The Relative Effectiveness of Different Types and Modes of Delivery of Therapeutic Exercise on pain and physical function for People with Knee and/or Hip Osteoarthritis: A Systematic Review Update and Individual Participant Data Network Meta-analysis.

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Background

Osteoarthritis (OA), most commonly of the knee and/or hip, is a leading cause of pain and disability worldwide. Total direct and indirect costs associated with OA are now conservatively estimated at 1-2.5% of gross domestic product in high-income countries (1). The high burden of knee and hip OA is predicted to rise even further with the ageing, increasingly obese and multimorbid population (2). As there is no cure for OA, treatments that reduce symptoms and slow functional decline are the focus of healthcare (3).

The National Institute for Health and Care Excellence (NICE), along with multiple international clinical guidelines, currently recommend therapeutic exercise, alongside information, and weight management (if appropriate), as a first line treatment for all people with knee and/or hip OA (4). Therapeutic 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 knee and/or hip OA. It encompasses general aerobic exercise, strengthening, flexibility, balance, or body-region specific exercises (5). Systematic reviews and meta-analyses of randomised controlled trials (RCTs) have consistently shown that such exercise is beneficial for pain and physical function among people with knee and/or hip OA (6-9). 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 RCT participants achieved a clinically important treatment response (10-13). This could be due to individual variability in response to exercise, and to characteristics of exercise interventions.

In collaboration with the OA Trial Bank we recently undertook a large individual participant data (IPD) meta-analysis using data from RCTs comparing therapeutic exercise to non-exercise controls among people with knee and/or hip OA (the STEER OA study) (14). Analyses of data from 31 RCTs and 4241 participants revealed that individuals with higher pain and worse physical function at baseline benefited more from exercise than those with lower pain and better physical function at baseline (14). However, on average the benefits of exercise were small compared to controls, and in contrast to previous systematic reviews of aggregate RCT data, were of questionable clinical importance (14). Whilst our findings suggest that targeting exercise to those with higher OA-related pain and disability might be of merit, the heterogeneity of exercise interventions included in our analyses means there is considerable uncertainty about the relative effectiveness of different characteristics of exercise interventions, including exercise type and mode of delivery.

Two network meta-analyses including up to 103 RCTs of exercise for knee and/or hip OA have previously been undertaken to explore the relative effectiveness of different types of exercise. However, due to differences in design they have differing conclusions (7, 9). In addition, as they both utilised aggregate RCT data, they are also at risk of ecological bias and confounding (15). Conducting network meta-analyses based on a large database of IPD has several key advantages. It allows better harmonisation of data and better checking of data quality and risk of bias; enables a multivariate approach allowing for all time points together, accounting for their correlation and thus using more information; enables adjustment for prognostic factors to focus on conditional treatment effects, which mirrors individuals being treated in clinical practice; and allows for interactions in the network, if needed (15). Given that we previously identified that baseline pain and physical function moderate the effect of exercise, if these have a different distribution across RCTs providing direct and indirect evidence, they would need to be accounted for to ensure consistency in the network. An IPD network meta-analysis therefore offers important new knowledge about the relative effectiveness of different types and mode of delivery of therapeutic exercise for people with knee and/or hip OA (16), in a way that would support provision of individualised care in clinical practice (the right exercise programme for the right person).

Aim

This study aims to summarise, compare and rank the effectiveness of different types and modes of delivery of therapeutic exercise on pain and physical function at 3, 6 and 12 months for people with knee and/or hip OA in an IPD network meta-analysis, in terms of: (a) the overall effect (across all individuals); and b) the effect in specific subgroups that cause heterogeneity in effects (effect moderators), if inconsistency of evidence is identified in analysis.

Methods

We will update our previous systematic review and 'Master' IPD database (14) with newly identified eligible RCTs and after agreement and data sharing from RCT leads, undertake IPD network meta-analyses. Our systematic review and meta-analysis will be completed in accordance with methods advocated by the Cochrane IPD meta-analysis group (16), and reported according to PRISMA-IPD guidance (17). We will work in collaboration with the OA Trial Bank, an initiative established in 2012 to collect and analyse IPD of published RCTs of interventions for people with OA (18). The updated IPD database will be deposited with the OA Trial Bank for future analyses, providing ongoing benefit for the wider OA research community.

Phase 1: RCT identification

We will update our previous systematic review (14) to identify new RCTs that compared exercise to non-exercise or other exercise controls among people with knee and/or hip OA. We will seek IPD from new eligible RCTs identified in addition to again seeking IPD from those RCT teams that did not previously share their IPD. We will combine new IPD with the IPD previously obtained from 48 RCTs and 6365 participants with knee and/or hip OA (note that data was obtained for both exercise vs exercise and exercise vs non-exercise RCTs but analysis in the STEER study included only exercise vs non-exercise RCTs).

The previous search strategy will be re-run from February 2019 (the date of the previous search) until 10 January 2024 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). Bibliographies of relevant review articles and included articles will be examined for additional potentially relevant RCTs. There will be no language restriction imposed.

Study Selection

In line with our previous systematic review, we will evaluate RCTs against the following inclusion criteria:

Study population: Adults aged 45 years and above with knee and/or hip OA (diagnosed by appropriate imaging, clinical criteria, health care professionals diagnosis or self-reported)**.**

Intervention: Any land or water based therapeutic exercise intervention regardless of content, duration, frequency, or intensity.

Comparator: Other forms of exercise or no exercise control group (including usual care, waiting list, placebo, attention control, or no treatment).

Outcome measure: At least one measure of self-reported pain or physical function.

Study design: RCTs. Trials will be excluded if they focus on pre- or post-operative exercise, when exercise is combined with interventions other than advice/education/self-management/motivational techniques (meaning treatment effects cannot clearly be attributed to the exercise), or if intervention and comparator groups receive identical exercise interventions.

Titles and abstracts of identified RCTs and subsequently full papers will be independently screened by two reviewers. A third reviewer will be consulted to resolve any disagreements. Two reviewers will independently classify exercise interventions of included RCTs, based on the following a priori defined criteria:

Type of exercise

Exercise types will be classified according to the American College of Sports Medicine recommendations (19).

1. Strengthening/resistance exercise: exercise that aims to improve the muscle's ability to exert force and involves applying resistance against a contracting muscle.
2. Aerobic exercise: exercise that aims to improve cardiorespiratory fitness and involves repetitive movement of large muscle groups, performed at moderate to vigorous intensity for prolonged periods of time.
3. Flexibility exercise: exercise that improves the ability to move a joint throughout its range of motion and includes various types of stretching exercises.

4. Neuromotor exercise: exercise that improves motor skills such as balance and coordination.
5. Mind-body exercise: exercise that combines a physical exercise with mental concentration like meditation or mindfulness, for example Tai Chi, Qi Chong, Yoga, Pilates.
6. Mixed exercise: interventions will be categorised as mixed exercise when they include more than one core exercise type listed above, or when the authors did not specify it as a single component exercise.

Exercises included as part of a warm up or cool down component of an exercise intervention will not be included in the exercise categorisation.

Mode of delivery of exercise

1. Delivered in a group, supervised face-to-face
2. Delivered in a group, supervised remotely
3. Delivered individually, supervised face-to-face
4. Delivered individually, supervised remotely
5. Delivered individually, unsupervised
6. Mixed delivery of exercise: interventions will be categorised as mixed mode of delivery when they include more than one core exercise delivery mode listed above).

Total number of protocolised prescribed exercise sessions

Total number of prescribed exercise sessions (number per week (as specified by authors) multiplied by programme duration in weeks) (8).

Non-exercise control interventions

Two reviewers will also independently classify non-exercise controls of included RCTs (where applicable), based on the following a priori defined criteria (8):

1. Placebo, sham, or attention control (any intervention that was designed to control for contextual/placebo effects and described by the authors as 'placebo' or 'sham', and/or an 'attention control' involving more than one bout of synchronous interaction with study personnel/care provider (excluding contact to obtain outcome measures)).
2. No treatment (no defined allocated intervention), usual care (where the authors stated that participants could receive 'normal/usual care', but this was not controlled by the trial), limited education (provided with a one-off information resource), or usual activity.
3. Other advice or education interventions that were also offered or provided, equally, as a co-intervention in the exercise group.

Heterogeneity within all groups will be explored and additional sub-categories will be developed where appropriate.

Phase 2: Collection, checking and standardising IPD

Following the procedures of the OA Trial Bank, we will seek permission to analyse the data already collected for the purpose of this study (data from 48 RCTs and 6365 participants). We will also contact lead authors of new eligible RCTs identified from the systematic review update and of previously identified RCTs for which IPD has not yet been shared, to inform them about the study and invite them to share IPD. Once a data sharing agreement is in situ, new datasets will be accepted in any form, provided all data are anonymised and variables and categories are adequately labelled in English. To ensure accurate pooling of data into the 'Master' dataset, each RCT dataset will be harmonised to a common format and variables re-named in a consistent manner.

Variables of interest
IPD analysed will include the following:
Baseline factors: Participant characteristics will be summarised to describe the sample, including age, sex, ethnicity/race, and body mass index,
Outcome measures: All self-report pain and physical function outcome data at time-points ≤3 months, 4-11 months, and ≥12 months post randomisation. If more than one measure of self-reported pain and physical function are reported, we will choose the highest in the hierarchy of outcome measures, as recommended by the Cochrane Musculoskeletal Review Group (20).

Data quality assurance
We will evaluate the IPD from each RCT to ensure the ranges of included variables are reasonable, and missing data will be checked against the original trial publication. We will attempt to reproduce the results included in each RCT publication, including baseline characteristics and self-reported pain and physical function at a time-point of interest (≤3 months, 4-11 months, and ≥12 months) post randomisation. Discrepancies or missing information will be discussed and clarified with original RCT authors. Where discrepancies cannot be explained the RCT data will be excluded from the analysis. Individual RCT datasets will be combined to form a new 'Master' dataset with a variable added to indicate the original RCT.

Assessment of risk of bias
Two researchers will independently grade risk of bias of newly included RCTs using the Cochrane Collaboration's tool (V1), based on their publications (21). A third reviewer will resolve any differences and if necessary, trial design, conduct and analysis methods will be clarified with the RCT authors. Additionally, IPD will be directly checked for key potential biases, including whether baseline participant characteristics are balanced by intervention arm. It will also be checked to ensure that data on all or as many randomised participants as possible are included.

Phase 3: Data Synthesis
The networks will be displayed using two network maps depicting a) which types of exercise interventions are compared against others, and b) which modes of delivery of exercise interventions are compared against others. Nodes in each network map will correspond to each intervention group as defined previously. Before analysis, transitivity will be assessed by comparing the distribution of potential effect moderators in RCTs that provide direct and indirect evidence for each exercise characteristic contrasted, to identify any concerns about pooling the set of RCTs in the network.

Following retrieval, cleaning and harmonisation of the IPD from each RCT, a two-stage IPD network meta-analysis (NMA) will be undertaken. All self-report pain and physical function outcome data will be analysed separately at each time-point of interest (≤3 months, 4-11 months, and ≥12 months) post randomisation. For continuous outcomes, we aim to summarise the intervention effect as mean differences (or standardised mean difference if different measures are used for similar constructs) with respective 95% confidence intervals (CIs). All analyses will be conducted in Stata using different modules such as *metan*, *mvmeta* and *network*.

In the first stage of the IPD NMA, each RCT will be analysed separately (which accounts for clustering of participants within RCTs) to produce RCT-specific estimates, following methodological guidance provided by Riley et al (22). Conditional treatment effects will be estimated in each RCT by fitting a mixed-effects multivariable regression that accounts for participant-level outcome values at multiple

time-points (longitudinal data) and allows for their correlation. A linear regression model for continuous outcomes will be fitted, and covariates of age, sex, body mass index, baseline pain, baseline physical function score, and symptom duration (less than or greater than two years) will be adjusted for in the models (14). Missing prognostic factor values will be handled using mean imputation or the missing indicator method, which is appropriate for RCTs (23). Missing outcome values at some time-points will be naturally handled by the mixed effects model. Restricted maximum likelihood (REML) estimation will be used to fit the models for the continuous outcomes.

In the second stage, a NMA model will be fitted for each outcome separately, allowing for exercise type and mode of delivery at each time-point, separately. Further, the models will include random-effects to allow for unexplained between-trial heterogeneity, and be fitted using REML estimation or the methods of moments, with 95% CIs derived using an approach to account for uncertainty in the estimate of heterogeneity (tau-squared) such as the Hartung-Knapp-Sidik-Jonkman approach (25). The between-trial variance of intervention effects will be assumed common (i.e. the same for each intervention effect) at a particular time-point, but allowed to be different across time-points, whilst accounting for between-trial correlation. If this fails to converge, then simplifications will be used including allowing for a common between-trial variance for all time-points and an auto-regressive between-trial correlation structure; or by analysing each time-point independently. We will conduct a sensitivity analysis that accounts for the correlation across time-points in a multivariate NMA model for each outcome separately, where possible (24).

Following each NMA, the consistency assumption will be assessed for each exercise characteristic comparison and time-point where there is direct and indirect evidence (visible as a closed loop within the network plot), using a global approach via the Wald test and comparisons within each loop. To summarise the NMA results, summary treatment effects will be provided for every pair of exercise characteristics, and characteristics will be ranked using the mean rank and the Surface Under the Cumulative RAnking (SUCRA) curve, accompanied with appropriate plots such as rankograms (26).

Including effect moderators

Where concerns of inconsistency arise, we will expand the NMA models to allow for interactions with effect moderators where possible. This includes both patient-level characteristics (baseline pain severity, physical function and pain duration) and exercise programme characteristics (exercise type, mode of delivery and the total number of protocolised prescribed exercise sessions). We will thus tailor results (and rankings) to specific intervention groups (defined by values of the effect modifiers). To do this, we will follow the approach described by Donegan et al (27) that includes treatment-covariate interaction terms.

Small trial effects and sensitivity analyses

If ten or more RCTs are in a meta-analysis, network funnel plots will be presented to examine small-trial effects (potential publication bias) (28). Egger's test of asymmetry will be used for continuous outcomes. We will also conduct additional subgroup and sensitivity analyses to explore potential sources of heterogeneity: this includes re-running the analyses in people with knee and hip OA separately, and limiting the analyses to trials at low risk of bias.

GRADE

The quality of evidence will be rated using GRADE guidelines (Grading of Recommendations, Assessment, Development, and Evaluations) (29).

Dissemination, Outputs and Anticipated Impact

Our findings about the relative effectiveness of type and mode of delivery of exercise interventions for people with knee and/or hip OA, will be taken forward to Work Package 2 where we will co-develop recommendations about how to provide sustainable, easily accessible, evidence informed, best practice exercise for people with knee and/or hip OA. These recommendations will have important clinical, commissioning, workforce planning and academic applications; including wider roll out or testing of the proposed recommendations for of exercise provision to establish its impact on patient outcomes and health care services.

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