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Moderators of the effect of therapeutic exercise for knee and hip osteoarthritis: a systematic review and individual participant data meta-analysis

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See **Online** for appendix

Summary

Background Many international clinical guidelines recommend therapeutic exercise as a core treatment for knee and hip osteoarthritis. We aimed to identify individual patient-level moderators of the effect of therapeutic exercise for reducing pain and improving physical function in people with knee osteoarthritis, hip osteoarthritis, or both.

Methods We did a systematic review and individual participant data (IPD) meta-analysis of randomised controlled trials comparing therapeutic exercise with non-exercise controls in people with knee osteoarthritis, hip osteoarthritis, or both. We searched ten databases from March 1, 2012, to Feb 25, 2019, for randomised controlled trials comparing the effects of exercise with non-exercise or other exercise controls on pain and physical function outcomes among people with knee osteoarthritis, hip osteoarthritis, or both. IPD were requested from leads of all eligible randomised controlled trials. 12 potential moderators of interest were explored to ascertain whether they were associated with short-term (12 weeks), medium-term (6 months), and long-term (12 months) effects of exercise on self-reported pain and physical function, in comparison with non-exercise controls. Overall intervention effects were also summarised. This study is prospectively registered on PROSPERO (CRD42017054049).

Findings Of 91 eligible randomised controlled trials that compared exercise with non-exercise controls, IPD from 31 randomised controlled trials (n=4241 participants) were included in the meta-analysis. Randomised controlled trials included participants with knee osteoarthritis (18 [58%] of 31 trials), hip osteoarthritis (six [19%]), or both (seven [23%]) and tested heterogeneous exercise interventions versus heterogeneous non-exercise controls, with variable risk of bias. Summary meta-analysis results showed that, on average, compared with non-exercise controls, therapeutic exercise reduced pain on a standardised 0–100 scale (with 100 corresponding to worst pain), with a difference of –6·36 points (95% CI –8·45 to –4·27, borrowing of strength [BoS] 10·3%, between-study variance [τ^2] 21·6) in the short term, –3·77 points (–5·97 to –1·57, BoS 30·0%, τ^2 14·4) in the medium term, and –3·43 points (–5·18 to –1·69, BoS 31·7%, τ^2 4·5) in the long term. Therapeutic exercise also improved physical function on a standardised 0–100 scale (with 100 corresponding to worst physical function), with a difference of –4·46 points in the short term (95% CI –5·95 to –2·98, BoS 10·5%, τ^2 10·1), –2·71 points in the medium term (–4·63 to –0·78, BoS 33·6%, τ^2 11·9), and –3·39 points in the long term (–4·97 to –1·81, BoS 34·1%, τ^2 6·4). Baseline pain and physical function moderated the effect of exercise on pain and physical function outcomes. Those with higher self-reported pain and physical function scores at baseline (ie, poorer physical function) generally benefited more than those with lower self-reported pain and physical function scores at baseline, with the evidence most certain in the short term (12 weeks).

Interpretation There was evidence of a small, positive overall effect of therapeutic exercise on pain and physical function compared with non-exercise controls. However, this effect is of questionable clinical importance, particularly in the medium and long term. As individuals with higher pain severity and poorer physical function at baseline benefited more than those with lower pain severity and better physical function at baseline, targeting individuals with higher levels of osteoarthritis-related pain and disability for therapeutic exercise might be of merit.

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Introduction

Osteoarthritis, particularly of the knee and hip, is a leading cause of disability worldwide, with an estimated global age-standardised point prevalence of 3754·2 (95% uncertainty interval [UI] 3389·4–4187·6) per 100 000 people in 2017.[1] This is an increase of 9·3% (95% UI 8·0–10·7) from 1990.[1] The burden of osteoarthritis is rising with an ageing, increasingly obese population.[2] International clinical guidelines, such as those from the American College of

Research in context

Evidence before this study

Although international clinical guidelines consistently recommend therapeutic exercise for individuals with knee and hip osteoarthritis, improvements in pain and physical function are, on average, small to moderate compared with non-exercise controls. This could be due to individual variability in response to exercise. Previous exploratory secondary analyses of randomised controlled trials of knee osteoarthritis provide tentative evidence that not all people with osteoarthritis respond similarly to therapeutic exercise. However, these post-hoc analyses have low statistical power to detect treatment-effect moderators. Individual participant data (IPD) meta-analyses can provide a more robust investigation of individual response to therapeutic exercise. This approach enables inclusion of more participants and has greater power to identify treatment-effect moderators and avoid the risk of aggregation (ecological) bias. We did a systematic review and IPD meta-analysis to explore whether potential moderators were associated with short-term (12 weeks), medium-term (6 months), and long-term (12 months) effects of exercise on pain and physical function among people with knee osteoarthritis, hip osteoarthritis, or both, in comparison with non-exercise controls. Overall intervention effects were also summarised. We searched Medline, EMBASE, Allied and Complementary Medicine Database, Health Management Information Consortium, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Controlled Trials Register, and the NHS Economic Evaluation Database from March 1, 2012, to Feb 25, 2019, and, in collaboration with the OA Trial Bank, invited leads of eligible randomised controlled trials to share IPD for inclusion in our IPD meta-analysis.

Added value of this study

This study is, to the best of our knowledge, the first IPD meta-analysis of therapeutic exercise for people with knee or hip osteoarthritis, or both, and the largest international IPD meta-analysis of an intervention for osteoarthritis. It highlights a small, positive overall effect of therapeutic exercise on pain and physical function in individuals with knee or hip osteoarthritis, compared with non-exercise controls. However, this benefit is of questionable clinical importance, particularly in the medium and long term. Most importantly, our findings suggest that individuals with higher pain severity and poorer physical function at baseline might benefit more from therapeutic exercise than those with lower pain severity and better physical function at baseline.

Implications of all the available evidence

Given the small overall positive effect of therapeutic exercise on pain and physical function compared with non-exercise controls (which is of questionable clinical importance), targeting individuals with higher levels of osteoarthritis-related pain and disability for therapeutic exercise might be of merit.

Rheumatology/Arthritis Foundation,[3] Osteoarthritis Research Society International,[4] and the UK National Institute for Health and Care Excellence,[5] recommend therapeutic exercise as a core treatment for knee osteoarthritis, hip osteoarthritis, or both. Therapeutic exercise (subsequently referred to as exercise) involves participation in physical activity that is planned, structured, repetitive, and purposeful for the improvement or maintenance of a specific health condition such as osteoarthritis. It encompasses general aerobic exercise, strengthening, flexibility, balance, or body-region specific exercises.[6] Systematic reviews and meta-analyses of randomised controlled trials have consistently shown that such exercise is beneficial for pain and physical function.[7–10] However, the observed effect sizes are small to moderate compared to non-exercise controls, can decline over time, and only up to approximately 50% of participants achieve a clinically important treatment response.[11–14] This could be due to individual variability in response to exercise. Better targeting of individuals with knee osteoarthritis, hip osteoarthritis, or both, for exercise could potentially lead to improved overall mean treatment effects and reduced variability in outcomes, as well as more efficient use of health-care services.

Some previous research has examined whether outcomes from exercise for individuals with osteoarthritis vary for subgroups defined by individual-level characteristics (treatment-effect moderators).[15] Exploratory secondary analyses of randomised controlled trials provide tentative evidence that not all people with osteoarthritis respond similarly to exercise.[15] However, these post-hoc analyses have low statistical power to detect significant subgroup effects.[16] A more robust method to investigate individual response to exercise is to conduct a meta-analysis of individual participant data (IPD).[17,18] This approach enables the inclusion of more participants and has greater power to identify treatment-effect moderators, and avoids the risk of aggregation bias and study-level confounding.[17,18]

The aim of the Subgrouping and TargetEd Exercise pRogrammes for knee and hip OsteoArthritis study (STEER OA) was to identify moderators of the effect of exercise in people with knee osteoarthritis, hip osteoarthritis, or both, thus facilitating better targeting of future exercise interventions. Specific analytical objectives were to ascertain the short-term (12 weeks), medium-term (6 months), and long-term (12 months) overall effects of exercise on pain and function in people with knee osteoarthritis, hip osteoarthritis, or both, compared with non-exercise controls. To address the main aim, we then identified individual-level characteristics (ie, treatment-effect moderators) that are

associated with the short-term, medium-term, and long-term effects of exercise on pain and physical function.

Methods

Search strategy and selection criteria

We updated a previous systematic review[8] and conducted an IPD meta-analysis with embedded Patient and Public Involvement and Engagement (PPIE), reported with the PRISMA IPD systematic reviews guidelines.[19] The full protocol has previously been published.[20] Ethical approval was not required as no new data were collected.[21,22] This study is prospectively registered on PROSPERO (CRD42017054049). The other aims and analytical objectives of STEER OA, as outlined in the protocol, will be addressed separately and reported elsewhere.

We updated our previous search strategy to identify randomised controlled trials comparing the effects of exercise with non-exercise or other exercise controls on pain and physical function outcomes among people with knee or hip osteoarthritis, or both.[8] The search was re-run from the date of the previous search (March 1, 2012) up to Feb 25, 2019, in the following electronic databases: Medline, EMBASE, Allied and Complementary Medicine Database (AMED), Health Management Information Consortium (HMIC), Cumulative Index to Nursing and Allied Health Literature (CINAHLPlus), Web of Science, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane Controlled Trials Register (CCTR), and the NHS Economic Evaluation Database (NHS EED); the search strategy is summarised in the appendix (pp 1–2). Bibliographies of relevant review articles and selected articles were also examined. No language restrictions were applied. Two investigators (either MAH, JR, ELH, JQ, or AL) independently screened titles and abstracts and subsequent full texts to identify which randomised controlled trials met the eligibility criteria (appendix pp 3–4). In line with the specific analytical objectives detailed above, randomised controlled trials that compared exercise with non-exercise controls were the focus of this study.

In collaboration with the OA Trial Bank, we requested IPD from leads of all eligible randomised controlled trials. The terms of collaboration were specified in a data sharing agreement. De-identified, transferred data were assessed for integrity. Original results from randomised controlled trials were re-analysed (by MH) to ensure that they could be reproduced. Discrepancies were discussed and clarified with trial leads; if not resolved, the data were not included in the meta-analysis. After harmonisation of potential treatment-effect moderators (appendix pp 5–6) and outcome measures, individual trial datasets were combined within Stata 16 to form a new master dataset with a variable added to indicate the original randomised controlled trial.

For the **data sharing agreement** see https://www.oatrialbank.com/procedures/

Data analysis

From the original publications and IPD, the following study-level data were extracted into tables: sample size, site of osteoarthritis (knee, hip, or mixed), exercise intervention or interventions, comparator, and outcome assessment.[20]

Before obtaining IPD and analysing the data, a consensus process was undertaken with a large international group of STEER OA collaborators to identify the most important potential treatment-effect moderators for exercise.[23] The following moderators that could be considered in the available IPD were prioritised: pain severity, physical function, age, BMI, physical activity, arthritis self-efficacy, mental wellbeing, co-morbidity, muscle strength (quadriceps), educational attainment (as a proxy measure of socioeconomic status), pain duration, and radiographic joint structure (appendix pp 5–6). Outcomes of interest were self-reported pain and physical function in the short term (nearest timepoint to 12 weeks), medium term (nearest timepoint to 6 months), and long term (nearest timepoint to 12 months). If more than one measure of pain or physical function was used within randomised controlled trials, we chose the highest in the hierarchy of outcome measures, as recommended by the Cochrane Musculoskeletal Review Group.[20,24]

We used the Cochrane Collaboration's tool (version 1.0) for assessing the risk of bias, based on their published reports.[25] Two investigators (either MAH, JR, ELH, JQ, or AL) independently graded the risk of bias (unclear, high, or low) for sequence generation, allocation concealment, masking of outcome assessors, incomplete outcome data, selective outcome reporting and other reasons (eg, uncertainty about baseline data being collected before randomisation). If necessary, the IPD obtained for each randomised controlled trial were used to inform the risk of bias assessment.

All meta-analyses used a two-stage approach whereby each randomised controlled trial was analysed separately in the first stage (which accounts for clustering of participants within randomised controlled trials) to produce study-specific estimates, which were then synthesised in the second stage to produce summary meta-analysis results.[17,18] All analyses were done in Stata 16 on an intention-to-treat principle, with all estimates reported with 95% CIs. Under a missing-at-random assumption, individuals and randomised controlled trials were included even if they did not record outcomes at all timepoints of interest, as partially missing outcome values were handled naturally in the first stage (via a longitudinal model) and second stage (via a multivariate meta-analysis model).[26,27]

This study had two objectives. First, for the meta-analysis to estimate an overall treatment effect, all available comparisons were grouped into any exercise intervention versus non-exercise controls. Outcomes were continuous and, given the use of different scales

across randomised controlled trials, were standardised to a 0–100 scale (pain: 0=no pain, 100=worst pain; physical function: 0=best physical function, 100=worst physical function). Longitudinal models were fitted in the first stage to account for participant-level correlation between outcome values at multiple timepoints,[26] with time included as a discrete factor (12 weeks, 6 months, or 12 months). For each randomised controlled trial, the model included baseline pain or function, treatment, time, and treatment-by-time interaction terms. The second stage required a multivariate meta-analysis framework, which jointly synthesises the treatment-effect estimates from multiple timepoints across randomised controlled trials, accounting for within-trial and across-trial correlations between the multiple timepoints.[27] The correlation matrix was unstructured, both within and between studies, and thus allows distinct variances for each timepoint and distinct correlations between each pair of timepoints. Given the anticipated heterogeneity in treatment effects across randomised controlled trials (eg, due to variability in participant characteristics and exercise interventions), we assumed a multivariate random-effects meta-analysis model to estimate the summary results of interest using restricted maximum likelihood estimation, and with 95% CIs for the summary effect derived with the Hartung-Knapp approach for multivariate meta-analyses.[28] Heterogeneity in treatment effects across randomised controlled trials was summarised by the estimated between-trial variance (τ^2). The gain in information from analysing correlated outcomes using a multivariate meta-analysis over a univariate meta-analysis was quantified with the borrowing of strength (BoS) statistic.[29]

Second, IPD were further analysed to examine treatment-effect modification at the individual level; that is, whether individual participant characteristics (potential moderators) were associated with differences in the effect of exercise compared with non-exercise controls. Under a missing-at-random assumption, missing baseline characteristics within randomised controlled trials were imputed (before stage 1) through the following methods: continuous measures were imputed by use of mean imputation and binary measures with the missing indicator method, since such single imputation approaches are appropriate for randomised controlled trials.[30] To test effect modification, longitudinal models were fitted as described above for the first objective and also included interaction terms between the intervention and potential moderators of interest. The pooled interaction effects for each timepoint were obtained by a multivariate random-effects meta-analysis of the interaction effect estimates from each randomised controlled trial. We explored non-linear relationships for the potential moderators since a linear association might not always be appropriate. To fit a non-linear relationship, we modelled the potential treatment-effect moderator using restricted cubic splines with 3 knots.[17,31] Longitudinal models were fitted with the baseline pain or function, treatment, time, treatment-by-time interaction terms, and the interaction terms between the intervention and potential moderators. The potential moderator of interest was included in the longitudinal model with the spline functions that had been fitted. The pooled interaction effects for each timepoint for each spline function were obtained by a multivariate random-effects meta-analysis of the parameter estimates defining the (non-linear) interaction estimate from each randomised controlled trial. These were plotted with the respective 95% CIs, such that the function of the interaction could be visually explored.

In sensitivity analyses, effect estimates were explored with data only from randomised controlled trials that were deemed to be at a low risk of bias across all domains assessed. Contour-enhanced funnel plots and tests for asymmetry were used to investigate small study effects and the potential for publication bias.

Patient and public involvement

A STEER OA Patient Advisory Group consisting of five members of the public with experience of exercise and osteoarthritis was convened ahead of acquiring study funding and this advisory group was actively involved in all project stages, including informing the research objectives and outcomes of interest, identifying and prioritising important potential moderators for analyses, and interpretation of results, as well as clinical and research implications (described in more detail elsewhere[32]).

Role of the funding source

The funders had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the Article for publication.

Results

We downloaded 5808 unique references from the updated electronic search into Covidence, which were combined with the 60 randomised controlled trials from the original systematic review, and nine randomised controlled trials identified from other sources (including manually checking reference lists and collaborator knowledge). After screening the title and abstract, 433 full-text articles were assessed. Following full-text screening, 133 randomised controlled trials met the inclusion criteria. Of the 91 randomised controlled trials that compared exercise with non-exercise controls (9519 participants), we were unable to gain permission to include IPD from 52 studies. This was due to not being able to establish contact (n=29), communications not resulting in IPD sharing despite extensive effort (n=14), or IPD being unavailable (n=9). We obtained formal written permission to analyse 39 IPD datasets. However,

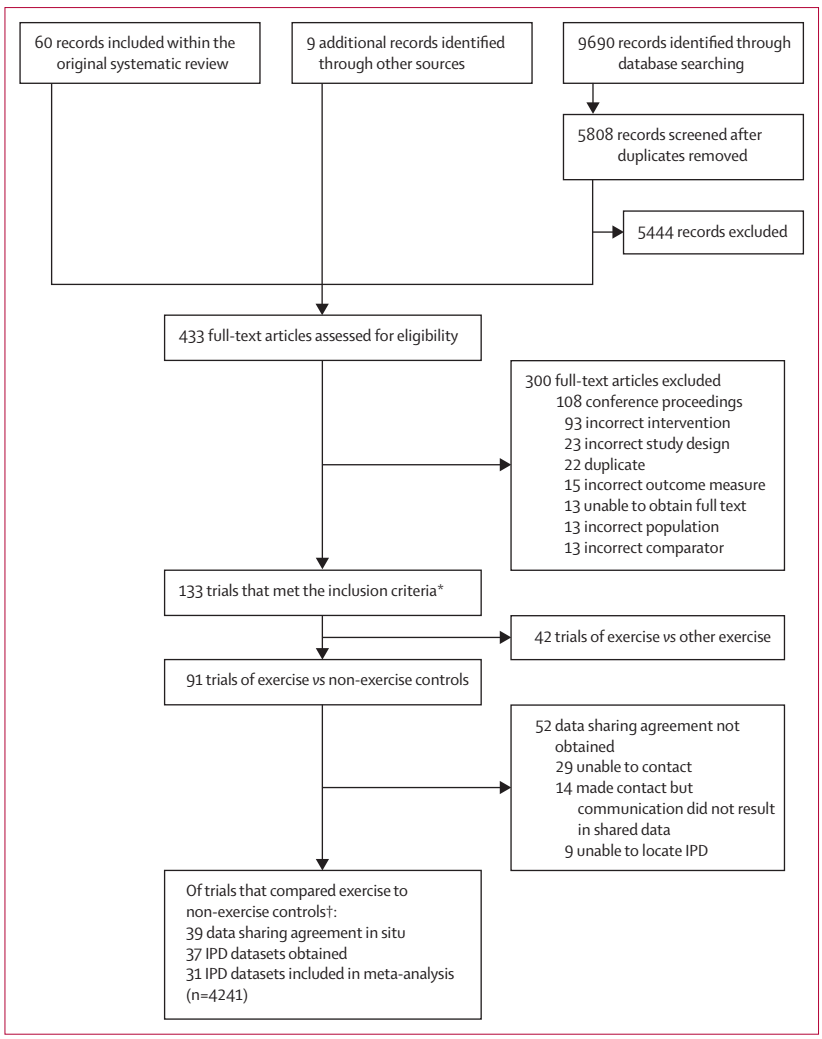

Figure 1: **Study selection**
*Our broad search strategy aimed to identify randomised controlled trials comparing the effect of exercise with non-exercise or other exercise controls on pain and physical function outcomes among people with knee or hip osteoarthritis, or both. Only randomised controlled trials that compared exercise with non-exercise controls were the focus of this study. †Data were not delivered for two randomised controlled trials (no reason was provided), and data were delivered but not useable from six randomised controlled trials.

data from two randomised controlled trials were not subsequently shared, despite reminders. Of the 37 datasets shared, six were unusable (eg, data not coded or labelled, imputed dataset). Therefore, 31 randomised controlled trials that compared exercise with non-exercise controls, comprising 4241 participants, were included in the meta-analysis (figure 1).[33–63]

The 31 randomised controlled trials for which IPD were included were predominantly published in the past 15 years (24 [77%]), and were done in different continents, including Europe (18 [58%]), North and South America (seven [23%]), and Australasia (six [19%]; table).[33–63] Randomised controlled trials were of variable size (32–786 participants) and included participants with knee (18 [58%]), hip (six [19%]), or mixed knee and hip (seven [23%]) osteoarthritis. Within randomised controlled trials, the proportion of female participants ranged from 25% to 100%, the mean age ranged from 57 years to 79 years, and the mean BMI ranged from 25 kg/m² to 36 kg/m² (appendix pp 10–14). Overall, participants had a mean baseline pain score (on a standardised 0–100 scale) of 39·7 (SD 22·3, range 0–100), and a median baseline physical function (on a standardised 0–100 scale) of 36·8 (IQR 20·3–52·9, range 0–100).

Within the 31 randomised controlled trials, 37 different exercise interventions were tested (appendix pp 15–19). Most were land based (31 [84%]), included different types of exercise (15 [41%] mixed, 14 [38%] strengthening, six [16%] general aerobic [eg, walking], and two [5%] mind-body [eg, yoga]), and were predominantly of moderate intensity (31 [84%]) and low impact (34 [92%]). The duration of exercise interventions varied (27 [73%] were ≤12 weeks, ten [27%] were >12 weeks; range 4–104 weeks). The number of exercise sessions also varied (range 6–728), as did exercise delivery (17 [46%] individual sessions, 15 [41%] group sessions, two [5%] individual and group sessions, one [3%] based on preference, and two [5%] not stated). 24 (65%) exercise interventions were supervised, seven (19%) included supervised and unsupervised home exercise, and six (16%) comprised unsupervised home exercise only. Most exercise interventions were delivered face to face in person (33 [89%]), most commonly by a health-care professional (19 [51%]) or exercise instructor (ten [27%]).

Exercise interventions were compared with heterogenous non-exercise controls, including being on a waiting list or no intervention (n=14), education or advice alone (n=6; either delivered at minimal intensity such as leaflet only [n=3] or as a more intense education or self-management programme [n=3]), usual medical care (n=5), maintenance of usual medication or activities (n=4), or another form of attention control (n=2; table).

Although some potential treatment-effect moderators were frequently measured in randomised controlled trials (eg, age, pain severity, physical function, and BMI), others were less common (eg, physical activity, arthritis self-efficacy, education, and radiographic joint structure; appendix pp 5–6). The majority of randomised controlled trials (27 [87%]) had a short-term follow-up. 14 (45%) had a medium-term follow-up and 13 (42%) had a long-term follow-up. The most common measures of pain were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[64] (17 [55%]) and overall pain measured by a visual analogue scale or numerical rating scale (nine [29%]). The majority of randomised controlled trials (24 [77%]) measured physical function via the WOMAC physical function subscale[64] (table).

The risk of bias from included randomised controlled trials varied (appendix p 20). Selective reporting was deemed as having an unclear or high risk of bias in one (3%) randomised controlled trial, as was random

	Country	Osteoarthritis site*	Osteoarthritis diagnosis†	Total participants‡	Intervention or interventions	Pain outcome‡§	Function outcome¶	Follow-up data available‡‖	Funding source
Allen et al (2018)[33]	USA	Knee	X-ray, clinical, or self-report	350 (210 relevant)	1) internet-based exercise training; 2) control (waiting list)	WOMAC pain subscale	WOMAC disability subscale	Short term, long term	Patient-Centered Outcomes Research Institute Award
Bearne et al (2011)[34]	UK	Hip	Clinical	48	1) rehabilitation group; 2) control (usual GP care)	WOMAC pain subscale	WOMAC disability subscale	Short term, medium term	Physiotherapy Research Foundation
Bennell et al (2010)[35]	Australia	Knee	Combined	89	1) hip strengthening group; 2) control (no intervention)	Pain overall (NRS)	WOMAC disability subscale	Short term	National Health and Medical Research Council
Bossen et al (2013)[36]	Netherlands	Mixed	Self reported	199	1) automated web-based physical activity intervention; 2) control (waiting list)	Pain overall (VAS)	Composite disability score other than WOMAC (KOOS/HOOS function)	Short term, long term	Not stated
Brosseau et al (2012)[37]	Canada	Knee	Combined	222	1) walking and behavioural intervention; 2) walking intervention; 3) control (education leaflet)	WOMAC pain subscale	WOMAC disability subscale	Short, medium, and long term	Canadian Institutes of Health Research; University Research Chair; the Ministry of Human Resources
Cochrane et al (2005)[38]	UK	Mixed	Clinical	312	1) water-based exercise; 2) control (education leaflet)	WOMAC pain subscale	WOMAC disability subscale	Medium term, long term	National Institute of Health Research, Health Technology Assessment
de Rooij et al (2017)[39]	Netherlands	Knee	Clinical	126	1) individualised, co-morbidity adapted exercise programme; 2) control (waiting list)	Pain overall (NRS)	WOMAC disability subscale	Short term, medium term	Merck Sharp & Dohme; Royal Dutch Society for Physical Therapy
Fernandes et al (2010)[40]	Norway	Hip	Combined	109	1) patient education plus supervised exercise; 2) control (patient education alone: "hip school", 1× individual physical therapy visit, 3× group based sessions, 20 h of education in total)	WOMAC pain subscale	WOMAC disability subscale	Short term, long term	Norwegian Foundation for Health and Rehabilitation; Norwegian Rheumatism Association; South Eastern Norway Regional Health Authority
Fransen et al (2007)[41]	Australia	Mixed	Clinical	152	1) hydrotherapy classes; 2) Tai Chi classes; 3) control (waiting list)	WOMAC pain subscale	WOMAC disability subscale	Short term	National Arthritis and Musculoskeletal Conditions Improvements grant
French et al (2013)[42]	Ireland	Hip	Combined	143 (88 relevant)	1) exercise therapy; 2) control (waiting list)	Pain on activities other than walking (NRS)	WOMAC disability subscale	Short term	Health Research Board, Ireland
Hale et al (2012)[43]	New Zealand	Mixed	Self-reported osteoarthritis or pain	39	1) water-based programme; 2) control (time-matched computer training program)	WOMAC pain subscale	WOMAC disability subscale	Short, medium, and long term	Not Stated (no commercial party had a direct financial interest in the results)
Hay et al (2006)[44]	UK	Knee	Self-reported osteoarthritis or pain	325 (217 relevant)	1) community physical therapy; 2) control (advice leaflet reinforced by telephone call)	Pain overall (NRS)	WOMAC disability subscale	Short, medium, and long term	Arthritis Research Campaign; North Staffordshire Primary Care Research Consortium; Department of Health National Co-ordinating Centre for Research Capacity Development
Henriksen et al (2014)[45]	Denmark	Knee	Combined	48	1) supervised exercise therapy; 2) control (no intervention)	Other algofunctional scale (KOOS pain)	Composite disability score other than WOMAC (KOOS function)	Short term	Danish Council for Independent Research; Danish Physiotherapists association; Lundbeck Foundation; Oak Foundation

(Table continues on next page)

	Country	Osteoarthritis site*	Osteoarthritis diagnosis†	Total participants‡	Intervention or interventions	Pain outcome‡§	Function outcome¶	Follow-up data available‡‖	Funding source
(Continued from previous page)									
Hinman et al (2007)[46]	Australia	Mixed	Combined	71	1) aquatic physical therapy; 2) control (continue with usual daily activities and medication)	WOMAC pain subscale	WOMAC disability subscale	Short term	Australian Government Department of Health and Aging
Hopman-Rock and Westhoff (2000)[47]	Netherlands	Mixed	Self-reported osteoarthritis or pain	105	1) self-management and exercise programme; 2) control group (no intervention)	Other algofunctional scale (IRGL pain subscale)	Other algofunctional scale (IRGL mobility subscale)	Short term, medium term	The Netherlands Health Research and Development Council
Hurley et al (2007)[48]	UK	Knee	Self-reported osteoarthritis or pain	418	1) individual rehabilitation programme; 2) group rehabilitation programme; 3) usual primary care	WOMAC pain subscale	WOMAC disability Subscale	Short, medium, and long term	Arthritis Research Campaign
Krauß et al (2014)[49]	Germany	Hip	Clinical	218	1) exercise therapy; 2) placebo ultrasound treatment; 3) control (no intervention)	WOMAC pain subscale	WOMAC disability subscale	Short term	Supported with training materials by the companies Theraband and Ludwig Artzt; no other financial support stated
Levinger et al (2018)[50]	Australia	Knee	Clinical	28	1) high speed resistance training; 2) high speed resistance training plus balance exercises; 3) control (usual activities)	WOMAC pain subscale	WOMAC disability subscale	Short term	Arthritis Australia
Lim et al (2008)[51]	Australia	Knee	Combined	107	1) quadriceps strengthening group 2) control (no intervention)	Pain on walking (VAS)	WOMAC disability subscale	Short term	in part by United Pacific Industries through a grant from the Physiotherapy Research Foundation, Australia
Messier et al (2004)[52]	USA	Knee	Combined	316 (158 relevant)	1) exercise only; 2) control (education: group meetings 1xmonth for 3 months, monthly phone contact during months 4–6, contact every other month during months 7–18)	WOMAC pain subscale	WOMAC disability subscale	Medium term, long term	NIH grants
Multanen et al (2014)[53]	Finland	Knee	Combined	80	1) supervised progressive exercise; 2) control (no intervention)	WOMAC pain subscale	WOMAC disability subscale	Long term	Academy of Finland; Finnish Ministry of Education and Culture; Yrjö Jahnsson Foundation
Munukka et al (2016)[54]	Finland	Knee	Combined	87	1) aquatic resistance exercise; 2) control (usual level of physical activity)	WOMAC pain subscale	WOMAC disability subscale	Short term, long term	Academy of Finland; Social Insurance Institution of Finland; Finnish Cultural Foundation; Yrjo Jahnsson Foundation
Simão et al (2012)[55]	Brazil	Knee	Combined	32	1) Squat exercises on a vibratory platform; 2) squat exercises without vibration; 3) control (usual activities/physical activity)	WOMAC pain subscale	WOMAC disability subscale	Short term	Not stated
Tak et al (2005)[56]	Netherlands	Hip	Clinical	109	1) strength training; 2) control (no intervention)	Pain overall (VAS)	Other algofunctional scale (GARS)	Short term	Not stated

(Table continues on next page)

	Country	Osteoarthritis site*	Osteoarthritis diagnosis†	Total participants‡	Intervention or interventions	Pain outcome‡§	Function outcome¶	Follow-up data available‡‖	Funding source
(Continued from previous page)									
Takacs et al (2017)[57]	Canada	Knee	X-ray	40	1) Dynamic balance and strength training; 2) control (no intervention)	Pain overall (NRS)	WOMAC disability subscale	Short term	Arthritis Health Professions Association
Talbot et al (2003)[58]	USA	Knee	Combined	34	1) pedometer-driven walking program with arthritis self-management; 2) control (12-hour self-management program)	Other algofunctional scale (Pain rating scale from the McGill Pain Questionnaire)	None	Short term, medium term	Fund for Geriatric Medicine and Nursing; Johns Hopkins University; Intramural Research Program of the National Institute on Aging
Teirlinck et al (2016)[59]	Netherlands	Hip	Clinical	203	1) exercise therapy plus GP care; 2) control (GP care)	Pain overall (NRS)	Composite disability score other than WOMAC (HOOS function)	Short, medium, and long term	Netherlands Organization for Health Research and Development; Dutch Arthritis Foundation for their centre of excellence "Osteoarthritis in primary care"
Thomas et al (2002)[60]	UK	Knee	Self-reported osteoarthritis or pain	786 (391 relevant)	1) exercise therapy; 2) control (no intervention)	WOMAC pain subscale	WOMAC disability subscale	Medium term, long term	Department of Health
Tsai et al (2013)[61]	USA	Knee	Clinical	55	1) sun style Tai Chi classes; 2) control (health education, culture-related activities and other social activities. The length and frequency of activities closely matched sun style Tai Chi classes)	WOMAC pain subscale	WOMAC disability subscale	Short term, medium term	National Institute of Nursing Research; National Center for Research Resources
van Baar et al (2001)[62]	Netherlands	Mixed	Clinical	200	1) GP treatment plus physical therapist-led exercise; 2) GP treatment	Pain overall (VAS)	Other algofunctional scale (IRGL)	Short term, medium term	Dutch Fund of Investigative Medicine of the Dutch Health Insurance Council
Wallis et al (2017)[63]	Australia	Knee	X-ray	46	1) walking programme; 2) usual care (pharmacological and non-pharmacological treatment delivered at health service's hip and knee clinic. Advised not to include a prescription of physical activity in the 12-week study)	Pain overall (VAS)	WOMAC disability subscale	Short term	La Trobe University's research focus area on Sport, Exercise and Rehabilitation

GARS=Groningen Activity Restriction Scale. GP=General Practitioner. HOOS=Hip Disability and Osteoarthritis Outcome Score. IRGL=Impact of Rheumatic diseases on General Health and Lifestyle scale. KOOS=Knee Injury and Osteoarthritis Outcome Score. NRS=Numerical Rating Scale. VAS=Visual Analogue Scale. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index. *Osteoarthritis site categorised as knee, hip, or mixed (knee and hip). †Osteoarthritis diagnosis categorised as radiographic (X-ray), clinical, combined radiographic and clinical, and self-reported osteoarthritis or pain. ‡Data shown in the table are derived from individual participant data. Some slight discrepancies might therefore exist between data in the table and the published report. §Pain outcome chosen in accordance with the hierarchy recommended by the Cochrane Musculoskeletal Review Group,[24] as follows: pain overall; pain on walking; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale; pain on activities other than walking; WOMAC global scale; Lequesne osteoarthritis index global score; other algofunctional scale; patient's global assessment; physician's global assessment; other outcome; and no continuous outcome reported. ¶Physical function outcome chosen in accordance with the hierarchy recommended by the Cochrane Musculoskeletal Review Group,[24] as follows: global disability score, walking disability, WOMAC disability subscale, composite disability scores other than WOMAC, disability other than walking, WOMAC global scale, Lequesne osteoarthritis index global score, and other algofunctional scale. ‖Follow-up time period categorised as follows: short-term corresponds to nearest timepoint to 12 weeks, medium-term corresponds to nearest timepoint to 6 months, long-term corresponds to nearest timepoint to 12 months.

Table: **Summary of randomised controlled trials that shared individual participant data**

allocation in two (6%) randomised controlled trials. In five (16%) randomised controlled trials, blinding of outcome assessors was judged as having an unclear or high risk of bias, as was allocation concealment in six (19%) randomised controlled trials, and incomplete outcome data in eight (26%). Six (19%) randomised controlled trials were judged as having an unclear or high risk of bias from other sources resulting from a range of issues (eg, uncertainty about baseline data being collected before randomisation). In total, 14 (45%) randomised controlled

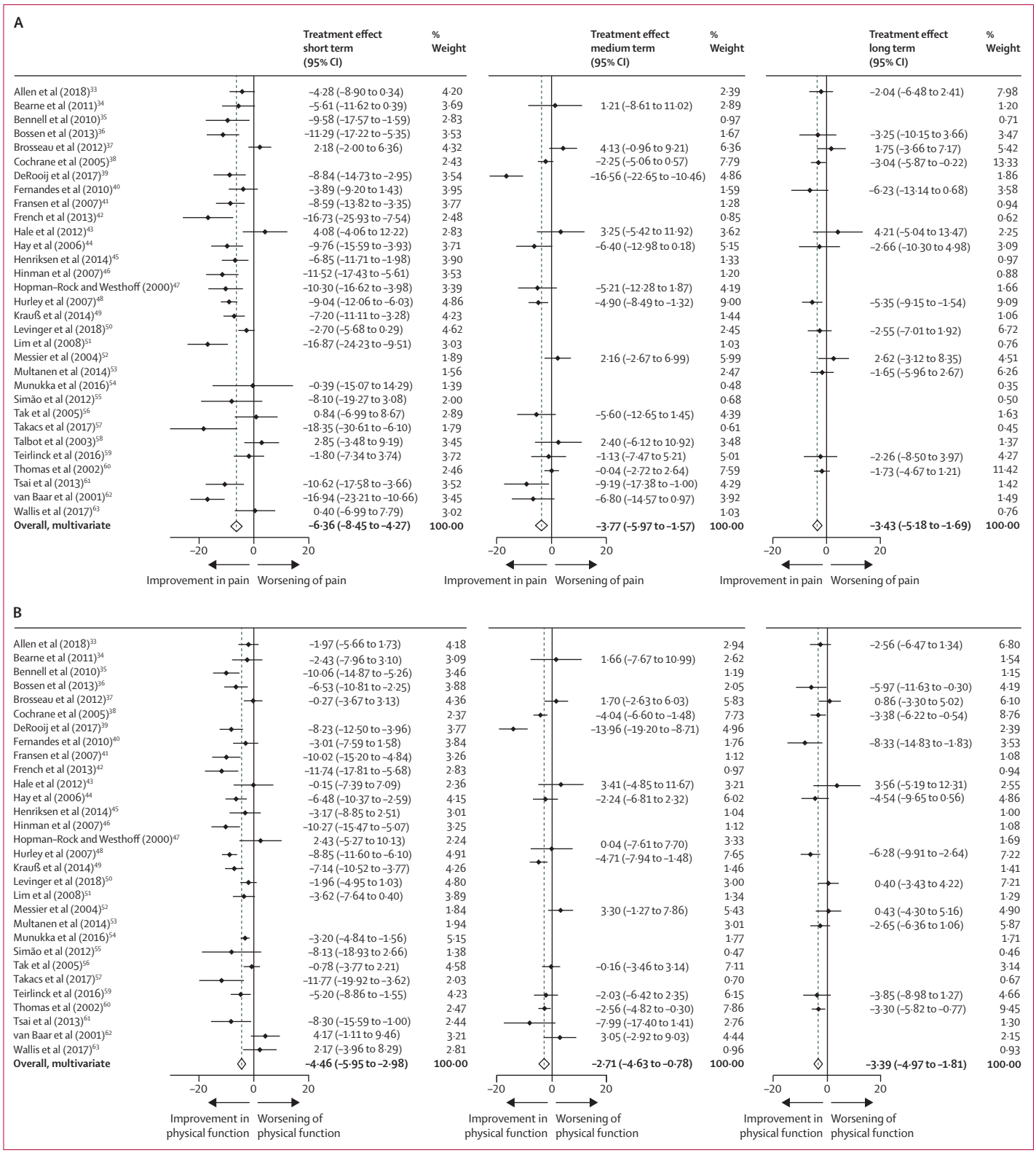

***Figure 2*: Forest plots showing overall effects of therapeutic exercise versus non-exercise controls on pain (A) and physical function (B) outcomes at various timepoints**
Short term=nearest timepoint to 12 weeks. Medium term=nearest timepoint to 6 months. Long term=nearest timepoint to 12 months. Weights are based on user-defined quantiles.

trials were deemed as having a low risk of bias across all domains assessed and were thus included in the sensitivity analysis.

Tables describing randomised controlled trials that did not share IPD are provided in the appendix (pp 21–35). There were some differences between randomised controlled trials that did and did not share IPD (appendix p 58). Compared to randomised controlled trials that did share IPD (or data were unusable), a higher proportion of those that did not share IPD were older (published before 2006), completed in North or South America and Asia, included short-term follow-up only, included fewer participants, and included participants with knee osteoarthritis only. Exercise interventions and non-exercise controls were heterogenous between randomised controlled trials that did and did not share IPD. However, compared to randomised controlled trials that did share IPD, a higher proportion of those that did not share IPD tested mind-body exercise interventions, and exercise interventions that combined group and individual exercise sessions. Randomised controlled trials that did not share IPD were also more likely to have a high risk of bias in one or more domains compared with those that shared IPD (low risk of bias in all domains: 14 [23%] non-IPD and 14 [45%] IPD).

Summary meta-analysis results from the included 31 randomised controlled trials showed that, on average, compared with non-exercise controls, exercise reduced pain on a standardised 0–100 scale, with a difference of –6·36 points (95% CI –8·45 to –4·27, borrowing of strength [BoS] 10·3%, between-study variance τ^2 21·6) in the short term, –3·77 points (–5·97 to –1·57, BoS 30·0%, τ^2 14·4) in the medium term, and –3·43 points (–5·18 to –1·69, BoS 31·7%, τ^2 4·5) in the long term (figure 2A). Pooled results from 30 randomised controlled trials showed that, on average, exercise also improved physical function on a standardised 0–100 scale, with a difference of –4·46 points in the short term (95% CI –5·95 to –2·98, BoS 10·5%, τ^2 10·1), –2·71 points in the medium term (–4·63 to –0·78, BoS 33·6%, τ^2 11·9), and –3·39 points in the long term (–4·97 to –1·81, BoS 34·1%, τ^2 6·4; figure 2B).

Baseline pain severity moderated the effect of exercise on pain in comparison with non-exercise controls. There was a non-linear association in the short term, with the benefit of exercise gradually increasing as baseline pain increased, but plateauing around a baseline pain score of 40 out of 100 and higher (figure 3A). A similar pattern was observed in the long term. There was some evidence to suggest that baseline pain severity was a moderator for physical function at short-term and long-term follow-ups (figure 3B).

As shown in figure 4, baseline physical function was found to moderate the effect of exercise on pain and physical function outcomes. Those with a higher baseline physical function score (ie, poorer physical function) benefited more from exercise than those with a lower baseline physical function score, with the evidence most certain for this moderator in the short term.

There was no evidence to suggest that age, BMI, physical activity, arthritis self-efficacy, mental wellbeing,

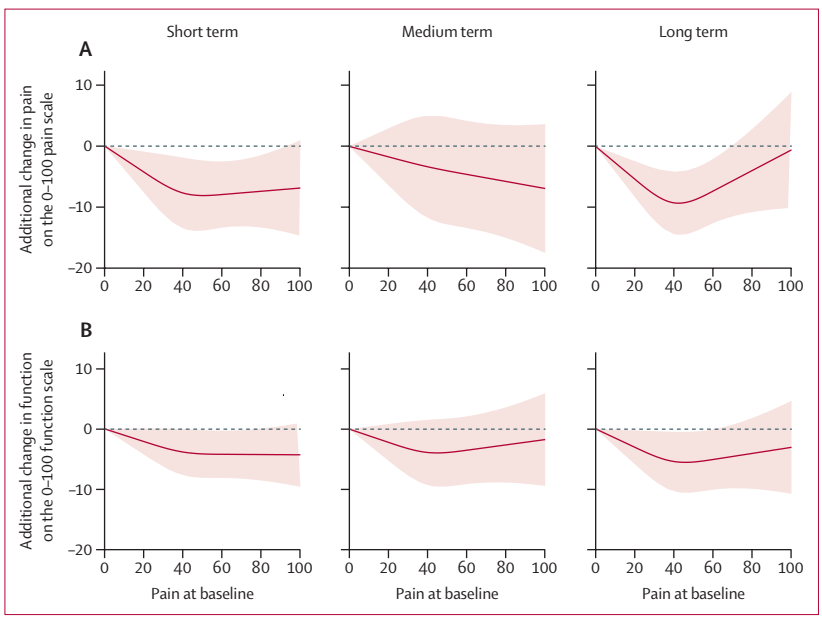

Figure 3: **Moderating effect of baseline pain severity on therapeutic exercise versus non-exercise controls on pain (A) and physical function (B) outcomes at various timepoints**
Short term=nearest timepoint to 12 weeks. Medium term=nearest timepoint to 6 months. Long term=nearest timepoint to 12 months. Solid lines represent the predicted treatment covariate interaction. The shaded area represents 95% CIs.

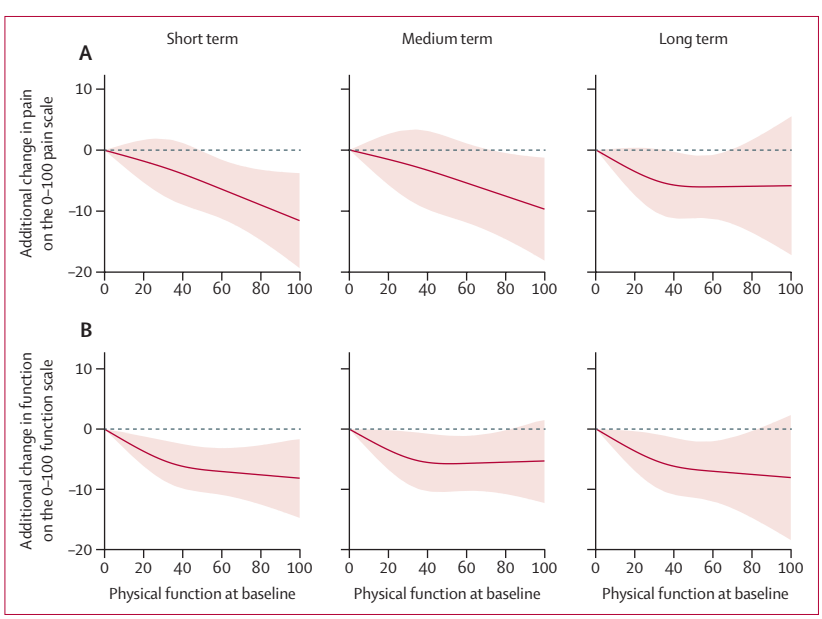

Figure 4: **Moderating effect of baseline physical function on therapeutic exercise versus non-exercise controls on pain and physical function outcomes at various timepoints**
Short term=nearest timepoint to 12 weeks. Medium term=nearest timepoint to 6 months. Long term=nearest timepoint to 12 months. Solid lines represent the predicted treatment covariate interaction. The shaded area represents 95% CIs.

comorbidity, muscle strength (quadriceps), education, pain duration, or radiographic joint structure moderated the effect of exercise on pain and physical function in the short, medium, or long term (appendix pp 62–67).

Sensitivity analyses revealed broadly similar results to the summary meta-analyses when restricted to the 14 randomised controlled trials deemed to be at low risk of bias across all domains assessed, for pain (–6·70 points [95% CI –9·47 to –3·93] in the short term, –5·55 points [–10·38 to –0·72] in the medium term, and –3·47 points [–6·28 to –0·67] in the long term) and physical function (–5·42 points [95% CI –7·54 to –3·30] in the short term, –5·56 points [–9·81 to –1·32] in the medium term, and –5·18 points [–8·64 to –1·72] in the long term). There was no evidence of small study effects or publication bias (appendix p 68).

Discussion

There are two important findings from this large, international, IPD meta-analysis of 4241 participants from 31 randomised controlled trials. First, we found a differential response to exercise among people with knee, hip, or mixed knee and hip osteoarthritis; individuals who report higher pain severity and poorer self-reported physical function at baseline have greater pain relief and improved physical function after exercise than do those with lower pain severity and better physical function at baseline. Second, although the summary results showed evidence of the overall benefits of exercise for pain and physical function in the short, medium, and long term in comparison with non-exercise controls, the magnitude of the benefit was small and of questionable clinical importance.

We identified two moderators of the effect of exercise for people with knee, hip, or mixed osteoarthritis: baseline pain severity and physical function. Allowing for non-linear associations, we found that individuals with more severe pain and poorer physical function at baseline generally benefited more from exercise, with the evidence most certain in the short term. This outcome could be expected, given that the most symptomatic individuals might have the greatest benefits to gain, although additional benefits often plateaued around a baseline pain score of about 40 out of 100. Whether these additional benefits are maintained over time is less clear, as there was more uncertainty at later timepoints (the 95% CIs were wider). Of the 12 individual-level characteristics explored, no other treatment-effect modifiers were identified. This could be because the magnitude of benefit from exercise is the same for people regardless of other characteristics. If so, this finding could provide important reassurance to anyone prescribing exercise and to patients when individual-level characteristics act as barriers to optimal exercise prescription and adherence (eg, obesity or the presence of comorbidities).[65–67] However, some of the characteristics explored might not have been detected as treatment-effect moderators due to lack of power (leading to false negative findings). Although we had a large dataset overall, some potential moderators were measured inconsistently, so the amount of data available for each analysis was variable. The large heterogeneity of included exercise interventions might also have masked important moderators that are only relevant for certain exercise characteristics (eg, exercise type, intensity, duration, frequency, and mode of delivery). Other moderators of the effect of exercise might exist but were not explored in this study.

We reported small overall effects of exercise on pain and physical function compared with non-exercise controls, particularly in the medium and long term. Although our 0–100 standardised scales might not be directly comparable with other outcome measures, our effect sizes do not appear to reach previously used thresholds for the minimum clinically important difference for non-surgical osteoarthritis interventions (eg, range of minimum clinically important difference values used for a between-group difference in pain on a 0–100 visual analogue scale: 8·4–20·0).[68] They also appear to be smaller than those reported in previous systematic reviews of aggregate data.[7,9,10] This discrepancy could be due to inclusion of different randomised controlled trials (with differences in inclusion and exclusion criteria between this systematic review and previous ones, and the fact that the present study included participants with knee, hip, or mixed knee and hip osteoarthritis), methodological differences (with IPD meta-analyses having several key advantages[18]), or as discussed below, the inability to include IPD from all eligible randomised controlled trials in our meta-analysis. Our findings question the magnitude of expected benefit from exercise in people with knee, hip, or mixed osteoarthritis, adding to a growing body of evidence that raises uncertainty about the role of exercise in osteoarthritis.[69–74] For example, a recently published randomised controlled trial suggests that improvements from exercise might primarily be driven by placebo response phenomena, contextual factors, the natural course of the disease, and regression to the mean.[72]

Our study has various strengths. Doing an IPD meta-analysis enabled us to explore individual-level treatment-effect moderators of exercise in people with knee, hip, or mixed knee and hip osteoarthritis more robustly than ever before,[15] using participant data from many international randomised controlled trials. This is a key strength of the study, as participant-level relationships cannot be modelled directly with only study-level (aggregate) data, which is prone to aggregation bias and study-level confounding. IPD also allowed us to standardise outcome scores from 0 to 100, and to perform advanced analyses that accounted for the correlation among outcomes over time, both at the participant level and the randomised controlled trial level.

This study also has some limitations. The process of obtaining IPD (including identifying and tracking down

randomised controlled trial leads with regular reminders and follow-up emails, agreeing suitable terms in a data sharing agreement, and facilitating data transfer), checking IPD (including numerous correspondences with randomised controlled trial leads to resolve ambiguity and discrepancies), and harmonising IPD (including recoding variables and standardising variables before combining into one dataset with a variable identifying the randomised controlled trial) was extremely time intensive, taking approximately 3·5 years to complete. Despite substantial efforts, we only obtained IPD from approximately 40% of all eligible randomised controlled trials. Although this is better than previous IPD meta-analyses of other interventions for osteoarthritis,[75–77] this limitation could potentially introduce bias in our findings. Within the included randomised controlled trials, there was large heterogeneity, which could have influenced our findings. Furthermore, although key baseline participant characteristics were broadly similar between randomised controlled trials that did and did not share IPD, there were some differences. Randomised controlled trials that provided IPD were larger, had longer follow-up, and a lower risk of bias across all domains assessed compared with randomised controlled trials for which IPD could not be obtained, meaning that there might have been some self-selection, with IPD shared from teams reporting higher-quality randomised controlled trials. There were also some differences in the characteristics of exercise interventions. Some exercise types were underrepresented in our dataset (eg, mind-body exercise) whereas others were overrepresented (eg, unsupervised home exercise). If these exercise characteristics are associated with the overall treatment effect, this could partly explain why the overall treatment effect in this study was smaller than in previous systematic reviews and meta-analyses. This observation highlights the importance of data sharing, which is becoming increasingly recognised as a key requirement in health research,[78] but currently remains suboptimal.[79] The predominant reason why IPD were not obtained was due to the inability to contact or get a response from randomised controlled trial teams. This limitation supports the ongoing need for condition-specific repositories such as the OA Trial Bank, as well as broader data-sharing initiatives.[80] Our search was run up to Feb 25, 2019. For a systematic review, one might argue that an update of the search strategy is warranted. However, given the time-consuming efforts of sharing and then harmonising data, this was not feasible for the present study.

One previous systematic review explored moderators of the effects of exercise for people with knee and hip osteoarthritis, synthesising findings from individual randomised controlled trials with subgroup analyses investigating potential treatment-effect moderators.[15] The systematic review included four randomised controlled trials that had explicitly carried out interaction tests for moderation.[44,48,51,81] Knee varus malalignment was identified as a treatment-effect moderator of pain, whereas obesity, anxiety and depression, presence of comorbidity, and exercise confidence and beliefs were not. Although joint alignment was deemed an important potential moderator by our collaborators,[23] it was not possible to explore the effect of this moderator within our IPD meta-analyses because of the absence of consistent measurements across randomised controlled trials. However, our findings support the view that obesity, anxiety and depression, and comorbidity do not moderate the effect of exercise on pain in individuals with knee, hip, or mixed knee and hip osteoarthritis.[15] Recent secondary analyses of randomised controlled trials by Henriksen and colleagues[82,83] found that people with knee osteoarthritis who take analgesics or report constant knee pain appeared to show clinically relevant benefits on knee pain from the Good Life with osteoArthritis in Denmark exercise and education programme when compared to an open-label placebo. Although direct comparisons are not possible (as baseline pain and physical function were not explored as potential moderators in these analyses), our results support these findings given that people with more severe pain are more likely to take analgesics.[82] In line with our study, BMI, age, and radiographic disease severity were not found to moderate the effect of exercise compared to an open-label placebo control.[82]

Three previous IPD meta-analyses have explored treatment-effect moderators for intra-articular glucocorticoids, oral glucosamine, and topical non-steroidal anti-inflammatory drugs (NSAIDs) in individuals with osteoarthritis.[75–77] Similarly to the present study, pain severity was found to be a treatment-effect moderator for the effects of both intra-articular glucocorticoids and topical NSAIDs.[75,77] Additionally, age, BMI, duration of complaints, and radiographic osteoarthritis severity were not found to moderate the effect of topical NSAIDs.[75]

Our findings indicate that there is a differential response to exercise in people with knee, hip, or mixed knee and hip osteoarthritis, but the overall effects are likely to be small and of questionable clinical importance. Targeting individuals with higher levels of osteoarthritis-related pain and disability for exercise might therefore be of merit. Our data suggest that none of the other individual-level characteristics we explored (age, BMI, physical activity, arthritis self-efficacy, mental wellbeing, comorbidity, muscle strength [quadriceps], educational attainment, pain duration, or radiographic joint structure) can be used to target individuals for exercise therapy. Although our findings question the magnitude of expected therapeutic benefit from exercise in people with knee, hip, or mixed osteoarthritis, we acknowledge that exercise is unlikely to be harmful[84] and can have multifaceted benefits for general health and for comorbid conditions, irrespective of osteoarthritis.[85]

The large heterogeneity in the included randomised controlled trials highlights the need to further examine

and compare the different characteristics of exercise programmes accounting for the effect modifiers identified. This can be achieved by an IPD network meta-analysis. Additionally, data sharing should continue to be supported. How to best measure important potential treatment-effect moderators should be agreed and included within future randomised controlled trials to facilitate further IPD meta-analyses.

In conclusion, this large international IPD meta-analysis showed a differential response to therapeutic exercise among people with knee, hip, or mixed knee and hip osteoarthritis; individuals with higher pain severity and poorer physical function at baseline benefited more from exercise than did those with lower pain severity and better physical function at baseline. Therapeutic exercise had an overall positive effect on pain and physical function compared with non-exercise controls. However, the magnitude of the overall effect was small and of questionable clinical importance, particularly in the medium to long term. Targeting individuals with higher levels of osteoarthritis-associated pain and disability for exercise therapy might therefore be of merit. Our data suggest that none of the other individual-level characteristics we explored can be used to target individuals for exercise therapy.

Contributors

MAH contributed to the conception and design of the study, acquisition of funding, acquisition of data, analysis and interpretation of data, drafting and revising the Article, and final approval of the submitted version. MH, JR, RDR, ELH, and JQ contributed to the conception and design of the study, acquisition of data, and analysis and interpretation of data, drafting and revising the Article, and final approval of the submitted version. DAvdW and KD contributed to the conception and design of the study, acquisition of funding, acquisition of data and interpretation of data, drafting and revising the Article, and final approval of the submitted version. MvM contributed to the conception and design of the study, acquisition of data, interpretation of data, drafting and revising the Article, and final approval of the submitted version. DB contributed to the conception and design of the study, acquisition of funding, drafting and revising the Article, and final approval of the submitted version. NC contributed to the conception and design of the study, acquisition of data, drafting and revising the Article, and final approval of the submitted version. AL contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and revising the Article, and final approval of the submitted version. SB-Z contributed to the conception and design of the study, acquisition of data, interpretation of data, drafting and revising the Article, and final approval of the submitted version. NEF contributed to the conception and design of the study, acquisition of funding, acquisition of data, interpretation of data, drafting and revising the Article, and final approval of the submitted version. MAH, RDR, and NEF are responsible for the overall content as guarantors. The guarantors accept full responsibility for the work or conduct of the study, or both, had access to the data, and controlled the decision to publish the manuscript. The guarantors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are no discrepancies from the study as originally planned. All authors had full access to all the output data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors had final responsibility for the decision to submit for publication. MH and RDR directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

RDR receives royalties for two books: *Individual Participant Data Meta-analysis: A Handbook for Healthcare Research* and *Prognosis Research in Healthcare: Concepts, Methods and Impact*. SB-Z receives consulting fees from Infirst Healthcare and Pfizer, and payment from Osteoarthritis Cartilage as a deputy editor. DAvdW is a member of PROGRESS Medical Research Council Prognosis Research Strategy (PROGRESS) Partnership (G0902393/99558). JQ was an unpaid member of the UK National Institute for Health and Care Excellence osteoarthritis guideline committee (2019–22). SB-Z, MvM, KD, and MAH are unpaid members of the OA Trial Bank Steering Committee. All other authors declare no competing interests.

Data sharing

Keele University is a member of the UK Reproducibility Network and committed to the principles of the UK Concordat on Open Research Data. The Keele University School of Medicine has a long-standing commitment to sharing data from our studies to improve research reproducibility and to maximise benefits for patients, the wider public and the health and care system. De-identified IPD that underlie the results from this study will be made available to bona-fide researchers on reasonable request via the OA Trial Bank, and with permission from the original randomised controlled trial leads. Data requests and enquiries should be directed to m.holden@keele.ac.uk. We encourage collaboration with those who collected the data, to recognise and credit their contributions. Release of data will be subject to a data use agreement between the OA Trial Bank, original randomised controlled trial leads, and the third party requesting the data. De-identified IPD will be encrypted on transfer.

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