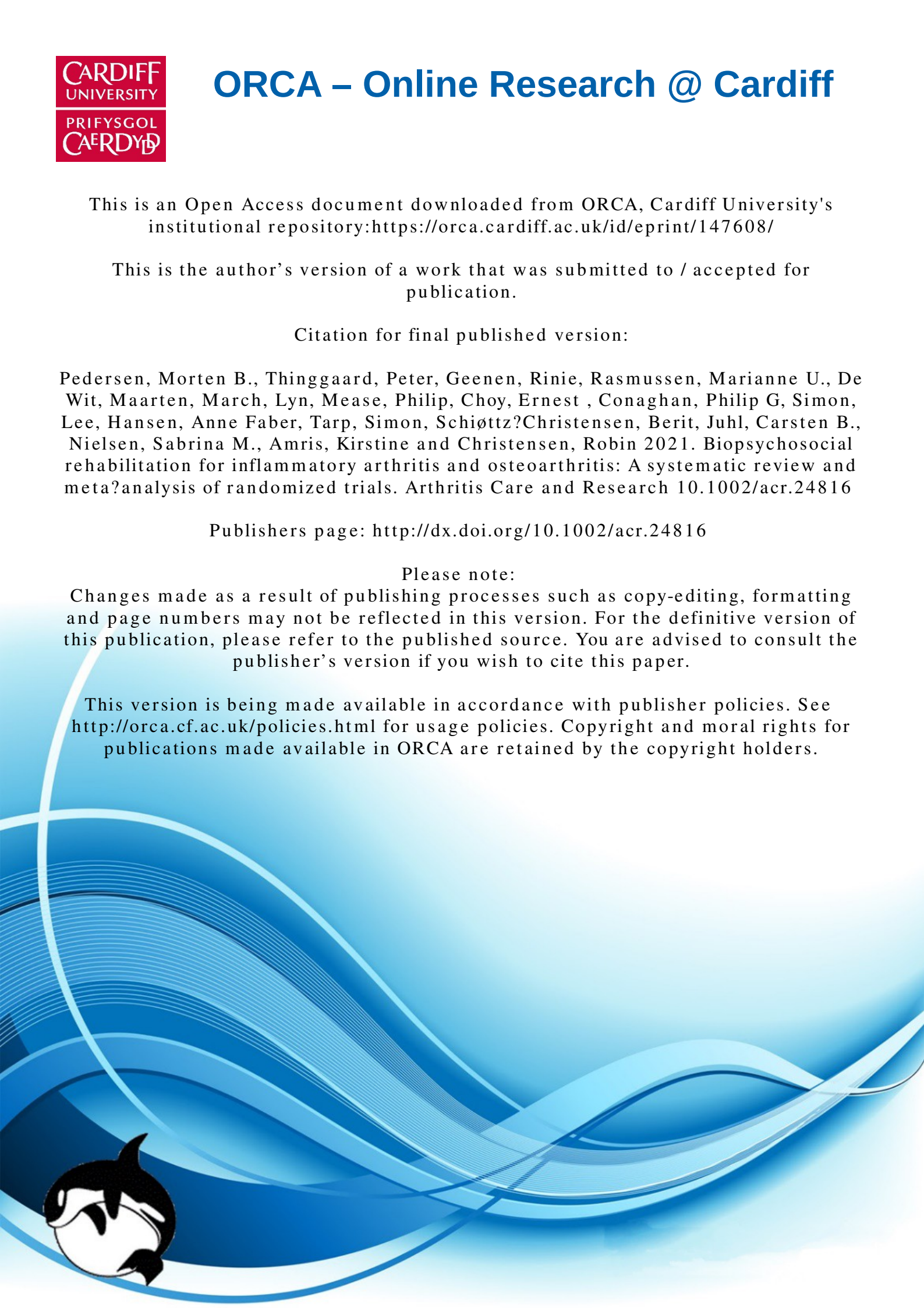

Biopsychosocial rehabilitation for inflammatory arthritis and osteoarthritis: A systematic review and meta-analysis of randomised trials

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ABSTRACT

OBJECTIVE:

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

DESIGN:

Systematic review and meta-analysis of randomised and quasi-randomised controlled trials.

DATA SOURCES:

Electronic searches of CENTRAL, Medline, Embase, PsycINFO, and CINAHL databases up to March 2019, supplemented by hand searching of reference lists and forward citation tracking of included trials.

ELIGIBILITY CRITERIA:

Randomised and quasi-randomised controlled trials examining the effect of biopsychosocial rehabilitation in adults with IA and/or OA were eligible. Studies were restricted to English, German, or Scandinavian languages, and excluded if biopsychosocial rehabilitation was an adjunct to surgery.

REVIEW METHODS:

Two reviewers independently selected studies, extracted data, and assessed risk of bias and certainty of the evidence. The effect of biopsychosocial rehabilitation was compared with usual care, waiting lists, and other types of control comparators. The main outcome we studied was pain, examined as standardised mean differences (SMDs). Outcomes were assessed and analysed according to the time closest to 12 months post-randomisation. Our analysis used a random-effects model and explored statistical heterogeneity.

RESULTS:

Of the 27 trials meeting the eligibility criteria, 22 trials (3,750 participants) reported sufficient data to be included in the quantitative analysis. Of the 27 eligible trials, 17 included patients with IA and 10 with OA.

Moderate-certainty evidence suggested that biopsychosocial rehabilitation was superior to control with regard to effects on pain relief (SMD -0.19 [95% CI, -0.31 to -0.07], k = 17), a modest effect on observed disability/physical function (SMD -0.34 [95% CI, -0.57 to -0.10], k = 8), and no difference for patient global scores, health-related quality of life, fatigue, and

number of withdrawals from the trials. Very low to low-certainty evidence suggested a large effect on physician global score (SMD -0.72 [95% CI, -1.18 to -0.26], k = 1), and no difference for self-reported disability/physical function, mental well-being, inflammation, reduction in pain intensity ≥30%, adverse events, and risk of serious adverse events. A moderate amount of statistical heterogeneity was observed for the pain outcome (I^2 = 47.3%), of which 59.2% could be explained through stratifying by intensity of intervention.

CONCLUSIONS:

On average, biopsychosocial rehabilitation produces a small beneficial effect at best on patient-reported outcomes among patients with IA and OA. Methodological weaknesses was observed in the included trials, suggesting low to moderate confidence in the estimates supporting biopsychosocial rehabilitation in these patients.

PROSPERO Registration number: CRD42019127670

Keywords: Biopsychosocial rehabilitation, inflammatory arthritis, osteoarthritis, systematic review, meta-analysis.

INTRODUCTION

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 somatic 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). Both local (joint-specific) and generalised (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 its related effects on many bodily functions, the consequences of IA and OA are often chronic and are 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 specialised 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).

International guidelines and recommendations on managing IA and OA recommend using biopsychosocial interventions, or parts thereof, for rehabilitation (9-14). These rehabilitation programs involve, along with ongoing pharmacological treatment, a physical component and a psychological or work/social-related component, preferably delivered by a team of clinicians of varying medical professions. 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 randomised 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.

METHODS

This systematic review was carried out in accordance with the recommendations from the Cochrane Collaboration guidelines (15) and was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)(16). Our protocol describing the methods was registered on PROSPERO (identifier: CRD42019127670) prior to performing the systematic review (**Appendix 1**).

Eligibility criteria

We included randomised and quasi-randomised controlled trials comparing biopsychosocial rehabilitation with any control, regardless of publication date or status. We included trials published in English, German, or Scandinavian languages that enrolled adults with IA and OA of any type (e.g., RA, SpA or PsA) and any location in the body (e.g., knee or hand). 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 medical professions; however, no specific professional background was required. Interventions could be of any intensity, approach (interdisciplinary or multidisciplinary), supervision (group-based or individual), and setting.

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)(16). However, only studies presenting quantitative data were included in the quantitative evidence synthesis (17, 18).

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 references and forward citation using Web of Science from relevant reviews and trials also was performed. The full search strategy can be found in the protocol (**Appendix 1**).

Study selection

The initial screenings of title/abstract and subsequent full-text assessment were performed in a standardised and unblinded manner by two independent reviewers (MLP and PT) using Covidence online tool (19). Any disagreements in study selection were resolved by discussion or through consultation with a third reviewer (KA/RC). Inter-rater agreement was calculated for both the title/abstract screening and full-text review stage using Cohen's kappa (κ)(20).

Data collection process and data items

Data were extracted for study and patient characteristics and predefined outcomes of interest, based on recommendations from Cochrane Musculoskeletal Group (aligned with Outcome Measures in Rheumatology [OMERACT])(21). The outcomes for benefit were pain (considered our primary outcome), patient global, observed disability/physical function, self-reported disability/physical function, health-related quality of life, mental well-being, fatigue, inflammation, physician global, and pain responders dichotomised into reduction in pain intensity ≥30% and <30%. The outcomes for harm were total number of withdrawals, number of patients experiencing adverse events, number of patients experiencing 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. When studies

reported their findings only as final scores, these were converted to change scores where possible; if needed the corresponding author of the trials was contacted for further data (22). Due to possible carry-over effects, data from cross-over trials were extracted from the first period only (23). 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 (MLP and PT) for all eligible trials using Cochrane's Risk of Bias (RoB) tool (24). Trials were assessed as high, low, or unclear risk of bias in various domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources. Each randomised controlled trial (RCT) was assigned an overall risk of bias in terms of low risk (low for all bias), unclear risk (unclear for ≥1 bias item with no high-risk items) or high risk (high for ≥1 bias item). Other sources of potential bias included presence of concomitant psychoactive medications/treatments, pre-existing mental illnesses, or co-morbid fibromyalgia. As recommended by the Cochrane Collaboration, the blinding and incomplete outcome data domains were assessed at the outcome level (25). Discrepancies were resolved through discussion or by consultation with a third reviewer (RC).

Summary measures and synthesis of results

When an outcome domain is measured using several outcome measurement instruments, it requires standardisation to be combined in a meta-analysis (26). Continuous outcomes were summarised using standardised mean differences (*SMD*) with 95% confidence intervals (95%CI) by dividing the differences in mean change from baseline by the pooled standard deviation (*SD*); to adjust for small-sample bias, Hedges' g value was applied (27). Our interpretation of the SMD was inspired by Cohen's standard; SMD values of <0.2 were interpreted as trivial, 0.2 as small, 0.5 as moderate, and >0.8 as large (28). To avoid double counting, trials with more than one eligible experimental intervention group had the number of patients in the comparator (control) group divided by the number of comparisons.

Dichotomous outcomes were analysed 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 (i.e, imputing approximately half event in the intervention and the control groups, adjusted by the number of participants in the groups) (29).

Our analysis anticipated significant heterogeneity between studies due to real differences in the treatment effect in each study as well as sampling variability (30). We therefore performed meta-analyses using restricted maximum likelihood (REML) models (31). We quantified and interpreted the heterogeneity in the meta-analyses by the I^2 inconsistency index and T^2 (an estimate for τ^2) for the variation across trials (32); I^2 values of less than 25% were loosely interpreted as 'low' and more than 75% as 'substantial' between-trial heterogeneity (33). A fixed-effect meta-analysis model was also applied for the purpose of sensitivity analysis; if the point estimate from the fixed-effect analysis was not included in the 95%CI from the REML-based random-effects model, we would rate down our certainty of the evidence (i.e., serious inconsistency). Furthermore, funnel plot and Egger's test were applied to investigate publication bias.

Risk of bias across studies and additional analyses

Prespecified sensitivity analyses were carried out to explore the robustness of our findings, and the potential impact of systematic errors from RoB by stratifying according to the individual RoB items and the overall risk (34). Prespecified stratified analyses of the primary effectiveness outcome (effect size for pain) were performed by condition category (i.e, IA or OA), treatment modalities/components, approach to care (i.e, interdisciplinary, multidisciplinary or other), supervision of intervention (i.e, group-based, individual, unsupervised or other), and comparator/control (i.e, usual care, waitlist, physical treatment, surgery, or other). The following covariates were included using meta-regression analysis: proportion of patients with chronic widespread pain (CWP) at baseline; mean pain at baseline; physical function at baseline; health-related quality of life at baseline; intensity of intervention (the number of hours used in consultations per week); length of intervention in weeks; trial duration in months from baseline until last follow-up; coping/self-management skills at baseline (normalised to 0-100 visual analog scale units [VAS]); average age of patients at baseline; proportion of female participants at baseline;

and duration of symptoms at baseline. All analyses were conducted using STATA, version 15.1.

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 (35), by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias for all outcome measures (36). The estimates of effect was re-expressed as Weighted Mean Differences (WMDs), calculated from the SMDs using pooled standard deviations of baseline scores from studies included in the analyses.

RESULTS

Study selection

Figure 1 shows the flow diagram of study selection. From 8,572 identified citations, 27 trials met the eligibility criteria. 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. Of the 27 trials, 22 trials were published as full reports, two trials were published as abstracts only (37, 38), and three trials were ongoing (39-41). One of the abstracts (37) and one of the full reports (42) presented insufficient data concerning effect. The corresponding authors of these two trials were contacted, but we received no response. The remaining 22 trials included 30 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. Most of the IA trials were based on patients with RA (13 trials), whereas only 3 trials included patients with SpA and 1 trial with early onset IA. Of the OA trials, one focused on general OA, two included patients with hand OA, and the remaining seven trials focused on knee OA. Among the 22 trials reporting age, the average of the mean age was 54 years, with means ranging from 30 to 65 years. Gender distribution was reported in 23 trials: 74% of enrolled patients were female, with proportions ranging from 17 to 100%. Among 19 of the eligible trials, the average of the reported mean pain scores at baseline (normalised to VAS-units) was 44 mm VAS (ranging from 30 to 66 mm). As reported in 17 of the trials, the mean duration of disease of the participants ranged from 1.4 to 17.5 years, with an average of the mean duration of 10.9 years.

Risk of bias within studies

Appendix 2 summarises the risk-of-bias assessments. All the included trials were randomised 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 patient-reported outcome measures (PROMs). The objectively assessed measures allowed for blinding of the trial assessors which led to 11 (46%) trials having a low risk of detection bias for objective measures. Seven (29%) trials were assessed low risk of attrition bias and 7 (29%) were assessed a 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, due to the trials' having high risk of performance and detection bias.

Synthesis of results

Figure 2, 3 and **Appendix 3** present the results of individual studies for all outcome measures. The certainty of evidence for the outcomes with sufficient data for meta-analyses is shown in Table 2.

Pain – On the basis of 17 trials (2,906 patients), we found that biopsychosocial rehabilitation on average had a small or even trivial statistically significant effect reducing pain compared with control (SMD -0.19 [95% CI, -0.31 to -0.07]; I^2 = 47.3%; **Figure 2**). The certainty of the evidence was evaluated as moderate; rated down from high due to (*i*) serious risk of bias, and (*ii*) high risk of publication bias indicated by visual inspection of forest plot and significant result from the Egger's test (**Appendix 4.1 and Table 2**). A positive dose-response relationship was found, however, increasing our confidence in the estimate by 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 intensity of the intervention with a 59.2% decrease in T^2 (P = 0.01; **Table 3**).

Patient global – On the basis of nine trials (1,745 patients), we found a trivial but statistically significant difference in effect between biopsychosocial rehabilitation and control (SMD -0.13 [95% CI, -0.26 to -0.00]; I^2 = 24.5%; **Appendix 3.2**). The outcome was evaluated as moderate certainty evidence; rated down once due to serious risk of bias.

Observed disability/physical function – On the basis of eight trials (777 patients), we found that biopsychosocial rehabilitation led to a small, statistically significant difference in effect compared to control (SMD -0.34 [95% CI, -0.57 to -0.10]; I^2 = 54.8%; **Appendix 3.3**).

The outcome was evaluated as moderate certainty evidence, which was rated down due to serious risk of bias.

Self-reported disability/physical function – On the basis of 19 trials (3,292 patients), we found that biopsychosocial rehabilitation did not result in a more favourable outcome than control (SMD -0.09 [95% CI, -0.21 to 0.03]; I^2 = 51.8%; **Appendix 3.4**). The outcome was evaluated as low certainty evidence which was rated down twice due to (*i*) serious risk of bias, and (*ii*) serious imprecision as the extremes of the 95% CI overlaps a SMD of 0 (no effect) with a wide ranged including no diffence to a small effect.

Health-related quality of life – On the basis of 12 trials (2,543 patients), we found that biopsychosocial rehabilitation does not result in a statistically better effect than control (SMD -0.07 [95% CI, -0.19 to 0.05]; I^2 = 33.9%; **Appendix 3.5**). The outcome was evaluated as moderate certainty evidence; rated down due to serious risk of bias, whereas the certainty was not rated down for imprecision because the 95% CI precisely indicated no difference between groups.

Mental well-being – On the basis of 14 trials (1,880 patients), we found that biopsychosocial rehabilitation had no statistically significant effect when compared to control (SMD -0.11 [95% CI, -0.24 to 0.03]; I^2 = 39.8%; **Appendix 3.6**). The outcome was evaluated as low certainty evidence; rated down twice due to (*i*) serious risk of bias, and (*ii*) serious imprecision as the extremes of the 95% CI overlaps a SMD of 0 (no effect) with a wide ranged including no diffence to a small effect.

Fatigue – On the basis of eight trials (1,151 patients), we found that biopsychosocial rehabilitation had no statistically significant difference in effect when compared to control (SMD 0.02 [95% CI, -0.11 to 0.15]; I^2 = 17.2%; **Appendix 3.7**). The outcome was evaluated as moderate certainty evidence; rated down due to serious risk of bias, whereas the certainty was not rated down for imprecision because the 95% CI precisely indicated no difference between groups.

Inflammation – On the basis of two trials (140 patients) biopsychosocial rehabilitation showed no statistically significant effect when compared to control (SMD 0.08 [95% CI, -0.26 to 0.41]; I^2 = 0.0%; **Appendix 3.8**). The outcome was evaluated as very low certainty evidence; rated down due to (*i*) serious risk of bias, and twice for (*ii*) very

serious imprecision as the 95% CI was only based on a small sample size with the extremes potentially favouring different interventions.

Physician global – One trial with 80 participants reported a global score evaluated by a physician. The trial found that biopsychosocial rehabilitation led to a moderate effect when compared to control (SMD -0.72 [95% CI, -1.18 to -0.26]; **Appendix 3.9**). The outcome was evaluated as very low certainty evidence; rated down due to (*i*) serious risk of bias, and for twice for (*ii*) very serious imprecision as the 95% CI was based on a small sample size with the extremes ranged from a small to a large effect.

Reduction in pain intensity ≥30% – One trial (146 participants) reported this outcome. The trial found that biopsychosocial rehabilitation had no statistically significant difference in effect when compared to control (RR 1.24 [95% CI, 0.80 to 1.91]; **Appendix 3.10**). The outcome was evaluated as very low certainty evidence; rated down due to (*i*) serious risk of bias, and twice for (*ii*) very serious imprecision as the 95% CI was based on a small sample size with the extremes favouring different interventions.

Number of withdrawals – On the basis of 20 trials (3,265 patients), we found no difference in the number of withdrawals from the trials when comparing biopsychosocial rehabilitation and control (RR 0.99 [95% CI, 0.82 to 1.18]; I^2 = 0.0%; **Figure 3**).). The outcome was evaluated as moderate certainty evidence; rated down due to serious risk of bias.

Adverse events – On the basis of 10 trials (1,164 patients), we found that biopsychosocial rehabilitation had no statistically significant effect when compared to control (RR 1.18 [95% CI, 0.47 to 2.94]; I^2 = 0.0%; **Appendix 3.12**).). The outcome was evaluated as low-certainty evidence; rated down due to (*i*) serious risk of bias, and (*ii*) serious imprecision as the 95% CI was wide with the extremes favouring different interventions.

Serious adverse events – On the basis of 10 trials (1,164 patients), we found no reduction in risk of adverse events in patients receiving biopsychosocial rehabilitation compared to control (RR 0.96 [95% CI, 0.37 to 2.52]; I^2 = 0.0%; **Appendix 3.13**).). The measure was evaluated as low-certainty evidence; rated down due to (*i*) serious risk of bias, and (*ii*)

serious imprecision as the 95% CI was wide with the extremes favouring different interventions.

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 analyses showed no significant interaction for type of condition, treatment modalities/components, comparator/control, pain at baseline, physical function at baseline, health-related quality of life at baseline, length of intervention, trials duration, age of patients at baseline, proportion of female participants at baseline, and duration of symptoms at baseline. The analysis for intensity of the intervention showed a significant interaction (P = 0.01), with a 59.2% decrease in T^2, suggesting that the intervention's effect is enhanced by an increase in the contact time patients have with a medical 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. Three of the prespecified stratifications could not be carried out because some studies did not report sufficient 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, due to the SMD point estimate of the analysis being within the 95% CI of the random-effects analysis. 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 (**Appendix 4 and Table 2**).

DISCUSSION

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 statistically significant but clinically trivial improvements in pain and patient global; small improvements in observed disability/physical function; and large improvements in physician global. No difference was observed in health-related quality of life, fatigue, self-reported disability/physical function, mental well-being, inflammation, and reduction in pain intensity ≥30%. Compared with any type of control, biopsychosocial rehabilitation showed no increased number of withdrawals or increased risk in adverse events or serious adverse events.

The effect of biopsychosocial rehabilitation was associated with the intensity of the intervention and supervision of the intervention. The analysis for intensity 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 analysis for supervision indicated that group-based rehabilitation experienced a larger effect than individual rehabilitation or other types of rehabilitation. There was no association, however, between baseline characteristics, type of condition, treatment modalities/components, or type of comparator/control group.

Two trials were excluded from some of the analyses because they did not report variations for some of their measures. Riemsma et al. (44) and Taal et al. (42) reported a 0.02 and 0.31 difference in change on a 0-10 pain scale, favouring control. Had these results been included, the estimated effect on pain would have been slightly reduced, and further heterogeneity might have been introduced.

Cost-effectiveness was not analysed 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 more focused programs.

Comparison with other studies - Systematic reviews by Bearne et al. (45) and Finney et al. (46) have previously assessed the effect of multidisciplinary team care in patients with IA and multidisciplinary approaches in patients with OA, respectively. Bearne et al. (45) based their quantitative analysis on a limited number of studies, whereas Finney et al. (46) could not perform any quantitative analyses due to them including only four studies in total. However, both studies concur with our findings, reporting a small or insignificant effect on patient-reported pain of their respective interventions.

Although international guidelines and recommendations for managing IA and OA generally recommend the use of biopsychosocial interventions for rehabilitation, the current analyses did not yield strong evidence for the effectiveness of these interventions. This finding is at odds with the extent to which these interventions are used and encouraged in clinical practice.

Limitations – As seen in most other systematic reviews, a common – yet important – limitation is the small number 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. (47). However, when using the inclusion criteria from Kamper et al., we experienced a large variation in both study populations and the interventions content and approach, which may be the result of our inclusion criteria being too broad. Additionally, the majority of IA trials included only RA patients; therefore, the effect of the intervention may differ in other IA conditions. Further, we found that many of the included studies used a structured treatment program, with no room for adaptation based on patient needs and preferences, thus straying from the core principle of rehabilitation's being patient-centred and based on the needs of the individual. Finally, as biopsychosocial rehabilitation is already recommended in most guidelines, usual care in some of the included trials may be using rehabilitation 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.

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

analyses. 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, structured 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. Although statistically insignificant, the stratified analysis for comparator/control group on pain suggested that biopsychosocial rehabilitation is not better than usual care but better than nothing (waitlist); we suggest future systematic reviews to further explore this finding when more trials using waitlist as comparator are published.

CONCLUSIONS

This meta-analysis found on average a statistically significant but clinically trivial beneficial effect of biopsychosocial rehabilitation on patient-reported pain in patients with IA and OA, with a small effect on observed disability, but close to no improvement for the remaining outcome measures. No harm done either, as there was no differences for adverse events 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). Although this study does not refute the possible effectiveness of specific biopsychosocial interventions customized to the patient with specific problems, our findings challenge the uniform and potentially naïve application of non-specific biopsychosocial group programs in rehabilitation.

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expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

FIGURES AND TABLES:

Figure 1: Flowchart depicting the identification of trials for inclusion in the review and meta-analysis

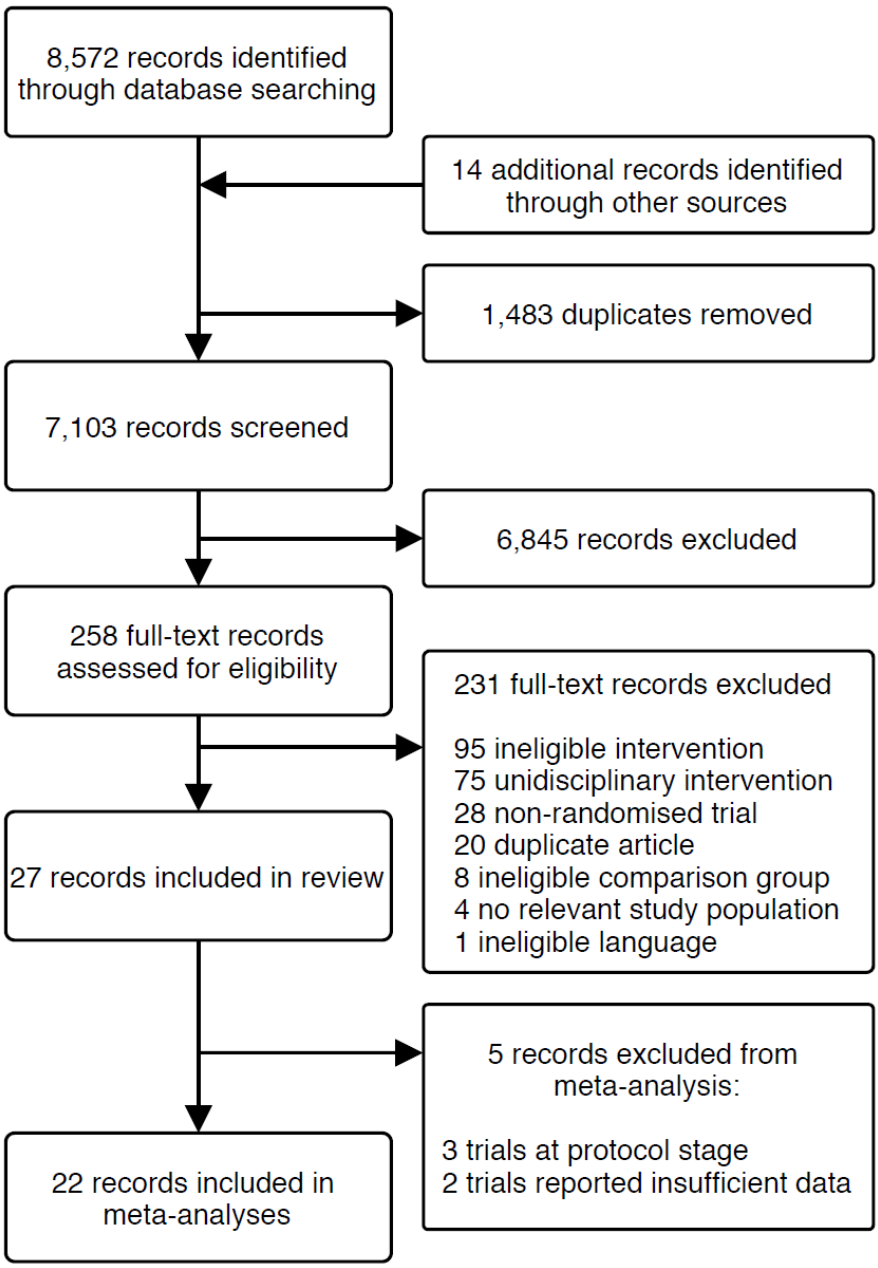

Table 1 Key characteristics of included studies in review

Author (year)	Primary diagnosis	No. of participants (% female)	Age, Disease duration: mean (SD) (years)	Intervention details	Comparison details
Ahlmen (1988)(48)	RA (IA)	60 (100)	58.5 (9.4) 11.4 (10.3)	MDT education (N/A weeks) Intensity: 5 × 2h 5 disciplines: RT, nurse, PT, OT, SW	Usual care 1-5 professions: physician, nurse, PT, OT, SW as required
Bennell (2017)(49)	Knee OA	168 (63)	62.3 (7.4) N/A	Coaching and exercise (25 weeks) Intensity: 5.5h + 6-12 coaching sessions 2-4 disciplines: psychologist, nurse, PT, OT	Other: Exercise (20 weeks) Intensity: 5.5h 1 profession: PT
Breedland (2011)(50)	RA (IA)	34 (71)	48.0 (10.9) 8.0 (11.5)	MDT education and exercise (8 weeks) Intensity: 4h/week 5 disciplines: psychologist, dietician, PT, OT, SW	Waitlist
Coleman (2012)(51)	Knee OA	146 (75)	65 (8.3) N/A	MDT education program (6 weeks) Intensity: 2.5h/week 3 disciplines: nurse, PT, OT	Waitlist
Giraudet-Le Quintrec (2007)(52)	RA (IA)	208 (86)	54.8 (13.2) 13.1 (9.9)	MDT education & 4h booster session at 6 months (8 weeks) Intensity: 6h/week 7 disciplines: RT, rehabilitation specialist, SW, dietician, nurse, PT, OT	Usual care + information leaflets
Helminen (2015)(53)	Knee OA	111 (69)	63.6 (7.2) 7.8 (6.9)	CBT intervention including education and relaxation exercises + usual care (6 weeks) Intensity: 2h/week 2 disciplines: psychologist, PT	Usual care
Karpouzas (Ongoing: estimated 2021)(40)	RA (IA)	N/A	N/A N/A	MDT care + nurse education (52 weeks) Intensity: N/A 4+ disciplines: nurse, PT, RT, psychologist	Usual care
Keefe (2004)(54)	Knee OA	38 (63)	59.0 (11.9) N/A	Spouse assisted coping skills training and exercise (12 weeks) Intensity: 4.2h/week 2 disciplines: psychologist, exercise physiologist	Usual care
Kjeken (2013)(55)	SpA (IA)	100 (34)	49.0 (9.9) 15.5 (10.8)	Patient-tailored PT and OT treatments (3 weeks) Intensity: Inpatient 4 disciplines: physician, PT, nurse, OT	Usual care 1-3 professions: PT, physician, RT
Lahiri (2018)(38)	RA (IA)	131 (86)	56.6 (11.6) 5.5 (6.7)	Single visit to 6-member MDT care (1 day) Intensity: Single visit 6 disciplines: RT, nurse, SW, PT, OT, podiatrist	Usual care

Liang (2019)(56)	SpA (IA)	100 (21)	30.2 (9.8) 6.3 (5.5)	Nurse-led MDT care; rehabilitation, education and interviews (26 weeks) Intensity: Depending on patient' needs 2-4 disciplines: nurse, RT, psychology specialists, rehabilitation specialists	Usual care; routine nursing and education by doctor
Lindroth (1997)(57)	RA (IA)	96 (88)	55.0 (13.6) 12.0 (10.2)	Education sessions by different professions (8 weeks) Intensity: 2.5h/week 6 disciplines: doctor, nurse, PT, OT, SW, dietician	Waitlist
Moe (2016)(58)	OA	391 (86)	61.2 (7.9) N/A	Education and individual MDT consultations as needed (1 day) Intensity: 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)(41)	RA (IA)	N/A	N/A N/A	Single visit to MDT + routine care (1 day) Intensity: 1 session 2+ disciplines: MDT, other unspecified	Usual care
Rezende (2016)(59) Group 1A Group 1B Group 2A Group 2B Group 3A Group 3B	Knee OA	 37 (74) 37 (74) 36 (78) 36 (78) 36 (76) 36 (76)	45+ N/A	MDT education and exercise workshops Group 1A, 2A, 3A received guidance telephone calls every 2 months (4 to 13 weeks) Intensity: 10h/day for 2 days 7 disciplines: Orthopedic surgeon, psychologist, PT, nutritionist, OT, physical educator, SW	Other: booklet and video with all lectures from intervention. Required to watch video 3 times. Group 4A (control for group 1A, 2A, 3A) received guidance telephone calls.
Rezende (2018)(37)	Knee OA	N/A	N/A N/A	MDT education + usual care (9 weeks) Intensity: 1 lecture/month 2+ disciplines: MDT, other unspecified	Usual care
Rezende (Ongoing: estimated 2021)(39)	Knee OA	N/A	N/A N/A	MDT education, exercise, nutritional guidance and psychotherapy (22 weeks) Intensity: 18 sessions 6+ disciplines: psychologist, PT, orthopaedist, OT, SW, nutritionist	Other: MDT education (9 weeks) Intensity: 2 sessions 6+ professions: PT, psychologist, OT, orthopaedist, SW, nutritionist
Riemsma (1997)(44) Group A Group B	RA (IA)	 105 (66) 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) Intensity: Depending on patients' needs 4 disciplines: RT, general practitioner, PT, nurse	Usual care
Rodriguez-Lozano (2013)(60)	SpA (IA)	802 (81)	45.5 (11.5) 17.5 (10.5)	Education, exercise, and video material (1 day) Intensity:2h 3 disciplines: RT, nurse, PT	Usual care by RT

Schned (1995)(61)	Early Onset Chronic IA	107 (75) 1.4 (0.8)	43.1 (14.2)	Comprehensive care program (N/A) Intensity: Based on patient needs 8 disciplines: RT, MHS, SW, podiatrist, nurse, dietician, PT, OT	Usual care by physicians and RT
Scholten (1999)(43)	RA (IA)	68 (79) 8.9 (1.2)	48.3 (5.6)	Education, exercise, and psychological counselling (2 weeks) Intensity: 9 afternoons 5 disciplines: RT, orthopaedist, PT, psychologist, SW	Waitlist
Stoffer-Marx (2018)(62)	Hand OA	153 (85) 7.8 (9.4)	59.6 (10.7)	Education and exercise. Telephone consultation at 1 month (1 day) Intensity: 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)(63)	Hand OA	151 (17) 4.0 (6.5)	59.0 (8.1)	Education and exercise (4 sessions) Intensity: 3h/session 2 disciplines: OT, nurse	Other: 30 min. nurse-led education and written information + usual care.
Taal (1993)(42)	RA (IA)	75 (74) 4.3	49.6	Education, exercise, self-help guide and written material (5 weeks) Intensity:2h/week 2-3 disciplines: nurse, PT, SW	Other: referred to PT
Tijhuis (2002)(64) Group A Group B	RA (IA)	 106 (78) 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 Intensity: 9 treatment days 5 disciplines: RT, nurse, OT, PT, SW	Other: nurse specialst care, with possibility for referral to other professions (12 weeks) Intensity: 3 visits 1-5 profession: nurse, RT, OT, PT, SW
Tonga (2016)(65)	RA (IA)	40 (95) 8.8 (4.1)	53.6 (10.9)	Education, exercise and patient-centred OT (10 PT, 4+ OT sessions) Intensity: 45-90min/session 2 disciplines: PT, OT	Other: education and exercise (10 sessions) Intensity: 45min/session 1 profession: PT
Vliet Vlieland (1997)(66)	RA (IA)	80 (70) 3.5	55.5	Nursing care, exercise, OT, and social support. 6 weeks PT following hospitalization (1.5 weeks) Intensity: Inpatient 4 disciplines: nurse, OT, SW. PT	Usual care

IA = inflammatory arthritis; OA = osteoarthritis; RA = rheumatoid arthritis; SpA = spondyloarthritis.
MDT = Multidisciplinary Team; MHS = Mental Health Specialist; OT = Occupational Therapist; PT = Physio Therapist; RT = Rheumatologist; SW = Social Worker.

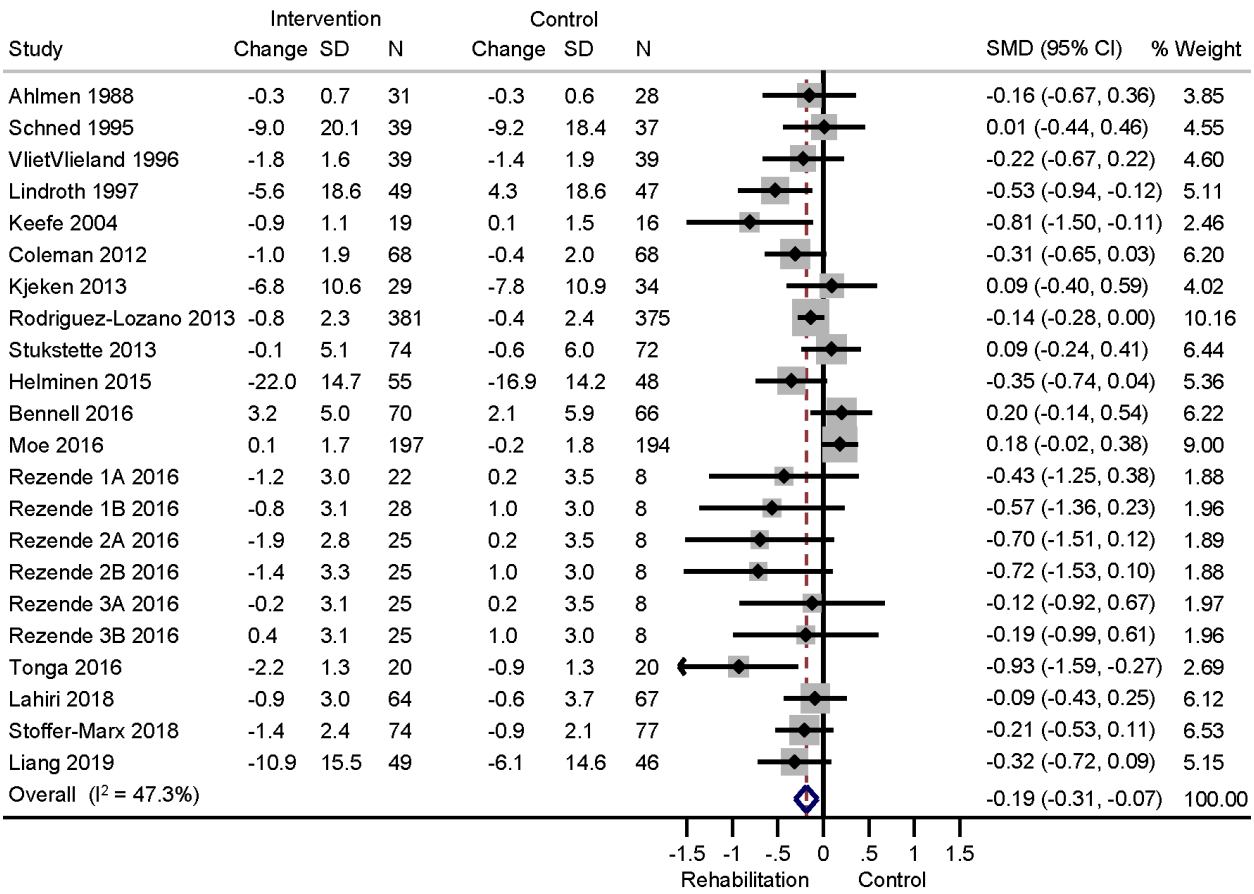

Figure 2: Forest plot of the standardised mean difference (SMD adjusted into Hedges' g) of changes in patient-reported pain intensity between the intervention and control groups.
95% CI = 95% confidence interval, N = number of patients, SD = standard deviation, SMD = standardized mean difference. Estimates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

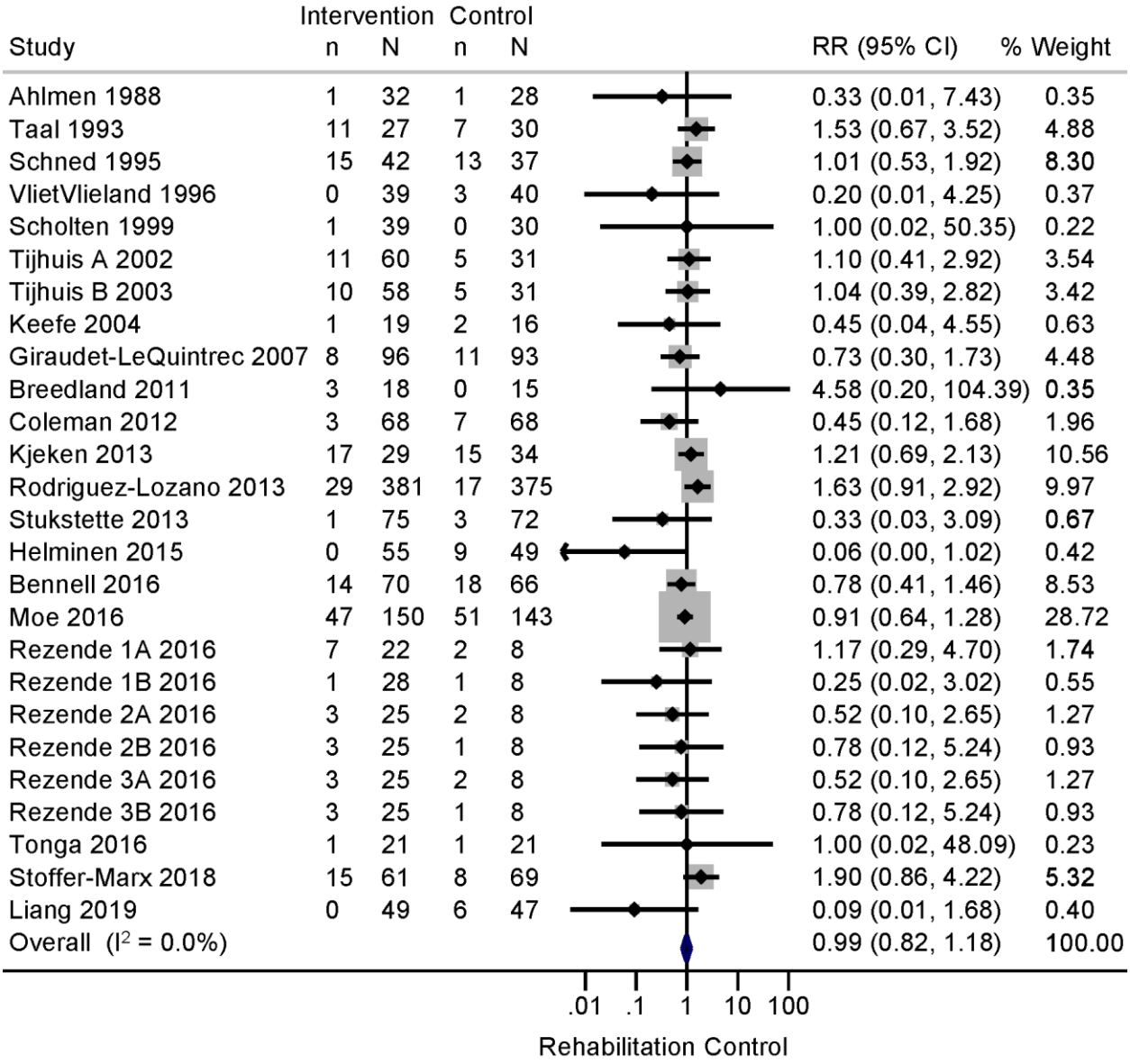

Figure 3: Forest plot of the relative risk (RR) of withdrawals in the intervention and control groups. 95% CI = 95% confidence interval, n = number of events, N = number of patients, RR = risk ratio.

Estimates were calculated using a random-effects meta-analysis model.

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]	Inconsistency, I^2 [b]	Serious Indirectness[c]	Serious Imprecision[d]	*P* Value for Publication Bias[e]	Relative measure SMD (95% CI)	Absolute measure[f] WMD (95% CI)	Absolute measure tool, range	Certainty of Evidence
Pain	17	2906	9.3	Yes	47.3%	No	No	0.02	-0.19 (-0.31, -0.07)	-4.56 (-7.44, -1.68)	VAS pain 0 to 100 ⇩	Moderate
Patient global	9	1745	9.2	Yes	24.5%	No	No	0.85	-0.13 (-0.26, -0.00)	2.22 (-4.45, -0.00)	SF36 GH 0 to 100 ⇧	Moderate
Observed disability/physical function	8	777	6.1	Yes	54.8%	No	No	0.89	-0.34 (-0.57, -0.10)	-0.58 (-0.99, -0.18)	TUG 0 and up ⇩	Moderate
Self-reported disability/physical function	19	3292	9.7	Yes	51.8%	No	Yes	0.43	-0.09 (-0.21, 0.03)	3.96 (-9.24, 1.32)	SF36 PF 0 to 100 ⇧	Low
Health related quality of life	12	2543	9.2	Yes	33.9%	No	No	0.57	-0.07 (-0.19, 0.05)	-0.09 (-0.24, 0.06)	AIMS2 0 to 10 ⇩	Moderate
Mental well-being	14	1880	8.6	Yes	39.8%	No	Yes	0.53	-0.11 (-0.24, 0.03)	1.66 (-0.38, 3.69)	SF36 MH 0 to 100 ⇧	Low
Fatigue	8	1151	9.4	Yes	17.2%	No	No	0.11	0.02 (-0.11, 0.15)	-0.04 (-2.31, 3.15)	SF36 VT 0 to 100 ⇧	Moderate
Inflammation	2	140	18	Yes	0.0%	No	Yes, twice	N/A	0.08 (-0.26, 0.41)	2.53 (-8.06, 13.11)	ESR 0 and up ⇩	Very low
Physician global	1	80	24	Yes	N/A	No	Yes, twice	N/A	-0.72 (-1.18, -0.26)	-0.50 (-0.83, -0.18)	Disease Activity 0 to 3 ⇩	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)	RD 0.06 (-0.06, 0.19)		Very low
Number of withdrawals	20	3265	9.8	Yes	0.0%	No	No	0.29	RR 0.99 (0.82, 1.18)	RD -0.02 (-0.04, 0.00)		Moderate
Adverse events	10	1164	9.0	Yes	0.0%	No	Yes	0.50	RR 1.18 (0.47, 2.94)	RD 0.00 (-0.01, 0.02)		Low
Serious adverse events	10	1164	9.0	Yes	0.0%	No	Yes	0.30	RR 0.96 (0.37, 2.52)	RD 0.00 (-0.01, 0.01)		Low

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

Measure tool abbrevations: AIMS2 = Arthritis Impact Measurement Scale 2; ESR = Erythrocyte Sedimentation Rate; SF36 (Subscales: GH, MH, PF, VT) = Short Form 36 (Subscales: General Health, Mental Health, Physical Functioning, Vitality); TUG = Timed Up and Go; VAS = Visual Analog Scale.

⇧ indicates a higher score is better, ⇩ indicates a lower score is better.

[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 a funnel plot and the Egger's test. *P* values of <0.05 suggest the presence of publication bias.

[f] Re-expressed estimate calculated from the SMD using pooled standard deviations of baseline scores from studies included in the analyses.

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		
All trials (Fixed-effect model)		17	-0.13 (-0.20, -0.05)	0.030		
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)			
Intensity of 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.

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