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## **Exercise treatment effect modifiers in persistent low back pain: An individual participant data meta-analysis of 27 randomized controlled trials**

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## ABSTRACT (250 words)

**Background:** Low back pain is one of the leading causes of disability worldwide. Exercise therapy is widely recommended to treat persistent non-specific low back pain. While evidence suggests exercise is, on average, moderately effective, there remains uncertainty about which individuals might benefit from exercise the most.

**Methods:** In parallel with a Cochrane review update, we requested individual participant data (IPD) from high quality randomized clinical trials of adults with our primary outcomes of interest, pain and functional limitations, and calculated global recovery. We compiled a master dataset including baseline participant characteristics, exercise and comparison characteristics, and outcomes at short, moderate and long-term follow-up. We conducted descriptive analyses, and one-stage IPD meta-analysis using multilevel mixed-effects regression of the overall treatment effect, and pre-specified potential treatment effect modifiers.

**Results:** We received IPD for 27 trials (3514 participants). For studies included in this analysis, compared to no treatment/usual care, on average exercise therapy reduced pain ~~by a statistically significant, but not clinically important amount~~ [mean effect/100 (95% CI): -10.7 (-14.1, -7.4)], ~~a result most compatible with a clinically important 20% smallest worthwhile effect,~~ and reduced functional limitations ~~with a clinically important 23% improvement~~ [mean effect/100 (95% CI): -10.2 (-13.2, -7.3)] at the short-term follow-up in included trials. Not having heavy physical demands at work and medication use for low back pain were potential treatment effect modifiers – they were associated with superior exercise outcomes relative to non-exercise comparisons. Lower BMI was also associated with better outcomes in exercise compared to no treatment/usual care. This study was limited by inconsistent availability and measurement of participant characteristics.

**Conclusions:** This study provides potentially useful information to help treat patients and design future studies of exercise interventions that are better matched to specific subgroups.

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## SUMMARY

**What is already known on this topic:** Low back pain is a leading cause of disability. While there is no consensus on the best course of treatment, exercise therapy is on average moderately effective for persistent low back pain and is recommended by clinical guidelines. It is important to understand which individual characteristics (e.g., work status, pain medication use) are associated with better or worse treatment outcomes to choose the most appropriate care for patients.

**What this study adds:** The research team obtained datasets for 27 randomized controlled trials, each of which examined the impact of various forms of exercise on pain or function for people with persistent low back pain. Trial data were merged into a large dataset of 3514 individuals and analyzed.

Exercise therapy appeared to be more effective than other treatments for people who did not have heavy physical demands at work and who used medication for low back pain.

Future studies of exercise therapy should prospectively test the modifying effect of factors identified in this study, and other untested factors, alone and in combination.

## INTRODUCTION

Low back pain is one of the leading causes of disability worldwide and has a substantial socioeconomic impact<sup>1-4</sup>. The majority of the cost associated with low back pain is generated by a small percentage of individuals with persistent symptoms<sup>2,5</sup>. Both the prevalence and the cost of persistent low back pain are increasing<sup>2</sup>. Exercise therapy is widely recommended to treat persistent low back pain and is one of several interventions which is moderately effective in reducing pain and improving function<sup>6</sup>.

Identifying subgroups of individuals who may benefit more from treatment, and potential treatment effect modifiers (also known as moderators or treatment-covariate interactions), is an important goal in health research. There are difficulties with most existing subgroup/classification systems for patients with low back pain; these include unclear reliability or validity in clinical practice, lack of comprehensive predictor variables, and inclusion of measures or information that are not useful, nor feasibly collected in practice<sup>7</sup>. Furthermore, most low back pain trials are not designed to detect treatment effect modifiers<sup>8,9</sup>.

Our team conducted a Cochrane review in which we concluded that exercise therapy appears to be effective in decreasing pain and improving function in adults with persistent low back pain; however, this work was limited by inclusion of only published ‘aggregate’ data, such as overall treatment effects and average patient characteristics<sup>10-12</sup>. Individual participant data (IPD) meta-analysis standardizes analyses across trials, allowing for more powerful and reliable examination of differential treatment effects across subgroups of individuals<sup>13,14</sup>, since within-trial information can be used to estimate how individual characteristics modify treatment benefit<sup>15</sup>.

Our primary objective in this study was to assess the treatment effect of exercise therapy for reducing pain and functional limitations in adults with persistent low back pain as well as any modification of treatment effect by important individual characteristics. We aimed to identify characteristics of persons with low back pain who are more likely to benefit from exercise therapy.

## MATERIALS AND METHODS

We used standard systematic review methods advocated by Cochrane Back and Neck to identify eligible trials<sup>16</sup>. For this IPD meta-analysis, we identified randomized controlled trials from an updated search conducted in 2013 for the Cochrane review, ‘Exercise therapy for treatment of chronic low back pain’. Complete descriptions of the full search strategy, screening, selection and trial-level data extraction for the related Cochrane review are reported elsewhere<sup>10</sup>. This IPD study was approved by the Dalhousie University Research Ethics Board (REB), and the protocol was published<sup>17</sup>.

Eligible trials evaluated all forms of exercise therapy compared to any or no other interventions in adults (> 18 years of age) with non-specific persistent (> 12 weeks duration) low back pain (alone or with leg pain). Trials with mixed subacute (> 6 weeks duration) and persistent low back pain populations were eligible for the IPD meta-analysis if it was possible to extract information exclusively for those participants experiencing persistent low back pain.

For retrieval of IPD, we selected trials included in the updated Cochrane review that were rated as moderate to low risk of bias. We defined moderate to low risk of bias following Cochrane Back and Neck Methods Guidelines as at least six of twelve recommended items rated as having low risk of bias<sup>18</sup>; these risk of bias items align with the current Cochrane Back and Neck Methods Guidelines<sup>16</sup>.

### Data collection and management

The original IPD were requested from the authors of 56 eligible trials. We extracted trial-level information about each eligible trial (details can be found in our Cochrane review protocol<sup>10</sup>) and included IPD reported characteristics of the trial sample, variables collected at baseline and at follow-up periods, and subgroup and treatment effect modifiers investigated and presented in the trial report.

For eligible trials that provided their IPD, each raw dataset was saved on a secure server at Dalhousie University in its original format before being converted to a common format. We evaluated the IPD received from each trial and compared it to the available related publication(s) based on descriptive summary, range of included variables and missing observations. We attempted to use the IPD from each trial to replicate results reported in the original publications, including baseline characteristic descriptive analyses, and advanced analyses of outcome data at each available follow-up period, by reproducing the statistical analyses as reported by the trial authors. We discussed and clarified any discrepancies or missing information between our results and those presented in each original publication with the original trial authors. Ultimately, we included only trial data where we could reproduce published trial findings or explain/clarify discrepancies. Once data checks were complete and satisfactory, individual trial datasets were combined to form a new master dataset with a variable added to indicate the original trial.

## **Data Preparation**

We used a pre-specified framework for mapping, classifying and re-naming sufficiently similar variables (defined following the variable map presented in Hayden *et al.*, 2010<sup>5</sup>). Potential treatment effect modifiers included variables in the following broad domains: participant sociodemographic characteristics, lifestyle factors, overall health, psychological status, previous low back pain, characteristics of the current episode, and physical examination findings. For all variables, we preferentially selected the most valid and reliable measures available in each dataset, based on supporting literature. Whenever possible, we maintained variables measured continuously in their continuous data form, while also creating categorical or dichotomous variables, as necessary, for homogeneity across studies. We assessed participant-level missing data on variables and outcomes. Individual subjects with missing data within each trial were excluded from specific analyses, as necessary.

## **Data analysis**

*Descriptive analyses:* We described trial-level and participant-level characteristics of included trials. We compared trial-level characteristics from trials included in the IPD analysis with those from eligible trials from the Cochrane review update to determine whether the IPD trials available were a representative sample of the full set of eligible trials<sup>19</sup>.

Meta-analyses of overall effect of any type of exercise therapy compared to no treatment, non-exercise usual care, and other conservative treatments, was conducted as part of the associated Cochrane review based on aggregate data presented in the publications of primary studies (in preparation<sup>10</sup>). In this study, we compared published aggregate treatment effect results of exercise therapy versus any non-exercise comparisons from trials available for the IPD analysis with those from eligible studies in the Cochrane review update that did not provide IPD.

Our primary outcomes of interest were pain intensity, back-related functional limitations, and a composite measure of global recovery. Pain and back-related functional limitations outcomes were self-reported as continuous measures and mainly analysed on the continuous scale to avoid losing power. To achieve this, as outcome scales varied across studies, we converted each trial's outcome data to a common 0 to 100 scale to facilitate synthesis across studies and interpretability of the IPD meta-analysis results. We also calculated global recovery as a dichotomous measure of clinically important individual pain or functional limitations response as any improvement in score  $\geq 30\%$  of its baseline value with a minimum value of 20-point (/100) improvement in pain<sup>20</sup> or 10-point (/100) improvement in function<sup>21-23</sup>. We collected existing outcome data for all available time periods. We assessed outcomes at short-term follow-up (post-treatment time period closest to 3 months) for primary analyses, and for moderate-term (time period closest to 6 months) and long-term follow-up (time period closest to 12 months) in sensitivity analyses.

*IPD Syntheses:* For synthesis of IPD, we employed a one-stage meta-analysis approach, as specified in our protocol, using multilevel mixed-effects linear regression for continuous pain and functional limitations outcomes using restricted maximum likelihood estimation, and multilevel mixed-effects logistic regression for dichotomous global recovery outcome using maximum likelihood estimation, accounting for the clustering of individuals within studies<sup>24,25</sup>. These models specified a random treatment effect (to allow for between-trial heterogeneity in effect), trial-specific intercepts (to account for clustering), and random effects for baseline values of outcome variables (to allow for between-trial heterogeneity). We assessed the effectiveness of exercise therapy compared to no treatment or usual care, and compared to other conservative treatments, including adjustment for the baseline value of the outcome of interest (i.e. pain or functional limitations, as appropriate; functional limitations for global recovery outcome).

We extended the one-stage IPD meta-analysis framework to assess potential treatment effect modifiers (i.e. differences between subgroups) related to effectiveness of exercise therapy compared to any other studied non-exercise treatments. We identified candidate treatment effect modifiers from available data by considering potential mechanisms for modification of treatment response (biological reasoning and by understanding the mechanism by which response is modified), and from existing prognostic research (treatment effect modification studies<sup>26</sup> and prognostic factor studies<sup>27</sup>). These were: age, sex, level of education, current smoker, physical activity, body mass index, history of low back pain, work status, past 12-month sick leave, heavy physical demands at work, general health, general mental health, fear avoidance beliefs, social support, low back pain duration, baseline pain and functional limitations, leg pain symptoms, and medication use for low back pain.

To identify potential treatment effect modifiers, we examined interaction terms between treatment and each variable to assess subgroup effects using unadjusted and adjusted models. Interaction coefficients for dichotomous variables are interpreted as the effect of exercise treatment, relative to non-exercise comparisons, in those with the baseline characteristic compared to those who do not have the characteristic. Interaction coefficients for continuous variables are interpreted as the additional benefit of exercise therapy, relative to non-exercise comparisons, for every one-unit increase in the continuous variable. Unadjusted models included fixed effects at the participant level and random effects at the trial level: baseline pain or functional limitations (corresponding with the outcome; functional limitations variable was included for global recovery outcome), the potential treatment effect modifying variable, treatment group (exercise or comparison), and the variable-treatment group interaction. To assess whether effect modifiers remained after further adjustment, we also adjusted interaction analyses for age and sex (at the random and fixed effects levels). We centered the participant-level covariates about their trial-specific means to remove the contribution of across-trial associations of covariates and treatment effects (removing the impact of potential ecological bias on the effect modifier estimates)<sup>28,29</sup>. **Appendix 1** describes the treatment effect modifier statistical model and sample code. For each model, participants missing data on any of the included variables were not included in the corresponding analysis.

We performed secondary analyses to explore the robustness of our results. We repeated the adjusted treatment effect modifier analyses described above to separately assess potential treatment effect modifiers for exercise therapy compared to no treatment/usual care comparison groups, or to other conservative comparison groups. We assessed potential treatment effect modifiers for pain, functional limitations and global recovery outcomes in adjusted analyses at moderate-term (time period closest to 6 months) and long-term follow-up (time period closest to 12 months).

We considered ~~minimal clinically important differences in mean treatment effect as a 20-point (out of 100) the smallest worthwhile effect for exercise treatment compared to no treatment/usual care on pain and functional limitation outcomes to be a 20% change from baseline<sup>30,31</sup> (ref) improvement in pain<sup>20</sup> and a 10-point (out of 100) improvement in functional limitations outcomes<sup>24</sup>~~. We considered a variable as a potential treatment effect modifier ~~using statistical and clinical importance of results. We report if the 95% confidence intervals of summary treatment-variable interaction coefficients and exact p-values was statistically significant at  $p < 0.05$ .~~



For easier interpretation of results, we computed and present the observed treatment effect sizes (as mean differences (MD) for continuous outcomes, and as odds ratios (OR) for dichotomous outcomes, with 95% confidence intervals (CIs)) from available trial data for subgroups of potential treatment effect modifiers, categorizing continuous variables at clinically relevant cut-points when possible, or based on the observed median. For this forest plot presentation, we used uncentered values of the potential treatment effect modifier to calculate the mean treatment effect across categories. Models to determine the effect of potential treatment effect modifiers were adjusted using the same centered covariates as are described for primary analyses. For our primary analyses, we discuss treatment effect modifiers as potentially important in size where a level of the participant characteristic modified-changed the direction of the mean effect, with results compatible with a clinically important effect in one group and opposite effect in another group, or if a clinically important difference between covariate groups is greater than the proposed smallest worthwhile effect for exercise treatment (20% change from baseline on pain and functional limitation outcomes, and positive OR of 2.0 or greater)<sup>30 31</sup> ~~(ref) the average effectiveness of exercise therapy compared to other treatments by 3.3 points or more (MD), or by a difference in odds ratio of 0.7 or more;~~ we consider these results exploratory.

Descriptive analyses and one-stage IPD overall treatment effect meta-analyses were conducted using Stata v.15.0<sup>32</sup>; extension of the one-stage IPD models to include treatment effect modifiers were conducted in R v.3.5.2; Review Manager v.5.3<sup>33</sup> was used for meta-analyses of published aggregate data; IPD data checking and replication was conducted in SPSS v.24.0 and SAS v.9.4<sup>34 35</sup>.

## RESULTS

Authors from 27 eligible trials, published between 2000 and 2012<sup>36-72</sup>, provided IPD for this study (**Table 1**). Each trial included between 28 and 264 participants (median, 109), randomized to 1-3 exercise groups, and 0-2 comparison groups (the most common design compared two exercise groups; 10 trials). The mean sample size per group in included trials was 56 participants: four trials included more than 100 participants per group, seven trials included less than 30 participants per group. Trials were conducted in Australia (4 trials), Denmark (4), Italy (3), the Netherlands (3), United Kingdom (2), United States (2), Finland (2), one in each of Hong Kong, Spain, Switzerland, Sweden, Norway, Brazil, and one multi-country trial. Most trials were conducted in healthcare settings (10 trials in secondary care settings, and 6 in primary care settings); 5 trials were conducted in occupational settings, and 6 in general population or mixed settings. The mean age by trial was between 37.0 and 60.1 years, and studies included 0 to 78% female participants. Twenty-six of the 27 included trials reported pain (96%) outcomes and 25 reported functional limitation outcomes (93%). All studies reported participant outcomes at short-term follow-up, with 19 and 15 respectively reporting pain or functional limitations at moderate- and long-term follow-up. Twenty-nine eligible studies were unable to provide their data or did not respond after four attempted requests for data (**Figure 1**); the only characteristic on which these trials differed significantly was design of exercise program (non-included trials had standardized exercises more often) (**Table 2**). Aggregate meta-analysis of published estimates comparing treatment effect results from studies included in the IPD analysis with those from eligible studies not providing data found smaller pain improvement, and similar functional limitation improvement with exercise therapy relative to non-exercise comparisons for included studies, than with eligible studies not providing data [pain (0-100 scale) MD (95% CI), included: -2.3 (-8.1, 3.5) vs. not included: -10.2 (-16.4, -4.1) (**Figure 2**); functional limitations (0-100 scale) MD (95% CI), included: -3.6 (-8.7, 1.4) vs. not included: -2.9 (-6.2, 0.3)]. (**Appendix 2**).

Data from 3514 trial participants were available for our IPD meta-analyses (510 participants were excluded from two trials due to not having persistent low back pain, or having missing data on both outcomes): 2568 participants were randomized to receive exercise therapy, and 946 participants were randomized to receive a non-exercise comparison (142 placebo/no treatment, 125 usual care, 679 other conservative treatments, including manual therapy, education, or psychological therapy; see Table 2 for full list). The mean age of participants was 45.7 years (95% CI: 45.2, 46.1) and 55.5% (1945 of 3504) were female. From trials reporting these variables, more than two thirds of participants reported previous history of low back pain (598 of 877;

68%), and 52% had been on sick leave in the previous 12 months (943 of 1801). At baseline, the median low back pain episode duration for participants was 14 months (IQR= 6-48 months; n=1692), with mean pain intensity 53.5 on a 100-point scale (95% CI=52.6, 54.3; n=3411); over 60% of participants reported leg pain with their low back pain (1354 of 2145). Missing data for variables of interest ranged from 0.2% (sex) to 75% (history of low back pain) (**Table 3**). There was heterogeneity in measurement of potential treatment effect modifiers.

### IPD integrity

For all included IPD, we were able to replicate aggregate results that were reported in each of the associated publications. Of the 27 IPD datasets that were received, trial information was fully replicated at the data verification stage for 12 datasets. The remaining 15 trials were partially replicated and required further author contact to confirm the data.

### Pain and functional limitation outcomes

One-stage random effects IPD meta-analysis of included trials found that, on average exercise therapy was more effective than no treatment or usual care on pain outcome [MD (95% CI): -10.7 (-14.1, -7.4); 26 studies, 2466 participants] at short-term follow-up, ~~though not at the level that we pre-specified as being minimal clinically important a result most compatible with a clinically important 20% smallest worthwhile effect~~. Other conservative treatment was found to be more effective than exercise therapy, though, again, not by a ~~minimal clinically important amount~~ [MD (95% CI): 3.7 (1.3, 6.0); 26 studies, 2850 participants].

For functional limitations outcome, exercise therapy was associated with ~~statistically significant, and~~ clinically important 23% improvement compared to no treatment or usual care [MD (95% CI): -10.2 (-13.1, -7.3); 25 studies, 2366 participants] at short-term follow-up. Other conservative treatment was found to be more effective than exercise therapy, though, ~~again~~, not by clinically important amount [MD (95% CI): 1.9 (0.03, 3.8); 25 studies, 2778 participants] at short-term follow-up. We observed similar results in meta-analyses of global recovery, where exercise therapy was more effective compared to usual care or no treatment [OR (95% CI): 3.8 (2.6, 5.7); 25 studies, 2366 participants] and similarly effective as other conservative treatments [OR (95% CI): 0.9 (0.7, 1.1); 25 studies, 2777 participants] at short-term follow-up.

### Exploring individual characteristics that modify exercise therapy treatment effect

We identified several variables that may modify the treatment effectiveness of exercise therapy relative to non-exercise comparison groups. Observed results were consistent between unadjusted and adjusted models for each of pain (**Table 4**), functional limitations (**Table 5**), and global recovery outcomes (**Table 6**).

For pain outcomes adjusted analyses, ~~we found no variables associated with lower (improved) pain intensity in the exercise treatment group relative to non-exercise comparisons at short term at a statistically significant level~~. **Figure 3** depicts the mean difference in pain outcomes of exercise compared ~~to other/no treatments to non-exercise comparisons at short-term~~ for subgroups of participants based on levels of characteristics of potential treatment effect modifiers. We observed ~~improved clinically important~~ outcome improvements with exercise therapy in participants with the following characteristics (exploratory results, ~~based on  $|MD| \geq 3.3$~~ ): ~~beyond high school education~~, normal BMI (compared to underweight and obese), ~~previous history of low back pain~~, sick leave in the previous 12 months, ~~no heavy physical demands, having low fear avoidance beliefs, higher pain at baseline~~, and any medication use for low back pain at baseline.

For functional limitation outcomes adjusted analyses, we found two variables ~~associated most compatible~~ with lower (improved) functional limitations with receiving exercise treatment relative to non-exercise comparisons for treatment-variable interactions: not having heavy physical demands at work (adjusted MD (aMD) (95% CI): 6.0 (1.0, 11.0), p=0.~~02019~~), and any medication use for low back pain (aMD (95% CI): -4.8 (-8.7, -0.9), p=0.~~02016~~). **Figure 4** presents the mean difference in functional limitations with exercise therapy compared to other/no treatments for subgroups of participants based on potential treatment effect modifiers. Participants with

the following characteristics had better functional limitation outcomes with exercise (exploratory results, based on  $|MD| \geq 3.3$ ): aged less than 35 years (compared to 65+ years), normal BMI (compared to underweight), sick leave in the previous 12 months, no heavy physical demands, having low fear avoidance beliefs, worse functioning at baseline, and any medication use for low back pain at baseline.

For global recovery outcome with adjusted analyses, any medication use for low back pain at baseline was significantly associated most compatible with improved outcomes from exercise relative to non-exercise comparisons (aOR (95% CI): 1.7 (1.0, 2.8),  $p < 0.05 = 0.046$ ). **Figure 5** displays the size of global recovery treatment effects for subgroups of participants. Participants with the following characteristics reported greater global recovery with exercise compared to other/no treatments (exploratory results, based on  $|OR \text{ difference}| \geq 0.7$ ): normal BMI (compared to underweight and obese), sick leave in the previous 12 months, no heavy physical demands, good general health, poor mental health, longer chronic episode duration of back pain, and worse functioning at baseline any medication use for low back pain at baseline.

The mean size and direction of the interaction effect for potential treatment effect modifiers were consistent across moderate- and long-term follow-up time periods for the characteristics: no physical demands at work and any medication use for low back pain, though not always statistically significant. Other potential treatment effect modifiers that were important in size and statistically significant most compatible with positive treatment effect modification, at moderate- or long-term follow-up were: pain outcome – beyond high school education, not having a history of low back pain, lower fear avoidance beliefs, and shorter episode duration; for functional limitations outcome – any medication use for low back pain; and for global recovery outcome – female sex (**Appendices 3-5**).

Secondary analyses to explore potential treatment effect modifiers for exercise therapy compared to no treatment/usual care comparison groups, or to other non-exercise conservative comparisons found on average individuals with lower BMI experienced statistically significantly more improvement on all three outcomes with exercise compared to no treatment/usual care comparison groups. Individuals with worse baseline function and any medication use for low back pain had improved functional limitations with exercise compared to either no treatment/usual care comparison groups or other non-exercise conservative comparisons. Compared to non-exercise comparisons individuals with the following characteristics had better outcomes with exercise treatment: functional limitations outcome – lower fear avoidance beliefs; and for global recovery outcome – any medication use for low back pain (**Appendices 6-8**). **Appendix 9** provides a summary of observed potential effect modifiers that were statistically significant and clinically important in size.

## DISCUSSION

In this study, we used original data from 27 randomized controlled trials of exercise therapy to explore individual characteristics and identify subgroups based on participants' likely response to exercise treatment. Comparisons of trial characteristics were not noticeably different from eligible trials not providing data. However, analysis limited to other treatment group comparisons suggested that the average treatment effect for exercise therapy was smaller and not clinically important for studies providing IPD (MD = -2.3 for pain outcome) compared to the effect of treatment in eligible trials not providing IPD (MD = -10.2 for pain outcome).

One-stage random effects meta-analysis of data from included trials found exercise therapy to be statistically significantly more effective than no treatment or usual care on pain, functional limitations, and global recovery outcomes at short-term follow-up; however, minimally clinically important treatment effects were observed only for improvements in functional limitations, most compatible with a clinically important improvement. Exercise therapy was observed to be similarly effective to other included comparison treatments (here including manual therapy, education, or psychological therapy) for all outcomes. However, these results should be interpreted cautiously as the trials included in this study may underestimate exercise treatment effect and represent fewer than 10% of the randomized controlled trials now available.

Our study has provided exploratory evidence that not having heavy physical demands at work and using pain medication are potential treatment effect modifiers for exercise therapy outcomes compared to other treatments at short term follow up. This indicates that individuals with these characteristics may benefit more from exercise

therapy. One could hypothesize that characteristics that may facilitate compliance with an active treatment program (e.g. using medication to alleviate low back pain symptoms, and not having physical demands at work which could lead to strain and/or a flare up of symptoms) may be associated with improved outcomes with exercise compared to other treatments. Lower BMI was consistently associated with improved outcomes from exercise interventions compared to usual care or no treatment at the follow-up period closest to 3 months.

These results suggest two directions for future research to advance management of persistent low back pain. First, further research is needed to validate and extend our findings. We tested many potential effect modifiers, so our findings may be coincidental. Future trials of exercise therapy, including prospectively planned multicentre trials, should consistently measure and test these and other theoretically-driven potential treatment effect modifiers. Second, future studies may test incorporation of these characteristics into prediction models to select individuals for exercise treatment. If prediction models are confirmed accurate in future studies, and with alternate strategies for subgroups who do poorly with exercise, then persistent low back pain outcomes could be improved with more tailoring of treatments received.

IPD meta-analysis is the gold standard for systematic review<sup>24</sup>, and we followed current recommendations for robust analyses. There are three key advantages of IPD meta-analysis that we have benefited from in this study. First, the availability of data from 27 trials identified through a systematic review and rated as moderate to low risk of bias resulted in a large sample size available to investigate subgroup effects. Second, we were able to attain consistent presentation of data; direct derivation of information independent of reporting, and standardization of analyses across studies allowed more usable data for meta-analyses. Third, we were able to conduct additional analyses to explore heterogeneity (more extensive use of available data to explore trial-level and participant-level factors in meta-analyses, and assessment of the variation in summary effects within participant subgroups to allow better understanding of the effects of exercise treatment).

A limitation of our IPD study is the small sample size of included trials. Small trials, common with low back pain treatment studies, are not individually powered to detect a meaningful treatment or moderating effect, may be lower quality, or reflect publication bias. A benefit of meta-analysis is providing sufficient power through synthesis. However, inclusion of invalid trials in our study may have led to misleading results, particularly related to overall treatment effect. We addressed study internal validity by selecting trials judged to not be at high risk of bias using the Cochrane Back and Neck group recommended criteria, but may have missed other sources of bias. We do not think that systematic bias related to our primary treatment effect modification results is likely, however still interpret our results cautiously. A challenge of smaller studies that should be considered by future researchers undertaking IPD meta-analyses, relates to feasibility. Small studies add little information relative to the time required to test, map, and include their data. However, this should be balanced against enhanced generalizability of results with trials representing real heterogeneity in populations and exercise interventions.

A second limitation of this study was inconsistent availability and measurement of some individual characteristics, limiting the ability to assess all potential treatment effect modifiers with the most valid, reliable continuous measures. Although the overall sample size was large, some potential treatment effect modifiers were available and measured consistently in only a small subset of studies. For example, 8 trials, 1386 participants provided usable data on heavy physical demands at work, and 13 trials, 1774 participants provided usable data on use of pain medication at baseline, analyzed as a dichotomous measure, including analgesic, anti-inflammatory or opioids. Almost 40% of trials compared different exercise types, with no non-exercise comparison available.

We were unable to explore treatment effect modifiers for specific exercise therapies, ~~or~~ non-exercise comparisons, [or for no treatment separate from placebo or usual care comparisons](#) due to insufficient homogeneous types across included trials. Furthermore, we were unable to investigate some potential treatment effect modifiers we had originally planned due to low availability across studies, including presence and number of comorbidities, alcohol use, and socioeconomic status. While we only received data from approximately half of requested trials and the observed effect of exercise vs. other comparisons was smaller for pain outcomes, trial-level characteristics did not significantly differ between those received and requested. A commonly stated

benefit of IPD meta-analysis is a more consistent presentation of data and approach to analysis across included trials, allowing for more homogeneity. However, this is achievable only if the necessary participant characteristics and outcome variables are reported; in our study we did not find our IPD meta-analysis to have lower heterogeneity than previous aggregate meta-analyses. A limitation of our IPD analysis includes our assumption of linear interactions for continuous variables, which may have missed non-linear relationships. Finally, a challenge of the IPD approach was the considerable amount of time and effort that was involved in gathering, testing and compiling data from individual studies, which were published before 2013. However, we think that it is unlikely that newer trial data would be different for treatment effect modification results, which is the focus of this project.

Patients with low back pain are heterogeneous and treatment is complex. We will need large datasets of reliably and consistently measured variables to better understand treatment effect modifiers and identify relevant treatment subgroups for exercise overall, and specific types of exercise (i.e. yoga, aerobic exercise, etc.). Specifically, the factors that we identified in our study to be potential treatment effect modifiers should be further investigated. Future trials should measure a comprehensive set of variables to define potential subgroups, evaluate treatment effect modification, and include non-exercise comparisons. This is unlikely to be feasible with small individual studies, so it will need to be facilitated by increased international collaboration, prospective planning of multisite and multi-country trials, standardizing measurement of prognostic factors, and potentially by sharing of data through accessible repositories. Future prospective coordination and collaboration for more consistent data collection will help researchers identify treatment effect modifiers. This will further advance a personalized management approach for persistent low back pain.

## Conclusions

Our IPD meta-analysis combined data from 27 randomized trials, which allowed us to examine a large sample with consistent data. We assessed the effectiveness of exercise therapy to provide context to our study, and explored the impact of potential treatment effect modifiers. In our sample, exercise therapy was minimally effective for persistent non-specific low back pain ~~function~~-outcomes, and it appears that for individuals using medication for low back pain, and possibly for those with no heavy physical demands at work, they may benefit more from exercise than other treatments. This study provides potentially useful information to help design future studies of exercise interventions that are better matched to specific subgroups.

## Abbreviations

Cochrane B&N: Cochrane Back & Neck; individual participant data: IPD; LBP: low back pain; LBP-IPD Group: Chronic Low Back Pain IPD Meta-analysis Group; NSHRF: Nova Scotia Health Research Foundation; RCT: randomized controlled trial; REB: Research Ethics Board.

**Competing interests:** MWvT and members of the Chronic LBP IPD Meta-analysis Group are investigators of the individual trials included in the IPD dataset.

**Authors' contributions:** JAH conceived the protocol. JAH and JLC developed and drafted the initial protocol with input from RDR and MWvT. JLC, AS, and MW tested and mapped data variables. JAH, MW and SS conducted analyses with guidance from RDR. Members of the Chronic LBP IPD Meta-analysis Group contributed IPD and guidance to this study. JAH and MW drafted the initial manuscript. All members of the Chronic LBP IPD Meta-analysis Group were sent draft versions of the protocol and manuscript and were invited to comment and contribute changes. All authors approved the final protocol manuscript.

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**Supplemental material:**

**Appendix 1.** Statistical model for one-stage IPD treatment effect modifier analysis and sample statistical code

**Appendix 2 (Figure).** Aggregate meta-analysis results from published data, functional limitations

**Appendix 3 (Table).** Pain outcome, moderate and long-term follow-up

**Appendix 4 (Table).** Functional limitations outcome, moderate and long-term follow-up

**Appendix 5 (Table).** Global recovery outcome, moderate and long-term follow-up

**Appendix 6 (Table).** Pain outcome, by comparison group type

**Appendix 7 (Table).** Functional limitations outcome, by comparison group type

**Appendix 8 (Table).** Global recovery outcome, by comparison group type

~~**Appendix 9 (Table).** Summary of statistically significant and clinically important potential effect modifiers~~

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**Table 1.** Characteristics of 27 studies with data available for IPD meta-analysis.

Trial author, year	Country	Population source	Participants	% Female	Mean age	Trial groups		Outcomes available		Follow-up periods		
						# Ex; Comp	Comparison category	Pain intensity	Functional limitations	Short	Mod.	Long
Albaladejo, 2010	Spain	Primary care	264	68.2	50.9	1; 2	Education <sup>†</sup>	VAS	RMDQ <sup>  </sup>	+	+	-
Cecchi, 2010	Italy	Primary care	210	66.7	58.8	2; 1	Manual therapy	Pain Rating Scale	RMDQ	+	+	+
Chan, 2011	Hong Kong	Primary care	46	78.3	46.6	2; 0	N/A	VAS	Aberdeen <sup>¶</sup>	+	-	+ <sup>††</sup>
Costa, 2009	Australia	Primary care	154	60.4	53.7	1; 1	∅/Usual	NRS	RMDQ	+	+	+
Dufour, 2010	Denmark	Secondary care	286	55.9	40.9	2; 0	N/A	VAS	RMDQ	+	+	+
Ferreira, 2007	Australia	Primary care	240	68.8	53.7	2; 1	Manual therapy	VAS	RMDQ	+	+	+
Gudavalli, 2006	United States	Mixed	235	37.5	41.6	1; 1	Manual therapy	VAS	RMDQ	+	-	-
Hartvigsen, 2010	Denmark	Secondary care	136	71.4	46.6	2; 1	Education	LBPRS - P	LBPRS - F	+	+	+
Helmhout, 2004	Netherlands	Occupational	81	0.0	40.9	2; 0	N/A	-	RMDQ	+	+	+
Kool, 2007	Switzerland	Occupational	151	21.2	42.3	2; 0	N/A	NRS	-	+	-	-
Koumantakis, 2005	United Kingdom	Primary care	52	53.9	37.0	2; 0	N/A	VAS	RMDQ	+	-	-
Kuukkanen, 2000	Finland	Occupational	60	50.0	40.5	1; 1	∅/Usual	Borg CR-10	ODI	+	+	+
Long, 2004	Multisite*	Secondary care	133	51.1	41.6	3; 0	N/A	VAS	RMDQ	+	-	-
Macedo, 2012	Australia	Mixed	172	59.3	49.2	2; 0	N/A	NRS	RMDQ	+	+	+
Machado, 2007	Brazil	Secondary care	33	69.7	43.5	1; 1	Psychological therapy	VAS	RMDQ <sup>#</sup>	+	+	-
Mehling, 2005	United States	Mixed	28	64.3	49.3	2; 0	N/A	VAS	RMDQ <sup>**</sup>	+	+	-
Morone, 2011	Italy	Secondary care	70	64.3	60.1	1; 1	∅/Usual	VAS	ODI	+	+	-
Morone, 2012	Italy	Secondary care	75	72.0	55.3	1; 2	Multiple <sup>‡</sup>	VAS	ODI	+	+	-
Petersen, 2011	Denmark	Secondary care	224	56.3	37.1	2; 0	N/A	VAS <sup>§</sup>	RMDQ	+	-	+
Rasmussen-Barr, 2009	Sweden	Mixed	71	50.7	38.1	2; 0	N/A	VAS	ODI	+	+	+
Ryan, 2010	United Kingdom	Secondary care	38	65.8	45.3	1; 1	Education	NRS	RMDQ	+	-	-
Sjögren, 2006	Finland	Occupational	90	73.3	45.7	1; 1	∅/Usual	Borg CR-10	-	+	+	-
Smeets, 2006	Netherlands	Secondary care	223	47.1	41.6	3; 1	∅/Usual	VAS	RMDQ	+	+	+
Sorensen, 2010	Denmark	Secondary care	207	52.2	39.1	1; 1	Education	NRS	RMDQ	+	+	+
Staal, 2004	Netherlands	Occupational	39	7.7	38.2	1; 1	∅/Usual	NRS	RMDQ	+	+	+
Unsgaard-Tøndel, 2010	Norway	Mixed	109	69.7	40.1	3; 0	N/A	NRS	ODI	+	-	+ <sup>††</sup>
Wajswelner, 2012	Australia	General	87	55.2	49.6	2; 0	N/A	NRS	PSFS	+	+	-

RMDQ=Roland Morris Disability Questionnaire; ODI=Oswestry Disability Index; LBPRS=Low Back Pain Rating Scale (P=pain scale; F=function scale); SNQ=Standardized Nordic Questionnaire for activity restrictions; QBPDS=Quebec Back Pain Disability Scale; ∅='No treatment' comparison; \*Multisite (Canada, United States, Germany, United Kingdom, Kuwait); †Both comparison groups are education; ‡Group 1 is ∅/Usual, group 2 is back school; §Sum of three VAS scales; ||Spanish RMDQ; ¶Chinese Aberdeen scale; #Brazilian/Portuguese RMDQ; \*\*16-item RMDQ; ††Function outcome only; ‡‡pain outcome only.

**Table 2.** Trial and group-level characteristics for 27 IPD included studies compared to 29 eligible trials that did not provide data. Data presented describe number and percentage for each characteristic unless otherwise noted.

<b>Trial Characteristic</b>	<b>Included IPD trials (N=27) Number (%)*</b>	<b>Not included eligible trials (N=29) Number (%)*</b>
<b>Median number of subjects (IQR)</b>	109 (65-209)	90 (60-132)
<b>Population source</b>		
<i>Health care</i>	16 (59%)	20 (69%)
<i>Occupational</i>	5 (19%)	2 (7%)
<i>General or mixed</i>	6 (22%)	7 (24%)
<b>Mean age of sample, years (95% CI)</b>	45.7 (45.2, 46.1)	42.9 (40.1-45.6)
<b>Proportion of sample female (95% CI)</b>	55.5 (53.9, 57.2)	44.3 (36.0-52.7)
<b>Mean severity of pain at baseline (95% CI)</b>	53.5 (52.6, 54.3)	50.9 (44.6-57.1)
<b>Number of exercise groups available</b>		
<i>1 exercise group</i>	11 (41%)	11 (46%)
<i>2 exercise groups</i>	13 (48%)	15 (63%)
<i>3 exercise groups</i>	3 (11%)	3 (13%)
<b>Number of comparison groups available</b>		
<i>1 comparison group</i>	13 (48%)	15 (63%)
<i>2 comparison groups</i>	2 (7%)	1 (4%)
<b>Exercise group types (46 groups)</b>		
<i>Strengthening</i>	4 (9%)	5 (8%)
<i>Stretching</i>	1 (2%)	2 (3%)
<i>Core strengthening</i>	10 (22%)	10 (15%)
<i>Flexibility/mobilizing</i>	1 (2%)	0 (0%)
<i>Aerobic</i>	4 (9%)	2 (3%)
<i>McKenzie</i>	2 (4%)	0 (0%)
<i>Functional restoration</i>	1 (2%)	1 (2%)
<i>Yoga</i>	0 (0%)	5 (8%)
<i>Other</i>	4 (9%)	0 (0%)
<i>Mixed (&gt;2 types)</i>	19 (41%)	25 (37%)
<b>Design of exercise program</b>		
<i>Individualized</i>	15 (33%)	6 (12%)
<i>Partially individualized</i>	21 (46%)	18 (36%)
<i>Standardized</i>	9 (20%)	26 (52%)
<i>Not specified</i>	1 (2%)	0 (0%)
<b>Delivery of exercise program</b>		
<i>Independent</i>	5 (11%)	1 (2%)
<i>Independent with FU</i>	2 (4%)	1 (2%)
<i>Group</i>	18 (39%)	30 (60%)
<i>One-on-one</i>	17 (37%)	16 (32%)
<i>Not specified</i>	4 (9%)	2 (4%)
<b>Comparison group types (17 groups)</b>		
<b>No treatment /usual care comparisons</b>	7 (41%)	4 (24%)
<i>No treatment</i>	3 (18%)	2 (12%)
<i>Usual care</i>	4 (24%)	2 (12%)
<b>Other conservative treatment comparisons</b>	10 (59%)	13 (77%)
<i>Advice/education</i>	5 (29%)	5 (29%)
<i>Back school</i>	1 (6%)	0 (0%)
<i>Electrotherapy</i>	0 (0%)	4 (24%)
<i>Manual therapy</i>	3 (18%)	1 (6%)
<i>NSAIDs/analgesics</i>	0 (0%)	1 (6%)
<i>Physiotherapy</i>	0 (0%)	1 (6%)
<i>Psychological therapy</i>	1 (6%)	0 (0%)
<i>Relaxation</i>	0 (0%)	1 (6%)

IQR=interquartile range; \*Number (%) unless otherwise noted.

**Table 3.** Characteristics of persistent low back pain participants with available follow-up data for IPD analyses (n=3514). Percentage of missing data for each participant characteristic is noted. Data presented describe number and percentage for each characteristic unless otherwise noted.

<b>Participant characteristic at baseline</b> (% missing)	<b>Number participants</b>	<b>%</b>
<b>Age</b> (mean, 95% CI) (missing = 0.4%)	3499	45.7 (45.2-46.1)
<b>Sex</b> (missing = 0.3%)		
<i>Male</i>	1559	44.5
<i>Female</i>	1945	55.5
<b>High school education</b> (missing = 56%)		
<i>High school completed or less</i>	691	45.0
<i>Beyond high school</i>	843	55.0
<b>Current smoker</b> (missing = 57%)		
<i>No</i>	980	65.0
<i>Yes</i>	527	35.0
<b>Regularly physically active</b> (missing = 47%)		
<i>No</i>	916	49.0
<i>Yes</i>	954	51.0
<b>BMI</b> (mean, 95% CI) (missing = 33%)	2352	26.3 (26.1-26.5)
<b>History of LBP</b> (missing = 75%)		
<i>No</i>	279	31.8
<i>Yes</i>	598	68.2
<b>Sick leave (past 12 months)</b> (missing = 49%)		
<i>No</i>	858	47.6
<i>Yes</i>	943	52.4
<b>Work status</b> (missing = 22%)		
<i>Unemployed</i>	1076	39.2
<i>Employed</i>	1669	60.8
<b>Heavy physical demands at work</b> (missing = 57%)		
<i>No</i>	976	63.9
<i>Yes</i>	552	36.1
<b>General health</b> (0-100; mean, 95% CI) (missing = 56%)	1529	57.3 (56.3-58.2)
<b>Mental health</b> (0-100; mean, 95% CI) (missing = 71%)	1034	63.4 (62.1-64.7)
<b>Fear avoidance beliefs</b> (0-100; mean; 95% CI) (missing = 66%)	1182	39.4 (38.1-40.8)
<b>Social support available</b> (missing = 56 %)		
<i>No</i>	480	30.8
<i>Yes</i>	1080	69.2
<b>Episode duration</b> (months, median; IQR) (missing = 52%)	1692	14.0 (6.0-48.0)
<b>Pain intensity</b> (0-100; mean, 95% CI) (missing = 0.3%)	3411	53.5 (52.6-54.3)
<b>Functional limitations</b> (0-100; mean, 95% CI) (missing = 0.8%)	3247	44.6 (43.8-45.4)
<b>Any leg pain</b> (missing = 39%)		
<i>No</i>	791	36.9
<i>Yes</i>	1354	63.1
<b>Any LBP medication use</b> (missing = 44%)		
<i>No</i>	927	47.3
<i>Yes</i>	1032	52.7

LBP=low back pain

**Table 4.** Size and statistical significance of treatment-variable interactions (unadjusted and adjusted results) on continuous pain outcome (0-100) at follow-up closest to 3 months. \* A negative interaction coefficient indicates decreased pain for the variable level (e.g. females) with exercise vs. any non-exercise comparison (i.e. all other conservative and no treatment/usual care comparisons).

Variable	Unadjusted				Adjusted			
	Studies	Participants	Interaction MD (95% CI)	p-value	Studies	Participants	Interaction MD (95% CI)	p-value
<b>Age (years)</b>	26	3091	0.09 (-0.05, 0.23)	0.22	26	3091	0.09 (-0.05, 0.23)	0.22
<b>Sex</b>								
Male	26	3095	--	--	26	3091	--	--
Female			-0.98 (-4.49, 2.53)	0.59			-0.96 (-4.39, 2.46)	0.58
<b>High school education</b>								
High school or less	12	1401	--	--	12	1399	--	--
Beyond high school			-3.94 (-8.90, 1.02)	0.12			-3.69 (-8.65, 1.27)	0.15
<b>Current smoker</b>								
No	9	1411	--	--	9	1407	--	--
Yes			2.07 (-3.15, 7.29)	0.44			1.38 (-3.86, 6.63)	0.61
<b>Regular physical activity</b>								
No	11	1695	--	--	11	1693	--	--
Yes			-1.05 (-5.79, 3.68)	0.66			-0.67 (-5.4, 4.06)	0.78
<b>BMI</b>	17	2173	0.23 (-0.27, 0.74)	0.37	17	2170	0.22 (-0.27, 0.71)	0.38
<b>History of LBP</b>								
No	8	827	--	--	8	827	--	--
Yes			-4.03 (-13.88, 5.82)	0.42			-3.92 (-13.76, 5.92)	0.44
<b>Sick leave (past 12 months)</b>								
No	14	1578	--	--	14	1575	--	--
Yes			-2.27 (-9.15, 4.61)	0.52			-2.15 (-8.92, 4.62)	0.53
<b>Work status</b>								
Unemployed	18	2446	--	--	18	2444	--	--
Employed			-3.81 (-9.07, 1.45)	0.16			-4.22 (-9.26, 0.82)	0.10
<b>Heavy physical demands</b>								
No	8	1388	--	--	8	1386	--	--
Yes			4.45 (-1.84, 10.74)	0.17			4.92 (-1.35, 11.19)	0.12
<b>General health (0-100)</b>	10	1319	0.05 (-0.11, 0.20)	0.54	10	1316	0.05 (-0.11, 0.21)	0.55
<b>Mental health (0-100)</b>	6	877	-0.05 (-0.19, 0.10)	0.54	6	874	-0.04 (-0.18, 0.11)	0.61
<b>Fear avoidance beliefs (0-100)</b>	8	1012	0.08 (-0.03, 0.20)	0.16	8	1011	0.09 (-0.03, 0.20)	0.15
<b>Social support</b>								
No	10	1451	--	--	10	1450	--	--
Yes			-1.05 (-5.65, 3.55)	0.66			-1.38 (-5.97, 3.20)	0.55
<b>Episode duration (months)</b>	13	1572	0.02 (-0.03, 0.07)	0.37	13	1569	0.02 (-0.04, 0.08)	0.58
<b>Functional limitations (0-100)</b>	24	2880	0.01 (-0.08, 0.11)	0.81	24	2876	0.02 (-0.07, 0.12)	0.66
<b>Pain intensity (0-100)</b>	26	3095	-0.06 (-0.15, 0.03)	0.23	26	3091	-0.05 (-0.14, 0.04)	0.26
<b>Any leg pain</b>								
No	14	1837	--	--	14	1833	--	--
Yes			1.60 (-3.57, 6.77)	0.54			1.46 (-3.73, 6.64)	0.58
<b>Any LBP medication use</b>								
No	13	1776	--	--	13	1774	--	--
Yes			-4.04 (-9.66, 1.58)	0.16			-3.90 (-9.40, 1.60)	0.16

\* Unadjusted models include baseline pain, the potential treatment effect modifying variable, treatment group (exercise or comparison treatment), and trial at the random effects level, and the variable-treatment group interaction at the fixed effects level. Adjusted models add age and sex (at the random effects level). All participant-level covariates are centered about their trial-specific means; LBP=low back pain.

**Table 5.** Size and statistical significance of treatment-variable interactions (unadjusted and adjusted results) on continuous function outcome (0-100) at follow-up closest to 3 months. \* A negative interaction coefficient indicates decreased function for the variable level (e.g. females) with exercise vs. any non-exercise comparison (i.e. all other conservative and no treatment/usual care comparisons).

Variable	Unadjusted				Adjusted			
	Studies	Participants	Interaction MD (95% CI)	p-value	Studies	Participants	Interaction MD (95% CI)	p-value
<b>Age (years)</b>	25	2996	0.07 (-0.04, 0.19)	0.21	25	2996	0.07 (-0.04, 0.19)	0.21
<b>Sex</b>								
Male	25	3000	--	--	25	2996	--	--
Female			-1.62 (-4.38, 1.15)	0.25			-1.71 (-4.44, 1.02)	0.22
<b>High school education</b>								
High school or less	10	1204	--	--	10	1202	--	--
Beyond high school			-0.53 (-4.83, 3.77)	0.81			-0.24 (-4.54, 4.05)	0.91
<b>Current smoker</b>								
No	9	1420	--	--	9	1416	--	--
Yes			0.16 (-3.99, 4.30)	0.94			-0.36 (-4.52, 3.80)	0.87
<b>Regular physical activity</b>								
No	12	1758	--	--	12	1756	--	--
Yes			-0.96 (-4.59, 2.67)	0.60			-0.75 (-4.38, 2.89)	0.69
<b>BMI</b>	15	1984	0.11 (-0.31, 0.52)	0.61	15	1981	0.11 (-0.30, 0.52)	0.60
<b>History of LBP</b>								
No	8	830	--	--	8	830	--	--
Yes			0.16 (-8.23, 8.56)	0.97			0.39 (-7.99, 8.76)	0.93
<b>Sick leave (past 12 months)</b>								
No	13	1451	--	--	13	1448	--	--
Yes			-0.35 (-6.65, 5.94)	0.91			-0.03 (-6.24, 6.17)	0.99
<b>Work status</b>								
Unemployed	17	2321	--	--	17	2319	--	--
Employed			0.96 (-2.93, 4.85)	0.63			0.58 (-3.24, 4.40)	0.76
<b>Heavy physical demands</b>								
No	8	1391	--	--	8	1389	--	--
Yes			5.81 (0.73, 10.88)	0.03			6.02 (1.00, 11.04)	0.02
<b>General health (0-100)</b>	10	1337	-0.06 (-0.25, 0.14)	0.56	10	1334	-0.06 (-0.25, 0.14)	0.56
<b>Mental health (0-100)</b>	7	956	-0.03 (-0.20, 0.15)	0.75	7	953	-0.02 (-0.19, 0.15)	0.82
<b>Fear avoidance beliefs (0-100)</b>	9	1110	0.09 (-0.003, 0.18)	0.06	9	1109	0.09 (-0.002, 0.18)	0.05
<b>Social support</b>								
No	9	1381	--	--	9	1380	--	--
Yes			2.2 (-2.08, 6.48)	0.31			1.94 (-2.40, 6.29)	0.38
<b>Episode duration (months)</b>	13	1573	0.01 (-0.01, 0.04)	0.29	13	1570	0.02 (-0.01, 0.04)	0.25
<b>Functional limitations (0-100)</b>	25	3000	-0.08 (-0.18, 0.02)	0.14	25	2996	-0.06 (-0.16, 0.03)	0.21
<b>Pain intensity (0-100)</b>	24	2923	0.03 (-0.04, 0.10)	0.38	24	2919	0.03 (-0.04, 0.10)	0.36
<b>Any leg pain</b>								
No	15	1950	--	--	15	1946	--	--
Yes			0.86 (-3.21, 4.94)	0.68			0.54 (-3.53, 4.61)	0.80
<b>Any LBP medication use</b>								
No	13	1795	--	--	13	1793	--	--
Yes			-5.11 (-9.03, -1.19)	0.01			-4.81 (-8.72, -0.90)	0.02

\* Unadjusted models include baseline functional limitations, the potential treatment effect modifying variable, treatment group (exercise or comparison treatment), and trial at the random effects level, and the variable-treatment group interaction at the fixed effects level. Adjusted models add age and sex (at the random effects level). All participant-level covariates are centered about their trial-specific means; LBP=low back pain.

**Table 6.** Size and statistical significance of treatment-variable interactions (unadjusted and adjusted results) on important global recovery in pain or function outcome (dichotomous) at follow-up closest to 3 months. \* An interaction coefficient above 1 indicates increased likelihood of recovery for the variable level (e.g. females) with exercise vs. any non-exercise comparison (i.e. all other conservative and no treatment/usual care comparisons).

Variable	Unadjusted				Adjusted			
	N studies	n participants	Interaction OR (95% CI)	p-value	N studies	n participants	Interaction OR (95% CI)	p-value
<b>Age (years)</b>	25	2995	1.01 (0.99, 1.02)	0.43	25	2995	1.01 (0.99, 1.02)	0.43
<b>Sex</b>								
Male	25	2995	--	--	25	2995	--	--
Female			1.33 (0.91, 1.94)	0.15			1.32 (0.90, 1.93)	0.16
<b>High school education</b>								
High school or less	10	1204	--	--	10	1202	--	--
Beyond high school			1.32 (0.73, 2.40)	0.36			1.32 (0.72, 2.40)	0.37
<b>Current smoker</b>								
No	9	1421	--	--	9	1417	--	--
Yes			0.98 (0.54, 1.80)	0.96			1.04 (0.56, 1.93)	0.90
<b>Regular physical activity</b>								
No	12	1758	--	--	12	1756	--	--
Yes			0.94 (0.56, 1.57)	0.80			0.90 (0.54, 1.52)	0.70
<b>BMI</b>	15	1986	0.95 (0.89, 1.00)	0.07067	15	1983	0.95 (0.89, 1.00)	0.054
<b>History of LBP</b>								
No	8	830	--	--	8	830	--	--
Yes			1.05 (0.40, 2.79)	0.92			1.05 (0.39, 2.78)	0.93
<b>Sick leave (past 12 months)</b>								
No	13	1450	--	--	13	1447	--	--
Yes			1.33 (0.61, 2.92)	0.48			1.26 (0.57, 2.80)	0.56
<b>Work status</b>								
Unemployed	17	2319	--	--	17	2317	--	--
Employed			0.93 (0.56, 1.55)	0.78			0.94 (0.56, 1.58)	0.82
<b>Heavy physical demands</b>								
No	8	1393	--	--	8	1391	--	--
Yes			0.56 (0.26, 1.21)	0.14			0.55 (0.26, 1.19)	0.13
<b>General health (0-100)</b>	10	1335	1.00 (0.98, 1.03)	0.88	10	1332	1.00 (0.98, 1.03)	0.92
<b>Mental health (0-100)</b>	7	954	0.99 (0.97, 1.02)	0.55	7	951	0.99 (0.97, 1.01)	0.46
<b>Fear avoidance beliefs (0-100)</b>	9	1106	1.00 (0.98, 1.01)	0.69	9	1105	1.00 (0.98, 1.01)	0.71
<b>Social support</b>								
No	9	1380	--	--	9	1379	--	--
Yes			1.14 (0.66, 1.97)	0.64			1.17 (0.67, 2.02)	0.58
<b>Episode duration (months)</b>	13	1575	1.00 (1.00, 1.01)	0.41	13	1572	1.00 (1.00, 1.01)	0.43
<b>Functional limitations (0-100)</b>	25	2999	1.01 (1.00, 1.02)	0.28	25	2995	1.01 (0.99, 1.02)	0.32
<b>Pain intensity (0-100)</b>	24	2925	1.00 (0.99, 1.01)	0.79	24	2921	1.00 (0.99, 1.01)	0.81
<b>Any leg pain</b>								
No	15	1950	--	--	15	1946	--	--
Yes			0.98 (0.54, 1.78)	0.95			1.01 (0.55, 1.86)	0.97
<b>Any LBP medication use</b>								
No	13	1795	--	--	13	1793	--	--
Yes			1.72 (1.03, 2.85)	0.0374			1.68 (1.01, 2.81)	<0.0465

\* Unadjusted models include baseline functional limitations, the potential treatment effect modifying variable, treatment group (exercise or comparison treatment), and trial at the random effects level, and the variable-treatment group interaction at the fixed effects level. Adjusted models add age and sex (at the random effects level). All participant-level covariates are centered about their trial-specific means; LBP=low back pain.