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ORIGINAL RESEARCH

# Efficacy of non-pharmacological interventions: a systematic review informing the 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases

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## ABSTRACT

**Objective** To identify the best evidence on the efficacy of non-pharmacological interventions in reducing fatigue in people with inflammatory rheumatic and musculoskeletal diseases (I-RMDs) and to summarise their safety in the identified studies to inform European Alliance of Associations for Rheumatology recommendations for the management of fatigue in people with I-RMDs.

**Methods** Systematic review of randomised controlled trials (RCTs) including adults with I-RMDs conducted according to the Cochrane Handbook. Search strategy ran in Medline, Embase, Cochrane Library, CINAHL Complete, PEDro, OTseeker and PsycINFO. Assessment of risk of bias, data extraction and synthesis were performed by two reviewers independently. Data were pooled in meta-analyses.

**Results** From a total of 4150 records, 454 were selected for full-text review, 82 fulfilled the inclusion criteria and 55 RCTs were included in meta-analyses. Physical activity or exercise was efficacious in reducing fatigue in rheumatoid arthritis (RA) (standardised mean differences (SMD)=−0.23, 95% CI=−0.37 to −0.1), systemic lupus erythematosus (SLE) (SMD=−0.54, 95% CI=−1.07 to −0.01) and spondyloarthritis (SMD=−0.94, 95% CI=−1.23 to −0.66); reduction of fatigue was not significant in Sjögren's syndrome (SMD=−0.83, 95% CI=−2.13 to 0.47) and systemic sclerosis (SMD=−0.66, 95% CI=−1.33 to 0.02). Psychoeducational interventions were efficacious in reducing fatigue in RA (SMD=−0.32, 95% CI=−0.48 to −0.16), but not in SLE (SMD=−0.19, 95% CI=−0.46 to 0.09). Follow-up models in consultations (SMD=−0.05, 95% CI=−0.29 to 0.20) and multicomponent interventions (SMD=−0.20, 95% CI=−0.53 to 0.14) did not show significant reductions of fatigue in RA. The results of RCTs not included in the meta-analysis suggest that several other non-pharmacological interventions may provide a reduction of fatigue, with reassuring safety results.

**Conclusions** Physica activity or exercise and psychoeducational interventions are efficacious and safe for managing fatigue in people with I-RMDs.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interventions to manage fatigue are complex, difficult to implement and evidence for non-pharmacological interventions is still scarce, hindering effective clinical decision-making.

### WHAT THIS STUDY ADDS

⇒ This systematic review reinforces the importance of implementation of non-pharmacological interventions for managing fatigue in people with inflammatory rheumatic and musculoskeletal diseases (I-RMDs), as they are efficacious and safe.

⇒ There is strong evidence that physical activity or exercise and psychoeducational interventions are efficacious in reducing fatigue. More evidence regarding follow-up models in consultations, multicomponent interventions and other interventions is still required to allow firm conclusions regarding these other non-pharmacological treatment strategies.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This systematic review highlights the importance of incorporating non-pharmacological interventions to manage fatigue in routine clinical care.

⇒ Future research should explore the efficacy and safety of interventions where evidence is still scarce and the extent to which patients with rarer I-RMDs might benefit from interventions tested primarily in patients with more common I-RMD.

## INTRODUCTION

Inflammatory rheumatic and musculoskeletal diseases (I-RMDs) are highly prevalent conditions and major contributors to the global disability burden. They require complex treatment regimens, which, if started early, reduce the risk of long-term structural damage, the need for surgeries and number of complications.[1]

Chronic fatigue is a common and poorly managed problem in people with I-RMDs, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), gout, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SjS), idiopathic inflammatory myopathies (IIMs), vasculitis and undifferentiated arthritis, among others.[2]

In RA, international consensus has been reached that fatigue should be measured in all clinical trials.[3] In 2006, international delegates at the Outcome Measures in Rheumatology eighth meeting, endorsed fatigue as an addition to the 'core set' of outcome measures for all future studies, highlighting the importance of investigating this symptom.[3] However, despite these efforts, it is widely recognised by the rheumatology community that there is still a large gap in the current management of fatigue, which is mainly due to the lack of evidence on the cost-effectiveness of providing fatigue therapies using different treatment modalities, the lack of training available for healthcare professionals to provide evidence-based fatigue therapies,[2 4 5] and the complexity of fatigue itself, since it is a multidimensional symptom that varies from patient to patient and over time,[6] making it more challenging to manage effectively.

Several European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of people with specific I-RMDs have highlighted the importance of non-pharmacological interventions in the management of the condition, including fatigue.[7–12] However, these recommendations are either disease specific or focusing on a single intervention, and lack an integrated view of the overall evidence for non-pharmacological fatigue management in the wider context of all I-RMDs.

To inform the task force responsible for the 2023 EULAR recommendations for the management of fatigue in people with I-RMDs, we performed a systematic review (SR) that aimed to identify and evaluate the evidence on the efficacy of non-pharmacological interventions in reducing fatigue in people with I-RMDs and to describe their safety in the included studies.

## METHODS

This SR was conducted according to the Cochrane Handbook[13] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14]

The steering group of the EULAR task force (BF, EJFS, ED and PMM) established and published the SR protocol in PROSPERO (CRD42021282899). Although this protocol refers to all interventions to manage fatigue, the interventions were subsequently divided into pharmacological and non-pharmacological ones, and two SRs were generated given the high number of included studies. The SR for pharmacological interventions was published elsewhere.

The outlined research questions, as approved by the task force at the first meeting, were:

1. Which non-pharmacological interventions are efficacious in reducing fatigue in people with I-RMDs?
2. Which non-pharmacological interventions are safe in reducing fatigue in people with I-RMDs?

These questions were framed and structured according to the EULAR standardised operating procedures[15] using the 'Patients, Intervention, Comparator or Control, Outcome, Type of study' format, as follows:

### Participants

A study was eligible for inclusion if the participants included were adults (aged 18 years or over) with I-RMDs, specifically, RA, axSpA, peripheral spondyloarthritis (pSpA), PsA, gout, SLE, SSc, SjS, IIM (dermatomyositis, polymyositis, immune-mediated necrotising myopathy, anti-synthetase syndrome, inclusion body myositis) and primary systemic vasculitis (large-vessel vasculitis: giant cell arteritis (GCA) (and the related condition polymyalgia rheumatica), Takayasu's arteritis; medium-vessel vasculitis: polyarteritis nodosa; small-vessel vasculitis limited to the ANCA-associated vasculitis: granulomatosis with polyangiitis (GPA, previously named Wegener's granulomatosis), microscopic polyangiitis and eosinophilic GPA (previously named Churg-Strauss); and variable-vessel vasculitis: Behçet syndrome, also known as Behçet disease). Only studies in which patients were formally diagnosed with I-RMDs or who met internationally accepted disease classification criteria were included to maximise accuracy.[16–19] Studies focusing on other concomitant diseases were summarised separately and by subgroups whenever possible.

### Interventions

We included all non-pharmacological interventions, defined as interventions that do not involve registered drugs.[20] Additionally, these interventions should be promoted/endorsed/referred to by a health professional which is defined as a provider of healthcare treatment and advice based on formal accredited training and experience, such as physicians, nurses and physiotherapists, among others.

### Comparator or control

The comparator was placebo or usual (standard) care.

### Context

There were no contextual constraints.

### Outcomes

Regarding outcomes, the core concept was fatigue. Fatigue is a complex, multifaceted phenomenon. Importantly,

most people have experienced fatigue during their everyday life, but qualitative research suggests differences between fatigue associated with chronic diseases and tiredness or premorbid fatigue.[21] The most distinguishing features of fatigue associated with chronic diseases include the perception of the fatigue as having no obvious 'explanation', a lack of improvement with rest, variability in severity, unpredictability and profound or overwhelming fatigue.[21] In that sense, we accepted self-reported measures of fatigue using quantitative and validated scales, such as: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F),[22] Rheumatoid Arthritis Impact of Disease-Fatigue,[23 24] Fatigue-Visual Analogue Scale (VAS),[25] 36-Item Short Form Survey vitality scale,[26] the Multidimensional Assessment of Fatigue,[27] Profile of Mood States-subscale fatigue,[28] Checklist Individual Strength,[29] Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF),[30 31] BRAF Numerical Rating Scales for severity, effect and coping,[30 31] among others.

### Type of study

Only randomised controlled trials (RCTs) or controlled clinical trials were eligible because they are considered the most robust study designs and represent the strongest evidence.[32] The studies integrating SRs were extracted for joint analysis with the remaining primary studies. SRs were not analysed.

### Search Strategy and Study Selection

A search strategy was run in Medline through PubMed, Embase, Cochrane Library, CINAHL Complete, PEDro, OTseeker and PsycINFO. The start date was the date of inception of the database, and the end date was 27 December 2021. Studies published in English, French, Portuguese, Spanish and Turkish, with no restriction on the publication date, were considered for inclusion. Details on complete search strategies are provided in online supplemental material S1.

All identified citations were uploaded into an EndNote V.X9 (Clarivate Analytics, Pennsylvania, USA) library and the duplicates removed. Two independent reviewers (BF and EJFS) screened titles and abstracts to assess eligibility criteria. The full articles were retrieved for all studies that met or had insufficient information to assess inclusion criteria, and two reviewers (BF and EJFS) independently examined them in detail. Any disagreements between the reviewers were resolved through discussion or adjudication by a third reviewer (PMM). The study selection was performed using Rayyan.

### Risk of Bias (Quality) Assessment

Two reviewers (BF and EJFS) assessed the risk of bias in each included study using the Cochrane Collaboration's tool for RCTs.[33] Any disagreements between the reviewers were resolved through discussion or adjudication by a third reviewer (PMM).

### Data Extraction and Synthesis

Data were extracted from the selected reports by the same two independent reviewers (BF and EJFS), and disagreements were discussed until consensus was achieved, or with adjudication by the third reviewer (PMM), whenever necessary. There was no need to contact the authors of the papers to request additional information.

Studies were pooled for statistical meta-analysis using Review Manager V.5.2.8. and SPSS Statistics, V.28 (IBM), if the needed statistics were available. Effect sizes were expressed as final postintervention standardised mean differences (SMD), and their 95% CIs were calculated. The selection of SMD was determined primarily because all studies report the outcome using different scales/metrics.[13] We imputed SD where necessary according to sections 6.5.2.2 and 6.5.2.3 of the Cochrane Handbook.[13] Additionally, if not available, the mean and SD were estimated from the median, range and/or IQR, according to the method proposed by Wan *et al*.[34] Heterogeneity was assessed statistically using the standard $x^2$ and $I^2$ tests. For a value of $I^2$ equal to 0%, we assume no heterogeneity between studies (homogeneity), around 25% low heterogeneity, around 50% moderate heterogeneity and around or greater than 75% high heterogeneity.[35] Statistical analyses were performed using random effects models only in the presence of moderate to high heterogeneity ($I^2$>50%), and, in their absence, fixed effect models were used instead.[36 37] A funnel plot was generated to assess publication bias if there were 10 or more studies included in a meta-analysis.[38 39] Egger's regression test for funnel plot asymmetry were performed and it was considered that publication bias existed when the p value was less than 0.05.[13] Where statistical pooling was impossible, the findings were presented in narrative form, including tables and figures, where appropriate. Subgroup analyses were conducted if sufficient data was provided, with subanalyses based on the different disease categories. Sensitivity analyses were conducted to test the decisions made. The level of evidence was assigned for each intervention using the 2011 Oxford Centre for Evidence Based Medicine Levels of Evidence.[32]

## RESULTS

The results of the searches are shown in a flow diagram (figure 1). Out of a total of 4150 records, 454 were selected for full-text review, 82 studies fulfilled the inclusion criteria and were included in this SR. Of these, 55 RCTs were included in the meta-analysis. There was no need to contact the authors of the papers to request additional information. Fatigue was a primary outcome in only 29 of the 82 RCTs included of which 11 were included in the meta-analysis.

### Methodological quality

The critical appraisal results for each of the studies are summarised in figure 2 and online supplemental material S2. There was agreement among the reviewers to

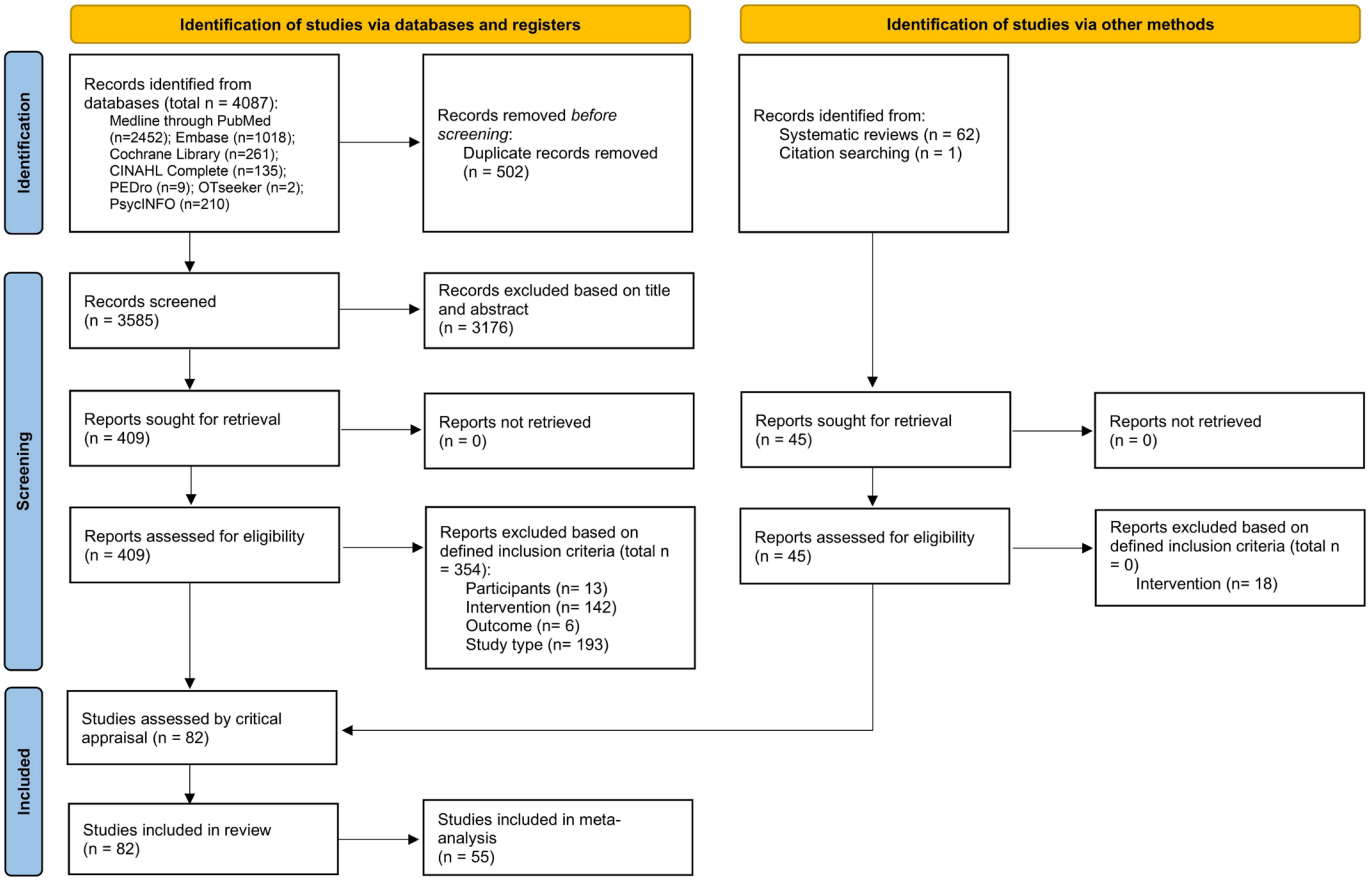


**Figure 1** Flow chart of the study selection and inclusion process.

include all the studies that were appraised. Most of the RCTs included were of moderate to high quality, except for four of low quality.[40–43] These studies had at least four criteria deemed to have high or unclear bias and had some kind of issue in the random sequence or allocation concealment. Most RCTs had issues with blinding participants, personnel and outcomes, which might be expected given the nature of the intervention (methodologically, it is challenging to blind non-pharmacological interventions). A smaller percentage of RCTs had problems with allocation concealment.

## Characteristics of included studies and interventions

Study characteristics are detailed ine online supplemental material S3. Regarding interventions, the most studied among the 82 RCTs were physical activity or

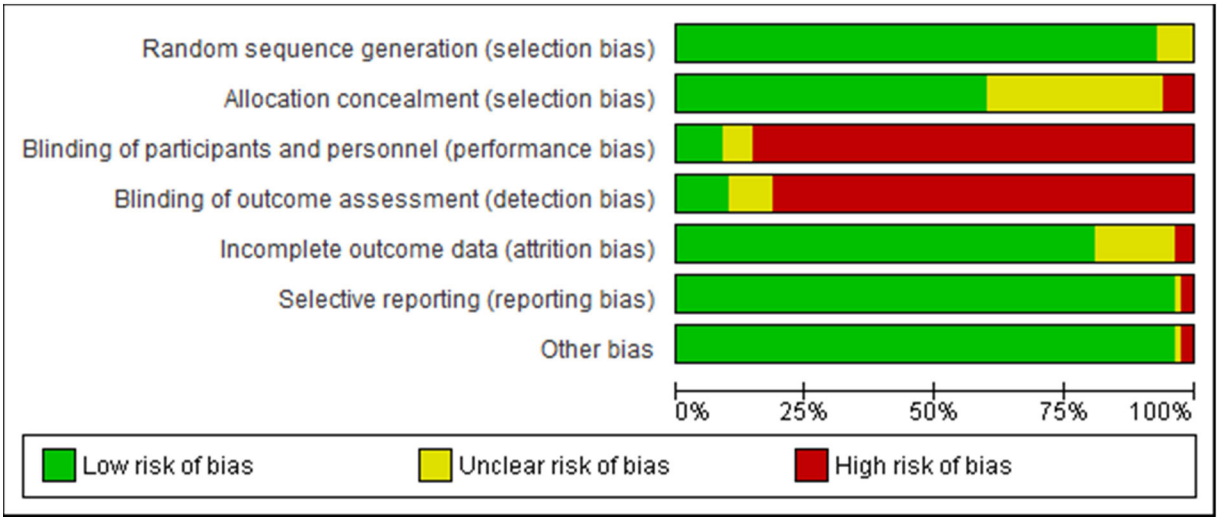


**Figure 2** Risk of bias summary graph for included clinical trials. Review authors' judgements about each risk of bias item presented as percentages across all included studies using the Cochrane RoB tool. RoB, risk of bias.

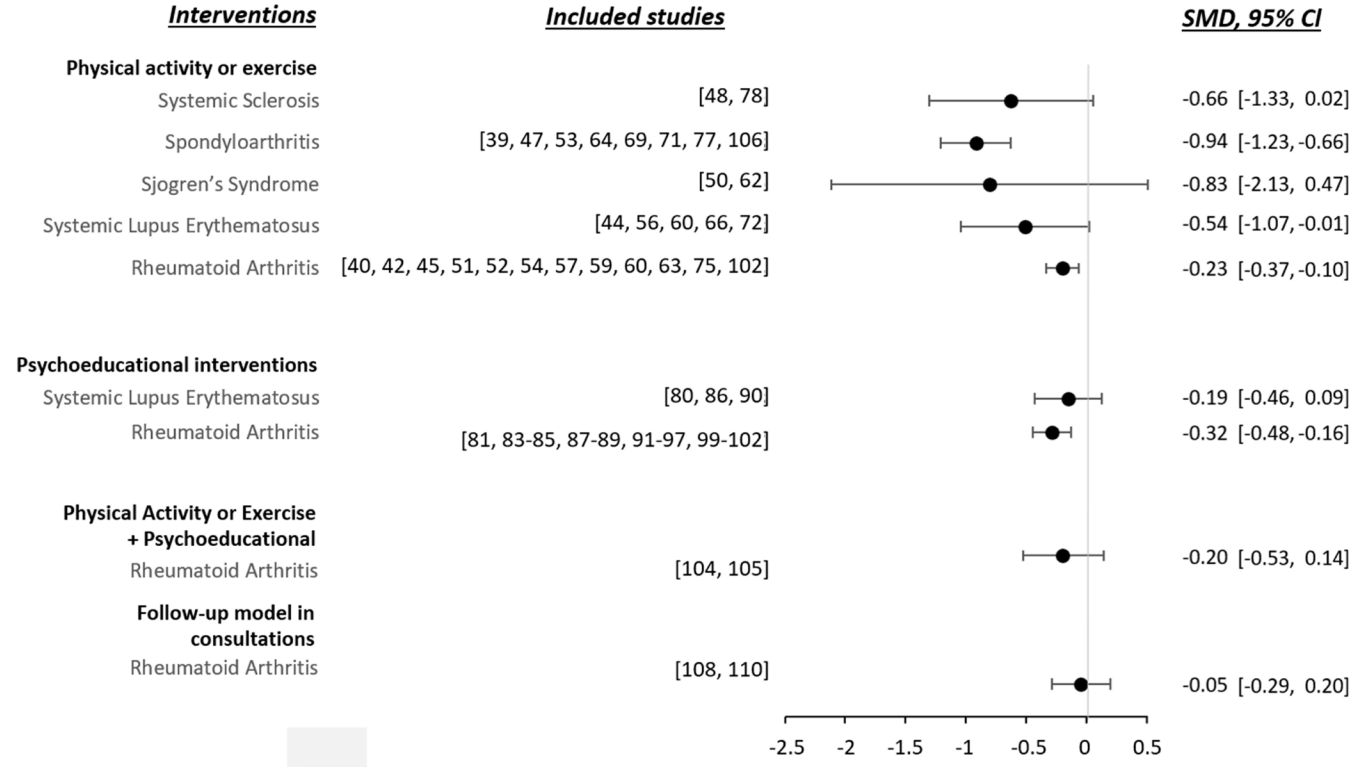


**Figure 3** Meta-analyses summary. SMD, standardised mean differences.

exercise (n=41),[40–80] psychoeducational interventions (n=22),[81–102] multicomponent interventions: physical activity or exercise and psychoeducational interventions (n=6),[103–108] follow-up models in consultations, which includes the different follow-up consultation systems, like the follow-up by a clinical nurse specialist or by a medical doctor or other models (n=4),[109–112] traditional Chinese medicine (n=2),[113 114] diet (n=2),[115 116] balneotherapy (n=1),[117] transcranial direct current stimulation (n=1),[118] transcutaneous auricular vagus nerve stimulation (n=1),[119] whole body vibration (n=1)[120] and aromatherapy (n=1).[121]

The most widely used fatigue assessment scale was the Fatigue-VAS (21 studies), followed by Fatigue Severity Scale (15 studies) and the (FACIT-F; 10 studies). A very high number of different scales were used, indicating a clear lack of standardisation.

## Meta-analysis

A meta-analysis of the results is detailed in online supplemental material S4. A summary of the meta-analyses was grouped into a single forest plot (figure 3).

In comparison to usual care, physical activity or exercise in RA was efficacious in reducing fatigue (SMD=−0.23, 95% CI=−0.37 to −0.1, p<0.001). No publication bias was observed according to the funnel plot and Egger's regression test (−0.1, 95% CI=−0.49 to 0.3, p=0.6). The superiority of physical activity or exercise versus control was also observed in SLE (SMD=−0.54, 95% CI=−1.07 to −0.01, p=0.04) and spondyloarthritis (SMD=−0.94, 95% CI=−1.23 to −0.66, p<0.001). In the case of SjS and SSc, the reduction in fatigue was not statistically significant (SMD=−0.83, 95% CI=−2.13 to 0.47, p=0.21; SMD=−0.66, 95% CI=−1.33 to 0.02, p=0.06, respectively).

Regarding the comparison between psychoeducational interventions versus control, in RA, the meta-analysis showed that psychoeducational interventions were efficacious in reducing fatigue (SMD=−0.32, 95% CI=−0.48 to −0.16, p<0.001). No publication bias was observed according to the funnel plot and Egger's regression test (−0.1, 95% CI=−0.59 to 0.39, p=0.67). In the case of SLE, a reduction in fatigue by means of psychoeducational interventions was not statistically significant (SMD=−0.19, 95% CI=−0.46 to 0.09, p=0.18).

Finally, in RA, regarding the comparison between follow-up models in consultations vs control (SMD=−0.05, 95% CI=−0.29 to 0.20, p=0.71), and the comparison between multicomponent interventions (physical activity or exercise+psychoeducational intervention) versus control (SMD=−0.20, 95% CI=−0.53 to 0.14, p=0.24), the reductions in fatigue were not statistically significant.

It should be noted that in four of the meta-analyses performed there was no heterogeneity ($I^2$=0%) (physical activity or exercise in RA, psychoeducational intervention in SLE, follow-up model in consultations in RA, and physical activity or exercise+psychoeducational in RA). In four of the meta-analyses, we found moderate heterogeneity ($I^2$<75%) (physical activity or exercise in SLE, SpA and SS, and psychoeducational interventions in RA). In one meta-analysis, heterogeneity was high ($I^2$=90%) (physical activity or exercise in SjS).

### Narrative synthesis

The narrative results of the RCTs not included in the meta-analysis showed that multicomponent interventions (physical activity or exercise+psychoeducational interventions) reduced fatigue in vasculitis,[104] but not in IIMs.[75 108] In SjS, transcranial direct current stimulation also reduced fatigue,[118] but not traditional Chinese medicine.[113] In PsA, physical activity or exercise reduced fatigue.[101] In SLE, traditional Chinese medicine, diet and transcutaneous auricular vagus nerve stimulation reduced fatigue.[114 115 119] Lastly, in RA, aromatherapy, whole body vibration and balneotherapy reduced fatigue.[117 120 121]

Regarding the safety of the interventions, most studies did not address it. The 31 RCTs reporting safety data did not find any serious or clinically significant adverse effects.[41 43 49–51 56 60 62 63 65 66 72 74–76 78 80 86 97 102–104 106 111–116 118 119]

## DISCUSSION

This SR shows evidence that physical activity or exercise[40–80] and psychoeducational interventions[81–102] are efficacious in reducing fatigue in people with I-RMDs. However, these interventions' optimal parameters and components are not yet fully established. Some beneficial effects were observed for follow-up models in consultations[109–112] and multicomponent interventions.[103–108] To a lesser degree, there was also some evidence that other interventions such as traditional Chinese medicine,[113 114] diet,[115 116] balneotherapy,[117] transcranial direct current stimulation,[118] transcutaneous auricular vagus nerve stimulation,[119] whole body vibration[120] and aromatherapy,[121] are efficacious in reducing fatigue in people with I-RMDs. However, in the case of these interventions, more robust studies are still needed before strong conclusions can be made.

Safety results were reassuring. However, safety information was often lacking in the retrieved studies and mentioning safety in detail in future non-pharmacological interventions addressing fatigue is advisable. Even if no adverse events or side effects are observed, this should be clearly reported in future studies.

The interventions were delivered by various healthcare professionals, including rheumatologists/physicians, nurses, psychologists, nutritionists, physiotherapists, occupational therapists, social workers and dieticians. Besides them, the multidisciplinary teams that delivered the interventions also included laypersons, pairs of lay leaders, counsellors and yoga teachers, although with smaller participation.

Regarding the quality of the included studies, most of them were of high or moderate quality, as mentioned previously, corresponding to a level of evidence 1 or 2 according to the 2011 Oxford Centre for Evidence Based Medicine Levels of Evidence.[32] Even so, no RCTs addressed cost-effectiveness analysis, which is important in determining the optimal framework for the non-pharmacological management of fatigue in I-RMDs.

Another research gap is that although fatigue has been identified as one of the most challenging symptoms to manage and a priority for patients with I-RMDs, very few RCTs have studied fatigue as the primary outcome. This limitation does not seem to be specific for I-RMDs, and it is also observed in non-inflammatory RMDs.[122] Fatigue was more often studied as a secondary outcome or side effect. It is possible that interventions of which the primary aim is to reduce fatigue have another content than interventions of which the primary aim is to increase mental well-being or physical functioning. Thus, some of the evaluated interventions may be better suited to reach other outcomes than a reduction of fatigue. Moreover, in several I-RMDs, the evidence to support the use of non-pharmacological interventions to manage fatigue is still very poor or non-existent, particularly in rarer conditions such as SSc, IIMs, vasculitis and GCA, among others. Future research should explore how fatigue-related support needs of people with I-RMDs, particularly rarer I-RMDs, can be met by existing evidence-based interventions or whether novel interventions are needed. Another point to consider is that, while assessing general fatigue is relevant, it is also important to assess the multidimensional aspects of fatigue, such as physical fatigue, mental fatigue, reduced activity and reduced motivation. Differentiated effects on outcomes may be observed, hence a multidimensional scale for measuring fatigue or specific elements of fatigue (depending on the type of intervention/mechanism of action) may be more suitable than a one-dimensional scale.

Finally, our SR also raised the need for standardisation and validation of fatigue measures across and within specific RMDs, especially if interventions target more than one disease group. This problem has been previously highlighted, and several suggestions have been proposed until a gold-standard measure can be recommended.[2 6] This prevented the integration of some studies into the meta-analysis. Moreover, blinding was highlighted as a limitation in most of the included studies, although there are intrinsic difficulties in blinding non-pharmacological interventions; blinding of outcome assessments might be possible, but there are many circumstances where participants cannot be blinded. In this regard, the use of better or alternative research designs is encouraged. For example, placebo drug controls as an alternative intervention, or cognitive-behavioural interventions that are known not to affect fatigue.

Lastly, we intentionally tried to include all I-RMDs and all non-pharmacological interventions with the potential to reduce fatigue, and this naturally led to clinical heterogeneity. To decrease clinical heterogeneity and enable a better understanding of the evidence, results were presented by disease rather than globally, and interventions were grouped by category (eg, physical activity or exercise, psychoeducational interventions, among others). The levels of heterogeneity found in the meta-analyses were mostly absent to moderate. Based on the number of studies included in each meta-analysis and the

magnitude of the SMDs, which ranged from low to high, we may conclude that the results are robust and precise. It should be noted that meta-analyses composed of three or fewer RCTs showed higher levels of heterogeneity and no statistical significance, thus translating into greater imprecision. Although most studies did not refer to 'clinically relevant differences', given the high number of studies comprising the different meta-analyses, their statistical significance, as well as their magnitude we can conclude that clinically there are unequivocal benefits. Still, future studies should be conducted to analyse whether fatigue reduction is clinically relevant/meaningful.

Compared with other robust SRs previously published,[123] which focused only on a particular disease (eg, RA), we can highlight that our review, being more recent and including a greater number of studies, namely in the meta-analysis, has led to improved effect sizes and magnitudes. This improvement has resulted in higher precision and lower heterogeneity levels, while observing a similar direction of effect.

In conclusion, this SR provides evidence on the efficacy and safety of several non-pharmacological interventions for the management of fatigue in people with I-RMDs and provides new insights into the management of fatigue across the entire spectrum of I-RMDs. More specifically for RA, this evidence is robust.

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**Contributors** All authors are members of the EULAR's task force for the development of 2023 EULAR Recommendations for the management of fatigue in people with inflammatory rheumatic diseases. EJFS and BF were the fellows. ED was the convenor. PMM was the methodologist and is responsible for the overall content as guarantor. All authors have contributed to the work, read and finally approved the manuscript for submission.

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