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Biopsychosocial Rehabilitation for Inflammatory Arthritis and Osteoarthritis Patients: A Systematic Review and Meta-Analysis of Randomized Trials

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Objective. To assess the benefits and harms associated with biopsychosocial rehabilitation in patients with inflammatory arthritis 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 inflammatory arthritis 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 (standardized mean difference [SMD] –0.19 [95% confidence interval (95% CI) –0.31, –0.07]), had a small effect on patient global assessment score (SMD –0.13 [95% CI –0.26, –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, –0.10]), a large effect on physician global assessment score (SMD –0.72 [95% CI –1.18, –0.26]), and no effect on inflammation. No difference in harms existed in terms of the number of withdrawals, adverse events, or serious adverse events.

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

INTRODUCTION

Inflammatory arthritis 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 inflammatory arthritis describes a group of rheumatic conditions characterized by inflammation, such as rheumatoid arthritis

SIGNIFICANCE & 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 a 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.

(RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). Despite inflammatory arthritis and OA having different pathologies, their nonpharmacologic 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 inflammatory arthritis or OA, caused directly by inflammation or damage of various joints, and centrally modulated by neurobiologic, psychological, and social factors. Because of the permanence of the patient's disease and disease-related disability, the consequences of inflammatory arthritis 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, nonpharmacologic and pharmacologic 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, to reduce pain and achieve optimal social participation (9).

Until recent years, the biomedical model has been the predominant paradigm in the treatment of inflammatory arthritis and OA, focusing on the physical processes of the diseases. We are now seeing a shift in paradigms toward 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 inflammatory arthritis and OA recommend using biopsychosocial interventions, or parts thereof, for rehabilitation (9,11–15). These rehabilitation programs involve, along with ongoing pharmacologic treatment, a physical component and a psychological or work/social-related component, delivered by a team of health care 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 inflammatory arthritis and OA (9), there is no clear summary of evidence to confirm its effectiveness.

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 inflammatory arthritis and OA based on its effects on pain, disability, health-related quality of life, and adverse events.

MATERIALS 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 was registered on PROSPERO (identifier: CRD42019127670) (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816).

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' countries of origin) that enrolled adults with inflammatory arthritis (i.e., RA, axial SpA, 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 inflammatory arthritis 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., the amount of time clinicians were in contact with participants during the intervention).

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 March 15, 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 and European Alliance of Associations for Rheumatology conference abstracts were searched from 2014 through March 15, 2019. Handsearching was performed of relevant references and included studies. Forward citation tracking of included studies, relevant reviews, and trials was performed using Web of Science. For a detailed search strategy, see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816.

Study selection. The initial screenings of title/abstract and subsequent full-text assessment were performed in a standardized manner by 2 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 or 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 the Cochrane Musculoskeletal Group (22), guidance from the Outcome Measures in Rheumatology initiative, and the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (23). The patient-reported outcome measures for benefit were pain (primary outcome), patient global assessment score, 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 assessment score. The outcomes for harm were the number of withdrawals, adverse events, serious adverse events, 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 2 independent reviewers (MBP and PT) using Cochrane's risk-of-bias 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 (SMDs) with 95% confidence intervals (95% CIs); 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 with a 95% CI. Sweeting's adjustment was applied to calculate the relative risk 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 the 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 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-effects meta-analysis model was applied for the purpose of sensitivity analysis. Furthermore, a 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 the risk of bias (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 SDs of baseline scores from studies investigating the minimum clinically important differences (MCIDs) in the target population (33). 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, with 27 trials meeting the eligibility criteria (Figure 1). The agreement between the 2 trial assessors corresponded to an interrater reliability of $\kappa = 0.48$ (95% CI 0.41, 0.55) for the title/abstract

screening, and κ = 0.93 (95% CI 0.86, 1.00) for the full-text assessment. Two of these trials were published as abstracts only (36,37), and 3 trials were ongoing (38–40). The corresponding authors of 2 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 inflammatory arthritis and 10 with OA. The mean age was 54 years, with mean ages ranging from 30 to 65 years. A total of 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 visual analog scale [VAS] units) was 44-mm VAS (ranging 30–66 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. Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816, summarizes the
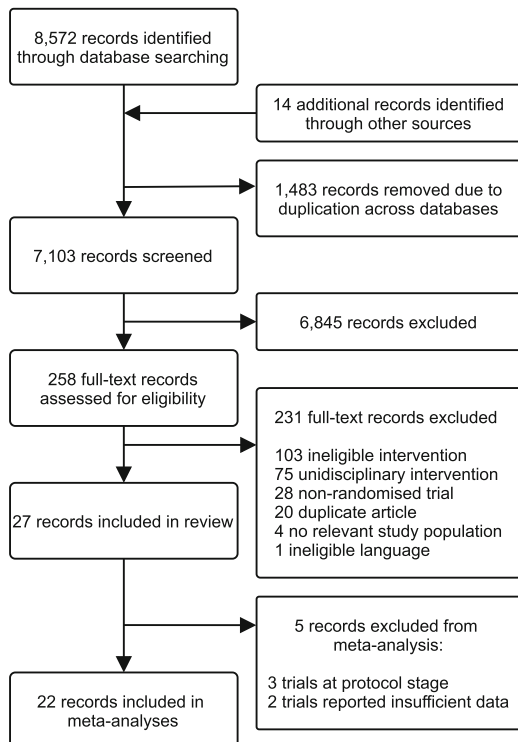

Figure 1. Flow chart depicting the identification of trials for inclusion in the review (qualitative synthesis) and meta-analysis (quantitative synthesis).

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 patient-reported outcome measures.

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 having low risk-of-attrition bias, and 7 (29%) were assessed as having 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 biases.

Synthesis of results. Figures 2 and 3 and Supplementary Figures 2–14, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816, 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). Supplementary Figures 15–26, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816, show funnel plots for all outcome measures.

The majority of estimates indicated no significant difference between biopsychosocial rehabilitation and control interventions for either benefit or harm. For patient-reported outcome measures, pain and patient global assessment score reached a statistically significant difference in effect. For clinician measured outcomes, observed disability/physical function and physician global assessment score were statistically significant. Radiographic damage was not reported in any of the included studies. The magnitude of improvement in pain, patient global assessment score, and observed disability/physical function were nominally small, favoring biopsychosocial rehabilitation.

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

Table 1. Key characteristics of included studies in review[*]

Author, year (ref.)	Primary diagnosis	Participants, no. (% female)	Age; disease duration, mean ± SD years	Intervention details	Comparison details
Ahlmen et al, 1988 (42)	RA	60 (100)	58.5 ± 9.4; 11.4 ± 10.3	MDT education (NA weeks); contact time: 5 × 2 ours; 5 disciplines: RT, nurse, PT, OT, SW	Usual care; 1–5 professions: physician, nurse, PT, OT, SW as required
Bennell et al, 2017 (47)	Knee OA	168 (63)	62.3 ± 7.4; NA	Coaching and exercise (25 weeks); contact time: 5.5 hours +6–12 coaching sessions; 2–4 disciplines: psychologist, nurse, PT, OT	Other: exercise (20 weeks); contact time: 5.5 hours; 1 profession: PT
Breedland et al, 2011 (55)	RA	34 (71)	48.0 ± 10.9; 8.0 ± 11.5	MDT education and exercise (8 weeks); contact time: 4 hours/ week; 5 disciplines: psychologist, dietician, PT, OT, SW	Waitlist
Coleman et al, 2012 (56)	Knee OA	146 (75)	65 ± 8.3; NA	MDT education program (6 weeks); contact time: 2.5 hours/week; 3 disciplines: nurse, PT, OT	Waitlist
Giraudet-Le Quintrec et al, 2007 (57)	RA	208 (86)	54.8 ± 13.2; 13.1 ± 9.9	MDT education and 4-hour booster session at 6 months (8 weeks); contact time: 6 hours/week; 7 disciplines: RT, rehabilitation specialist, SW, dietician, nurse, PT, OT	Usual care + information, leaflets
Helminen et al, 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: 2 hours/week; 2 disciplines: psychologist, PT	Usual care
Karpouzas, ongoing: estimated 2021 (39)	RA	NA	NA; NA	MDT care + nurse education (52 weeks); contact time: NA; 4+ disciplines: nurse, PT, RT, psychologist	Usual care
Keefe et al, 2004 (59)	Knee OA	38 (63)	59.0 ± 11.9; NA	Spouse assisted coping skills training and exercise (12 weeks); contact time: 4.2 hours/week; 2 disciplines: psychologist, exercise physiologist	Usual care
Kjeken et al, 2013 (43)	SpA	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 et al, 2018 (37)	RA	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 et al, 2019 (44)	SpA	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 et al, 1997 (60)	RA	96 (88)	55.0 ± 13.6; 12.0 ± 10.2	Education sessions by different professions (8 weeks); contact time: 2.5 hours/week; 6 disciplines: doctor, nurse, PT, OT, SW, dietician	Waitlist
Moe et al, 2016 (48)	OA	391 (86)	61.2 ± 7.9; NA	Education and individual MDT consultations as needed (1 day); contact time: 3.5 hours education + consultations; 5 disciplines: surgeon, PT, OT, pharmacist, dietician	Usual care; nurse and RT with referral to other professions if needed

(Continued)

Table 1. (*Cont'd*)

Author, year (ref.)	Primary diagnosis	Participants, no. (% female)	Age; disease duration, mean ± SD years	Intervention details	Comparison details
NUH Singapore, ongoing: estimated 2019 (40)	RA	NA	NA; NA	Single visit to MDT + routine care (1 day); contact time: 1 session; 2+ disciplines: MDT, other unspecified	Usual care
Rezende et al, 2016 (61); groups: 1A, 1B, 2A, 2B, 3A, 3B	Knee OA	Groups 1A– 3B: 37 (74), 37 (74), 36 (78), 36 (78), 36 (76), 36 (76)	45+; NA	MDT education and exercise workshops; group 1A, 2A, 3A received guidance telephone calls every 2 months (4 to 13 weeks); contact time: 10 hours/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 et al, 2018 (36)	Knee OA	NA	NA; NA	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	NA	NA; NA	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 et al, 1997 (49)	RA	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
Rodríguez-Lozano et al, 2013 (62)	SpA	802 (81)	45.5 ± 11.5; 17.5 ± 10.5	Education, exercise, and video material (1 day); contact time: 2 hours; 3 disciplines: RT, nurse, PT	Usual care by RT
Schned et al, 1995 (45)	Early onset chronic IA	107 (75)	43.1 ± 14.2; 1.4 ± 0.8	Comprehensive care program (NA); contact time: based on patient needs; 8 disciplines: RT, MHS, SW, podiatrist, nurse, dietician, PT, OT	Usual care by physicians and RT
Scholten et al, 1999 (54)	RA	68 (79)	48.3 ± 5.6; 8.9 ± 1.2	Education, exercise, and psychological counseling (2 weeks); contact time: 9 afternoons; 5 disciplines: RT, orthopedist, PT, psychologist, SW	Waitlist
Stoffer-Marx et al, 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 provided a massage ball to roll gently on hand
Stukstette et al, 2013 (64)	Hand OA	151 (17)	59.0 ± 8.1; 4.0 ± 6.5	Education and exercise (4 sessions); contact time: 3 hour/session; 2 disciplines: OT, nurse	Other: 30 min. nurse-led education and written information + usual care.
Taal et al, 1993 (41)	RA	75 (74)	49.6; 4.3	Education, exercise, self-help guide and written material (5 weeks); contact time: 2 hours/week; 2–3 disciplines: nurse, PT, SW	Other: referred to PT
Tijhuis et al, 2002 (46)	RA	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

(Continued)

Table 1. *(Cont'd)*

Author, year (ref.)	Primary diagnosis	Participants, no. (% female)	Age; disease duration, mean ± SD years	Intervention details	Comparison details
Tonga et al, 2016 (65)	RA	40 (95)	53.6 ± 10.9; 8.8 ± 4.1	Education, exercise and patient-centered OT Contact time: 45–90 min/session; 2 disciplines: PT, OT	Other: education and exercise; contact time: 45 min./session; 1 profession: PT
Vliet Vlieland et al, 1997 (66)	RA	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

* CBT = Cognitive Behavioral Therapy; IA = inflammatory arthritis; MDT = multidisciplinary team; MHS = mental health specialist; min. = minutes; NA = not available; OA = osteoarthritis; OT = occupational therapist; PT = physiotherapist; RA = rheumatoid arthritis; ref. = reference; rehab. = rehabilitation; RT = rheumatologist; SpA = spondyloarthritis; SW = social worker.

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 assessment score, and reduction in pain intensity ≥30%) were rated down twice for very serious imprecision, as their 95% CIs were 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 health care 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).
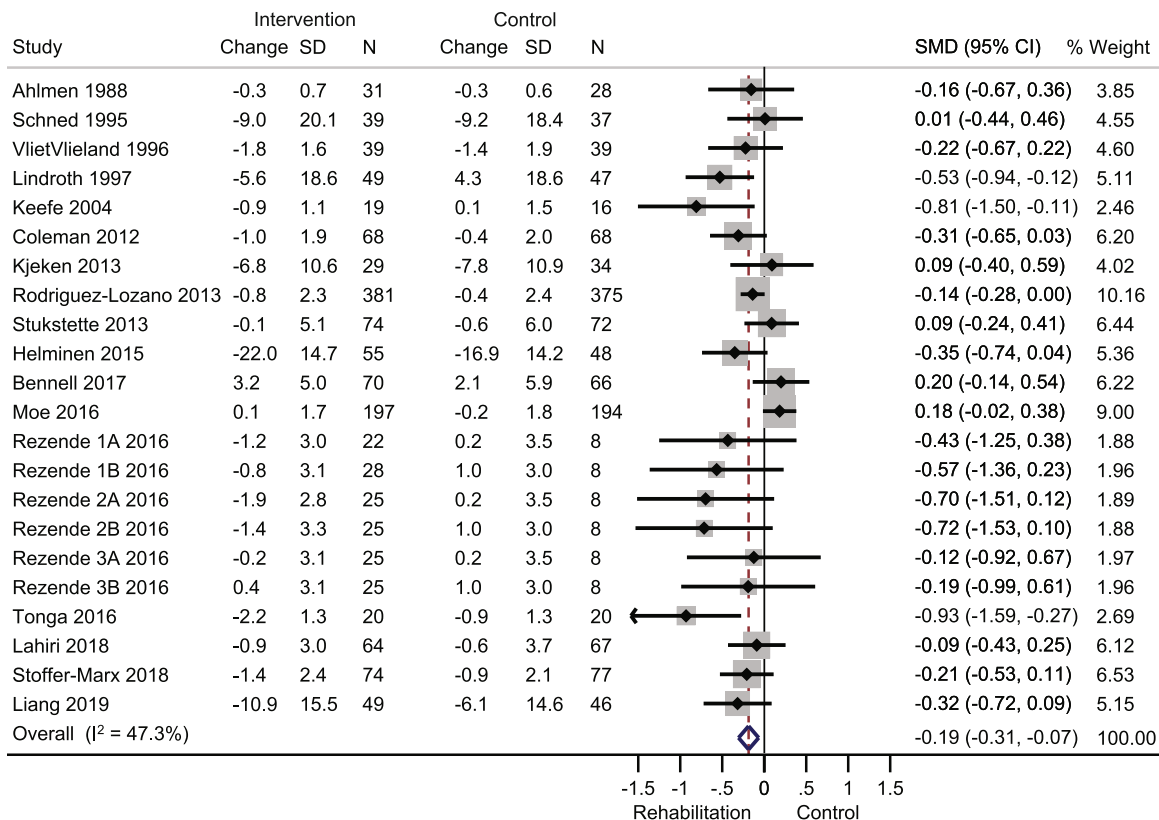

Figure 2. Forest plot of the standardized mean difference (SMD adjusted into Hedges' g) of changes in patient-reported pain intensity between the intervention and control groups. Estimates were calculated using a restricted maximum likelihood meta-analysis model. 95% CI = 95% confidence interval; N = number of patients; SMD = standardized mean difference.
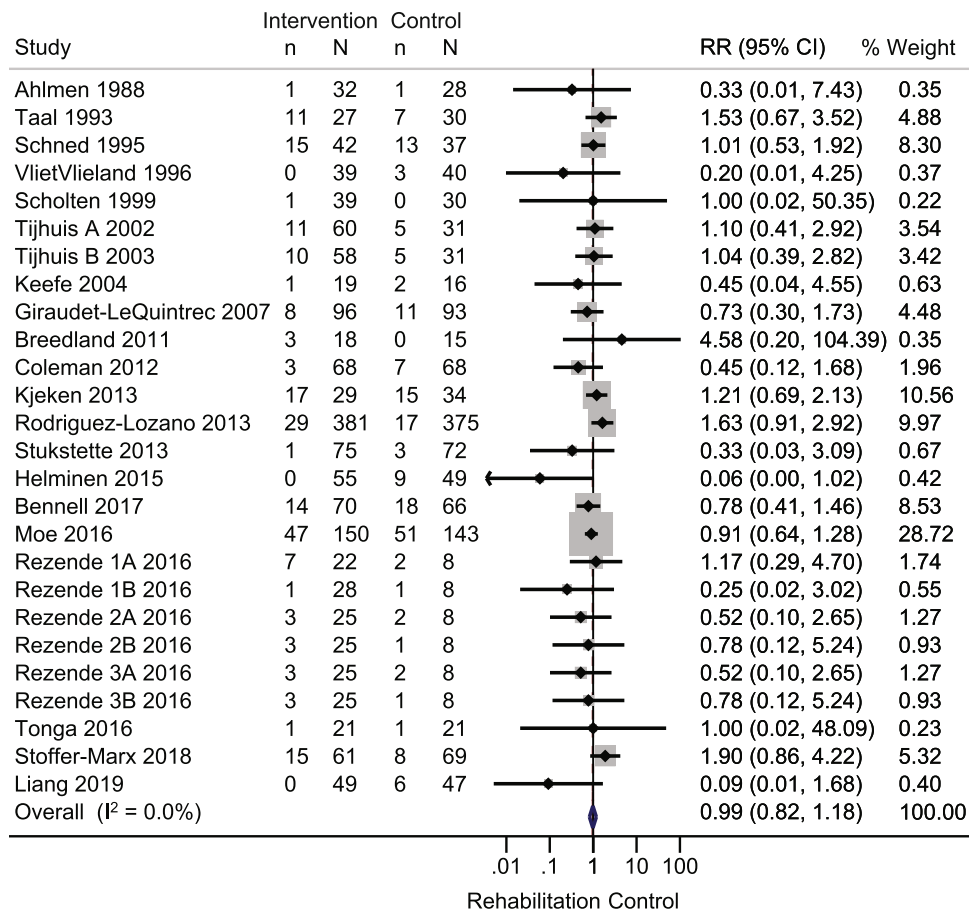
Study	Intervention n	Intervention N	Control n	Control N		RR (95% CI)	% Weight
Ahlmen 1988	1	32	1	28		0.33 (0.01, 7.43)	0.35
Taal 1993	11	27	7	30		1.53 (0.67, 3.52)	4.88
Schned 1995	15	42	13	37		1.01 (0.53, 1.92)	8.30
VlietVlieland 1996	0	39	3	40		0.20 (0.01, 4.25)	0.37
Scholten 1999	1	39	0	30		1.00 (0.02, 50.35)	0.22
Tijhuis A 2002	11	60	5	31		1.10 (0.41, 2.92)	3.54
Tijhuis B 2003	10	58	5	31		1.04 (0.39, 2.82)	3.42
Keefe 2004	1	19	2	16		0.45 (0.04, 4.55)	0.63
Giraudet-LeQuintrec 2007	8	96	11	93		0.73 (0.30, 1.73)	4.48
Breedland 2011	3	18	0	15		4.58 (0.20, 104.39)	0.35
Coleman 2012	3	68	7	68		0.45 (0.12, 1.68)	1.96
Kjeken 2013	17	29	15	34		1.21 (0.69, 2.13)	10.56
Rodriguez-Lozano 2013	29	381	17	375		1.63 (0.91, 2.92)	9.97
Stukstette 2013	1	75	3	72		0.33 (0.03, 3.09)	0.67
Helminen 2015	0	55	9	49		0.06 (0.00, 1.02)	0.42
Bennell 2017	14	70	18	66		0.78 (0.41, 1.46)	8.53
Moe 2016	47	150	51	143		0.91 (0.64, 1.28)	28.72
Rezende 1A 2016	7	22	2	8		1.17 (0.29, 4.70)	1.74
Rezende 1B 2016	1	28	1	8		0.25 (0.02, 3.02)	0.55
Rezende 2A 2016	3	25	2	8		0.52 (0.10, 2.65)	1.27
Rezende 2B 2016	3	25	1	8		0.78 (0.12, 5.24)	0.93
Rezende 3A 2016	3	25	2	8		0.52 (0.10, 2.65)	1.27
Rezende 3B 2016	3	25	1	8		0.78 (0.12, 5.24)	0.93
Tonga 2016	1	21	1	21		1.00 (0.02, 48.09)	0.23
Stoffer-Marx 2018	15	61	8	69		1.90 (0.86, 4.22)	5.32
Liang 2019	0	49	6	47		0.09 (0.01, 1.68)	0.40
Overall ($I^2 = 0.0\%$)						0.99 (0.82, 1.18)	100.00

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Rehabilitation Control

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

Risk of bias across studies. Stratified analyses of patient-reported pain on selection bias, attrition bias, 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 biases.

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 inflammatory arthritis (SMD −0.22 [95% CI −0.47, 0.03]) and OA (SMD −0.17 [95% CI −0.34, 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 chronic widespread pain at baseline, and coping/self-management skills at baseline.

Sensitivity analyses using a fixed-effects model indicated no sign of publication bias for any of the outcomes. However, the visual inspection of funnel plots and significant result from Egger's test indicated a high risk of publication bias for pain and self-reported disability/physical function (Table 2 and Supplementary Figures 15–26, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24816).

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

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

Outcome measure	Trials, no. (n = 22)	Patients, no. (n = 3,750)	Mean follow-up, months	Serious risk of bias†	Inconsistency, I²‡	Serious indirectness§	Serious imprecision¶	Publication bias#	Relative measure, SMD or RR (95% CI)	Certainty of evidence
Pain	17	2,906	9.3	Yes	47.3	No	No	0.02	−0.19 (−0.31, −0.07)	Moderate
Patient global assessment score	9	1,745	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	3,292	9.7	Yes	51.8	No	Yes	0.43	−0.09 (−0.21, 0.03)	Low
Health-related quality of life	12	2,543	9.2	Yes	33.9	No	No	0.57	−0.07 (−0.19, 0.05)	Moderate
Mental well-being	14	1,880	8.6	Yes	39.8	No	Yes	0.53	−0.11 (−0.24, 0.03)	Low
Fatigue	8	1,151	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	NA	0.08 (−0.26, 0.41)	Very low
Physician global assessment score	1	80	24	Yes	NA	No	Yes, twice	NA	−0.72 (−1.18, −0.26)	Very low
Reduction in pain intensity ≥30%	1	146	6.0	Yes	NA	No	Yes, twice	NA	RR 1.24 (0.80, 1.91)	Very low
Number of withdrawals	20	3,265	9.8	Yes	0.0	No	No	0.29	RR 0.99 (0.82, 1.18)	Moderate
Adverse events	10	1,164	9.0	Yes	0.0	No	Yes	0.50	RR 1.18 (0.47, 2.94)	Low
Serious adverse events	10	1,164	9.0	Yes	0.0	No	Yes	0.30	RR 0.96 (0.37, 2.52)	Low

* 95% CI = 95% confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NA = not available; RR = relative risk; SMD = standardized mean difference.
† Assessed using Cochrane risk of bias instrument.
‡ An I² value between 75% and 100% indicates that heterogeneity may be considerable, resulting in a downgrade for inconsistency.
§ Refers to the intervention, patients, or outcomes being different from the research question.
¶ Refers to situations in which the 95% CI includes both benefit and harm, unless there is no difference in effect.
# Tested using visual inspection of funnel plots and Egger's test. P values of <0.05 suggest the presence of publication bias.

Table 3. Stratified analyses of pain: primary outcome[*]

Variable	Trials, no.	Effect size (95% CI)	T²	Inconsistency explained, %	P for interaction
All trials, REML-based (I² = 47.3%)	17	−0.19 (−0.31, −0.07)	0.033	NA	NA
All trials, fixed-effects model	17	−0.13 (−0.20, −0.05)	0.030	NA	NA
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-related 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: 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. 95% CI = 95% confidence interval; NA = not available.

aspect (SMD −0.31 [95% CI −0.54, −0.07]) and the social aspect (SMD −0.26 [95% CI −0.42, −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-month 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, –1.36], MCID = 16 mm) and patient global assessment score (WMD –2.41 mm [95% CI –4.81, –0.07], MCID = 15 mm). No differences were observed among the remaining patient-reported outcome measures: 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, –2.03], MCID = 12 mm), large improvements in physician global assessment score (WMD –12.24 mm [95% CI –20.06, –4.42], MCID = 14 mm), and no difference in inflammation. For measures of harm, no difference was observed for the number of withdrawals or risk of adverse events or serious adverse events.

The meta-regression analysis for contact time indicated that an increase in hours of patient contact with health care professionals led to an increased effect of the intervention, or on the other hand, indicated 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 inflammatory arthritis 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.

Though some outcome measures proved statistically significant, the effect of biopsychosocial rehabilitation did not reach the MCID for any outcome measure, bringing into question 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, multidisciplinary clinics should consider allocating resources to ensure that their rehabilitative effort has a sufficient extent and is delivered by specialists in their respective fields.

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.

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 inflammatory arthritis trials included only RA patients; therefore, the effect of the intervention may differ in other inflammatory arthritis conditions. The majority of studies reported their measures at our preferred 12 months of follow-up, but a large proportion of the studies either reported at an earlier time point (41%) or later (14%). However, the median follow-up time for the pain outcome across trials was 12 months. This timing may have caused an overestimation of effect, as the effects of the interventions presumably diminish over time. No studies reported sufficiently on concomitant conditions, and thus we were unable to investigate to what 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 1 study demonstrated a mean age of ≥65 years, 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 age of 60–75 years. Age ranges of participants were reported in 6 studies, in which only Scholten et al (54) and Tijhuis et al (46) recruited participants age >75 years (79 years and 85 years, 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 that biopsychosocial factors, and thus interventions, are influenced by age. Therefore, our findings should be interpreted carefully when applied to an older population.

Future trials should include an economic analysis of their interventions to allow cost-benefit analyses. Concomitant conditions and treatments of participants should be reported and discussed in regard 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), 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 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.

From the present evidence synthesis, we found a significant but clinically small average beneficial effect following the use of biopsychosocial rehabilitation on patient-reported pain (WMD −3.69 mm [95% CI −6.01, −1.36], MCID = 16 mm) in patients with inflammatory arthritis and OA, with a small effect on observed disability (WMD −6.90 mm [95% CI −11.57, −2.03], MCID = 12 mm), and close to no improvement for the remaining outcome measures. No harm was done, as there were no differences for the number of withdrawals or adverse events. However, significant methodologic 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 finding 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Christensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Pedersen, Thinggaard, Geenen, Rasmussen, De Wit, March, Mease, Choy, Conaghan, Simon, Hansen, Tarp, Juhl, Nielsen, Amris, Christensen.

Acquisition of data. Pedersen, Thinggaard, Amris, Christensen.

Analysis and interpretation of data. Pedersen, Thinggaard, Schiøttz-Christensen, Amris, Christensen.

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