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Impact of non-pharmacological interventions targeting sleep disturbances or disorders in patients with inflammatory arthritis: A systematic review and meta-analysis of randomized trials

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ABSTRACT

Objectives Patients with inflammatory arthritis (IA) have a high risk of sleep disturbances and disorders. The objective was to evaluate the evidence of non-pharmacological interventions targeting sleep disturbances or disorders in patients with IA.

Methods A systematic search was undertaken from inception to September 8th, 2020. We included randomized trials concerning non-pharmacological interventions applied in adults with IA and concomitant sleep disturbances or disorders. Primary outcome was the sleep domain while secondary outcomes were core outcome domains for IA trials and harms. The Cochrane Risk of Bias tool was applied, and the overall quality of the evidence was assessed using GRADE. Effect sizes for continuous outcomes were based on the standardized mean difference, combined using random-effects meta-analysis.

Results Six trials (308 patients) were included in the quantitative synthesis; three of these reported improvement in sleep in favor of the non-pharmacological intervention(s). The meta-analysis of the sleep domains indicated a large clinical effect of -0.80 (95% CI, -1.33 to -0.28) in favor of non-pharmacological interventions targeting sleep disturbances or disorders. The estimate was rated down twice for risk of bias, and unexplained inconsistency; this was assessed as corresponding to low quality evidence. None of the secondary core outcomes used in contemporary IA trials indicated clinical benefit in favor of non-pharmacological interventions targeting sleep.

Conclusion Non-pharmacological interventions targeting sleep disturbances/disorders in patients with IA indicated a promising effect on sleep outcomes, but not yet with convincing evidence.
SIGNIFICANCE AND INNOVATIONS

- Up to 90% of patients with inflammatory arthritis (IA) have sleep disturbances or disorders, but few studies have examined the effect of non-pharmacological treatment on sleep domains in this population.
- Non-pharmacological treatment of sleep disturbances or disorders is potentially highly effective in improving sleep in IA. However, existing evidence is sparse and of low quality, while a positive effect on the usual core domains in clinical trials is uncertain.
- More rigorous research on non-pharmacological treatment of sleep disturbances and disorders is urgently needed to confirm the promising clinical utility of these novel treatment options based on high quality evidence.
INTRODUCTION

Inflammatory arthritis (IA) affects between 0.3% and 1.5% of the Western population and includes highly prevalent chronic rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthropathies (AxSpA) (1,2). Despite improved disease-modifying antirheumatic drugs, patients with IA are challenged in their everyday lives, because of the unpredictability, severity and chronicity of the disease (3). Some consequences hereof are reduced functional ability, health-related quality of life (HRQoL) and work ability, together with increased risk of disabling pain, fatigue, depression, anxiety, and sleep disturbances (4–6).

Sleep disturbances or disorders have been reported in 40-90% of patients with IA, and are thereby two to three times more prevalent in these patients compared to healthy controls (4,5,7). Sleep disturbances are not related to specific diagnosis codes, but are described as poor sleep quality or difficulties in initiating or maintaining sleep, and are associated with pain, fatigue, depression, and disease activity in IA (4,7–10). The most frequently reported sleep disorders in IA are insomnia, obstructive sleep apnea (OSA), and restless legs syndrome (RLS) (11–13). Treatment of sleep disturbances and disorders, such as insomnia and circadian rhythm sleep disorder, most often rely on hypnotic drugs. However, hypnotic drugs have several side effects, such as tolerance and dependency, cognitive impairment, falls resulting in fracture, motor vehicle accidents, and are also associated with increased risk of dementia and overall mortality (14–16). Thus, there is growing interest in non-pharmacological options. Currently there are no guidelines for non-pharmacological treatment targeting sleep disturbances or disorders in IA including structure, type and use, effectiveness and long-term effect of treatments.

The objective of this study was to evaluate the evidence of non-pharmacological interventions targeting sleep disturbances or disorders in patients with IA. Primary outcome was the sleep domain while secondary outcomes were core outcome domains for IA trials and harms (17–19).

METHODS

The project was conducted in accordance with the Cochrane Handbook for Systematic Reviews, and reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Eligibility criteria
Eligible studies were randomized controlled trials (RCTs) with people aged > 18 years with RA, PsA, or AxSpA (including ankylosing spondylitis) and sleep disturbances or disorders, comparing a non-pharmacological intervention targeting sleep disturbances or disorders to another non-pharmacological intervention, a pharmacological intervention or standard care.

Information sources, search strategy and trial selection
The search strategy was developed in collaboration with medical research librarians, in accordance with the 'PICO' framework (17). We identified potentially eligible RCTs in MEDLINE via PubMed (for MeSH terms used in the search strategy, see Table 1), Cochrane Central Register of Controlled Trials via CENTRAL, PsycINFO and CINAHL via Ebsco, and ClinicalTrials.gov, and conference proceedings at American College of Rheumatology (ACR) and European League against Rheumatism (EULAR), from inception to September 8th, 2020, available in English or Scandinavian languages (Supplementary file 2). No publication date or publication status restrictions were imposed. Screening of titles, abstracts, and subsequent full text assessment were conducted independently by KML and KBL using the Covidence tool. In the remainder of this article, the letter k represents the number of trials and the letter n represents the number of participants.

Data collection process and measures of treatment effect
The authors KML and KBL were responsible for the extraction and assessment of data, which were extracted from each trial based on the following characteristics: 1) design and setting, 2) participants, 3) type and content of intervention in each group, and 4) types of outcome measures. Results were collected at the follow-up time point closest to 26 weeks, to examine the long-term effect, or alternatively closest to end of treatment.
Whenever possible, we used results from intention-to-treat populations. When necessary, we approximated means and measures of dispersion from graphs reported in the trial manuscript. We summarized continuous outcomes using the standardized mean difference (SMD) with 95% confidence intervals (95% CI), based on the differences in mean changes from baseline values between treatment groups, divided by the pooled standard deviation (SD). When mean changes were unavailable, we used differences in mean values at end of treatment. If some of the required data were unavailable, we used approximations, as described in the Cochrane Handbook. Finally, we expressed our binary harm outcomes as risk ratios (RR), also with 95% CIs.

Risk of bias in individual studies
The authors KML and KBL independently assessed randomization, blinding, and adequacy of analyses using the Cochrane Collaboration's RoB tool, followed by justification for the rating (22). Disagreements were resolved at consensus meetings with RC.

Synthesis of the evidence
Continuous outcomes were analyzed as Cohen’s effect sizes (estimated as SMD). However, since the Cohen’s SMD value is biased in small samples, we applied Hedges’ adjustment in the meta-analysis, treating the variance as an estimate (23). Anticipating heterogeneity in the included trials, random effects meta-analysis was used to combine the trial results in Review Manager (24). To describe variability related to heterogeneity rather than chance, we quantified heterogeneity as inconsistency between trials using the $I^2$ statistic (25).

Quality of the evidence
Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to rate the quality of evidence (26). Evidence from RCTs starts at high quality with subsequent rating down in cases of serious study limitations (risk of bias), the degree of inconsistency, indirectness, imprecision, and the apparent risk of publication bias. The GRADE ratings of very low, low, moderate, or high quality evidence reflect the extent to which the effect estimates are
credible (27). The quality of the evidence across the included trials was independently assessed by KML and KBL, and disagreements were resolved at a consensus meeting with RC.

RESULTS

Our systematic searches yielded a total of 2,843 references, from which 389 duplicates were removed, while a further four references were identified through other sources (Figure 1). A total of 2,458 articles were screened for inclusion based on title and abstract, and 22 of these were eligible for full text screening. After full text review, we included six trials in the primary quantitative synthesis, with no disagreement between reviewers (28–33).

Characteristics of included trials and qualitative synthesis

As presented in Table 2, the trial duration varied from four to 12 weeks and number of included participants varied between 20 and 80, with a total number of 308 patients, all diagnosed with RA. Two trials included patients with the sleep disorder insomnia (31,32). The remaining four trials included patients with sleep disturbances, described as moderate to severe sleep problems (29), Pittsburgh Sleep Quality Index (PSQI) score > 5 (i.e. poor sleep) (28) or sleep disturbance for more than 30 minutes per night (30) (Table 2). The proportion of female participants ranged from 53% to 100% (average proportion 81%), ages ranged from 22-74 years (average mean 55 years), and duration of RA ranged from 1-31 years (average mean 12 years). All six trials reported data from a single follow-up time point, which was immediately upon termination of treatment. Three trials examined exercise (28,32,33), one examined foot reflexology (29), one examined yoga (30) and one examined auricular plaster therapy (31). The comparator in the control groups were; usual care in three trials (29,30,32); advice on benefits of exercise in two trials, and 1 mg of Estazolam in one trial (31). The questionnaire PSQI was used to measure sleep in five trials (28,29,31–33), while Insomnia Severity Index (ISI) was used in one trial (30). Furthermore, sleep was assessed objectively with polysomnography (PSG) in one trial (32).

Risk of bias and limitations of included trials

Four trials were judged to be at an overall high risk of bias (28–31), and two at an unclear risk of bias (32,33) (Table 2). The randomization process was rated with unclear or high risk of bias in
five trials, as they did not report how concealment was handled or how the sequence was
generated (28,29,31–33). Risk of deviation from intended intervention was rated as unclear or
high in all six trials, because of a potential for substantial impact on the results. Few participants
were lost to follow-up but data from intention-to-treat analyses were not reported (22).
Furthermore, in one trial, only 38% of participants reached the predefined threshold for
adherence to intervention (30). Risk of missing outcome data was rated as unclear or high in
50% of the trials, as two trials did not report if and how participants attended study visits (32,33),
and in one trial 12% of the participants were lost to follow-up or dropped out (29). Measurement
of outcome was rated as unclear or high risk of bias in all six trials, because outcomes were
measured by the participant or face-to-face, and thereby assessors were not blinded (22).
Selection of the reported results was a potential risk of bias in five trials, as the analysis plans in
each trial were insufficiently detailed to enable an assessment (28,29,31–33).

Evidence synthesis

Sleep domains

Five of the six trials found improved self-reported sleep measured with PSQI or ISI from baseline
to after treatment in the intervention groups (28–31,33), which was similar to the improved sleep
efficiency measured with PSG (32). When comparing intervention group with control group after
treatment, all trials showed a trend towards favoring the applied non-pharmacological
intervention; however, a statistically significant improvement on sleep was only found following
foot reflexology (29), auricular plaster therapy (31), and exercise (33).

The overall meta-analysis suggests that non-pharmacological interventions have a
potentially large effect size of -0.80 (95% CI, -1.33 to -0.28) on sleep (Figure 2). However, the
quality of the evidence was assessed as corresponding to low, given that the body of evidence
was rated down twice, due to serious study limitations and inconsistency (I² = 77%), as presented
in the GRADE profile (Table 3).

Core outcomes across inflammatory arthritis conditions

Pain was examined in three trials, of which one trial reported decrease in pain in favor of foot
reflexology (29); however, neither exercise nor yoga influenced pain (28,30). Based on the
evidence from these three trials, the overall meta-analysis suggested a potentially moderate effect on pain, corresponding to -0.56 (95% CI, -1.26 to 0.13) (Supplementary file 3).

Fatigue was examined in three trials, of which two reported a decrease in fatigue, both in favor of exercise (28,32); the third trial found that yoga did not influence fatigue (30). Based on the evidence from these three trials, the overall meta-analysis suggested a potentially small effect size, corresponding to -0.39 (95% CI, -1.00 to 0.21).

Mental well-being was examined in two trials, of which one trial reported a decrease in depression, in favor of exercise (32), and one trial found that yoga did not influence mental well-being (30). Based on the evidence from these two trials, the overall meta-analysis suggested that mental well-being had a potentially moderate effect, corresponding to -0.60 (95% CI, -1.20 to 0.01).

Physical function was examined in two trials, and neither exercise nor yoga influenced physical function (28,30). Based on the evidence from the two trials, the overall meta-analysis suggested a potentially small effect on physical function, corresponding to -0.40 (95% CI, -0.79 to -0.00).

HRQoL was examined in one trial, which found that yoga did not influence HRQoL (30). Thus, the evidence from that trial could indicate a potentially very small effect, if any, on HRQoL, with a SMD of 0.14 (95% CI, -0.65 to 0.93).

No trials reported data on soluble biomarkers of inflammation, such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).

**Harms**

Four trials reported on withdrawals, with a total of six participants in the intervention groups and seven participants in the control groups, corresponding to RR = 0.86 (95% CI, 0.30 to 2.45) (28–30,33). Three trials reported on withdrawals in connection with adverse events, with a total of three participants in the intervention groups and two participants in the control group, corresponding to RR = 1.17 (95% CI, 0.21 to 6.36) (28–30). Two trials reported having investigated the occurrence of serious adverse events, with a total of zero participants in the intervention groups and one participant in the control group (30,33) (Supplementary file 3.). The trial that had
identified one serious adverse event reported that the patient was admitted to the hospital in the trial period, without further elaboration on the clinical condition or severity (30).

**DISCUSSION**

This evidence synthesis provides evidence that non-pharmacological interventions targeting sleep reduce sleep disturbances and the sleep disorder insomnia, potentially corresponding to a large effect size. We estimated this to correspond to an average improvement of 34% when compared to the control groups. Although the effect was statistically highly significant, its importance for clinical recommendation may be minor, because of the overall quality of the evidence. The quality of the evidence was evaluated to correspond to low, supporting non-pharmacological interventions targeting sleep disturbances or disorders in patients with RA. Regarding secondary outcomes, none of the core outcome domains for IA indicate clinical benefit in favor of non-pharmacological interventions targeting sleep disturbances or disorders.

Unsurprisingly, the broad literature search, whose aim was to identify all non-pharmacological interventions targeting sleep disturbances or disorders, led to heterogeneity between the interventions in the included trials, with a very high degree of inconsistency ($I^2 = 77\%$) on sleep domains. Three trials had investigated the effect of exercise on sleep (28,32,33), of which only one trial found an improvement in sleep duration and sleep quality in favor of the intervention compared to controls (33). It is worth mentioning that advice on the benefits of exercise was the (active) comparator in two of the three trials (28,33). However, the two trials did not report whether the potential increase of exercise in the control groups had been measured. Consequently, if the participants in the (active) control groups exercised on their own, the observed effect size in these trials was potentially deflated. The varying conclusions on exercise are in agreement with evidence from other populations, such as cancer and fibromyalgia, which also have found inconclusive pooled results (34,35). In a previous meta-analysis, the effectiveness of exercise on sleep was examined in patients with fibromyalgia, showing a statistically significant but small effect size of -0.17 (95% CI, -0.32 to -0.01) in favor of exercise, compared to controls (35). Furthermore, an umbrella review of three previous meta-analyses investigated the effect of exercise on sleep in patients with OSA, cancer, and in older people (36). They found an effect size of -0.50 (95% CI, -0.72 to -0.28) on sleep.
quality in favor of exercise, compared to controls and, as in our present evidence synthesis, they also identified statistical heterogeneity and inconsistency as caveats. Thus, further research is required to determine the efficacy of exercise on sleep disturbances or disorders in people with IA, and in general, to explore the effects of exercise intervention characteristics, such as intensity, frequency and delivery settings.

Regarding the efficacy of foot reflexology, yoga and auricular plaster therapy, the evidence is sparse and of low quality, also in other populations. A previous meta-analysis found an improvement on sleep in the intervention group compared to the control group following treatment of foot reflexology \( (k = 18) \) (37). However, no RCTs were included and > 50% of the included studies were not peer-reviewed or were in the Korean language. Notwithstanding, the positive result has been confirmed in a recent RCT (38). Yoga has been examined comprehensively. A recent systematic review and meta-analysis included a diverse population of women with sleep disturbances \( (k = 19, n = 1832) \), and found an overall improvement in favor of yoga, with an SMD of \(-0.33\) (95% CI, \(-0.51\) to \(-0.15\)) (39). However, the moderator analysis suggested that the effect was not significant in the subgroup of postmenopausal women – a population similar in age and sex to that in the trial in our evidence synthesis that investigated the effect of yoga (30). The effect of auricular plaster therapy on sleep has been sparsely investigated. Additional to the one trial included in our evidence synthesis, we identified one study that examined the effect on sleep outcome (OSA); however, data on mean difference between groups after treatment were not reported (40).

To our knowledge, the effect of psychological and/or behavioral interventions have not been examined among people with IA and concomitant sleep disturbance or insomnia. However, high-quality research has been performed among patients with other conditions, such as cancer and fibromyalgia (41,42). Furthermore, there is emerging evidence for the use of mindfulness when used in combination with behavioral techniques (43). Several studies in various other populations have revealed evidence favoring cognitive behavioral therapy for insomnia (CBT-I) over comparators (44). Thus, it would be of importance for future research initiatives to address psychological or behavioral interventions. Such interventions may include CBT-I, brief behavioral treatment for insomnia, single-component therapies (sleep hygiene, stimulus
control, sleep restriction therapy), or mind-body interventions (relaxation training or, meditation).

Self-reported questionnaires were used to measure sleep in the trials included in our evidence synthesis. PSQI has a cut off at > five for poor sleep and ISI a cut off at > eight for threshold insomnia in rheumatic diseases (45). In this context, it is important to highlight the fact that the mean after treatment score in the intervention groups was 7.85 for PSQI and 8.5 for ISI. Thus, despite the statistically significant improvement in sleep identified in our current synthesis, the decreased level of sleep disturbances or disorders (specifically insomnia) did not reach a clinically relevant level.

Pain and fatigue are highly prevalent in people with IA and are associated with sleep disturbances, while fatigue correlates to pain, depression, physical function and HRQoL (46). In accordance with the 95% CI for pain and fatigue in our evidence synthesis, we did not find that non-pharmacological interventions targeting sleep disturbances or disorders improve pain or fatigue (Supplementary file 3). The evidence in this regard was assessed to be of very low quality, based on the GRADE approach.

Mental well-being, physical function, and HRQoL were only examined in one or two trials, respectively, and the findings were varying and vague. People with IA are at high risk of depression, and of reduced physical function and HRQoL. These outcomes are of primary importance for many people with IA and are core domains in clinical trials (4,17). Furthermore, given that sleep disturbances are associated with these outcomes, they are essential to future research on IA and sleep (7,8).

We also intended to investigate the effect of non-pharmacological interventions targeting sleep disturbances or disorders on biomarkers of inflammation, assessed by soluble biomarkers, as it is one of the IA core domains (18). However, none of the included trials reported data on soluble biomarkers of inflammation (CRP or ESR). One trial did, however, investigate the effect of yoga on disease activity, measured with Clinical Disease Activity Index (CDAI), but found no improvement on sleep (30). It has been suggested that inflammation is a plausible mechanistic link between sleep and the risk of several major diseases, such as cancer, diabetes, cardiovascular disease, and Alzheimer’s disease (47). In addition, in a meta-analysis of more than 50,000 adults, sleep disturbances were associated with higher levels of CRP (48). To our
knowledge, only a few studies have indicated that there is an association between sleep and inflammatory markers in arthritis (49). Thus, we lack knowledge on the effect of non-pharmacological interventions targeting sleep disturbances or disorders on inflammation.

The assessment of risk of bias for the trials included in our evidence synthesis highlighted methodological weaknesses, including weaknesses in reporting withdrawals and missing data, description of randomization, allocation concealment, and blinding. The interventions were also sparsely described, without providing knowledge of how and by whom the manual for the interventions was developed. Consequently, it is unknown whether a sleep expert participated in the preparation of the treatment interventions. Although the pooled data identify a statistically significant SMD between groups in favor of non-pharmacological interventions, none of the included trials determined the minimal clinically important difference. For that reason, we cannot conclude whether patients with IA and concomitant sleep disturbances or disorders would recognize as important the change identified in the evidence synthesis.

The sample sizes for the trials included ranged from 20 to 80, as both pilot studies and potentially confirmatory RCTs were included. Two trials reported a power-size and sample-size calculation (28,29). Of the remaining four trials, three were pilot studies or/and only conference abstract (30,32,33). One pilot study (30) elaborated on the deselection of sample size calculations following requirements for feasibility studies (50). However, the overall lack of power-size and sample-size considerations limits the credibility of the findings in our evidence synthesis, as it is questionable whether these trials would have had the statistical power to identify significant results should an effect have been found.

To our knowledge, this is the first systematic review and meta-analysis to investigate the extent of evidence across non-pharmacological interventions targeting sleep disturbances or disorders in patients with IA. The small number of trials and participants, the fact that populations were restricted to RA patients only, the heterogeneity of the interventions, lack of access to unpublished data and potentially unidentified gray literature, and the risk of bias prevent us from drawing firm conclusions and restrict the generalizability of the results. Also, sleep is often considered to be a secondary or even tertiary variable in clinical trials. So, even where the effect on sleep was investigated, because of the hierarchy of outcomes reporting, the findings related to sleep were potentially not available in publications.
Our evidence synthesis highlights that non-pharmacological interventions targeting sleep disturbances or disorders in patients with IA is a growing scientific area of interest in rheumatology. Such focus is also relevant and of utmost importance, because sleep disturbances and disorders have been under-recognized and poorly managed in patients with IA – as was the case for fatigue several years ago. Current knowledge encourages development of rigorous RCTs that include larger sample sizes, clearer identification of sleep disorders examined, blinding of assessors, well-described interventions and long-term follow-up. This will improve the quality of the evidence and allow a comparison of homogenous interventions, thereby informing and empowering the creation of consensus around optimal management of sleep disturbances, disorders and high-quality clinical guidelines. Non-pharmacological interventions may have the potential to persistently decrease symptom burden and increase quality of life in patients with IA and concomitant sleep disturbances or disorders, and for this reason it is also relevant to investigate the long-term perspectives of effectiveness.

In conclusion, more rigorous research on non-pharmacological treatment of sleep disturbances or disorders is needed; research that also aim at specific sleep disorders, in order to fully reveal the clinical utility of these novel treatment options. At this point, non-pharmacological treatment of sleep disturbances or disorders is promising and potentially highly effective.
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TABLES
Table 1. MESH terms used in the search strategy (MEDLINE)
Table 2. Characteristics of included trials
Table 3. GRADE evidence profile of non-pharmacological treatments

FIGURE LEGENDS
Figure 1. Flow Diagram showing the selection of the trials
   The letter $k$ represents the number of trials, the letter $n$ represents the number of participants.
Figure 2. Forest plot for self-reported sleep

SUPPLEMENTARY MATERIAL
Supplementary file 1. Impact of non-pharmacological interventions targeting sleep disorders in patients with inflammatory arthritis. Protocol for a systematic review and meta-analysis of RCTs
Supplementary file 2. Literature search in MEDLINE
Supplementary file 3. Forest plots (Random and fixed)
Table 1. MESH terms used in the search strategy (MEDLINE)

Table 2. Characteristics of included trials

<table>
<thead>
<tr>
<th>Trial/ year</th>
<th>Country</th>
<th>Design</th>
<th>Indication</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration of follow up</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durcan 2014 [28]</td>
<td>Ireland</td>
<td>RCT</td>
<td>RA n=80 (female 62.5%)</td>
<td>Exercise. 12-week home program of cardio, flexibility and resistance (n=40)</td>
<td>Advice on benefits of exercise (n=38)</td>
<td>Week 12</td>
<td>Sleep (PSQI), Pain (VAS), Fatigue (FSS), Physical function (HAQ)</td>
<td>Improvement on fatigue after treatment in favor of intervention, mean diff. between groups -8.20 (-16.10 to 0.30). No difference between groups after treatment on sleep, pain or physical function.</td>
<td>U/U/L/U/H/H</td>
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<tr>
<td>Bakir 2018 [29]</td>
<td>Turkey</td>
<td>RCT</td>
<td>RA n=68 (female 76.6%)</td>
<td>Foot reflexology. 30 mins. x 1 per week for six weeks (n=30)</td>
<td>Continued routine monitoring for RA (n=30)</td>
<td>Week 6</td>
<td>Sleep (PSQI), Pain (VAS)</td>
<td>Improvement on sleep and pain after treatment in favor of intervention, mean diff. between groups for sleep -5.30 (-7.00 to -3.60), for pain -12.00 (-16.84 to -7.16).</td>
<td>U/U/H/U/H</td>
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<tr>
<td>Ward 2018 [30]</td>
<td>New Zealand (P/A)</td>
<td>RCT</td>
<td>RA n=25 (female 96%)</td>
<td>Yoga. 75 min. x 1 per week for eight weeks in groups and 20 mins. x 3 per week at home (n=13)</td>
<td>Usual care for the management of RA (waitlist two-day yoga) (n=12)</td>
<td>Week 9</td>
<td>Sleep (ISI), Pain (VAS), Fatigue (BRAF-NSR), Mental well-being (HADS), Physical function (HAQ), Health-related Quality of Life (EQ-5D-L3)</td>
<td>No difference between groups after treatment on sleep, pain, fatigue, mental well-being, physical function or HRQoL.</td>
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<td>Lu 2019 [31]</td>
<td>China</td>
<td>RCT</td>
<td>RA n=76 (female n/a)</td>
<td>Auricular plaster therapy with beans. Compression of 1-2 mins. x 4-5 per day and before bedtime (n=38)</td>
<td>Estazolam 1 mg. each night before bedtime (n=38)</td>
<td>Week 4</td>
<td>Sleep (PSQI)</td>
<td>Improvement on sleep after treatment in favor of intervention, mean diff. between groups -3.30 (-5.38 to -1.88).</td>
<td>H/U/L/U/H</td>
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<table>
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<tr>
<th>Author</th>
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<th>Control/Usual Care</th>
<th>Improvement Measure</th>
<th>Effect Size</th>
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<tbody>
<tr>
<td>Løppenthin 2019</td>
<td>Denmark</td>
<td>RCT (P/A)</td>
<td>n=38 (female n/a)</td>
<td>Intermittent aerobic exercise (location unknown) x 3 per week for six weeks (n=17)</td>
<td>Usual care (n=21)</td>
<td>Week 6</td>
<td>Sleep (PSG) Sleep (PSQI) Fatigue (BRAF-MDO) Mental well-being (CESD)</td>
<td>Improvement on fatigue and mental well-being after treatment in favor of intervention, mean diff. between groups for fatigue -5.10 (-8.60 to -1.60), for mental well-being -6.80 (-11.71 to -1.89). No difference between groups after treatment on sleep.</td>
</tr>
<tr>
<td>McKenna 2020</td>
<td>Ireland</td>
<td>RCT P/A</td>
<td>n=20 (female 100%)</td>
<td>Exercise. 28 walking sessions for 8 weeks, supervised by a PT x 1 per week (n=10)</td>
<td>Advice on the benefits of exercise for people with RA (n=8)</td>
<td>Week 8</td>
<td>Sleep (PSQI)</td>
<td>Improvement on sleep after treatment in favor of intervention, mean diff. between groups -6.30 (-8.48 to -4.12).</td>
</tr>
</tbody>
</table>

RCT, Randomized Controlled Trial; RA, Rheumatoid arthritis; PSQI, Pittsburgh Sleep Quality Index; VAS, Visual Analog Scale; FSS, Fatigue severity scale; HAQ, Health Assessment Questionnaire; ISI, Insomnia Severity Index; P/A, Pilot study or Conference abstract; BRAF-NSR, Bristol Rheumatoid Arthritis Numerical Rating Scales; HADS, Hospital Anxiety and Depression Scale; EQ-5D-L3, European Quality of Life Five Dimension Three Level Scale; AIS, Athens Insomnia Scale; BRAF-MDO, Bristol Rheumatoid Arthritis Multi-Dimensional Questionnaire; CESD, Center for Epidemiologic Studies Depression Scale; PSG, Polysomnography, PT, Physiotherapist.

*Reported as low (L), unclear (U) or high (H) risk of bias
*Reference number
Table 3. GRADE profile of non-pharmacological treatment vs. comparators for patients with inflammatory arthritis included in eligible RCTs

<table>
<thead>
<tr>
<th>Outcome domain</th>
<th>No. of RCTs (k=6)</th>
<th>No. of Patients (N=308)</th>
<th>Duration range</th>
<th>Limita- tions</th>
<th>Inconsis- tency</th>
<th>Indirect- ness</th>
<th>Imprec- sion</th>
<th>Publication bias</th>
<th>QoE</th>
<th>SMD (95% CI)</th>
<th>Assumed Compara- tor: Mean (SD)</th>
<th>Average Added Value</th>
<th>Added Value %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>6</td>
<td>295</td>
<td>4-12 wks</td>
<td>Serious</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>10.8</td>
<td>(4.6)</td>
<td>-3.68 (-1.33 to -0.28)</td>
<td>10.8 (4.6)</td>
<td>34%</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
<td>160</td>
<td>6-12</td>
<td>Serious</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>V. Low</td>
<td>47.9</td>
<td>(21.0)</td>
<td>-11.76 (-16.26 to 0.31)</td>
<td>47.9 (21.0)</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>141</td>
<td>6-12</td>
<td>Serious</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>V. Low</td>
<td>15.5</td>
<td>(13.4)</td>
<td>-5.23 (-2.00 to 0.21)</td>
<td>15.5 (13.4)</td>
<td>34%</td>
</tr>
<tr>
<td>Mental Well-Being</td>
<td>2</td>
<td>63</td>
<td>6-12</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>5.8</td>
<td>(4.0)</td>
<td>-2.40 (-2.20 to 0.00)</td>
<td>5.8 (4.0)</td>
<td>47%</td>
</tr>
<tr>
<td>Physical Func- tion</td>
<td>2</td>
<td>103</td>
<td>9-12</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>0.8</td>
<td>(0.16)</td>
<td>-0.06 (-0.79 to -0.00)</td>
<td>0.8 (0.16)</td>
<td>8%</td>
</tr>
<tr>
<td>HR-QoL</td>
<td>1</td>
<td>25</td>
<td>12</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Low</td>
<td>0.14</td>
<td>(0.24)</td>
<td>0.03 (0.65 to 0.93)</td>
<td>0.14 (0.24)</td>
<td>4%</td>
</tr>
<tr>
<td>Soluble biomarkers of inflammation</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, Randomized Controlled Trials; QoE, Quality of Evidence; SMD, Standard Mean Difference; CI, Confidence Interval; SD, Standard Deviation; NA, Not applicable; HR-QoL, Health-Related Quality of Life.

- Assessed using Cochrane Risk of Bias tool
- *I* value > 75% indicates serious heterogeneity
- Occurs if the intervention, patients, or outcomes are different from the aim and research question
- Uncertainty about the results caused by risks of random error (few patients) and thus have a wide confidence interval (CI) around the estimate of the effect
- Systematic under- or over-estimation of the underlying beneficial or harmful effect
- Measured with Pittsburgh Sleep Quality Index (0-21, lower is better) and Insomnia Severity Index (0-28, lower is better)
- Measured with Visual Analog Scale (0-100, lower is better)
- Measured with Fatigue Severity Scale (9-63, lower is better), Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire physical component (0-22, lower is better) and Bristol Rheumatoid Arthritis Fatigue Numerical Rating (0-10, lower is better)
- Measured with Hospital Anxiety and Depression Scale (0-21, lower is better) and Center for Epidemiologic Studies Depression Scale (0-60, lower is better)
- Measured with Health Assessment Questionnaire (0-3, lower is better)
- Measured with European Quality of Life Five Dimension Three Level Scale (0-1, higher is better)
- No trials included soluble biomarkers of inflammation at follow-up

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Figure 1.

Records identified through database searching (k = 2,843)
- MEDLINE (k = 944)
- CENTRAL (k = 1,067)
- CINAHL (k = 715)
- PsycInfo (k = 112)

Duplicates removed (k = 389)

Records screened by title/abstract (k = 2,458)

Records excluded (k = 2,436)
- Wrong population (k = 2,141)
- Wrong study design (k = 274)
- Wrong intervention (k = 22)

Records screened by full-text (k = 22)

Records excluded (k = 16)
- Wrong population (k = 13)
- Wrong study design (k = 3)

Trials included in the qualitative synthesis (k = 6)

Trials included in the quantitative synthesis (k = 6)

Outcomes available:
- Sleep (k = 6)
- Pain (k = 3)
- Fatigue (k = 3)
- Mental well-being (k = 2)
- Physical function (k = 2)
- Health-related quality of life (k = 1)
- Inflammation (k = 0)
- Withdrawals (k = 4)
- Withdrawals due to adverse events (k = 3)
- Serious adverse events (k = 3)
Figure 2.

- Durcan (2014): -0.22 (-0.88 to 0.23)
- Bakir (2018): -1.56 (-2.14 to 0.37)
- Ward (2018): -0.42 (-0.23 to 0.36)
- Lu (2019): -0.71 (-0.17 to 0.14)
- Lappenthin (2019): -0.26 (-0.90 to 0.39)
- McKenna (2020): -2.33 (-3.59 to -1.06)

Random-Effects Model
Total (95% CI)

SMD

Test for overall effect: Z=2.97 (P=0.003)

Heterogeneity:
I² = 77%

Favors non-pharmacological treatment
Favors comparator