**Exercise interventions for persistent non-specific low back pain – does matching outcomes to treatment targets make a difference? A systematic review and meta-analysis**

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**ABSTRACT**

Exercise is a core treatment for persistent non-specific low back pain (NSLBP), but results from randomised controlled trials (RCTs) of exercise typically show only small to moderate standardised mean differences (SMDs) compared to non-exercise controls. The choice of primary outcome, and relationship to the specific targets of exercise may influence this. This systematic review aimed to explore whether primary outcomes match the exercise treatment targets used in NSLBP RCTs and the potential impact of matching on SMDs.

Included RCTs were conducted with patients with persistent NSLBP, compared exercise to no exercise, with sample sizes >60 per arm. Screening, data extraction and risk of bias assessment were independently undertaken by paired reviewers. Of 19272 initial titles, 27 RCTs were included with 31 treatment targets and 6 primary outcome domains identified. Only 25% of included RCTs had primary outcomes that matched the treatment targets. SMDs of exercise versus comparison arms were observed to be larger in the matched (SMD 0.54 (95% CI 0.23 to 0.85), p=0.0006) compared to the unmatched category (SMD 0.22 (95% CI 0.01, 0.44) p=0.04) but this difference was not statistically significant (p=0.10). These exploratory findings may have implications for future teams developing RCTs of exercise for NSLBP and warrant further investigation in larger datasets.

**Perspective: 50 words synopsis**

This review was an exploratory study that investigated the primary outcome and treatment targets used in RCTs of exercise for NSLBP. The SMDs of the matched group were descriptively larger than those of the unmatched group, but further analysis with larger sample sizes is required to have confidence in these results.

**Highlights:3-5 bullet points 85 characters each**

* 27 trials compared exercise to no-exercise with a sample sufficient to detect a moderate difference.
* RCTs had a variety of treatment targets, despite sometimes using the same exercise approach.
* Most RCTs did not match their primary outcome to their stated exercise treatment targets.
* Matched RCTs were more likely to conclude statistically significant results in favour of exercise.

**Key Words:**

Treatment targets, outcomes, exercise, low back pain, systematic review

**INTRODUCTION**

Exercise is a core recommended treatment for patients with persistent non-specific low back pain (NSLBP) in almost all international guidelines 49,62 with no evidence that one type of exercise is superior to another 41. NSLBP has the highest consultation prevalence among musculoskeletal conditions, and is most frequently managed in primary care 54. Despite the documented benefits of exercise more generally 5, 3, the standardised mean differences (SMDs) between exercise for NSLBP and non-exercise comparison/control interventions in randomised controlled trials (RCTs) are small to moderate 3,41, suggesting that they provide, at best, modest benefits over other treatments.

Exercise can be considered a complex intervention, with both physiological effects as well as impacts on the individual’s psychological well-being and social function 33. Complex interventions frequently have multiple treatment targets and treatment outcomes 18, where treatment targets reflect the aims and/or goals of exercise interventions 55. Treatment targets in this area are poorly defined, in comparison to other fields of medicine such as coronary heart disease 35 and diabetes 75. There is currently no consensus on the treatment targets for exercise in NSLBP, and publications of RCTs may or may not explicitly state the treatment goals that their exercise intervention is aiming to address. Outcomes, either in RCTs or clinical practice, should reflect the identified treatment targets 12,13. Although core outcome domains have now been agreed for RCTs of treatments for LBP (pain, physical functioning and health-related quality of life) 13, there remains a concern that single-domain outcome measures may not adequately detect or demonstrate important differences experienced by patients with persistent NSLBP. Further, single-domain primary outcome measures may not adequately reflect the range of key treatment targets of a complex intervention such as exercise.

RCTs have traditionally focussed on the average between-group difference on a single-domain primary outcome measure 4. The focus on one primary outcome upon which to draw conclusions about treatment effectiveness may not capture the often multiple treatment targets that complex interventions such as exercise aim to modify. Results from trials of exercise interventions may differ if outcomes better reflect the (multiple) targets of exercise interventions. The aims of this review were to i) describe the treatment targets and outcome domains of RCTs of exercise compared to no exercise for persistent NSLBP in a primary care or community setting, ii) explore to what extent outcome domains in these RCTs match the identified treatment targets of exercise and iii) explore whether matching of outcomes to exercise treatment targets changes the size of the between-group differences observed.

**METHODS**

The review protocol was published on the PROSPERO register (reference [CRD42017072023](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=72023)). Potential studies were identified by electronic database searches of PsycInfo and Cinahl (EBSCO); Web of Science; AMED, Embase and Medline (Ovid); PEDro and Cochrane Central trials registry (inception until the 18th September 2017, updated on the 5th August 2019). The search strategy was developed in consultation with information specialists, and used all key words and MeSH terms to explore the most important key terms: NSLBP, exercise therapy, RCTs (see supplementary file 1). Initial screening was performed by LW. Titles and abstracts were screened by LW and AB. Full text screening was performed by pairs of reviewers and checked against the inclusion criteria. Independent data extraction and quality assessment of included trials were undertaken by pairs of reviewers. Any disagreements were resolved by discussion with all authors. This review was performed in accordance with PRISMA guidance, ensuring a rigorous approach57.

**Study inclusion:**

RCTs of exercise interventions in comparison to no exercise controls in persistent NSLBP in primary and community care, were included. The definition used for persistent NSLBP was symptoms present for more than 12 weeks, with >50% participants with NSLBP. Included exercise interventions were required to be supervised or tailored to fulfil the requirement of a complex intervention. To be eligible, RCTs had to have a comparator group(s) that included no exercise treatment; RCTs may have compared exercise to usual care (e.g. physiotherapy, spinal manipulation, education, or GP led care), placebo interventions, brief interventions or waitlist controls as long as they did not include a supervised or tailored exercise component. All outcomes relevant to the exercise interventions were included, for the purposes of establishing the relationship between outcome domains and treatment targets. Outcome domains encompass the focus of the outcome (e.g. ‘what’ is measured), whereas outcome measures are the measurement instruments for each domain (e.g. ‘how’ it is measured) 5,12,77. All RCT outcomes (primary and secondary, where stated) were extracted, where relevant to the exercise intervention. To reduce the likelihood of high levels of bias in our results, only RCTs of adequate sample size were included; only those that were powered to detect at least a moderate between-group effect size were included. For a moderate effect size of 0.5 in a two-armed trial, 120 participants would be required at about 80% power (60 per arm)65.

**Study Exclusions:**

We excluded trials of specific causes of LBP, such as spinal stenosis, post-surgical pain, pregnancy-related LBP, lumbar instability etc., and we excluded serious spinal pathologies (cauda equina, spinal tumours, spinal fractures, spondyloarthopathies etc.). RCTs with patients with widespread chronic pain or systemic pain conditions (fibromyalgia, chronic fatigue etc.) and RCTs with healthy volunteers or asymptomatic participants were also excluded.

**Data Extraction:**

Pairs of reviewers independently extracted identified treatment targets, primary and secondary outcome domains, and outcome measures from each RCT. Documented exercise treatment targets (both explicit in methodology or protocol, and inferred in the background of each published paper with quotations where possible), were extracted. For the purposes of this review the primary outcome of each RCT was identified using the following process, moving to the next stage if the previous did not identify the primary outcome.

1. The primary outcome was explicitly stated by the authors.
2. If more than one primary outcome was used, then the first primary outcome mentioned was used
3. The outcome measure on which the sample size calculation was based
4. The first outcome measure referred to in the abstract or paper

This approach has also been taken in previous reviews 2,22,24,28,29. Secondary outcomes were also extracted. Primary outcome domains were classified as to whether they matched the reported treatment targets. The RCT was classified as ‘matched’ if the primary outcome matched (at least one of) the treatment targets identified within the paper describing the RCT. RCTs were classified as ‘unmatched’ if the primary outcome did not match any of the treatment targets identified.

**Data Synthesis:**

Descriptive statistics, frequency counts and percentages were used to summarise treatment targets, treatment outcome domains and outcome measures. Standardised mean difference(s) (SMDs) for exercise in comparison to non-exercise control arms were calculated for each individual RCT for between-group differences at the primary outcome time-point designated by the trial, or the soonest time-point post-intervention, if a primary outcome time-point was not specified by the authors. In trials including more than one arm with exercise, the arm that approximated the intervention requirement of supervised, tailored exercise was used. Where more than one intervention arm or control arm was included in a trial that was relevant, the results of both arms were combined according to the guidance given in the Cochrane Handbook for Systematic Reviews 44. Where possible, SMDs were compared to the reported minimum clinically important difference for each outcome measure, which was standardised. In order to determine whether the SMD was clinically meaningful or not, treatment success was then determined according to the recommendations from Dent and Raftery 20. Where possible, SMDs were compared to the reported minimum clinically important difference, which was standardised by:

In order to explore whether the SMD was clinically meaningful or not, treatment success was then determined according to the recommendations detailed by Dent and Raftery (2011) as demonstrated in Figure 1 below.

Figure 1: Modified graphic representation of interpretation of treatment success (Dent and Raftery; 2011)

**Analyses:**

Meta-analysis is the statistical combination of two or more studies in order to answer questions not answerable by individual studies46. Grouped SMDs were calculated for the categories of (a) matched; and (b) unmatched RCTs (as defined above); using the Revman 5.3 software, according to the guidelines referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions 46.  For the SMD approach, the standard deviations were used to standardize the mean differences to a single scale. In converting to a SMD scale, it was assumed that between-study variation in standard deviations reflected only differences in measurement scales and not differences in the reliability of outcome measures or variability among study populations46. Due to the expected high levels of heterogeneity given the wide variation in exercise types in these RCTs, random effects models were used for all meta-analyses. A sensitivity analysis was performed using the ratio of means30. The Mantel-Haenszel method was used for the random effects model when statistical heterogeneity was observed (I2>=50% or P<0.1). The I2 defines the amount of heterogeneity across trials in meta-analysis, and is frequently defined as low (25%), moderate (50%) or high (75%) 47. Subgroup analyses were performed to assess for differences in comparator arm, as well as to explore and describe differences in pain and physical function between matched and unmatched groups. A prediction interval for the estimated heterogeneity levels was calculated as recommended by the Cochrane Handbook19 using the calculation:

**Risk of Bias Assessment:**

The Cochrane Risk of Bias tool 64 was utilised to assess for risk of bias and includes the following domains: randomisation sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data (e.g. dropouts and withdrawals), and selective outcome reporting. Independent judgement of the risk of bias for each category was made by pairs of reviewers of the author team. Rating was determined as ‘high risk’, ‘low risk’ or ‘unclear risk’ if insufficient detail was present to reach a judgement. Disagreements between pairs of reviewers were discussed and resolved by discussion with all authors.

**RESULTS**

**Search results:**

The updated search yielded 19272 results, which resulted in full text screening of 121 papers before 27 RCTs were included (see Figure 2: PRISMA flow chart). 94 RCTs were excluded for various reasons summarised in the PRISMA chart. The most common reason for exclusion was that trials had sample sizes too small to be able to detect at least a moderate effect size.

Figure 2: PRISMA Flow chart to represent systematic review screening and selection

**Description of Included Trials:**

In the included RCTs there were a total of 5870 participants, of which 2916 were allocated to exercise and 2954 to non-exercise control interventions. Sample sizes varied from 121 to 768. Table 1 summarises the included RCTs. Of the 27 included trials, 25 were individually randomised and 2 were cluster randomised1,72. There were 16 two-arm8,11,17,23,32,36,38,48,51–53,58,61,69,72,73, 9 three-arm1,7,9,15,17,27,34,39,40,67, 1 four-arm59 and 1 six-arm66 RCTs of which only the arms meeting the inclusion criteria were included in our review. Seven trials included a general exercise component which included a regime of stretching and strengthening and/or education1,10,27,40,52,53,66. Four trials had a strengthening focussed exercise arm39,58,69,72, five were focussed on spinal stabilisation and motor control exercise7,8,17,27,34, and two trials had a stretching focussed exercise arm11,15. Three trials used yoga for their exercise intervention36,67,73, one used Pilates59 and one used Tai Chi38. Five trials used a specific exercise therapy approach such as McKenzie32,61, Godelieve Denys-Struyf23 or Cesar exercise therapy48,51. Most trials utilised a group exercise format10,11,15,27,34,36,38–40,52,53,58,66,67,69,72,74, fewer trials delivered their exercise intervention in a one-to-one format7,8,17,27,31,48,51,59,61. Only one trial used a mixed group and one-to-one format23 (27 included 2 exercise arms, so n=28 exercise arms). Three trials used a placebo intervention17,32,39, two trials compared exercise to usual care physiotherapy (excluding exercise)23,61, six trials compared exercise to spinal manipulation7,8,10,15,27,66, fourteen trials used a minimal intervention control group1,11,34,40,48,51–53,58,66,67,72, and four trials had waiting list control arms36,38,59,74 (n=29 comparator arms).

**Risk of Bias:**

There was substantial variation in the overall risk of bias across the 27 trials. At an individual trial level, only 22% of trials1,17,32,36,60,61 (n=6) demonstrated overall low risk of bias with five of the risk of bias domains met. Most trials described adequate sequence generation (22/27)1,7,34,36,38,40,51,53,60,61,66,67,8,74,9,11,15,17,23,27,32. No trials had low risk of bias for blinding, despite trial-specific measures specifically described by Costa et al. 17. The lack of blinding was agreed by the team due to the nature of participating in an exercise intervention in comparison to a non-exercise control. 37% (n=10) of trials1,7,17,32,36,38,40,60,61,72 had a low risk of attrition bias. 78% (n=21) of trials 1,7,38,40,48,51–53,60,61,66,67,9,72,11,15,17,27,32,34,36had low risk of bias for selective reporting, whilst 25% (n=6) had high risk of other biases34,38,48,51,72,74. Risk of bias findings are summarised in figure 3.

*Figure 3: Summary of the risk of bias components of included RCTs*

**Treatment Targets**

Treatment targets were specified in only 18 of the 27 included RCTs. We identified 31 different treatment targets in these 18 trials, with a range of 0 to 7 targets per trial (median of 3), but 19 of these were only mentioned in one trial each. The most frequently reported treatment targets were ‘reducing back pain’11,27,31,36,40,52,58,60,74, ‘increasing muscle strength’8,36,38,39,67,69,72,74, ‘targeting spinal stabilisation or altered spinal control or trunk stability’7,17,23,27,34,58,69, ‘stretching or improved flexibility’8,31,36,38,67,69,72 and ‘improved posture’17,48,72,74.

**Outcome Domains**

Twelve trials specified one primary outcome domain1,7,10,15,23,27,36,38,40,66,72,74, six trials27,31,52,60,61,67 specified two primary outcome domains, and three trials8,17,69 specified three primary outcome domains. Six trials11,34,39,48,51,58 did not explicitly identify any primary outcome domain and therefore the first mentioned outcome domain was taken to be their primary outcome domain. Six primary outcome domains were identified, of which the most frequently cited was physical function (n=14), pain (n=12), and global effect (including patient perceived recovery) (n=6). Figure 4 summarises the frequency of reported primary and secondary outcome domains in the included RCTs.

Figure 4: Frequency of outcome domains in included RCTs

**Categorisation**

RCTs were categorised into matched or unmatched by agreement between all four authors. Seven RCTs (26%) were classified as matched, and twenty RCTs (74%) were unmatched. In total, 1197 participants were included in seven trials judged to be matched. Statistically significant findings in favour of exercise therapy in the nominated or designated primary outcome domain were noted by the RCT authors in four of the seven trials (57%), but clinically important differences were only noted in Miyamoto et al. in one of their intervention arms (Pilates twice weekly) in both primary outcomes. Twenty trials of 4510 participants were judged to be unmatched, and only 15% of unmatched trials found statistically significant results in favour of exercise therapy in their primary nominated or designated outcome measure. Please see supplementary file 2 for the extracted treatment targets, outcomes and matched status.

**Standardised Mean Differences**

The overall SMD of all the included trials was 0.31 (95% CI 0.14,0.47), and was statistically significant in comparison to non-exercise control arms (p=0.0002) (see Figure 5). Ten trials provided sufficient information for the minimal clinically important difference of their primary outcome measure to be standardised. Only one trial demonstrated exercise treatment success that exceeded the standardised minimal clinically important difference (SMID)59. Most other trials (n=9), for which the SMID could be calculated had observed between-group differences that did not demonstrate the SMID1,17,31,38,53,61, and only three of these demonstrated statistical significance in favour of exercise versus their comparison arm 23,66,74.

**Meta-Analysis**

When SMDs were compared across the trials according to categorised status (matched, unmatched), a moderate between arm effect16 was seen in the matched trials (SMD 0.54 (95% CI 0.23 to 0.85)) which was statistically significant compared to non-exercise controls in those trials (p=0.0006), see Figure 5. The trials judged to not match the primary outcome to the treatment targets had SMDs of small to moderate effect in favour of exercise (SMD 0.22 (95% CI 0.01,0.44), p=0.04), see Figure 5. Total sample sizes in the included RCTs varied from 1296 in the matched category (based on 7 trials), to 4508 in the unmatched group (based on 20 trials). Hetereogeneity was high in both the matched (I2 92%) and unmatched (I2 95%) trial categories.

Figure 5: SMDs of unmatched trials in comparison to matched trials

When comparing the matched and unmatched groups described above, the difference between these groups was not statistically significant (p=0.10), prediction interval of (-0.12, 0.76). A sensitivity analysis was performed using the ratio of means, and this similarly found a greater between-group difference in favour of the intervention arms in comparison to their non-exercise controls in matched trials (10%) than unmatched trials (6%). The difference between groups (matched, unmatched) was slightly smaller than that found with the SMD and remained statistically non-significant (p=0.43).

Subgrouping within Matched Categories According to Comparator

Within each category, further subgrouping was performed to compare the effects of different comparator arms. In the matched group, all the comparator arms consisted of a brief intervention, usual care or waitlist control and thus further subgrouping was not possible. In the unmatched group, the effect size was altered according to the control arm but this was not sufficient to explain the differences across matched status (table 2).

*Table 2: Table to demonstrate effect of subgrouping according to comparators on SMDs across matched categories*

**Effectiveness Sensitivity Analyses**

A further sensitivity analysis of the weighted mean difference for pain and physical function was performed for the matched and unmatched categories.

**Physical Function**

The pooled mean difference in physical function demonstrated a statistically significant and larger clinically important effect in the matched group (8.89 (95% CI 1.32, 16.47) p=0.02) in comparison to the unmatched group of trials (1.95 (95% CI -0.20, 4.10). p=0.08). The difference between groups was not statistically significant (p=0.08), suggesting weak evidence in favour of the matched group. The heterogeneity was high (I2 76%). The overall effect of 3.28 (95% CI 1.33, 5.22) is similar to the effect reported by Hayden et al. 41 (3.00 (95%CI -0.53, 6.48).

**Pain**

A meta-analysis of 15 trials which included pain outcomes was performed. The synthesis resulted in a pooled weighted mean improvement of 1.79 (95% CI 0.11, 3.46; p=0.04) for exercise therapy compared to no exercise in matched trials. In trials which did not match their primary outcome to their exercise treatment targets (if specified), synthesis resulted in a lower pooled mean improvement of 0.65 (95% CI 0.08, 1.08; p=0.003). The unmatched values are similar to the pooled weighted mean difference found by Hayden et al., (2005) for all exercise interventions compared to all comparators of 0.73 points on a 10 point scale (7.29 points (95% CI 3.67, 10.91) on a 100 point scale, whereas the matched subgroup results are larger and clinically significant63. However, there was no statistically significant subgroup difference (p=0.20) suggesting no evidence in terms of the effect on pain outcomes in favour of the matched group of trials, and the heterogeneity was high (I2 98%).

**Risk of Bias Across RCTs**

A funnel plot was produced to check for publication bias (figure 6). The SMDs for each RCT primary outcome were plotted against the corresponding measure of precision (one over the standard error of the estimated effect). In the absence of publication bias, the plot should approximate the shape of a pyramid, with a symmetrical, “tapering funnel-like peak” 25, however as this study excluded all small trials, the base of the funnel has been lost, leaving only the peak, and making interpretation difficult.

Figure 6: Funnel plot to demonstrate small-study effect of 27 included trials

**DISCUSSION**

This review systematically identified, synthesised and analysed the treatment targets and outcomes of exercise trials for patients with persistent NSLBP with adequate statistical power to detect at least moderate effect sizes between exercise and comparison interventions. The 27 included trials reported 31 different exercise treatment targets, 19 of which were only mentioned in a single trial. A total of six different primary outcome domains were identified. Only seven trials appeared to clearly match the primary outcome domain and measure to the treatment targets of exercise described. The majority of included trials (n=20) did not match any of the outcomes to the treatment targets of exercise described. A greater proportion of trials (57%) in the matched category reported statistically significant findings in favour of exercise versus their comparator intervention, in contrast to only 15% of unmatched trials. Although meta-analysis found a SMD of moderate size for the matched trials (SMD 0.54 (95% CI 0.23 to 0.85) (p=0.0006)), and a smaller SMD for unmatched trials (SMD 0.22 (95% CI 0.01,0.44), p=0.04), this difference was not statistically significant. There was high heterogeneity, and trials with high risk of bias were included. This exploratory review provides some initial support for the hypothesis that better matching of outcome domains to the treatment targets of exercise interventions in RCTs of persistent NSLBP patients may be more likely to lead to statistically significant results, in favour of exercise compared to controls.

Although there is much evidence to support the benefits of exercise for physical and mental health 41,56,68, the mechanisms of action of exercise and the specific treatment targets of exercise for patients with persistent NSLBP are still a matter of debate 43,70,76. Exercise has been purported to improve motor control, patterns of movement and muscle activation, strength, endurance, flexibility, range of motion, general fitness, as well as mood and depression in persistent NSLBP 26,68. However, despite these wide and varied targets, few trials consistently measure these targets, or report them, demonstrating the lack of consensus amongst researchers and clinicians as to the treatment targets of exercise in persistent NSLBP.

This review found many mechanical exercise targets identified by the authors of the included RCTs (e.g. spinal stabilisation, muscle strengthening, stretching and flexibility), which was anticipated given the targeted physical performance aspects of many exercise trials (e.g. strength, flexibility) 26,71. Falla and Hodges 26 describe mechanical features of spinal pain that exercise can potentially alter such as suboptimal posture or alignment, altered patterns of muscle activation, and altered movement strategies resulting in poorly controlled motion or over-compression. However, our finding that 19 of the 31 different treatment targets were mentioned in only one trial each demonstrates clear uncertainty about the targets of exercise interventions for persistent NSLBP. Even in trials testing similar exercise regimes (e.g. McKenzie exercise approaches), many different treatment targets were mentioned in the trial papers 31,61. There is clearly a lack of consensus in the published literature about what exercise interventions are trying to achieve.

It is perhaps unsurprising that the most frequently cited primary and secondary outcome domains found in this review were those recommended in core outcome sets for RCTs in the field of LBP (pain, physical functioning or both, and health-related quality of life) 6,12,21. Thirteen included trials measured all three of these domains 1,7,8,23,34,36,51,53,59,66,67,69,73 , and in all three of these domains, the most frequently used outcome measures were again in line with published recommendations 14. The international LBP trials community has been using recommended core outcome domains for some time which is reflected in this review, but it is clear that the primary outcomes selected by trial teams are not usually specific to the intervention (in this review, exercise) being tested. Guidance on core outcome sets highlights the need for the primary outcome measure in RCTs to reflect the research question and the treatment being evaluated 12,13. Exercise is a complex intervention and therefore may have multiple treatment targets. The appropriateness of determining success or failure of such an intervention in comparison to a control based largely on one single primary outcome measure in a trial is uncertain. This raises the question as to whether multiple primary outcome domains might be more appropriate, or whether composite measures that capture information across several key domains should be considered for more accurate estimates of the treatment effectiveness of complex interventions.

RCTs were matched according to the author’s descriptions in the published protocol and trial results. Most RCTs (71%) specified treatment targets such as “the goal of the (exercise) program was to increase trunk muscle endurance and trunk stability”7 and these were directly compared to the primary and secondary outcomes of the RCT to determine matching status. This was a subjective process, and was performed by two authors, independently, to improve the validity of the process. However, most RCTs did not appear to match the outcomes to the identified treatment targets (74%). A greater percentage of matched trials found statistically significant results in favour of the exercise arm versus the comparator intervention, than the set of unmatched trials. This suggests that matching the primary outcome to the treatment targets of the intervention may result in statistically significant results in favour of exercise in comparison to a control intervention. The meta-analysis results supported this argument with larger SMDs seen within the matched trials in contrast to the unmatched trials. However due to the high levels of heterogeneity demonstrated within this meta-analysis and the non-statistically significant differences in the SMD between the two sets of trials (matched versus unmatched), it is not possible to draw firm conclusions. Further work to explore the impact of better matching is needed, in a larger sample of exercise RCTs for NSLBP, as well as in RCTs other than exercise for NSLBP.

**Strengths of this Review**

This review is the first to our knowledge that has examined the matching between primary outcomes and reported treatment targets in RCTs of exercise for persistent NSLBP. We found support from 27 RCTs that matching primary outcomes and exercise treatment targets in RCTs may result in a greater likelihood of finding a statistically significant result in favour of exercise. This finding may have implications for clinical practice and future research. The findings suggest that the effectiveness of exercise interventions for LBP may have been previously underestimated. This review was performed both in accordance with a published protocol as well as the PRISMA guidance, ensuring a rigorous approach 37. Independent reviewer selection, quality assessment and data extraction were performed by pairs of reviewers, strengthening the reliability of results 44. Publication bias appeared to be low due to the symmetry demonstrated in the funnel plot in figure 5 25.

Limitations of this Review

There are numerous trials of exercise interventions for persistent NSLBP 41. This review aimed to avoid inclusion of low-quality trials by using a criterion that would ensure included trials had adequate power to detect at least a moderate effect size between intervention arms. Trials with sample sizes sufficient to detect small to moderate changes are more likely to have lower risks of bias. Rubinstein et al. 65 support this theory with their post-hoc analysis. However, this theory does require further testing for confirmation, as this method is not established practice. Our application of this sample size criterion actually resulted in only five trials with lower risk of bias, and only half of the included trials meeting at least three of the seven domains of the risk of bias criteria. The majority of included trials in this review found small between-group SMDs: these are complex trials and there may be other factors that account for these effect sizes that are unaccounted for. Pooling trials when the heterogeneity is high is expected when combining trials of different exercise interventions, in different populations. However, this was controlled for by using a random effects model. When heterogeneity levels are large as was seen in this meta-analysis, the standard error of the pooled estimate is likely to be very large, which results in low power for the corresponding test to detect a difference between subgroups50. The likelihood of publication bias should be considered in light of the results gained from this review, as trials with more favourable results are more likely to have been published 45, and therefore included in this review. Further, almost all trials included in this review were considered to have a high risk of bias due to the lack of blinding of outcome measures and participants, which results in further caution in the interpretation of these results. The categorisation of trials into matched categories was a subjective process, and although independently performed by two members of the author team, it was not a formally validated process as none exists to our knowledge. A further limitation may be that trials might have used exercise interventions that did indeed match their primary outcome(s), but if this was not stated, it was assumed that they did not. This was a non-randomised comparison, and we have tried to adjust for other potential explanations for the results by considering sub-group analysis based on comparator interventions.

This review was exploratory in nature and was likely underpowered to test for a statistical difference between the matched and unmatched groups50, however the difference found between matched and unmatched groups was replicated across multiple subgroup analyses and sensitivity analyses.

**Implications for Practice**

The diversity of treatment targets used in trials of exercise interventions is highlighted in this review, and further work is required to agree the most important treatment targets in exercise interventions for persistent NSLBP as well as to explore the impact of matching outcomes of RCTs more clearly to intervention treatment targets. When treating patients with persistent NSLBP with exercise, use of the most appropriate outcomes, which reflect the treatment targets of exercise, may demonstrate greater patient benefits. Clinicians need to know what exercise interventions are targeting, and what the effects are of that targeted intervention to determine whether it is worth applying clinically. This review may have implications for trial teams developing future RCTs of exercise for NSLBP.

Conclusions

This exploratory review identified a lack of consensus about the treatment targets of exercise for patients with persistent NSLBP, and better understanding of these may provide more targeted treatment strategies for clinical practice. Most RCTs did not match the primary outcome to the treatment targets of the intervention although RCTs that did were more likely to find a statistically significant difference in favour of exercise. Our review suggests that the effectiveness of exercise interventions might be greater than current literature reports, if the treatment outcomes are better matched to the targets of the intervention. However, further research on this topic is needed.

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**Legend:**

Figures:

Figure 1: Modified graphic representation of interpretation of treatment success (Dent and Raftery; 2011)

Figure 2: PRISMA Flow chart to represent systematic review screening and selection

Figure 3: Risk of bias of included trials

Figure 4: Frequency of reported primary and secondary outcome domains in RCTs

Figure 5: Forest plots to demonstrate SMDs of matched in comparison to unmatched RCTs

Figure 6: Funnel plot to demonstrate risk of bias across included trials

Tables:

Table 1: Included Trials Characteristics (27 trials)

Table 2: Table to demonstrate effect of subgrouping according to comparators on SMDs across matched categories