity ranged from 55 % of VO_2 max to exhaustion for aerobic exercises, and 40–80 % of 1RM (Maximum Repetition) and 40–80 % of MVC (Maximum Voluntary Contraction). 4 studies [17,40,43,44] assessed the acute effect of exercise and 7 studies [42,45–50] evaluated the effect of maintained exercise. The exercise intervention duration, when specified, ranged between 20 and 60 min. Given the lack of consensus in the selected type of exercise interventions, their intensity and training periodization, it was not possible to identify the most convenient intervention for FM patients, however aerobic exercise were the most common ones.

Blood samples were extracted previous and posterior to EBIs in order to measure the changes in pro-inflammatory cytokines as: TNF-α [42,44,46–49], IL-1β [42,46–48,50], IL-2 [46,47], IL-8 [41–44,46,47], CRP [47], IFN-y [46,47]. Anti-inflammatory cytokines as: IL-4 [46,47], and IL-10 [40,44,46–49]; other stress and inflammation markers levels such as IGF-1 [43,45], NA [43,47,48,50], cortisol [44,47,50] and gene expression levels of genes involved in signalling and modulating fatigue and muscle pain [40] (**Supplementary Material 2**). IL-6 could be pro and anti-inflammatory effects [40–42,44,46–49]. The selected methods for the sample examination were enzyme-linked immunosorbent assay [43,45,47–50] and LUMINEX immunoassays [42,44,46]. Only one study used the real-time quantitative polymerase chain reaction (qPCR) [40] (**Supplementary Material 3**).

Risk of bias

The methodological quality of all the studies was evaluated using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (**Supplementary Material 4**). Domains with the highest risk of bias were bias in the measurement of the outcome. Domains with the lowest risk of bias

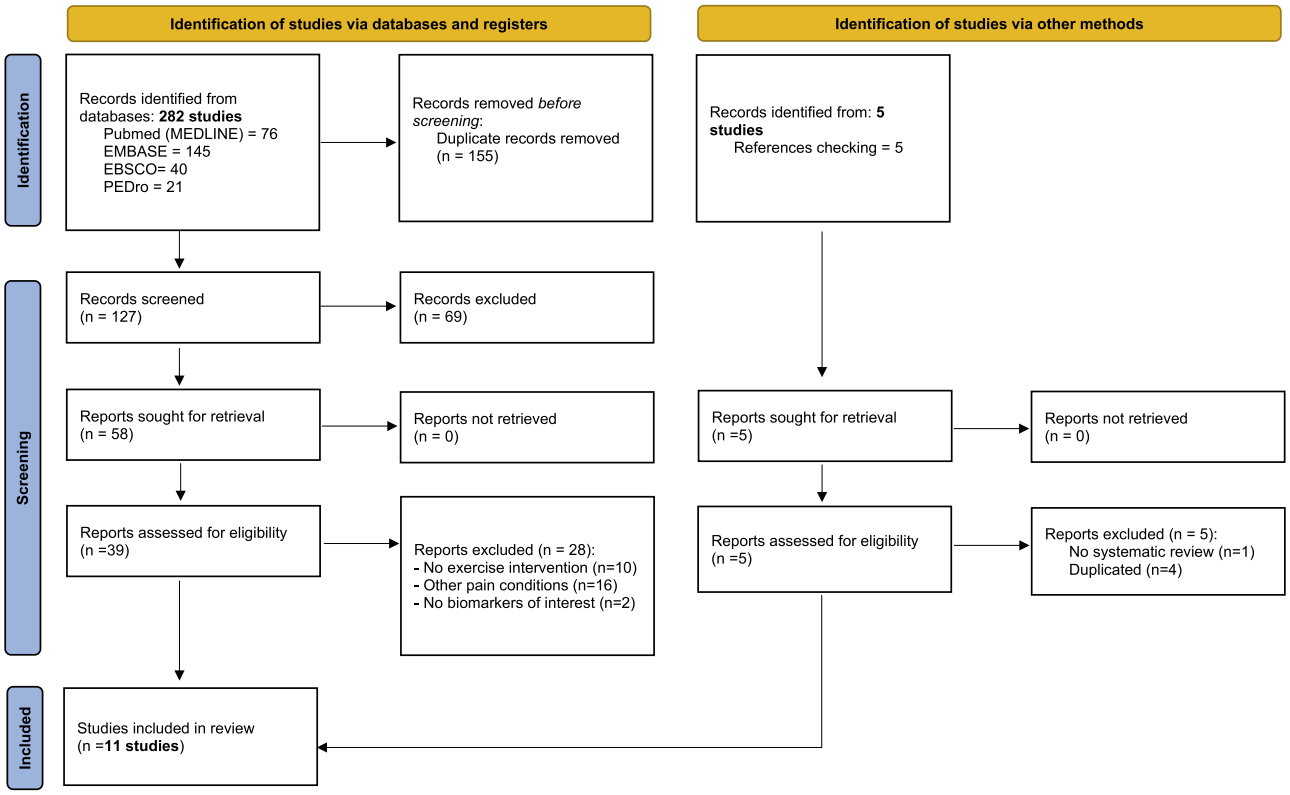

Fig. 1. Flow chart of participant selection according to PRISMA.

were randomization process and selection of the reported result The inter-rater reliability of the methodological quality assessment was high (κ = 0.838).

Methodological quality

Overall, the average PEDro score was 5.4 points across all included studies (min-max range: 4–7), indicating fair methodological quality. Items with good compliance were: eligibility criteria specified (90.9 %), random allocation (81.8 %), concealed allocation (63.6 %), baseline comparability (100 %), adequate follow-up (72.7 %), between-group comparison (100 %), point estimates and variability (72.7 %). The items with the lowest compliance were: blinding of subjects (9.1 %), blinding of therapists (0 %), blinding of assessor (18.2 %) and intention to treat (18.2 %). PEDro scores for the methodological quality of individual studies are reported in table **Supplementary Material 5.**

Meta-analysis results

Pro-inflammatory biomarkers

The meta-analysis showed statistically significant decrease in proinflammatory biomarkers by EBIs with a large clinical effect in 19 comparisons (SMD: 1.74; 95 % CI: 0.85–2.62; $p<0.05$) with evidence of significant heterogeneity ($p<0.01$, I2=89 %) (Fig. 2) and low certainty of evidence (**Supplementary Material 6**). The shape of DOI plot present asymmetry, and the LFK index showed asymmetry (LFK, 4.43) indicating a high risk of publication bias (**Supplementary Material 7A**).

IL8

The meta-analysis showed statistically significant decrease in IL8 by EBIs with a large clinical effect in 7 comparisons (SMD: 1.71; 95 % CI: 0.27–3.15; $p<0.05$) with evidence of significant heterogeneity ($p<0.01$, I2=92 %) (Fig. 2). The shape of DOI plot present asymmetry, and the LFK index showed asymmetry (LFK, 1.87) indicating a high risk of publication bias (**Supplementary Material 7A**).

TNF

The meta-analysis did not show statistically significant decrease in TNF by EBIs in 7 comparisons (SMD: 1.31; 95 % CI: 1.00–3.62; $p>0.05$) with evidence of significant heterogeneity ($p < 0.01$, I2=85 %) (Fig. 2). The shape of DOI plot present asymmetry, and the LFK index showed asymmetry (LFK, 3.45) indicating a high risk of publication bias (**Supplementary Material 7A**).

IL-1B

The meta-analysis did not show statistically significant decrease in IL-1B by EBIs in 5 comparisons (SMD: 2.30; 95 % CI: −0.54–5.13; $p>0.05$) with evidence of significant heterogeneity ($p<0.01$, I2=90 %) (Fig. 2). The shape of DOI plot present asymmetry, and the LFK index showed asymmetry (LFK, 3.79) indicating a high risk of publication bias (**Supplementary Material 7A**).

Anti-inflammatory biomarkers

IL10

The meta-analysis did not show statistically significant increase in IL10 by EBIs in 6 comparisons (SMD: −0.02; 95 % CI: −3.47–3.44; $p>0.05$) with evidence of significant heterogeneity ($p < 0.01$, I2=94 %) (Fig. 3) and very-low certainty of evidence (**Supplementary Material 6**). The shape of DOI plot present asymmetry, and the LFK index showed asymmetry (LFK, 1.91) indicating a high risk of publication bias (**Supplementary Material 7B**).

Exercise parameters

Duration

A meta-analysis was performed on the effect of EBIs on proinflammatory biomarkers, by classifying studies into those that performed

Table 1
Study characteristics.

Study	Design, participants, and age	Intervention	Outcomes	Results
Bjersing et al. 2012	RCT FM: 49 patients (49 GE) Age (median) 52 y FM patients diagnosed according ACR criteria.	Nordic Walking (moderate to high intensity program). Twice a week/ 40–45 min/ 15 weeks.	Blood samples at 15- and 30-weeks follow-up - IGF-1 - IGFBP-3	The baseline level of serum free IGF-1 did not change during high or low intensity of aerobic exercise. Changes in IGF-1 correlated positively with a variation in CSF SP, NPY, and pain threshold. These data indicate a beneficial role of IGF-1 during exercise in FM
Bote et al. 2012	RCT FM: 8 women Age FM (mean) 47±4 y FM patients diagnosed according ACR criteria.	A single bout of moderate exercise with arm-leg cycle ergometer (45 min at 55 % VO2max)	Blood sampling was carried out at basal state and immediately after exercise. - IL-8 - O_2 chemotaxis - O_2 production - IL-1β - TNF-a - IL-6 - IL-10 - IL-18 - Cortisol - NA -	Single sessions of moderate cycling can improve the inflammatory status in FM patients, reaching values close to the situation of aged-matched HW at their basal status. The neuroendocrine mechanism seems to be an exercise-induced decrease in the stress response of these patients.
Bote et al. 2014	RCT FM+*E*: 10 women Age range (53 ± 2y) FM: 10 women Age range (50 ± 4y) FM + *E* (Fibromyalgia patients exposed to exercise program FM patients diagnosed according ACR criteria.	Aquatic fitness program (A) 5 min stretching exercises; B)5 aerobic warm-up; C) 5 min passive stretching; D) 25 min aerobic; E) 15 min strength; F) 10 min cool down). Twice a week/ 60 min/ 8 months.	Blood sampling was carried out at basal status, 4 months, and at 8 months. - IL-8 - Noradrenaline (NA)	After 4 months of the exercise program, no significant changes were observed in neutrophil function (chemotaxis, phagocytosis, or fungicidal capacity) or in IL-8 and NA. At 8 months, a neuro-immuno-endocrine adaptation was observed, manifested by a significant decrease below basal state in neutrophil chemotaxis, IL-8, and NA. No significant changes in these parameters were observed during the same period in the group of non-exercised FM patients. After the 8 months of the exercise program, the FM patients had lower concentrations of IL-8 and NA with reduced chemotaxis of neutrophils compared to non-exercised FM women.
Ernberg et al. 2016.	RCT FM: 24 women Age FM (mean) 54 ± 8y Age FM (mean) 54 ± 9y FM patients diagnosed according ACR criteria.	FM Progressive resistance training (10 min bicycling, 50 min resistance training from low loads 40 % MVC, that progressed up to 80 % MVC) 60 min/ twice a week/ 15 weeks.	Blood sampling was carried out before and after the 15 week resistance training. Serum concentrations of - TNF - IL-1β - IL-6 - IL-8	At both sessions and for both groups the dynamic contractions increased pain ($P<$ 0.012) and fatigue ($P<0.001$). The levels of TNF were lower in the FMS at both sessions ($P<$ 0.05), but none of the other cytokines differed. IL-6 and IL-8 increased after the dynamic contractions in both groups ($P<$ 0.010), while TNF increased only in CG ($P<$ 0.05) and IL-1β did not change. Overall pain intensity was reduced after the 15 weeks of resistance exercise in FM ($P<$ 0.05), but there was no changes in fatigue or cytokine levels.
Jablochkova et al. 2019	RCT FM: 75 women Age FM (mean): 50.8 ± 9.6y FM patients diagnosed according ACR criteria.	FM - Resistance Intervention: Started at 40 % of MVC and developed up to 70–80 % of MVC (10 min warm-up, 50 min strength training). Twice per week/ 60 min/ 15 weeks - Relaxation Intervention: Mental exercises (Guided relaxation through body parts ended with stretching). Twice per week/ 25 min/ 15 weeks.	At baseline and after the 15 week intervention. - NGF BDNF IFN-ɣ IL-1β IL-2 - IL-4 - IL-6 - IL-8 - IL-10 - IL-17A - TNF-α - IL-1ra - IP-10	BDNF level was significantly higher ($p<0.001$) and NGF was significantly lower ($p<0.001$) in FM group than in CG. Exercise and relaxation interventions not affected the levels of BDNF and NGF. No significant correlations were found between BFNF or NGF in FM and cytokine levels or clinical variables.
Light et al. 2011	RCT FM: 18 patients - 15 women - 3 men Age (median) 51 Age (median) 45 FM patients diagnosed according ACR criteria.	1 bout of moderate exercise with arm-leg cycle ergometer (25 min at 70 % max age-predicted heart rate)	Blood samples evaluating mRNA expression at 4 fixed time points (0.5 h, 8 h, 24 h and 48 h after exercise) Metabolite detecting - ASIC3 - P2×4 - P2×5 - TRPV1 Adrenergic - α−2A - β−1 - β−2 - COMT Cytokine - IL-6 - IL-10	Moderate exercise increased most sensory and adrenergic receptor's and one cytokine gene's transcription for 48 h. These increases are correlated with behavioural measures of fatigue and pain. Moderate exercise decreased adrenergic a-2A receptor's transcription at all time-points. History of orthostatic intolerance was significantly more common in the a-2A decrease subgroup. FM-only patients showed no post-exercise alterations in gene expression, but their pre-exercise baseline mRNA for two sensory channels and one cytokine were significantly higher than controls.

(*continued on next page*)

Table 1 (*continued*)

Study	Design, participants, and age	Intervention	Outcomes	Results
Mannerkorpi et al. 2017	RCT FM: 22 women Age FM (mean): 44 ± 4y FM patients diagnosed according ACR criteria.	FM 2 bicycle test at moderate and high-intensity at 5–7th day of the menstrual cycle (15-min of ergometer cycle test/ 12–13 RPE ratings/ 15–17 RPE ratings)	After 15 min of exercise and 30 min rest -IGF-1 - Free IGF1 - S-IGFB3 - sCRP - IL-8	S-IGF-1 and S-IGFBP-3 increased both within the group with FM and in the healthy controls ($p < 0.01$). When bicycling at moderate or high intensity, the increases in S-IGF-1 did not significantly differ between the FM and CG (mean increase 11 ± 10 vs. 11 ± 15 ng/ml and 13 ± 10 vs. 19 ± 22 ng/ml) Self-reported pain and fatigue during exercise, irrespective of intensity, were higher in women with FM compared with healthy controls ($p < 0.001$).
Ortega et al. 2009	RCT FM: 14 women - Primary FM ($n = 10$) - Secondary FM ($n = 4$) Age FM (range) 30–60 y FM patients who fulfilled the ACR criteria. Physically inactive.	Aquatic fitness program (A) 5 min stretching exercises; B)5 aerobic warm-up; C) 5 min passive stretching; D) 25 min aerobic; E) 15 min strength; F) 10 min cool down). 3 times a week/ 4 months. A, B, C, F parts: - Low intensity (40–50 % of maximal heart rate). D part: - - Beginning program at low-moderate intensity (50–60 % of maximal heart rate) - - End of program (65–75 % of maximal heart rate)	Blood samples evaluating circulating concentrations of inflammatory markers before (pre-) and after 4 months of training (post) - SF-36 Health Survey questionnaire - Fibromyalgia Impact Questionnaire (FIQ) - 6-min walk test Serum concentrations of: - IFN-γ - TNF-α - IL-1β - IL-2 - IL-4 - IL-6 - IL-8 - IL-10 - CRP - NA - Cortisol	Whole FM group showed higher circulating levels of IL-8, IFNγ and CRP, as well as cortisol and NA than CG before the exercise program. Significant decrease in IL-8, IFNγ, CRP, cortisol but increased levels of NA were observed after the exercise program. Improvement in health-related quality of life and, FIQ and 6-min walk test scores in primary FM group were observed. Secondary FM group improved in social function, mental health and 6-min walk test but got worse in FIQ scores.
Ortega et al. 2012	RCT FM: 9 women Age FM (range) 30–60 y FM patients diagnosed according ACR criteria.	60-min indoor swimming pool sessions (A) 5 min stretching exercises; B)5 aerobic warm-up; C) 5 min passive stretching; D) 25 min aerobic; E) 15 min strength; F) 10 min cool down). A, B, C, F parts: - Low intensity (40–50 % of maximal heart rate). D part: - Beginning program at low-moderate intensity (50–60 % of maximal heart rate) - - End of program (65–75 % of maximal heart rate)	3 fixed time points (basal status, 4 months, and 8 months) 2 days after finishing last exercise session. - IL-1β - TNF-α - IL-6 - IL-10 - CRP	Increased IL-6 but decreased TNF release was found after 4 months of the exercise program. At 8 months, monocytes from FM patients showed diminished production of pro-/anti-inflammatory cytokines, (IL-1, I IL-6) with a similar spontaneous release of CG, but a lower production of TNF and higher of IL-10. Production of IL-1b, TNF, IL-6, CRP and IL-10 also decreased at the end of the exercise program, although IL-10 remained higher than CG. Exercise also improved the health-related quality of life of FM patients
Salm et al. 2019	RCT Aquatic exercise: 14 patients Age: 50.4 ± 7.9y FM patients diagnosed according ACR criteria.	Aquatic exercise 50 min aquatic exercise program with imprinted FIR emitting ceramics t-shirts. (5–7 min of stretching exercises; 5–7 min aerobic warm-up in the water, 5 min of passive stretching, 15 min of aerobic aquatic fast, 15 min of strength exercises, 10 min cool down). 3 times a week/ 6 weeks period)	Sampling was carried out before (pre) and at the end of the program (6 weeks, post), 1 day after finishing the last session of the program: - IL-6 - IL-10 -TNF	Pain scores did not differ. Patients showed significant reduction in IL-6 levels in intra-group analysis ($P = 0.04$). No differences were found in TNF and IL-10 levels.
Torgrimson-Ojerio et al. 2014	RCT FM: 20 women Age FM (mean) 52.0 ± 1.4y FM patients diagnosed according ACR criteria.	FM Exhaustive treadmill exercise to peak using the modified Balke protocol.	Blood was collected 3 times during the treadmill test; (immediately before exercise, peak exercise, and then 60-minutes after peak exercise). - IL-6 - IL-10 - TNF-α - IL-8 - ACTH - GH - Cortisol	FM participants failed to mount the expected anti-inflammatory response to exercise and experienced a worsening of symptoms post-exercise. Post-exertional symptoms changes were not mediated by post-exertional changes in pro-inflammatory cytokine levels.

FM: Fibromyalgia, RCT: Randomized control trial.

acute exercise (a single session) or maintained exercise (more than one session). A subgroup meta-analysis showed statistically significant differences for acute EBIs with large effect size (SMD: 1.58; 95 % CI: 0.54– 2.62; $p<0.05$) and chronic EBI with very large effect size (SMD: 2.10; 95 % CI: 0.65– 2.49; $p<0.05$). However, test for subgroup differences did not show statistically significant differences ($p = 0.52$) (Fig. 4).

Modality

A meta-analysis was performed on the effect of EBIs on proinflammatory biomarkers, by classifying studies into those that performed different EBI modality (aerobic exercise, resistance exercise and aquatic fitness exercise). A subgroup meta-analysis showed statistically significant differences for aerobic EBIs with large effect size (SMD: 1.58; 95 % CI: 0.54– 2.62; $p<0.05$) and aquatic EBIs with very large effect size (SMD: 2.92; 95 % CI: 1.15– 4.69; $p<0.05$). However, the meta-analysis did not show statistically significant difference for resistance exercise (SMD: −0.08; 95 % CI: −0.45– 0.29; $p>0.05$). Test for subgroup differences showed statistically significant differences ($p<0.01$). (Fig. 5).

Discussion

The present study aimed to evaluate the effect of EBIs on proinflammatory and anti-inflammatory biomarkers in FM patients. The results showed a significant decrease in pro-inflammatory cytokines, especially IL-8. These results are in line with previous studies that have demonstrated anti-inflammatory effects of exercise in chronic musculoskeletal pain conditions [17,51,52]. These results are also consistent with two recent meta-analyses that reported significant reductions in inflammatory markers (e.g., CRP) after aerobic exercise or resistance training in healthy middle age and older adults [53,54]. Aerobic and

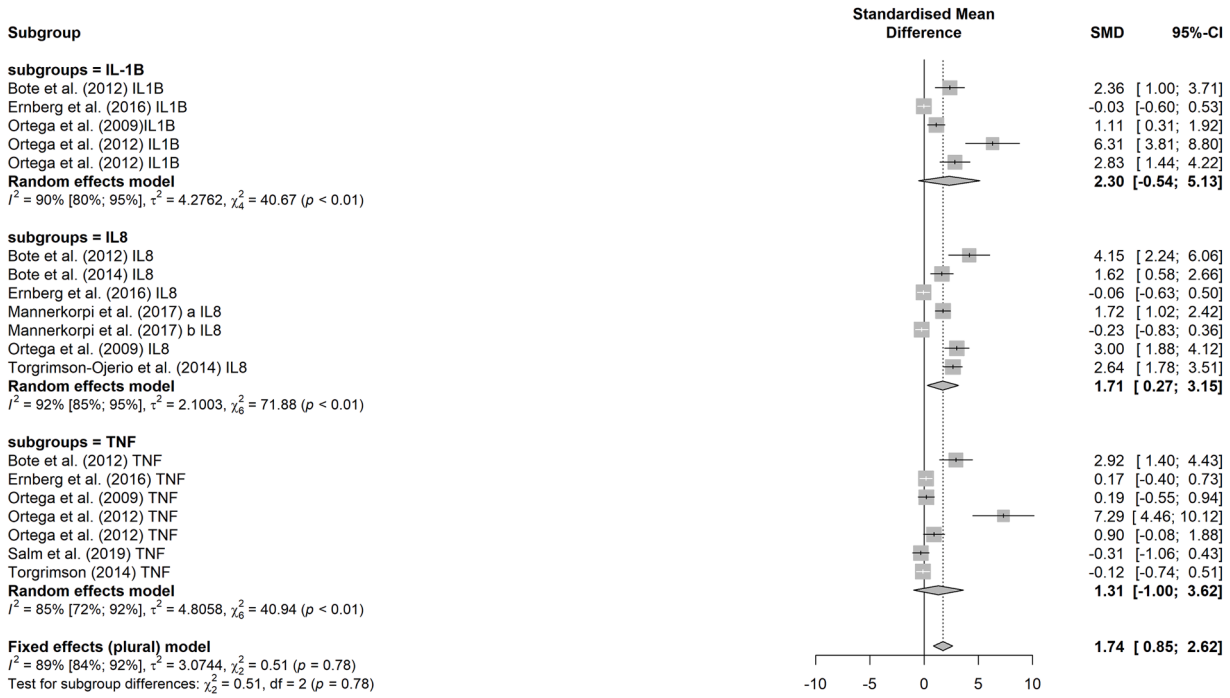

Fig. 2. Synthesis forest plot.
This forest plot summarizes the results of included studies in pro-inflammatory biomarkers (sample size, standardized mean differences [SMDs], and weight), divided in subgroups according to the type of cytokine (IL-1B, IL8, TNF). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95 % confidence interval (CI).

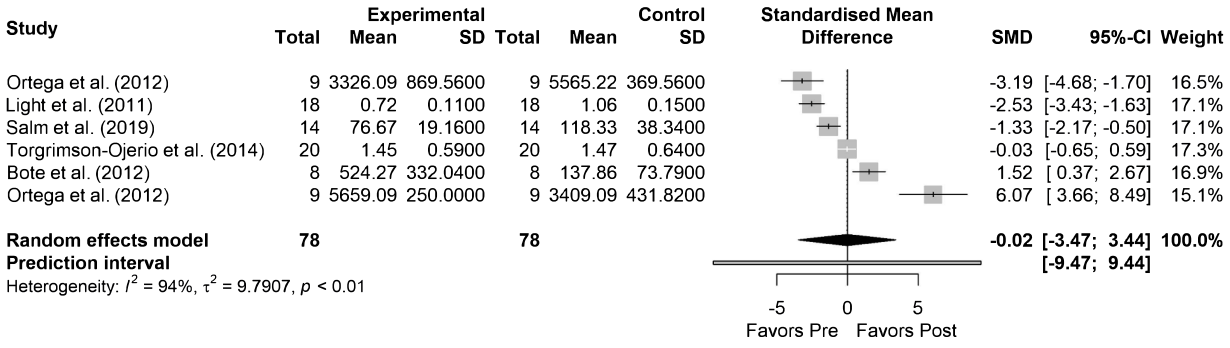

Fig. 3. Synthesis forest plot.
This forest plot summarizes the results of included studies in anti-inflammatory biomarkers (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95 % confidence interval (CI).

aquatic EBI showed a large and very large effect size respectively, which was superior to resistance exercise. Importantly, the effect of exercise on markers of inflammation was more pronounced in acute interventions (i.e. a single session). This is because the anti-inflammatory effects of exercise may be temporary and require regular exercise to maintain. Furthermore, these results should be interpreted with caution, as the certainty of evidence for these findings was low to very low.

The physiological mechanisms underlying the anti-inflammatory effects of exercise are not fully understood. The immune response is steered towards an anti-inflammatory state by regular, moderate-intensity exercise [55]. In fact, exercise can affect the immune system through the release of specific signaling molecules called cytokines, which are secreted by various tissues throughout the body [24]. Exercise may also have other benefits, such as improving muscle strength, flexibility, and cardiovascular fitness [19]. These may indirectly contribute to reducing inflammation. Additionally, inflammatory molecules in muscle tissue may be regulated by exercise [56]. Nevertheless, clinicians should be aware that exercise intensity may be a determining factor [57].

Different types of exercise may have different effects on markers of inflammation. For example, aerobic or aquatic exercise may have better results than muscular endurance exercise. Bote et al. showed that a single session of moderate cycling reduced systemic IL-8 levels [17]. Bidonde et al. found that aerobic exercise can reduce inflammation in FM patients [58]. Similarly, exercise interventions, including aerobic exercise, can reduce pro-inflammatory cytokines such as TNF-α, IL-1RA, IL-6 and IL-8 in FM patients, according to a systematic review and meta-analysis [59]. Aerobic exercise can also improve cardiovascular fitness, which may indirectly help to reduce inflammation. On the other hand, aquatic exercise can reduce stress and fatigue and improve FM symptoms [60]. This is important because stress might increase inflammation in painful conditions. In fact, in patients with chronic inflammatory diseases such as rheumatoid arthritis, stressful conditions may stimulate pro-inflammatory mechanisms due to dysfunctional

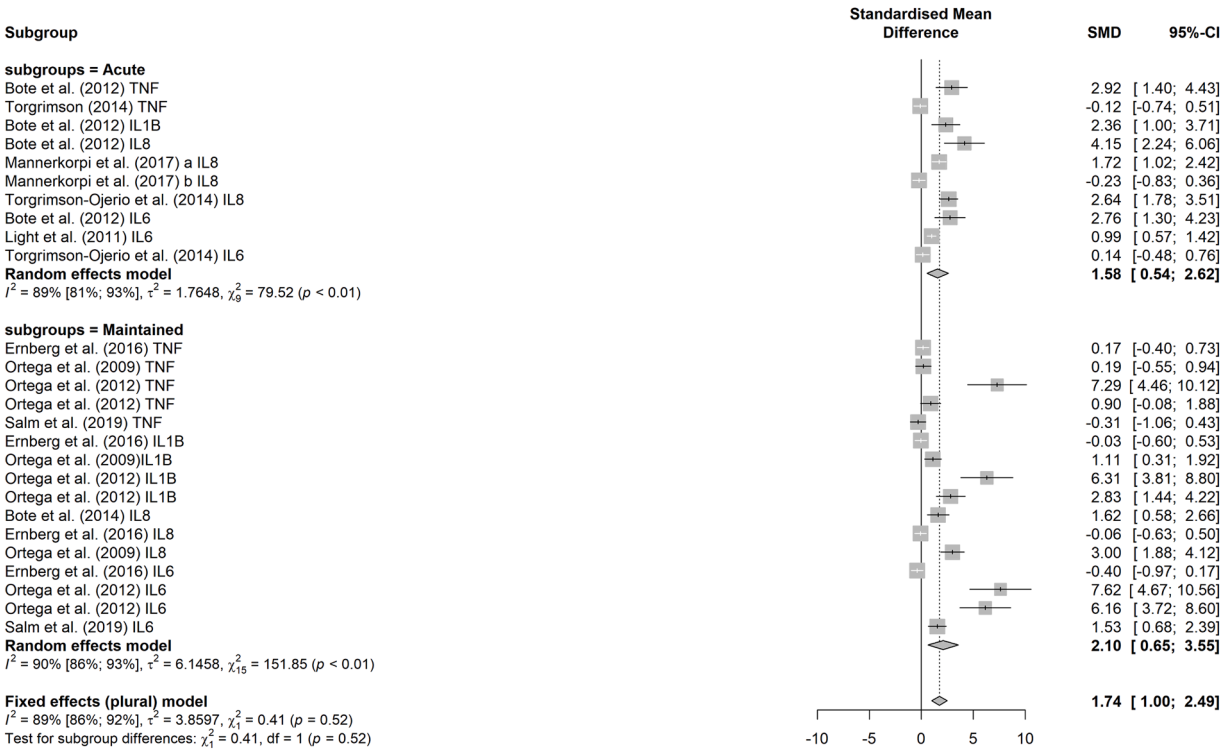

Fig. 4. Synthesis forest plot.
This forest plot summarizes the results of included studies in pro-inflammatory biomarkers (sample size, standardized mean differences [SMDs], and weight), divided in subgroups according to the type of exercise (acute, maintained). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95 % confidence interval (CI).

stress response systems (e.g. sympathetic nervous system and hypothalamic-pituitary-adrenal axis), which may lead to increased pain sensitivity [61]. In contrast, muscular resistance exercise may not have as significant an effect on inflammatory markers in FM patients. Although a combination of aerobic and endurance exercise is important for FM patients to enhance quality of life, pain relief and physical function [62], muscular endurance exercise may be more difficult for FM patients due to pain and fatigue.

In this regard, exercise can provide a non-pharmacological approach to managing the symptoms of FM through its anti-inflammatory effects [59]. However, it is important to note that exercise should be tailored to the needs and abilities of the individual and supervised by a healthcare professional. The long-term effects of exercise on markers of inflammation and the optimal type and intensity of exercise for people with FM should be investigated in future studies.

Limitations

This study has some limitations that need to be considered. First, ue to the low to moderate strength of evidence, future higher quality RCTs are needed to confirm our results. Despite similar mechanisms between exercise modalities, there is a high heterogeneity presents in our meta-analyses because we pooled different exercise modalities. Another limitation is the quality of the included studies, due to their methodological designs (i.e., different interventions in control groups). Although the methodological limitations found are common in the exercise sciences, the lack of blinding in the assessors and allocation concealment may be a limitation in the certainty of evidence. Future studies should focus on developing better designs to address this issue.

Conclusions

These results showed that EBIs are effective in inducing an immunomodulatory response in FM, characterized by decreased pro-inflammatory signaling. However, there was no evidence of an increase in anti-inflammatory biomarkers. Evidence was found for acute and maintained effects of exercise, with aerobic and aquatic exercise modalities showing better improvements than resistance exercise. However, these results should be interpreted with caution due to the low certainty of the evidence and the high heterogeneity of the interventions and outcomes assessed.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Luis Suso-Martí: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Rodrigo Núñez-Cortés:** Data curation, Writing – original draft, Methodology. **Alberto Sánchez-Sabater:** Writing – review & editing, Methodology, Data curation. **Miriam Garrigós-Pedrón:** Writing – review & editing. **Francisco José Ferrer-Sargues:** Writing – review & editing. **Rubén López-Bueno:** Writing – review & editing, Supervision, Methodology. **Joaquín Calatayud:** Writing – review & editing, Methodology, Data curation, Conceptualization.

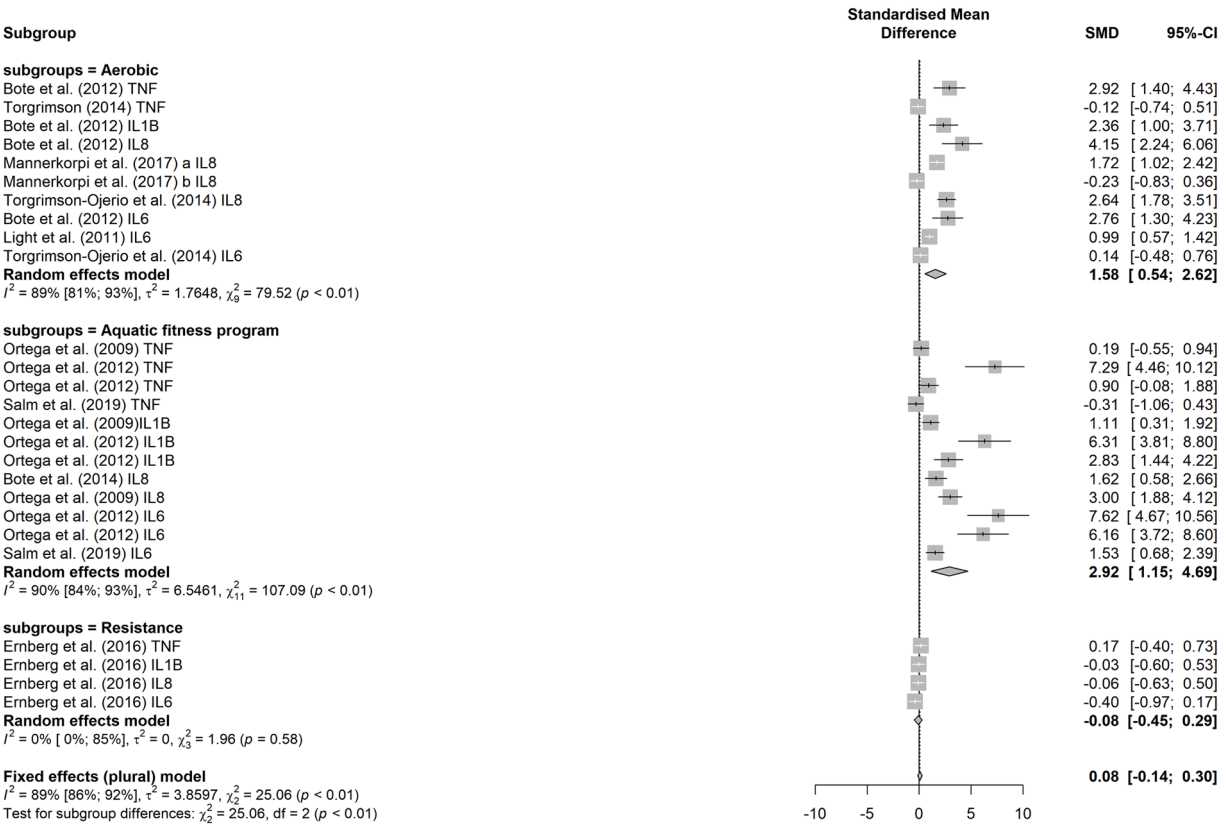

Fig. 5. Synthesis forest plot.
This forest plot summarizes the results of included studies in pro-inflammatory biomarkers (sample size, standardized mean differences [SMDs], and weight), divided in subgroups according to the modality of exercise (aerobic, aquatic fitness program, resistance). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95 % confidence interval (CI).

Declaration of competing interest

The authors declare no conflict of interest.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152377.

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