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SYSTEMATIC REVIEW

Allocation Concealment and Intention-To-Treat Analysis Do Not Influence the Treatment Effects of Physical Therapy Interventions in Low Back Pain Trials: a Meta-epidemiologic Study

Matheus Oliveira de Almeida, PhD,[a] Bruno Tirotti Saragiotto, PhD,[b] Chris Maher, PhD,[b] Leonardo Oliveira Pena Costa, PhD[a]

From the [a]Masters and Doctoral Programs in Physical Therapy, Universidade Cidade de São Paulo, Brazil; and [b]Sydney School of Public Health, Sydney Medical School, The University of Sydney, Sydney, Australia.

Abstract

Objective: To evaluate if allocation concealment and intention-to-treat (ITT) analysis influence the treatment effects of physical therapy interventions in low back pain (LBP) trials.

Data Sources: We searched on PubMed, Embase, Cochrane Database of Systematic Reviews, Physiotherapy Evidence Database (PEDro), and CINAHL up to February 2017.

Study Selection: We included LBP trials that compared physical therapy interventions to placebo or no intervention or minimal intervention with pain or disability outcomes.

Data Extraction: Information about allocation concealment and ITT analysis was extracted from PEDro and pain and disability outcomes converted to a 0-100 scale. A meta-regression was performed to evaluate the influence of these methodological features of interest on treatment effects. Other covariates included in the meta-regression were sample size and sequence generation.

Data Synthesis: We identified 128 eligible trials (pooled N = 20,555 participants). A total of 44.5% of the trials achieved allocation concealment, while 32% performed ITT analysis. Meta regression analyses showed no influence of allocation concealment on treatment effects for pain (regression coefficient 0.009; 95% confidence interval [CI] -2.91 to 2.91) and disability (regression coefficient 1.13; 95% CI -1.35 to 3.62), and no influence of ITT analysis for pain (regression coefficient 1.38; 95% CI -1.73 to 4.50) or disability (regression coefficient 1.27; 95% CI -1.39 to 3.64). For the other covariates, there was also no clinically significant influence on the treatment effects.

Conclusion: There is no influence of allocation concealment or ITT analysis on treatment effects of physical therapy interventions for pain and disability in LBP trials.

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Systematic reviews with meta-analysis provide the best available evidence to evaluate the effectiveness of healthcare interventions and are often used to support clinical decision-making and to promote changes in health policies.[1,2] Despite that, systematic reviews are not free of bias, since the summary estimates from these studies may be based on biased randomized controlled trials (RCTs), leading to inaccurate conclusions and misleading clinicians, policy-makers and researchers.[3] Authors of systematic reviews are responsible for reporting the nature and magnitude of bias in the included clinical trials and the possible impact on results. Clinicians who intend to use information from any study also need to be able to recognize the potential for biased conclusions before incorporating these findings into clinical practice.

In order to identify potential sources of biases in clinical research and to understand the impact of study level characteristics in RCTs,

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meta-epidemiologic studies have investigated the influence of these trial characteristics on the intervention effect estimates.[4,5] Important findings from initial meta-epidemiologic studies, such as Schulz et al[6] and Moher et al[7] demonstrated that treatment effect estimates were overestimated in low-quality trials with specific methodological characteristics. Methodological quality assessment tools, such as the Cochrane Collaboration's Risk of Bias[8] and the Physiotherapy Evidence Database (PEDro)[9] scale were developed taking into account the findings from these studies. However, other meta-epidemiologic studies performed in different medical areas have reported no significant influence between treatment effect estimates and trial characteristics considered as sources of bias.[10-13] Therefore, the influence of trial methodological features on treatment effects is still uncertain.

Allocation concealment and intention-to-treat (ITT) analysis are 2 methodological features not widely reported in physical therapy back pain trials,[14] but they may have an impact on the intervention effects and consequently on the findings of clinical trials.[15] Concealed allocation reduces the risk of selection bias (ie, systematic pre-treatment differences between the groups) preventing those who admit participants to a study from knowing the intervention assignment. Knowledge of the upcoming assignment can cause selective eligibility of participants on the basis of prognostic factors.[8] For example, participants with good prognostic factors could be directed to the appropriate intervention. ITT analysis is often defined as the pragmatic and least biased way to estimate intervention effects in RCTs.[8] The main principle of the ITT analysis is to include in the analysis all participants in the groups to which they were randomized, irrespective of what happened subsequently.[8] This principle preserves the benefits of the randomization and avoids the attrition bias and decreases the possibility of biased intervention effect estimates.[8,16]

Most meta-epidemiologic studies derived from reports of RCTs are from the field of medicine.[6,7,17,18] These studies are likely to be different from physical therapy trials, especially regarding the type of intervention and outcomes assessed. To our knowledge, there is only 1 meta-epidemiologic study that investigated the influence of sequence generation and allocation concealment on treatment effects in physical therapy interventions.[19] This study did not find association between these variables and treatment effects. However, this review included studies from different areas of physical therapy, selecting a wide range of different clinical conditions, leading to a large level of heterogeneity that may have influenced this likely association.

Therefore, we chose to focus our study on low back pain (LBP) trials, since LBP is the most prevalent, costly, and disabling musculoskeletal condition.[20,21] Additionally, this condition has the largest number of clinical trials in the physical therapy literature.[14] The objective of this study was to establish if adequate allocation concealment and the use of ITT analysis influence the estimates of treatment effect of physical therapy interventions in LBP RCTs.

List of abbreviations:

CI	**confidence interval**
ITT	**intention-to-treat**
LBP	**low back pain**
PEDro	**Physiotherapy Evidence Database**
RCT	**randomized controlled trial**

Methods

Study design

This is a meta-epidemiologic study. The study was prospectively registered in the International Prospective Register of Systematic Reviews, registration number CRD42016052347. All methodological steps of this study were published elsewhere.[22]

Identification and selection of studies

All RCTs included in systematic reviews with meta-analysis evaluating physical therapy treatment in adults with non-specific LBP that reported pain or disability (as continuous variables) as outcomes were included in this study. Non-specific LBP was defined as LBP not attributed to a specific pathology, such as nerve root compromise or serious spinal pathology.[23] We only included RCTs comparing a physical therapy intervention to no intervention or placebo or minimal intervention.

Potentially eligible RCTs were identified by searching for systematic reviews of physical therapy RCTs in the following databases from their inception up to February 2017: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase via OvidSP, Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/), PEDro (http://pedro.org.au/), and CINAHL (https://health.ebsco.com/products/the-cinahl-database). There was no restriction on language of publication. The search strategy combined validated filters related to "systematic reviews and meta-analyses," "physical therapy interventions," and "low back pain." Two review authors independently assessed and selected potential systematic reviews based on titles and abstracts. Any disagreement was resolved by consensus, and if necessary, a third assessor arbitrated the final decision. Full texts of selected systematic reviews were collected and evaluated in the same manner. From the identified systematic reviews we looked for the eligible RCTs and used the same process as for reviews to check eligibility.

Risk of bias assessment

We extracted the information about allocation concealment and ITT analysis from the PEDro for all included RCTs. We decided to use the PEDro scale due to the following reasons (1) the PEDro scale has high reliability for individual ratings and consensus ratings[9,24]; (2) the PEDro scale is strongly correlated ($r=0.83$; 95% confidence interval [CI] 0.76-0.88) with the Cochrane Risk of Bias tool[25]; (3) feasibility: as 2 authors from this study are raters from the PEDro database, we could easily download the PEDro scores for the included RCTs in our study. In cases where trial was not included in PEDro 2 independent assessors, not involved in the study, rated these trials using the PEDro scale. Any disagreements were resolved by discussion or arbitration by a third assessor when consensus cannot be reached.

The definitions used by the PEDro database for these domains are as follows: "Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation

schedule who was off-site"; "An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated."[9(p.721)] Each domain was rated as yes, when the criterion is clearly satisfied, or no when the criterion is not satisfied or the information is unclear in the text.

Data extraction

Two review authors independently extracted data from all trials included in the selected systematic reviews using a standardized data extraction form. Any disagreements were resolved by discussion or arbitration by a third reviewer when consensus could not be reached.

We extracted bibliographic data (authors, title, year of publication), study characteristics (sample size and interventions used), characteristics of the participants (sex, age, duration, and severity of the condition), outcomes results (mean and SD from each intervention group). We estimated data from graphs and figures when this information was not reported in tables or text. If information regarding SDs was missing, we calculated them from the standard error or CIs of the same study. When it was not possible to calculate the SD from the included trials, we estimated it using the mean SD from all trials. We only extracted outcome results for the short-term follow-up (closest to 4wk).

Data analysis and synthesis

In order to determine whether allocation concealment and ITT analysis influence estimates of treatment effect, a 2-level analysis was conducted. Initially, the treatment effects of each trial were calculated using mean differences with 95% CIs for between-group differences at short-term follow-up, or for between-group differences in change scores.[8,26] Data were converted to a common 0- to 100-point scale if trials had evaluated the same outcome on different scales.

After establishing the treatment effects for the trials included, we calculated the pooled treatment effect estimates using a random effects model (1) trials with allocation concealment; (2) trials without allocation concealment; (3) trials with ITT analysis; (4) trials without ITT analysis. This was calculated separately for pain and disability outcomes. As a post-hoc analysis, we calculated the pooled treatment effect estimates for trials with and without both characteristics (allocation concealment and ITT analysis). We also conducted a post-hoc analysis by calculating the differences in treatment effect estimates for pain and disability between trials with and without allocation concealment; ITT analysis and both characteristics. Review Manager (RevMan) version 5 software[a] was used for all meta-analyses and heterogeneity assessment.

The second stage of the analysis was a meta-regression to evaluate the influence of methodological characteristics of included trials on the estimates of treatment effect.[5] The dependent variable was the treatment effect (mean between-group difference) for the outcomes (pain or disability), while the independent variables were the methodological characteristics of interest (allocation concealment and ITT analysis). Additionally, we added 2 independent covariates in meta-regression analysis: sample size and sequence generation. We decided to investigate the effect of method of sequence generation and sample size since these variables have been associated with treatment effect estimates.[27] We also extracted the information about sequence generation from the PEDro database and is defined as adequate if subjects were randomly allocated to groups (eg, computer-generated random numbers, coin-tossing, and dice-rolling). It is rated as yes, when the criterion is clearly satisfied, or no when the criterion is not satisfied or the information is unclear in the article.[9] The sample size was considered as a continuous quantitative variable in the meta-regression model. Random-effects meta-regression was conducted using the metareg command in Stata 10[b] and weighted using effect size standard errors.[5]

A post hoc sensitivity analysis was also performed, investigating the influence of allocation concealment and ITT analysis on treatment effects based on types of physical therapy interventions (exercise therapy, electrophysical agents, manual therapy, acupuncture, multidisciplinary treatment, taping, traction, education, behavioral therapy).

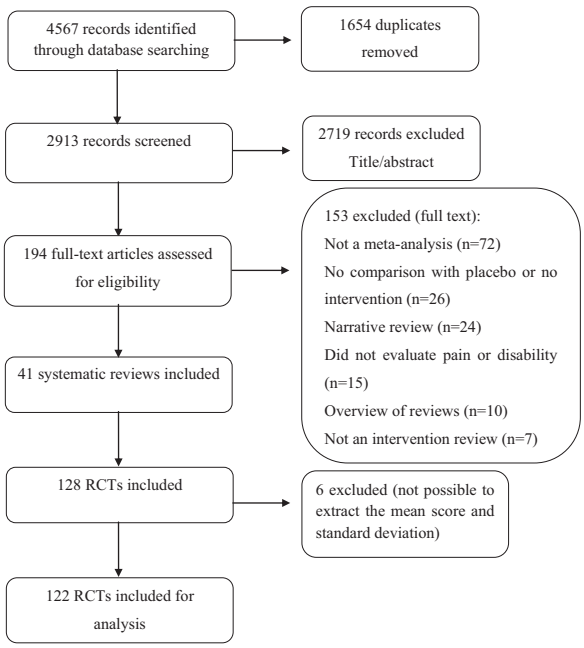

Fig 1 Study flow diagram (search period to February 7, 2017).

Results

The searches identified 194 systematic reviews, of these, 41 fulfilled our inclusion criteria, resulting in 128 RCTs included (pooled N = 20,555 participants), with 209 comparisons that contributed to our analysis (fig 1).

Table 1 describes the characteristics of the included trials. Of the 128 trials included, 40 evaluated exercise therapy, 25 electrophysical agents, 21 manual therapy, 14 acupuncture, 13 behavioral therapy, 10 advice or education, 6 multidisciplinary treatment, 3 taping, and 3 traction. Some trials evaluated more than 1 intervention and each comparison with no treatment or placebo or minimal intervention was included separately. It was

Table 1 Characteristics of included randomized clinical trials

Characteristics	Median (IQR), Mean ± SD, or n (%)
Sample size	91 (54-109)
Age, y	44.7±8.5
Duration of symptoms	
Acute/subacute	23 (18)
Chronic	87 (68)
Mix	16 (12.5)
Not reported	2 (1.5)

Abbreviation: IQR, interquartile range.

not possible to extract the mean score and corresponding SD of intervention and control groups from only 6 (4.7%) trials of all included RCTs, which were excluded from the analyses. Data was expressed as change from baseline values in 17 trials, whereas in the remaining trials data were expressed as values from the follow-up. The full raw data from the 122 included trials are provided in supplemental appendix S1 (available online only at http://www.archives-pmr.org/).

Allocation concealment and treatment effects

Fifty-seven of the 128 trials (44.5%) included in our study performed allocation concealment. The pooled treatment effect for pain of the trials with allocation concealment was -6.77 (95% CI -8.26 to -5.28), while for the trials without allocation concealment, it was -8.64 (95% CI -10.14 to -7.15) (fig 2A). For disability, the pooled treatment effect of the trials with and without allocation concealment was -5.17 (95% CI -6.32 to -4.02) and -6.51 (95% CI -8.59 to -4.44), respectively (fig 2B).

ITT analysis and treatment effects

Forty-one of the 128 trials (32%) included in our study performed ITT analysis. The pooled treatment effect for pain of the trials with ITT analysis was -5.84 (95% CI -7.40 to -4.28), while for the trials without ITT analysis, it was -9.22 (95% CI -10.82 to -7.61) (fig 2C). For disability, the pooled treatment effect of the trials with and without ITT analysis was -5.10 (95% CI -6.43 to -3.77) and -6.26 (95% CI -7.99 to -4.54), respectively (fig 2D).

Allocation concealment plus ITT analysis and treatment effects

Only 29 of the 128 trials (22.6%) included in our study had both characteristics.

The pooled treatment effect for pain of the trials with both characteristics was -7.08 (95% CI -9.11 to -5.04), while for the trials without both characteristics, it was -9.85 (95% CI -11.57 to -8.14) (fig 2E). For disability, the pooled treatment effect of the trials with and without both characteristics was -5.37 (95% CI -6.90 to -3.85) and -7.24 (95% CI -9.75 to -4.74), respectively (fig 2F).

The forest plots of the differences in treatment effect estimates for pain and disability between trials with and without allocation concealment, ITT analysis and both characteristics are provided in supplemental appendix S2 (available online only at http://www.archives-pmr.org/).

Meta-regression

The results of the meta-regression analyses are demonstrated in tables 2 and 3. There was no influence on treatment effects for allocation concealment and ITT analysis for both outcomes (pain and disability), as well as for the covariate sequence generation. For pain, the treatment effect was only influenced by the sample size, increased by 0.01 points (out of 100 points) for trials with a larger sample size (regression coefficient 0.01; 95% CI 0.002-0.018; $P=.01$). For disability, the treatment effect was also influenced only by sample size, decreased by 0.003 points (out of 100 points) for trials with a larger sample size (regression coefficient -0.003; 95% CI -0.006 to -0.0002; $P=.03$). In both cases, the influence was not clinically significant, since the regression coefficient was very small.

As a post hoc analysis, we also investigated the influence of the presence of both characteristics (allocation concealment plus ITT analysis) on the treatment effects and no statistically significant influence was found for both outcomes in the univariate analysis, as well in the multivariate analysis.

The post hoc sensitivity analyses were quite similar to the main analyses in that no statistically significant result was found for most of the analyses. Only in 3 out of 32 sensitivity analyses, a statistically significant result was found. We believe this type I error was due to multiple comparisons. The results of the sensitivity analyses were omitted from this article, but authors can provide these results upon request.

Discussion

We found no influence on estimates of treatment effects for allocation concealment and ITT analysis in LBP trials that investigated the effectiveness of physical therapy interventions. We did not find significant influence of the covariate method of sequence generation on the treatment effect estimates. For the other covariate analyzed, sample size, there was statistically significant, but not clinically relevant, influence on the treatment effect estimates. Therefore, we cannot assume these methodological characteristics as sources of bias, since the results from meta-regression analyses did not find significant findings.

Based on our findings, there is only a direction indicating the lack of allocation concealment and ITT analysis may inflate (in a very small magnitude) the treatment effects of continuous outcomes of physical therapy interventions in LBP trials. Despite our results demonstrating that these characteristics did not influence the treatment effect estimates, we recommend caution while interpreting our findings. To date, there is no strong evidence to discard these characteristics when conducting clinical trials or evaluating their quality.

Our results are largely consistent with previous meta-epidemiologic studies that investigated the influence of allocation and ITT analysis in continuous outcomes but in different clinical situations.[10,12,19,28-30] Four previous studies reported a very small, but not statistically significant, exaggeration of treatment effects in trials with inadequate allocation concealment and lack of ITT analysis.[10,12,19,30] However, 2 previous studies reported the influence in an opposite direction for allocation concealment and ITT analysis, but also without statistical significance.[28,29]

In contrast, among the meta-epidemiologic studies that evaluated the influence of allocation concealment on categorical

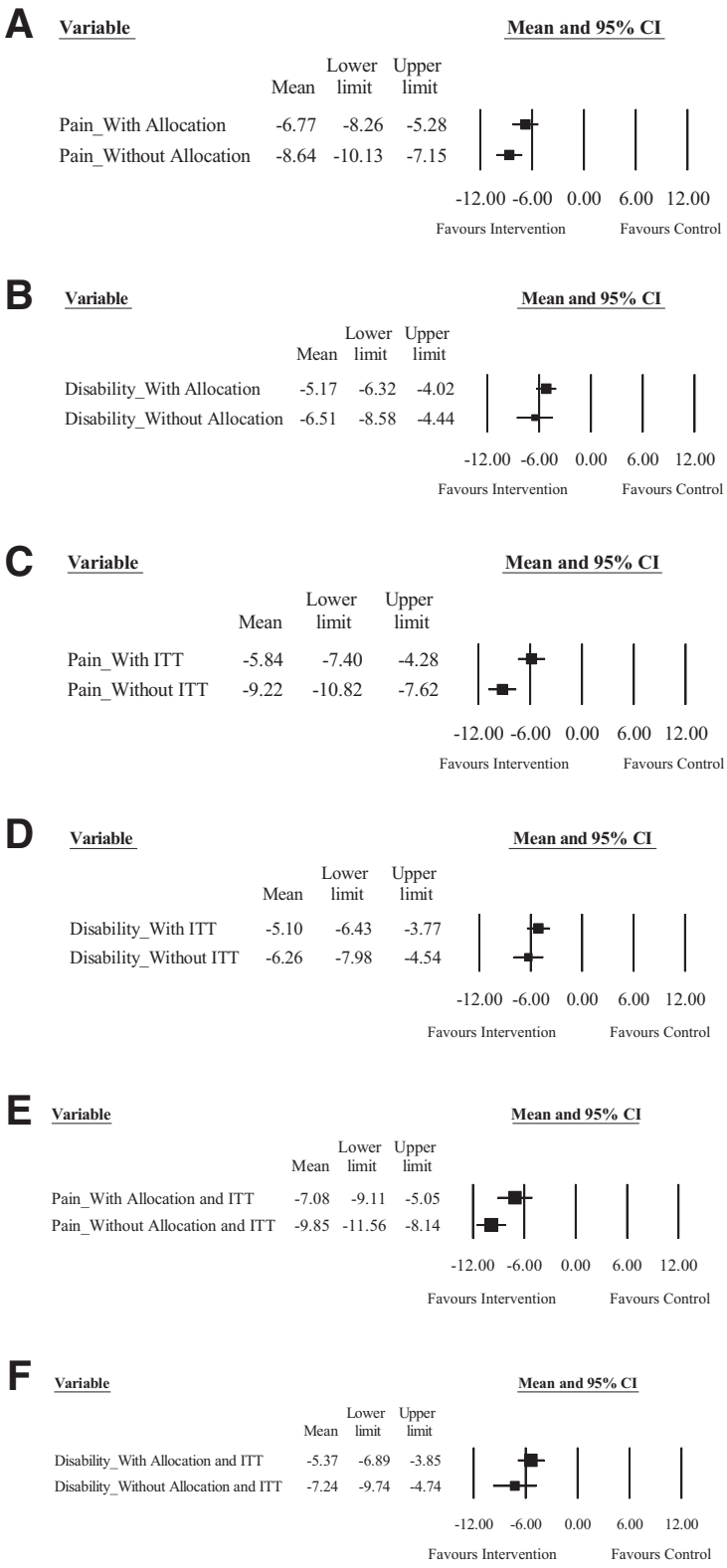

Fig 2 Descriptive forest plots of the pooled treatment effect for the outcomes: (A) pain of trials with and without allocation concealment; (B) disability of trials with and without allocation concealment; (C) pain of trials with and without ITT analysis; (D) disability of trials with and without ITT analysis; (E) pain of trials with and without allocation concealment plus ITT analysis; (F) disability of trials with and without allocation concealment plus ITT analysis.

Table 2 Meta-regression analyses on the association between treatment effect and methodological characteristics of included trials for pain

	Univariate Analysis		Multivariate Analysis	
Characteristics	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Allocation concealment	1.59 (-1.13 to 4.31)	.25	0.009 (-2.91 to 2.91)	.99
ITT analysis	2.91 (0.14-5.69)	.04*	1.38 (-1.73 to 4.50)	.38
Sequence generation	5.9 (-12.05 to 23.86)	.51	4.17 (-13.64 to 21.99)	.64
Sample size	0.01 (0.004-0.019)	.002*	0.01 (0.002-0.018)	.01*

* $P<.05$.

outcomes, some of them[7,13,31-33] found association between the lack of allocation concealment and overestimation of treatment effects (ratio of treatment effect ranging from 0.63 to 0.94), whereas other previous studies reported no association.[18,34-36] Regarding the influence of ITT analysis on treatment effects of categorical outcomes, most of them found no influence of this methodological characteristic.[11,13,37,38] Only Abraha et al,[39] using a different definition for deviation from ITT analysis without taking into account the occurrence of post-randomization exclusions, found that the treatment effect of trials that performed modified ITT analysis was overestimated by 17% compared with trials that performed ITT analysis. This variability in the results of the possible association among meta-epidemiologic studies, especially about allocation concealment that evaluated continuous and categorical outcomes may be explained by the fact meta-analysis that evaluate continuous outcomes are more likely to demonstrate heterogeneity, which may yield an impact on treatment effect estimates.[40] Another reason may be the fact that continuous scales are often used for subjective measures, such as pain and disability, while categorical outcomes are more often used to evaluate hard endpoints.

One possible explanation for the lack of influence of these 2 characteristics on the treatment effect estimates in our study is the modest effect size commonly found in the interventions used in LBP trials,[41] as well as in most fields of medicine.[42] Even when the interventions are compared to no or minimal intervention, the between-group differences are rarely large, which may explain the very small and not statistically significant differences favoring trials with no allocation concealment or ITT analysis.

Another possible explanation is the large heterogeneity (around 80%) found between trials included in our analyses, which can have an impact on treatment effects. This large heterogeneity could be explained by the inclusion of such different physical therapy interventions (with different characteristics of duration and dose), as well as different samples (acute, subacute, and chronic population were included). Therefore, we conducted sensitivity analyses investigating the influence of allocation concealment and ITT analysis on treatment effects based on types of physical therapy interventions. The results of the sensitivity analyses demonstrated that the large heterogeneity found in our study are unlikely to be explained by the inclusion of different types of physical therapy interventions. Another reason for the large heterogeneity may be due to the expected different effect estimates when we compare active and passive interventions. Future meta-epidemiologic studies that intend to investigate empirical bias should look for a large sample of homogeneous trials.

We cannot rule out the possibility of misleading reporting of research methods in the included trials. Although the Consolidated Standards of Reporting Trials has helped the authors to improve the quality of reporting of trials, this does not mean the quality of the trials themselves.[43] The possibility of discrepancies between what was reported and what was actually performed in the trials could affect our findings. This situation can happen due to lack of knowledge from researchers about fundamental methodological issues or a scientific ethical problem from the researchers despite their understanding of methodological issues. For example, Wu et al evaluated 3,137 studies reported to be RCTs and found that 86% failed to adhere to established methodological principles for RCTs.[44]

To our knowledge, this is the first study that investigated the influence of methodological characteristics (allocation concealment and ITT analysis) on the magnitude of the treatment effects of physical therapy interventions in LBP trials. Thus, our study yield novel evidence on this area, as previous studies have done in other healthcare areas (osteoarthritis, cardiorespiratory, childbirth, and others), that allocation concealment and ITT analysis do not significantly exaggerate treatment effect estimates.

Study limitations

Our study has some limitations and the results should be interpreted with caution. The first is that our study included only published data. We cannot rule out the possibility of publication

Table 3 Meta-regression analyses on the association between treatment effect and methodological characteristics of included trials for disability

	Univariate Analysis		Multivariate Analysis	
Characteristics	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
Allocation concealment	1.46 (-0.94 to 3.86)	.23	1.13 (-1.35 to 3.62)	.36
ITT analysis	1.24 (-1.18 to 3.67)	.31	1.27 (-1.39 to 3.64)	.37
Sequence generation	1.3 (-13.95 to 16.57)	.86	7.63 (-14.29 to 15.93)	.91
Sample size	-0.003 (-0.006 to -0.0008)	.04*	-0.003 (-0.006 to -0.0002)	.03*

* $P<.05$.

bias, and unpublished trials are likely to have lower methodological quality, as well as to find no significant differences between groups.[45] Another limitation is that our findings are restricted to meta-analyses of physical therapy interventions in non-specific low-back pain. Our results may have limited generalizability to other clinical conditions, as well to other type of interventions. So, a replication of our study is needed testing other conditions to evaluate if the findings are consistent.

Conclusion

In summary, there is no influence of allocation concealment and ITT analysis on treatment effect estimates of physical therapy interventions for pain and disability in LBP trials. Additionally, other important methodological characteristics, such as method of sequence generation and sample size, also did not influence the treatment effect estimates.

Suppliers

a. Review Manager (RevMan) version 5; Cochrane Collaboration.
b. Stata, version 10; StataCorp.

Keywords

Low back pain; Physical therapy modalities; Rehabilitation

Corresponding author

Matheus Oliveira de Almeida, PhD, Universidade Cidade de São Paulo. Rua Cesário Galeno, 448, Tatuapé, São Paulo, SP, Brazil, 03071-000. *E-mail address:* mathewsalmeida@hotmail.com.

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