Biopsychosocial rehabilitation for inflammatory arthritis and osteoarthritis: A systematic review and meta-analysis of randomized trials

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Funding: This work was indirectly supported by a core grant from the Oak Foundation. No financial support or other benefits were obtained from commercial sources.

Word count: 3.794 excluding title page, abstract, funding statement, data sharing statement, references, figures and tables.

ABSTRACT

OBJECTIVE:

To assess the benefits and harms associated with biopsychosocial rehabilitation in patients with inflammatory arthritis (IA) and osteoarthritis (OA).

METHODS:

We performed a systematic review and meta-analysis. Data were collected through electronic searches of Cochrane CENTRAL, Medline, Embase, PsycINFO, and CINAHL databases up to March 2019. Trials examining the effect of biopsychosocial rehabilitation in adults with IA and/or OA were considered eligible, excluding rehabilitation adjunct to surgery. The primary outcome for benefit was pain, and total withdrawals for harm.

RESULTS:

Of the 27 trials meeting the eligibility criteria, 22 trials (3,750 participants) reported sufficient data to be included in the quantitative synthesis. For patient reported outcome measures, biopsychosocial rehabilitation was slightly superior to control for pain relief (SMD -0.19 [95%CI, -0.31 to -0.07]), had a small effect on patient global (SMD -0.13 [95%CI, -0.26 to -0.00]), with no apparent effect on health-related quality of life, fatigue, self-reported disability/physical function, mental well-being, and reduction in pain intensity ≥30%. Clinician measured outcomes displayed a small effect on observed disability/physical function (SMD -0.34 [95%CI, -0.57 to -0.10]), a large effect on physician global score (SMD -0.72 [95%CI, -1.18 to -0.26]), and no effect on inflammation. No difference in harms for number of withdrawals, adverse events, or serious adverse events.

CONCLUSIONS:

Biopsychosocial rehabilitation produces a significant but clinically small beneficial effect on patient-reported pain among patients with IA and OA, with no difference in harm. Methodological weaknesses were observed in the included trials, suggesting low to moderate confidence in the estimates of effect.

PROSPERO Registration number: CRD42019127670

Keywords: Inflammatory arthritis, osteoarthritis, rehabilitation, systematic review, meta-analysis

Significance and Innovations:

- The biopsychosocial model is gaining increasingly widespread acceptance in clinical practice. The current study further supports this development, by indicating that biopsychosocial rehabilitation appears to have an overall beneficial effect, apparently with no harms when compared to control.
- While a core principle of biopsychosocial rehabilitation is being patient-centered and based on the needs and preferences of the individual patient, we found that the majority of published studies apply structured treatment programs, potentially masking the true effect of personalized rehabilitation.
- Our findings suggest a positive dose-dependent response between contact time with clinicians during rehabilitation and the achieved effect.

Inflammatory arthritis (IA) and osteoarthritis (OA) are highly prevalent rheumatic and musculoskeletal diseases having a detrimental effect on physical function and quality of life due to pain and other accompanying symptoms such as fatigue and stiffness (1-4). The term IA describes a group of rheumatic conditions characterized by inflammation, such as rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). Despite IA and OA having different pathologies, their non-pharmacological management bears a close resemblance, due to similarities in symptoms (e.g., pain) and symptom-interference with everyday life. Both local (joint-specific) and generalized (widespread) pain can be observed in patients with IA or OA, caused directly by inflammation or damage of various joints, and centrally modulated by neurobiological, psychological, and social factors. Because of the permanence of the patient's disease and disease related disability, the consequences of IA and OA are often associated with a large global socioeconomic burden (5-8) due to direct medical costs, decreased societal participation, and impaired ability to work and function normally. Early diagnosis, non-pharmacological and pharmacological treatment, and specialized management strategies are key factors in reducing the negative effects for the individual and society (1-3, 9). Biopsychosocial rehabilitation is thus considered essential for these patient groups, in order to reduce pain and achieve optimal social participation (9).

Until recent years, the biomedical model has been the predominant paradigm in the treatment of IA and OA, focusing on the physical processes of the diseases. We are now seeing a shift in paradigms towards the use of the biopsychosocial model, rooted in a patient-centered approach serving to integrate somatic, psychological and psychosocial aspects in patient care (10). International guidelines and recommendations on managing IA and OA recommend using biopsychosocial interventions, or parts thereof, for rehabilitation (9, 11-15). These rehabilitation programs involve, along with ongoing pharmacological treatment, a physical component and a psychological or work/social-related component, delivered by a team of healthcare professionals in a coordinated effort based on the biopsychosocial model (16). With an emphasis on patient choice and autonomy, biopsychosocial rehabilitation embraces a patient-centered standpoint, allowing the intervention to reflect the needs and preferences of the individual (17). However, despite the increasingly widespread acceptance of a biopsychosocial intervention for IA and OA (9), there is no clear summary of evidence to confirm its effectiveness.

In order to quantitatively estimate the magnitude of effect associated with biopsychosocial rehabilitation, we conducted a systematic review and meta-analysis of randomized trials. Our objective was to assess the benefits and harms associated with biopsychosocial rehabilitation in patients with IA and OA based on its effects on pain, disability, health-related quality of life, and adverse events.

PATIENTS AND METHODS

This systematic review was carried out in accordance with the recommendations from the Cochrane Collaboration guidelines (18) and was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)(19). Our protocol (**Supplement A**) was registered on PROSPERO (identifier: CRD42019127670).

Eligibility criteria

We included randomized and quasi-randomized controlled trials comparing biopsychosocial rehabilitation with any control comparator, including active comparator treatment arms, placebo, or management as usual. Studies were included regardless of publication date or status. We included trials published in English, German, or Scandinavian languages (based on the authors country of origin) that enrolled adults with IA (i.e., RA, AxSpA or PsA) and OA of any location in the body (e.g., knee, hip or hand). Trials were included regardless of concomitant conditions (e.g., chronic widespread pain syndrome, fibromyalgia, systemic lupus erythematosus) and timing of interventions and follow-ups. Trials where biopsychosocial rehabilitation was provided as an adjunct to surgery (e.g., total knee arthroplasty) were not considered eligible. Surgery is primarily indicated for patients with severely progressed joint damage, whereas biopsychosocial rehabilitation is indicated in earlier stages of IA and OA. Biopsychosocial rehabilitation applied at the same time as surgery focus on enhancing the effect of surgery, instead of investigating rehabilitation as the primary intervention.

Biopsychosocial rehabilitation was defined as an intervention including a physical component and one or both of a psychological or social/work-targeted component. The different components had to be delivered by a team of clinicians of varying health professional backgrounds; however, no specific professional background

was required. Interventions could be of any approach (interdisciplinary or multidisciplinary), supervision (group-based or individual), setting, and contact time (i.e., amount of time clinicians were in contact with participants during the intervention).

In order to assess and evaluate the likelihood of outcome-reporting bias, eligible trials were included independent of the outcome measures reported (i.e., included in qualitative synthesis)(19). However, only studies presenting quantitative data were eligible for the quantitative evidence synthesis (20, 21).

Information sources and search strategy

A search for relevant trials was conducted in MEDLINE, EMBASE, CENTRAL, PsycINFO, and CINAHL from inception through 15 March 2019. Completed, withdrawn, or terminated clinical trials were identified through ClinicalTrials.gov. Citation searches of all relevant articles were performed through Web of Science. In addition, American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conference abstracts were searched from 2014 through 15 March 2019. Handsearching of relevant references and included studies were performed. Forward citation tracking of included studies, relevant reviews and trials were performed using Web of Science. See Supplement A for a detailed search strategy.

Study selection

The initial screenings of title/abstract and subsequent full-text assessment were performed in a standardized manner by two independent reviewers (MBP and PT) using Covidence online tool. Any disagreements in study selection were resolved by discussion or through consultation with a third reviewer (KA/RC).

Data collection process and data items

Data were extracted for study and patient characteristics and predefined major outcomes of interest, based on recommendations from Cochrane Musculoskeletal Group (22), guidance from the Outcome Measures in Rheumatology (OMERACT) initiative, and the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT)(23). The patient-reported outcome measures (PROMs) for benefit were pain (primary outcome), patient global, self-reported disability/physical function, health-related quality of life, mental well-being, fatigue, and pain responders

dichotomized into reduction in pain intensity ≥30%. Clinician measured outcomes for benefit were observed disability/physical function, inflammation, and physician global. The outcomes for harm were number of withdrawals, adverse events, serious adverse events (SAE), and change in radiographic damage.

Dichotomous outcome measures were extracted as the number of participants experiencing the event of interest. Continuous outcome data were extracted as mean change from baseline, with their corresponding measure of dispersion. Data were collected for the follow-up measurement closest to 12 months after commencing treatment.

Risk of bias assessment in individual studies

The potential risk of bias was assessed by two independent reviewers (MBP and PT) using Cochrane's Risk of Bias (RoB) tool (24). Discrepancies were resolved through discussion or by consultation with a third reviewer (RC).

Summary measures and synthesis of results

Continuous outcomes were summarized using standardized mean differences (*SMD*) with 95% confidence intervals (95%CI); to adjust for small-sample bias, a bias-correction was performed by applying Hedges' g value (25, 26). Dichotomous outcomes were analyzed as a relative risk (*RR*) with 95% CI; Sweetings adjustment was applied in order to calculate the *RR* in trials reporting no events in either test group (27). This correction was inversely proportional to the relative size of the opposite of the study. For example, the continuity correction for the treatment arm was 1/(R+1), where R is the ratio of control group to treatment group sizes. Similarly, the continuity correction for the control arm was R/(R+1).

We performed meta-analyses using restricted maximum likelihood (REML) mixed effects models (28, 29). We quantified and interpreted the heterogeneity in the meta-analyses by T^2 (an estimate for τ^2) for the variation across trials and the I^2 inconsistency index (30, 31). A fixed-effect meta-analysis model was applied for the purpose of sensitivity analysis. Furthermore, funnel plot and Egger's test were applied to investigate publication bias.

Prespecified sensitivity and stratified analyses of the primary effectiveness outcome (effect size for pain) were carried out to explore the robustness of our findings,

and the potential impact of systematic errors from RoB (32). All analyses were conducted using STATA, version 15.1.

To guide clinical practice and future investigations on the efficacy of biopsychosocial rehabilitation compared to other approaches, estimates of effect were re-expressed as Weighted Mean Differences (WMDs), calculated from the SMDs using standard deviations of baseline scores from studies investigating the minimal clinical important differences (MCID) in the target population (33).

Certainty of evidence

The certainty of the body of evidence was assessed using the criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (34), by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias for all outcome measures (35).

RESULTS

Study selection

The final search identified 8,572 citations, whereof 27 trials met the eligibility criteria (**Figure 1**). The agreement between the two trial assessors corresponded to an inter-rater reliability of κ = 0.48 (95%CI, 0.41 to 0.55) for the title/abstract screening, and κ = 0.93 (95%CI, 0.86 to 1.00) for the full-text assessment. Two of these trials were published as abstracts only (36, 37), and three trials were ongoing (38-40). The corresponding authors of two trials (36, 41) were contacted as they presented insufficient data concerning effect, but we received no response. The remaining 22 trials included 30 randomized comparisons with 3,750 participants, having sample sizes ranging from 34 to 802.

Study characteristics

Table 1 shows the key characteristics of the included studies. Of the 27 eligible trials, 17 included patients with IA and 10 with OA. The average of the mean age was 54 years, with means ranging from 30 to 65 years. 74% of enrolled patients were female, with proportions ranging from 17 to 100%. The average of the reported mean pain scores at baseline (normalized to VAS-units) was 44 mm VAS (ranging from 30 to 66 mm). The mean duration of disease ranged from 1.4 to 17.5 years, with an average duration of

10.9 years. Only 5 studies (42-46) described their applied intervention as being able to adapt to the participants needs and preferences, with the remaining studies either having an unclear description (37, 47, 48), or applying a uniform or standardized intervention.

Risk of bias within studies

Supplement B summarizes the risk-of-bias assessments. All the included trials were randomized controlled trials, but only 10 (42%) had an adequate description of the performed sequence generation and allocation concealment. Due to the nature of biopsychosocial rehabilitation, trials were unable to completely blind clinicians and participants. This inability resulted in all trials receiving a high risk of performance and detection bias for PROMs.

The objectively assessed measures allowed for blinding of the trial assessors which led to 11 trials (46%) having a low risk of detection bias for objective measures. Seven trials (29%) were assessed as low risk of attrition bias and 7 (29%) were assessed as low risk of reporting bias. For other biases, no studies sufficiently described or assessed the risk of concomitant conditions or treatments, leading to all trials' receiving an unclear risk of other biases. The overall risk of bias was considered high for all assessed trials, in part due to the trials' having high risk of performance and detection bias.

Synthesis of results

Figure 2, 3 and **Supplement C** present the results of individual studies and meta-analyses for all reported outcomes. An overview of the meta-analyses and the certainty of evidence for the outcomes is shown in the GRADE evidence profile (**Table 2**). With **Supplement D** presenting funnel plots for all outcome measures.

The majority of estimates indicated no significant difference between biopsychosocial rehabilitation and control interventions for neither benefit nor harm. For PROMs, pain and patient global reached a statistically significant difference in effect. For clinician measured outcomes, observed disability/physical function and physician global were statistically significant. Radiographic damage was not reported in any of the included studies. The magnitude of improvement in both pain, patient global and

observed disability/physical function were nominally small, favoring biopsychosocial rehabilitation.

To re-express the statistically significant outcome domains in another interpretable way, standard deviations of baseline measures were derived from the study by Tubach et al. (33) for the estimates of pain (SD = 19.4), patient global (SD = 18.5), observed disability/physical function (SD = 20.3) and physician global (SD = 17). When re-expressed on a Visual Analog Scale (VAS), the estimates for pain (WMD -3.69 mm), patient global (WMD -2.41 mm), observed disability/physical function (WMD -6.90 mm), and physician global (WMD -12.24 mm) did not reach the minimal clinical important difference (MCID) of 16, 15, 12, and 14 mm, respectively (33).

The certainty of evidence varied from very low to moderate, the main reason for rating down being risk of bias and imprecision. All estimates were rated down due to overall high risk of bias (e.g., lack of blinding). Three estimates (inflammation, physician global, and reduction in pain intensity ≥30%) was rated down twice for very serious imprecision, as their 95% CI was excessively wide. For the pain outcome, our confidence in the estimate was subsequently increased from low to moderate due to a clear dose-response relationship; suggesting an increase in effectiveness of the intervention based on an increase of patient contact with healthcare professionals, as shown in the regression analysis for contact time during intervention with a 59.2% decrease in T^2 (P = 0.01; **Table 3**).

Risk of bias across studies

Stratified analyses of patient-reported pain on selection-, attrition- and reporting-bias showed a small reduction in heterogeneity (proportion of variance explained: 22.3%, -14.6%, and 22.1%, respectively) with no significant interaction among the groups (P = 0.06, 0.20, and 0.06, respectively) (**Table 3**). No further analyses were performed for the bias domains, where all trials were assessed as having the same risk of performance, detection, overall, and other bias.

Additional analyses

Stratified analyses were conducted only for the pain outcome using meta regression (**Table 3**). The analysis for contact time during intervention showed a significant interaction (P = 0.01), with a 59.2% decrease in T^2, suggesting an increase in effect

when increasing the contact time patients have with a health professional. The analysis for supervision of intervention showed a significant interaction (P = 0.04), with a 26.6% decrease in T^2, suggesting that group-based therapy may experience a better effect than individual rehabilitation or other types of rehabilitation. The analysis for type of condition showed no difference in effect between IA (SMD -0.22 [95% CI, -0.47 to 0.03]) and OA (SMD -0.17 [95% CI, -0.34 to 0.00] strata; test for subgroup difference, P = 0.91). Three of the prespecified stratifications could not be carried out due to insufficient data on the characteristics: approach in care, proportion of patients with CWP at baseline, and coping/self-management skills at baseline.

Sensitivity analyses using a fixed-effect model indicated no sign of publication bias for any of the outcomes. However, the visual inspection of funnel plots and significant result from the Egger's test indicated a high risk of publication bias for pain and self-reported disability/physical function (**Supplement D and Table 2**).

A *post-hoc* analysis was performed to further analyze the impact of employing the psychological and social aspects using disciplines specialized in their respective field (e.g., specialized psychological interventions employed by a psychologist). When compared to the primary analysis on pain, a meta-regression analysis for both the psychological aspect (SMD -0.31 [95% CI, -0.54 to -0.07]) and the social aspect (SMD -0.26 [95% CI, -0.42 to -0.10]) showed an increase in effect when the intervention was employed using specialized disciplines (i.e., psychologists or social workers).

DISCUSSION

For measures of benefit, moderate- to very-low-certainty evidence suggested that at 6-24 months follow-up biopsychosocial rehabilitation compared with any type of control was associated with significant but clinically small improvement in self-reported pain (WMD -3.69 mm [95% CI, -6.01 to -1.36], MCID = 16 mm) and patient global (WMD -2.41 mm [95% CI -4.81 to -0.07], MCID = 15 mm). No differences were observed among the remaining PROMs; health-related quality of life, fatigue, self-reported disability/physical function, mental well-being, and reduction in pain intensity ≥30%. Among clinician measured outcomes, a small but statistically significant effect was associated with observed disability/physical function (WMD -6.90 mm [95% CI, -11.57 to -2.03], MCID = 12 mm), large improvements in physician global (WMD -12.24 mm [95% CI, -20.06 to -4.42], MCID = 14 mm), and no difference in inflammation. For

measures of harm, no difference was observed for number of withdrawals or risk in adverse events or serious adverse events.

The meta-regression-analysis for contact time indicated that an increase in hours of patient contact with healthcare professionals led to an increased effect of the intervention, or, on the other hand, that studies including patients requiring more intense rehabilitation saw a larger effect. The subgroup analysis for supervision indicated that group-based rehabilitation experienced a larger effect than individual rehabilitation or other types of rehabilitation.

Riemsma et al. (49) and Taal et al. (41) did not report sufficient data to be included in the pain analysis. Had their estimates been included, our estimated effect on pain would have been slightly reduced, and further heterogeneity might have been introduced.

Cost-effectiveness was not analyzed in this review. To our knowledge, no review has performed an economic evaluation of biopsychosocial rehabilitation for IA and/or OA. However, with trials reaching 50+ hours of patient contact, the resource expenditure must be considered substantial. The costs of implementing biopsychosocial rehabilitation must be weighed against those of usual care or less intensive programs.

Clinical implications – Though some outcome measures proved statistically significant, the effect of biopsychosocial rehabilitation did not reach the MCID for any outcome measures, questioning its clinical significance. However, the rehabilitative effort shows a dose dependent response to contact time with clinicians as well as an increased effect when delivered by specialized disciplines. Thus, the structure, content and delivery may have a significant influence on the achieved effect. We found that many of the included trials used a structured treatment program, with no room for personalized adaptation based on patient needs and preferences, thus actually straying from the core principle of rehabilitation being patient-centered and based on the needs of the individual. Further, multi-disciplinary clinics should consider allocating resources to ensure that their rehabilitative effort has a sufficient extent and is delivered by specialists in their respective fields.

Comparison with other studies – Previous systematic reviews by Bearne et al. (50) and Finney et al. (51) included a limited number of studies in their analysis. However, both studies concur with our findings, reporting a small or clinically

insignificant effect on patient-reported pain, little or no apparent effect on function or disability, and varying effect on quality of life. Neither of the reviews investigated harm.

Limitations – As seen in most other systematic reviews, a common – yet important – limitation is the lack of studies with a low risk of bias, together with uncertainty over the presence and impact of publication bias. Furthermore, there is currently no consensus on the setting, content, and format of biopsychosocial rehabilitation. For this study, we used the definition put forward by Kamper et al. (52). The majority of IA trials included only RA patients; therefore, the effect of the intervention may differ in other IA conditions. The majority of studies reported their measures at our preferred 12 months follow-up, however, a large proportion of the studies either reported at an earlier (41%) or later (14%) time point. However, the median follow-up time for the pain outcome across trials was 12 months. This may have caused an overestimation of effect, as the effect of the interventions presumably diminish over time. No studies reported sufficiently on concomitant conditions, hence we were unable to investigate to which degree the presence of conditions such as chronic widespread pain syndromes and/or fibromyalgia could meta-confound the reported effect estimates (53). Finally, as biopsychosocial rehabilitation is already recommended in most guidelines, usual care in some of the included trials may be using rehabilitation approaches to some degree, effectively causing trials to compare an extensive biopsychosocial rehabilitation with a less intensive biopsychosocial rehabilitation, leading to an underestimation of the interventions' effect.

Only one study had a mean age at or above 65, suggesting that the older population were either directly or indirectly excluded. An age restriction for inclusion was reported in 12 of the included studies, 11 of which had an upper limit of 60-75 years. Age ranges of participants were reported in 6 studies, whereof only Scholten et al. (54) and Tijhuis et al. (46) recruited participants older than 75 years (79 and 85, respectively). Older participants may have been indirectly excluded by not meeting trials eligibility criteria due to comorbidities, and a history of joint replacement. A growing body of research suggests biopsychosocial factors, and thus interventions, are influenced by age. Therefore, our findings should be interpreted carefully when applied to an older population.

Recommendations for future studies – Future trials should include an economic analysis of their interventions in order to allow cost-benefit analyses. Concomitant

conditions and treatments of participants should be reported and discussed in regards to the main intervention applied. Due to the complexity of the intervention, studies need to describe their interventions in greater detail and report outcomes that are targeted (e.g., acceptance and coping strategies as an outcome), in order to assess patients from a perspective other than symptom reduction, which may be targeted in usual care. Future systematic reviews investigating the effect of biopsychosocial rehabilitation should further specify the intervention to include only trials true to the nature of rehabilitation. Predefined, standardized interventions should be excluded, as the intervention has to be responsive to the preferences and needs of the individual patient in order to assure a treatment where clinical decisions are guided by patient values. Future trials should carefully consider both the content and method of delivery when designing a biopsychosocial intervention, as indicated by the post-hoc analysis of the impact of employing the psychological and social aspects of the intervention using specialized disciplines.

CONCLUSIONS

From the present evidence synthesis, we found a significant but clinically small average beneficial effect following use of biopsychosocial rehabilitation on patient-reported pain (WMD -3.69 mm [95% CI, -6.01 to -1.36], MCID = 16 mm) in patients with IA and OA, with a small effect on observed disability (WMD -6.90 mm [95% CI, -11.57 to -2.03], MCID = 12 mm), and close to no improvement for the remaining outcome measures. No harm done either, as there were no differences for number of withdrawals or adverse events. However, significant methodological flaws were observed in the trials, leading to a reduced certainty in the calculated estimates (i.e., the true effect may be different from the effect estimated). This study does not refute the possible effectiveness of biopsychosocial interventions customized to address the specific needs of individual patients. However, this raises a concern for the growing body of evidence that continues to apply uniform and standardized biopsychosocial group programs in rehabilitation, potentially masking the true effect of the ideal individualized rehabilitation.

Funding statement

This work was supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL) given to The Parker Institute. PGC is supported in part by the National Institute for

Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data sharing statement:
The collected data has been presented in tables, graphs and supplement files. For further inquiries please contact the corresponding author.

6.0 REFERENCES

1. Hunter D, Bierna-Zeinstra S. Osteoarthritis. Lancet. 2019;393:1745-59.
2. Smolen J, Aletaha D, McInnes I. Rheumatoid arthritis. Lancet. 2016;388:2023-38.
3. Aletaha D, Smolen J. Diagnosis and Management of Rheumatoid Arthritis A Review. JAMA. 2018;320(13).
4. Ledingham J, Snowden N, Ide Z. Diagnosis and early management of inflammatory arthritis. BMJ. 2017;358(j3248).
5. Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9).
6. Hiligsmann M, Cooper C, Arden N, Boers M, Branco J, Brance M, et al. Health economics in the field of osteoarthritis: An Expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum. 2013;43(3):303-13.
7. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73:1316-22.
8. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010. Ann Rheum Dis. 2014;73:1323-30.
9. Geenen R, Overman C, Christensen R, Åsenlöf P, Capela S, Huisinga K, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018(77):797-807.
10. Meyer T, Gutenbrunner C, Bickenbach J, Cieza A, Melvin J, Stucki G. Towards a conceptual description of rehabilitation as a health strategy. J Rehabil Med. 2011;43:765-9.
11. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management (NICE guideline NG100). 2018.
12. National Institute for Health and Care Excellence. Osteoarthritis: care and management (Clinical guideline CG177). 2014.
13. American College of Rheumatology. Recommendations for the use of nonpharmacologic therapies in osteoarthritis of the hand, hip and knee. Arthritis Care Res. 2012;64(4):465-74.
14. EULAR. Recommendations for the non-pharmacological management of hip and knee osteoarthritis. Ann Rheum Dis. 2013;72:1125-35.

15. OARSI. OARSI recommendation for the management of hip and knee osteoarthritis, Part II: OARSI Evidence based expert consensus guidelines. Osteoarthritis Cartilage. 2008;16:137-62.
16. Engel G. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980;137:535-44.
17. Kogan AC, Wilber K, Mosqueda L. Person-Centered Care for Older Adults with Chronic Conditions and Functional Impairment: A Systematic Literature Review. J Am Geriatr Soc. 2016;64(1):e1-7.
18. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011.
19. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. BMJ. 2009;339(b2700).
20. Guyatt G, Oxman A, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.
21. Guyatt G, Thorlund K, Oxman A, Walter S, Patrick D, Furukawa T, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol. 2013;66(2):173-83.
22. Ghogomu E, Maxwell L, Buchbinder R, Rader T, Pardo P, Johnston R, et al. Updated method guidelines for cochrane musculoskeletal group systematic reviews and metaanalyses. J Rheumatol. 2014;41:194-205.
23. Dworkin R, Turk D, Whywich K, Beaton D, Cleeland C, Farrar J, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. The Journal of Pain. 2008;9(2):105-21.
24. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(d5928).
25. Hedges L. Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. Journal of Educational Statistics. 1981;6(2):107-28.
26. Murad M, Wang Z, Chu H, Lin L. When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. BMJ. 2019;364.
27. Sweeting M, Sutton A, Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.
28. Thompson S, Higgins J. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21:1559-73.
29. Riley R, Higgins J, Deeks J. Interpretation of random effects meta-analyses. BMJ. 2011;342(d549).
30. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
31. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
32. Jüni P, Altman D, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.
33. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand

osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. Arthritis Care Res. 2012;64(11):1699-707.
34. Hultcrantz M, Rind D, Akl E, Treweek S, Mustafa R, Iorio A, et al. The GRADE Working Group clarifies the construct of certanty of evidence. J Clin Epidemiol. 2017;87:4-13.
35. Guyatt G, Oxman A, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
36. Rezende MUR, Brito NLB, Hissadomi MIH, Pailo AFP, Frucchi RF, Pasqualin TP, et al. Two-year results of a two-day educational program about oa parqve ii (project arthritis recovering quality of life by education) improves function, strength and quality of life in respect to usual care. Osteoporos Int. 2018;29 (1 Supplement 1):S222-S3.
37. Lahiri M, Cheung PPM, Dhanasekaran P, Wong SR, Yap A, Tan D, et al. Does care by a multidisciplinary team improve outcomes in rheumatoid arthritis? a randomized controlled study. Arthritis and Rheumatology. 2018;70 (Supplement 9):310-1.
38. Rezende MU. P.A.R.Q.V.E III - Comparison of the Educational Program With and Without Multidisciplinary Care. Https://clinicaltrialsgov/show/nct02917655. 2016.
39. Karpouzas. Multidisciplinary Approach for Treat To Target In Rheumatoid Arthritis. Https://clinicaltrialsgov/show/nct02720874. 2016.
40. National University Hospital Singapore. Multidisciplinary Team Care in Rheumatoid Arthritis. Https://clinicaltrialsgov/show/nct03099668. 2017.
41. Taal E, Riemsma RP, Brus HL, Seydel ER, Rasker JJ, Wiegman O. Group education for patients with rheumatoid arthritis. Patient Educ Couns. 1993;20(2-3):177-87.
42. Ahlmen M, Sullivan M, Bjelle A. Team versus non-team outpatient care in rheumatoid arthritis. A comprehensive outcome evaluation including an overall health measure. Arthritis Rheum. 1988;31(4):471-9.
43. Kjeken I, Bo I, Ronningen A, Spada C, Mowinckel P, Hagen KB, et al. A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial. J Rehabil Med. 2013;45(3):260-7.
44. Liang L, Pan Y, Wu D, Pang Y, Xie Y, Fang H. Effects of multidisplinary team based nurse-led transitional care on clinical outcomes and quality of life in patients with ankylosing spondylitis. Asian Nurs Res. 2019.
45. Schned ES, Doyle MA, Glickstein SL, Schousboe JT, Reinertsen JL, Baglioni AJ, et al. Team managed outpatient care for early onset chronic inflammatory arthritis. J Rheumatol. 1995;22(6):1141-8.
46. Tijhuis GJ, Zwinderman AH, Hazes JM, Van Den Hout WB, Breedveld FC, Vliet Vlieland TP. A randomized comparison of care provided by a clinical nurse specialist, an inpatient team, and a day patient team in rheumatoid arthritis. Arthritis Rheum. 2002;47(5):525-31.
47. Bennell KL, Campbell PK, Egerton T, Metcalf B, Kasza J, Forbes A, et al. Telephone Coaching to Enhance a Home-Based Physical Activity Program for Knee Osteoarthritis: A Randomized Clinical Trial. Arthritis Care Res. 2017;69(1):84-94.
48. Moe RH, Grotle M, Kjeken I, Christoffer Olsen I, Mowinckel P, Haavardsholm EA, et al. Effectiveness of an integrated multidisciplinary osteoarthritis outpatient program versus outpatient clinic as usual: A randomized controlled trial. J Rheumatol. 2016;43(2):411-8.

49. Riemsma RP, Taal E, Brus HL, Rasker JJ, Wiegman O. Coordinated individual education with an arthritis passport for patients with rheumatoid arthritis. Arthritis Care Res. 1997;10(4):238-49.
50. Bearne LM, Byrne AM, Segrave H, White CM. Multidisciplinary team care for people with rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int. 2016;36(3):311-24.
51. Finney A, Healey E, Jordan JL, Ryan S, Dziedzic KS. Multidisciplinary approaches to managing osteoarthritis in multiple joint sites: a systematic review. BMC Musculoskelet Disord. 2016;17:266.
52. Kamper S, ATApeldoorn, Chiarotto A, Smeets R, Ostelo R, Guzman J, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. BMJ. 2015;350(h444).
53. Christensen R, Berthelsen D. Controversy and Debate on Meta-epidemiology. Paper 3: Causal inference from meta-epidemiology: a reasonable goal, or wishful thinking? J Clin Epidemiol. 2020;123:131-2.
54. Scholten C, Brodowicz T, Graninger W, Gardavsky I, Pils K, Pesau B, et al. Persistent functional and social benefit 5 years after a multidisciplinary arthritis training program. Arch Phys Med Rehabil. 1999;80(10):1282-7.
55. Breedland I, van Scheppingen C, Leijsma M, Verheij-Jansen NP, van Weert E. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. Phys Ther. 2011;91(6):879-93.
56. Coleman S, Briffa NK, Carroll G, Inderjeeth C, Cook N, McQuade J. A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health professionals. Arthritis Res Ther. 2012;14(1):R21.
57. Giraudet-Le Quintrec J, Mayoux-Benhamou A, Ravaud P, Champion K, Dernis E, Zerkak D, et al. Effect of a collective educational program for patients with rheumatoid arthritis: a prospective 12-month randomized controlled trial. J Rheumatol. 2007;34(8):1684-91.
58. Helminen EE, Sinikallio SH, Valjakka AL, Väisänen-Rouvali RH, Arokoski JP. Effectiveness of a cognitive-behavioural group intervention for knee osteoarthritis pain: a randomized controlled trial. Clin Rehabil. 2015;29(9):868-81.
59. Keefe FJ, Blumenthal J, Baucom D, Affleck G, Waugh R, Caldwell DS, et al. Effects of spouse-assisted coping skills training and exercise training in patients with osteoarthritic knee pain: A randomized controlled study. Pain. 2004;110(3):539-49.
60. Lindroth Y, Brattström M, Bellman I, Ekestaf G, Olofsson Y, Strömbeck B, et al. A problem-based education program for patients with rheumatoid arthritis: evaluation after three and twelve months. Arthritis Care Res. 1997;10(5):325-32.
61. Rezende MU, Hissadomi MI, de Campos GC, Frucchi R, Pailo AF, Pasqualin T, et al. One-Year Results of an Educational Program on Osteoarthritis: A Prospective Randomized Controlled Trial in Brazil. Geriatr Orthop Surg Rehabil. 2016;7(2):86-94.
62. Rodríguez-Lozano C, Juanola X, Cruz-Martínez J, Peña-Arrébola A, Mulero J, Gratacós J, et al. Outcome of an education and home-based exercise programme for patients with ankylosing spondylitis: a nationwide randomized study. Clin Exp Rheumatol. 2013;31(5):739-48.
63. Stoffer-Marx MA, Klinger M, Luschin S, Meriaux-Kratochvila S, Zettel-Tomenendal M, Nell-Duxneuner V, et al. Functional consultation and exercises improve grip strength in

osteoarthritis of the hand - A randomised controlled trial. Arthritis Res Ther. 2018;20 (1) (no pagination)(s13075-018-1747-0).
64. Stukstette MJ, Dekker J, den Broeder AA, Westeneng JM, Bijlsma JWJ, van den Ende CHM. No evidence for the effectiveness of a multidisciplinary group based treatment program in patients with osteoarthritis of hands on the short term; results of a randomized controlled trial. Osteoarthritis Cartilage. 2013;21(7):901-10.
65. Tonga E, DÜGer T, KarataŞ M. Effectiveness of Client-Centered Occupational Therapy in Patients With Rheumatoid Arthritis: Exploratory Randomized Controlled Trial. Arch Rheumatol. 2016;31(1):6-13.
66. Vliet Vlieland TP, Breedveld FC, Hazes JM. The two-year follow-up of a randomized comparison of in-patient multidisciplinary team care and routine out-patient care for active rheumatoid arthritis. Br J Rheumatol. 1997;36(1):82-5.

Figures and tables:

Figure 1: Flowchart depicting the identification of trials for inclusion in the review (qualitative synthesis) and meta-analysis (quantitative synthesis)

Figure 2: Forest plot of the standardized mean difference (SMD adjusted into Hedges' g) of changes in patient-reported pain intensity between the intervention and control groups. 95% CI = 95% confidence interval, N = number of patients, SD = standard deviation, SMD = standardized mean difference. Estimates were calculated using a restricted maximum likelihood (REML) meta-analysis model.

Figure 3: Forest plot of the relative risk (RR) of withdrawals in the intervention and control groups. 95% CI = 95% confidence interval, n = number of events, N = number of patients. Estimates were calculated using a random-effects meta-analysis model.

Table 1: Key characteristics of included studies in review.

Author (year)	Primary diagnosis	No. of participants (% female)	Age, Disease duration: mean years (SD)	Intervention details	Comparison details
Ahlmen (1988)(42)	RA (IA)	60 (100)	58.5 (9.4) 11.4 (10.3)	MDT education (N/A weeks) Contact time: 5 × 2h 5 disciplines: RT, nurse, PT, OT, SW	Usual care 1-5 professions: physician, nurse, PT, OT, SW as required
Bennell (2017)(47)	Knee OA	168 (63)	62.3 (7.4) N/A	Coaching and exercise (25 weeks) Contact time: 5.5h + 6-12 coaching sessions 2-4 disciplines: psychologist, nurse, PT, OT	Other: Exercise (20 weeks) Contact time: 5.5h 1 profession: PT
Breedland (2011)(55)	RA (IA)	34 (71)	48.0 (10.9) 8.0 (11.5)	MDT education and exercise (8 weeks) Contact time: 4h/week 5 disciplines: psychologist, dietician, PT, OT, SW	Waitlist
Coleman (2012)(56)	Knee OA	146 (75)	65 (8.3) N/A	MDT education program (6 weeks) Contact time: 2.5h/week 3 disciplines: nurse, PT, OT	Waitlist
Giraudet-Le Quintrec (2007)(57)	RA (IA)	208 (86)	54.8 (13.2) 13.1 (9.9)	MDT education & 4h booster session at 6 months (8 weeks) Contact time: 6h/week 7 disciplines: RT, rehabilitation specialist, SW, dietician, nurse, PT, OT	Usual care + information leaflets
Helminen (2015)(58)	Knee OA	111 (69)	63.6 (7.2) 7.8 (6.9)	CBT intervention including education and relaxation exercises + usual care (6 weeks) Contact time: 2h/week 2 disciplines: psychologist, PT	Usual care
Karpouzas (Ongoing: estimated 2021)(39)	RA (IA)	N/A	N/A N/A	MDT care + nurse education (52 weeks) Contact time: N/A 4+ disciplines: nurse, PT, RT, psychologist	Usual care
Keefe (2004)(59)	Knee OA	38 (63)	59.0 (11.9) N/A	Spouse assisted coping skills training and exercise (12 weeks) Contact time: 4.2h/week 2 disciplines: psychologist, exercise physiologist	Usual care
Kjeken (2013)(43)	SpA (IA)	100 (34)	49.0 (9.9) 15.5 (10.8)	Patient-tailored PT and OT treatments (3 weeks) Contact time: Inpatient 4 disciplines: physician, PT, nurse, OT	Usual care 1-3 professions: PT, physician, RT
Lahiri (2018)(37)	RA (IA)	131 (86)	56.6 (11.6) 5.5 (6.7)	Single visit to 6-member MDT care (1 day) Contact time: Single visit 6 disciplines: RT, nurse, SW, PT, OT, podiatrist	Usual care
Liang (2019)(44)	SpA (IA)	100 (21)	30.2 (9.8) 6.3 (5.5)	Nurse-led MDT care; rehabilitation, education and interviews (26 weeks) Contact time: Depending on patient' needs 2-4 disciplines: nurse, RT, psychology specialists, rehabilitation specialists	Usual care; routine nursing and education by doctor
Lindroth (1997)(60)	RA (IA)	96 (88)	55.0 (13.6) 12.0 (10.2)	Education sessions by different professions (8 weeks) Contact time: 2.5h/week 6 disciplines: doctor, nurse, PT, OT, SW, dietician	Waitlist
Moe (2016)(48)	OA	391 (86)	61.2 (7.9) N/A	Education and individual MDT consultations as needed (1 day) Contact time: 3.5h education + consultations 5 disciplines: surgeon, PT, OT, pharmacist, dietician	Usual care; nurse and RT with referral to other professions if needed
NUH Singapore (Ongoing: estimated 2019)(40)	RA (IA)	N/A	N/A N/A	Single visit to MDT + routine care (1 day) Contact time: 1 session 2+ disciplines: MDT, other unspecified	Usual care
Rezende (2016)(61) Group 1A	Knee OA	37 (74)	45+ N/A	MDT education and exercise workshops	Other: booklet and video with all lectures from intervention.

Group 1B Group 2A Group 2B Group 3A Group 3B		37 (74) 36 (78) 36 (78) 36 (76) 36 (76)		Group 1A, 2A, 3A received guidance telephone calls every 2 months (4 to 13 weeks) Contact time: 10h/day for 2 days 7 disciplines: Orthopaedic surgeon, psychologist, PT, nutritionist, OT, physical educator, SW	Required to watch video 3 times. Group 4A (control for group 1A, 2A, 3A) received guidance telephone calls.
Rezende (2018)(36)	Knee OA	N/A	N/A N/A	MDT education + usual care (9 weeks) Contact time: 1 lecture/month 2+ disciplines: MDT, other unspecified	Usual care
Rezende (Ongoing: estimated 2021)(38)	Knee OA	N/A	N/A N/A	MDT education, exercise, nutritional guidance and psychotherapy (22 weeks) Contact time: 18 sessions 6+ disciplines: psychologist, PT, orthopedist, OT, SW, nutritionist	Other: MDT education (9 weeks) Contact time: 2 sessions 6+ professions: PT, psychologist, OT, orthopedist, SW, nutritionist
Riemsma (1997)(49)	RA (IA)	Group A: 105 (66) Group B: 111 (66)	Group A: 57.0 (10.0) 13.9 (10.8) Group B: 58.6 (9.5) 12.9 (10.2)	MDT education, video, and self-help guide. Group A used an arthritis passport to coordinate rehab. (26 weeks) Contact time: Depending on patients' needs 4 disciplines: RT, general practitioner, PT, nurse	Usual care
Rodriguez-Lozano (2013)(62)	SpA (IA)	802 (81)	45.5 (11.5) 17.5 (10.5)	Education, exercise, and video material (1 day) Contact time:2h 3 disciplines: RT, nurse, PT	Usual care by RT
Schned (1995)(45)	Early Onset Chronic IA	107 (75)	43.1 (14.2) 1.4 (0.8)	Comprehensive care program (N/A) Contact time: Based on patient needs 8 disciplines: RT, MHS, SW, podiatrist, nurse, dietician, PT, OT	Usual care by physicians and RT
Scholten (1999)(54)	RA (IA)	68 (79)	48.3 (5.6) 8.9 (1.2)	Education, exercise, and psychological counselling (2 weeks) Contact time: 9 afternoons 5 disciplines: RT, orthopedist, PT, psychologist, SW	Waitlist
Stoffer-Marx (2018)(63)	Hand OA	153 (85)	59.6 (10.7) 7.8 (9.4)	Education and exercise. Telephone consultation at 1 month (1 day) Contact time: 1 session 2 of 4 disciplines: OT, PT, nurse, dietician	Usual care + placebo; Patients was provided a massage ball to roll gently on hand
Stukstette (2013)(64)	Hand OA	151 (17)	59.0 (8.1) 4.0 (6.5)	Education and exercise (4 sessions) Contact time: 3h/session 2 disciplines: OT, nurse	Other: 30 min. nurse-led education and written information + usual care.
Taal (1993)(41)	RA (IA)	75 (74)	49.6 4.3	Education, exercise, self-help guide and written material (5 weeks) Contact time:2h/week 2-3 disciplines: nurse, PT, SW	Other: referred to PT
Tijhuis (2002)(46)	RA (IA)	Group A: 106 (78) Group B: 104 (77)	Group A: 58 2.1 Group B: 57.9 1.6	Treatment program tailored to individual needs (2-3 weeks) Group A = inpatient Group B = outpatient Contact time: 9 treatment days 5 disciplines: RT, nurse, OT, PT, SW	Other: nurse specialist care, with possibility for referral to other professions (12 weeks) Contact time: 3 visits 1-5 profession: nurse, RT, OT, PT, SW
Tonga (2016)(65)	RA (IA)	40 (95)	53.6 (10.9) 8.8 (4.1)	Education, exercise and patient-centered OT Contact time: 45-90min/session 2 disciplines: PT, OT	Other: education and exercise Contact time: 45min/session 1 profession: PT
Vliet Vlieland (1997)(66)	RA (IA)	80 (70)	55.5 3.5	Nursing care, exercise, OT, and social support. 6 weeks PT following hospitalization (1.5 weeks) Contact time: Inpatient 4 disciplines: nurse, OT, SW. PT	Usual care

Abbreviations: IA = inflammatory arthritis; OA = osteoarthritis; RA = rheumatoid arthritis; SpA = spondyloarthritis; MDT = multidisciplinary team; CBT = Cognitive Behavioural Therapy; MHS = mental health specialist; OT = occupational therapist; PT = physiotherapist; RT = rheumatologist; SW = social worker

Table 2: GRADE evidence profile of biopsychosocial rehabilitation vs control for patients with inflammatory arthritis and osteoarthritis.

Outcome Measure	No. of Trials (N = 22)	No. of Patients (N = 3750)	Mean Follow-up, mos.	Serious Risk of Bias[a]	Inconsis-tency, I^2 [b]	Serious Indirect-ness[c]	Serious Impre-cision[d]	Publi-cation Bias[e]	Relative measure SMD (95% CI)	Certainty of Evidence
Pain	17	2906	9.3	Yes	47.3%	No	No	0.02	-0.19 (-0.31, -0.07)	Moderate
Patient global	9	1745	9.2	Yes	24.5%	No	No	0.85	-0.13 (-0.26, -0.00)	Moderate
Observed disability/physical function	8	777	6.1	Yes	54.8%	No	No	0.89	-0.34 (-0.57, -0.10)	Moderate
Self-reported disability/physical function	19	3292	9.7	Yes	51.8%	No	Yes	0.43	-0.09 (-0.21, 0.03)	Low
Health related quality of life	12	2543	9.2	Yes	33.9%	No	No	0.57	-0.07 (-0.19, 0.05)	Moderate
Mental well-being	14	1880	8.6	Yes	39.8%	No	Yes	0.53	-0.11 (-0.24, 0.03)	Low
Fatigue	8	1151	9.4	Yes	17.2%	No	No	0.11	0.02 (-0.11, 0.15)	Moderate
Inflammation	2	140	18	Yes	0.0%	No	Yes, twice	N/A	0.08 (-0.26, 0.41)	Very low
Physician global	1	80	24	Yes	N/A	No	Yes, twice	N/A	-0.72 (-1.18, -0.26)	Very low
Reduction in pain intensity ≥30%	1	146	6.0	Yes	N/A	No	Yes, twice	N/A	RR 1.24 (0.80, 1.91)	Very low
Number of withdrawals	20	3265	9.8	Yes	0.0%	No	No	0.29	RR 0.99 (0.82, 1.18)	Moderate
Adverse events	10	1164	9.0	Yes	0.0%	No	Yes	0.50	RR 1.18 (0.47, 2.94)	Low
Serious adverse events	10	1164	9.0	Yes	0.0%	No	Yes	0.30	RR 0.96 (0.37, 2.52)	Low

Abbreviations: CI, Confidence Interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RR = Relative Risk; RD = Risk Difference; SMD = Standardized Mean Difference.

[a] Assessed using Cochrane risk of bias instrument

[b] An I^2 value between 75% and 100% indicates that heterogeneity may be considerable, resulting in a downgrade for inconsistency.

[c] Refers to the intervention, patients, or outcomes being different from the research question.

[d] Refers to situations in which the 95% CI includes both benefit and harm, unless there is no difference in effect.

[e] Tested using visual inspection of funnel plots and the Egger's test. *P* values of <0.05 suggest the presence of publication bias.

Table 3: Stratified analyses of pain (primary outcome).

Variable	I^2	Trials (no.)	Effect size (95% CI)	T^2	Inconsistency explained, %	*P* for interaction
All trials (REML based)	47.3%	17	-0.19 (-0.31, -0.07)	0.033	n.a.	n.a.
All trials (Fixed-effect model)		17	-0.13 (-0.20, -0.05)	0.030	n.a.	n.a.
Selection bias				0.026	22.3%	0.06
Low		8	-0.04 (-0.21, 0.12)			
Unclear		8	-0.34 (-0.58, -0.11)			
High		1	0.01 (-0.56, 0.58)			
Attrition bias				0.038	-14.6%	0.20
Low		5	-0.06 (-0.31, 0.18)			
Unclear		10	-0.28 (-0.57, 0.01)			
High		2	0.05 (-0.44, 0.54)			
Reporting bias				0.026	22.1%	0.06
Low		6	-0.09 (-0.28, 0.11)			
Unclear		4	-0.01 (-0.32, 0.29)			
High		7	-0.36 (-0.62, -0.09)			
Type of condition				0.035	-5.7%	0.91
Osteoarthritis		8	-0.17 (-0.34, 0.00)			
Inflammatory arthritis		9	-0.22 (-0.47, 0.03)			
Treatment modalities/components				0.042	-25.9%	0.95
Physical and psychological element		3	-0.15 (-0.47, 0.17)			
Physical and social/work-related element		4	-0.21 (-0.63, 0.20)			
Physical, psychological, and social/work element		10	-0.20 (-0.56, 0.16)			
Supervision of intervention				0.017	26.6%	0.04
Group-based		7	-0.33 (-0.49, -0.17)			
Individual		7	-0.10 (-0.34, 0.14)			
Other		3	0.04 (-0.23, 0.32)			
Comparator/control				0.032	4.4%	0.38
Usual care		10	-0.13 (-0.29, 0.04)			
Waitlist		2	-0.41 (-0.80, -0.01)			
Other		4	-0.21 (-0.48, 0.05)			
Pain at baseline		17		0.037	-11.1%	0.80
Intercept			-0.11 (-0.79, 0.57)			
Slope			-0.00 (-0.02, 0.01)			
Physical function at baseline		15		0.034	-5.3%	0.30
Intercept			-0.02 (-0.35, 0.31)			
Slope			-0.00 (-0.01, 0.00)			
Health-related quality of life at baseline		9		0.060	-35.4%	0.51
Intercept			0.00 (-0.58, 0.58)			
Slope			-0.00 (-0.02, 0.01)			
Contact time during intervention (hours)		9		0.019	59.2%	0.01
Intercept			0.05 (-0.19, 0.29)			
Slope			-0.02 (-0.03, -0.00)			
Length of intervention (weeks)		14		0.047	-14.9%	0.93
Intercept			-0.23 (-0.43, 0.02)			
Slope			-0.00 (-0.02, 0.02)			
Trial duration (months)		17		0.034	-3.2%	0.32
Intercept			-0.30 (-0.56, -0.04)			
Slope			0.01 (-0.01, 0.04)			
Age of patients at baseline		16		0.036	-10.9%	0.70
Intercept			-0.33 (-1.31, 0.65)			
Slope			0.00 (-0.01, 0.02)			
Proportion of female participants at baseline		17		0.037	-13.2%	0.33
Intercept			0.00 (-0.42, 0.42)			
Slope			-0.00 (-0.01, 0.00)			
Duration of symptoms at baseline		11		0.014	42.4%	0.85
Intercept			-0.15 (-0.50, 0.20)			
Slope			-0.00 (-0.04, 0.03)			

Estimates were calculated using a restricted maximum likelihood (REML) meta-regression model.