

**Does Type of Sponsorship of Randomized Controlled Trials Influence Treatment Effect  
Size Estimates in Rehabilitation: A Meta-epidemiological Study**

**Short description:** Sponsorship bias arises due to potential inappropriate influence of funding on trial findings. The issues of detecting and quantifying the effects of sponsorship bias in the results of randomized controlled trials (RCTs) is of relevance for different decision makers. This study aimed to evaluate the influence of funding bias on treatment effect of RCTs, using a meta-epidemiological approach.

(60 words)

## **Abstract**

**Background:** Sponsorship bias could affect research results to inform decision makers when using the results of these trials. The extent to which sponsorship bias affect results in the field of physical therapy (PT) has been unexplored in the literature. Therefore, the main aim of this study was to evaluate the influence of sponsorship bias on the treatment effects of RCTs in PT area.

**Methods:** This was a meta-epidemiological study. A random sample of RCTs included in meta-analyses of physical therapy (PT) area were identified. Data extraction including assessments of appropriate influence of funders was conducted independently by 2 reviewers. To determine the association between biases related to sponsorship biases and effect sizes, a 2-level analysis was conducted using a meta-meta-analytic approach.

**Results:** We analyzed 393 trials included in 43 meta-analyses. The most common sources of sponsorship for this sample of PT trials were government (n=205 ,52%) followed by academic (n=44, 11%), and industry (n=39, 10%). The funding was not declared in a high percentage of the trials (n=85, 22%). The influence of the trial sponsor was assessed as being appropriate in 246 trials (63%) and considered inappropriate/unclear in 147 (37%) of them. We have moderate evidence to say that trials with inappropriate/unclear influence of funders tended to have on average a larger effect size than those with appropriate influence of funding (ES= 0.15; 95% CI - 0.03; 0.33).

**Conclusion:** Based on our sample of PT trials, it seems that most of the trials are funded by either government and academia and a small percentage are funded by the industry. Treatment effect size estimates were on average 0.15 larger in trials with lack of appropriate influence of funders as compared to trials with appropriate influence of funding. Contrarily to other fields, industry funding was relatively small and their influence perhaps less marked. All these results

could be explained by the relative youth of the field and/or the absence of clear industry interests. In front of the call for action by the World Health Organization to strengthen rehabilitation in health systems, these results raise the issue of the need of public funding in the field.(word count: 400)

## INTRODUCTION

Clinical research, in many cases, is funded by the industry as limited public money is available for funding. Sponsorship bias arises due to potential inappropriate influence of funding on trial findings. Inappropriate influence of funding may happen, for instance, if a trial receives commercial funding, and the sponsors have a say on trial design, analysis, and/or decision to publish results. Mechanisms to regulate conflicts of interest have been implemented. For example, journals and institutions request clear reporting of conflict of interest before submitting or publishing results from health research. These, however, do not protect against potential sponsorship bias that would affect research results to inform decision makers. The issues of detecting and quantifying the effects of sponsorship bias in the results of randomized controlled trials (RCTs) is of relevance for different decision makers in health care and thus it should be carefully discussed in different areas of health care.

The issue of sponsorship bias has been extensively discussed in medicine and drug trials for several years where funding of trials is generally done by the industry (e.g. pharmaceutical companies, industries promoting certain equipment/devices).<sup>1-7</sup> Also, some studies have been conducted in the area of dentistry where industry could play a role such as in the area of implantology<sup>8</sup> or restorative dentistry.<sup>9</sup> Numerous studies have concluded that when trials are sponsored by industry could provide exaggerated treatment effects.<sup>1-3,5-7</sup> In addition, industry sponsorship in some occasions can influence the publication and /or dissemination of the results of trials sponsored by industry.<sup>1</sup> For example trials that are sponsored by industry could be more likely to publish positive results or not published results which are not significant. This in turn, could create biases in the information that is actually disseminated to decisions makers. On the

contrary, some studies have found that the results of trials sponsored by industry are not significantly different than those funded by other means (e.g., government, academia, foundations or non-profit organizations) and thus the influence of the sponsors is actually limited or inexistent.<sup>4,8,9</sup>

In the area of rehabilitation, and specifically in the area of physical therapy, only few reports have looked at the issue of sponsorship.<sup>10,11</sup> However, these reports only looked at the association between funding and trial quality in a few trials in a specific area of PT. In fact, the evaluation of the funding was in general terms; that is, they classified trials as funded or not, but they did not evaluate whether the influence of funding was appropriate or not and if funding had an association with treatment effect.

Although, the role of the industry in the area of rehabilitation could have a more limited role than the areas of medicine and surgery; as far of our knowledge, there are no meta-epidemiological studies that have evaluated the influence of sponsorship bias on treatment effect size estimates within the field of rehabilitation and more specifically, in the physical therapy field. Importantly, it is not clear whether the previously mentioned conclusions from other health areas hold true in rehabilitation.

This study aimed to evaluate the influence of funding bias on treatment effect of RCTs, using a meta-epidemiological approach. More specifically, our objectives were: 1) to determine the most common types of funding in the area of physical therapy (PT); 2) determine appropriateness of its reporting in PT RCTs; 3) examine whether funding has an effect on treatment estimates in PT trials ; and 4) determine if these effects differ depending on characteristics of the meta-analyses analyzed, such as magnitude of effect size, meta-analysis

heterogeneity, type of outcome (subjective or objective), and whether the meta-analysis involves the musculoskeletal (MSK) area compared with other areas of research in physical therapy.

This study is targeted to clinicians, researchers, systematic reviewers, health technology assessments teams, and decisions makers. The results of this project will inform about the importance of evaluating sponsor bias in individual randomized controlled trials. It is hoped that the results help teams in the area of rehabilitation and specifically in the area of physical therapy to understand the importance of these biases when assessing, conducting and implementing results of these trials.

## **METHODS**

### **Design**

Meta-epidemiological approach

### **Study selection**

This project was part of a large project looking at the association between different biases and their association with treatment effects in randomized controlled trials in the physical therapy area. The methodology has been described in previous publications.<sup>12-16</sup> In short, a random sample of Randomized Controlled Trials (RCTs) included in meta-analyses in the PT discipline were identified by searching the Cochrane Database of Systematic Reviews from Jan 1, 2005 to May 25 2011 on PT interventions. Meta-analyses and RCTs included in these meta-analyses were included if they met the following eligibility criteria: 1) the meta-analysis included at least 3 RCTs comparing at least two interventions, with at least one of the interventions being part of PT scope of practice according to the World Confederation for Physical Therapy (WCPT)<sup>17</sup>; and 2) the main outcome or the outcome of the meta-analysis with the largest number of trials

conducted in the review was continuous.

### **Data extraction of treatment estimates and trial characteristics**

Two independent reviewers extracted specific data (e.g. type of interventions, type of outcomes (i.e. objective, subjective), PT area) for all trials included in the meta-analyses as well as data on means, standard deviations, and sample sizes. The primary outcome chosen for the analysis was the main outcome of interest reported in the review or determined from the meta-analysis that contained the largest number of trials in the review. Details on the reviewers' panel and training process can be found elsewhere.<sup>12,18</sup>

### **Data extraction on Key Characteristics**

#### **Risk of sponsorship bias**

We followed previous work to determine the funding of the trials.<sup>1</sup> Trials were specified either as being funded by for-profit, nonprofit, or unclear source of funding. Nonprofit funding included money received from both nonprofit organizations (e.g., internal academic institutional funding, non-profit foundations, or governmental funding) and not funded trials. For-profit organizations were defined as companies/industries that might acquire financial gains or losses depending on the outcome of the trial. Funding was defined as including provision of human resources (authorship, statistical analysis, or other assistance), study materials (devices/equipment, or similar materials), or grants. Sources of funding were extracted from the text, statements of sources of support, authors' affiliations, and acknowledgments.

Influence of sponsorship was judged as "appropriate" if either one of the following situations were met: 1) sponsor was acknowledged with clear statement regarding no involvement of a sponsor in the trial conduct, data management /analysis, or co-authorship; 2) sponsorship was



obtained from an academic institution, governmental agency, or foundation; 3) sponsor was acknowledged only as providing equipment or resources for the study but no one of the authors was paid by the company or the company had nothing to do with designing, analyzing, or disseminating the trial results.

Influence of funder was judged as “inappropriate” if sponsor was acknowledged with information provided that a co-author works for that company of that company was involved in conduct, analysis and dissemination of the study’ results. Influence of sponsorship was assessed as “unclear” if there was insufficient information to permit a judgment, or if the funding source was not reported.

## **Data Analysis**

Data on sponsorship bias were analyzed descriptively based on appropriate and inappropriate influence of funders. In order to determine whether sponsorship biases influenced treatment effect estimates, a 2-level analysis was conducted using a meta-meta-analytic approach with a random-effects model to allow for within and between meta-analyses heterogeneity as suggested by Sterne et al.<sup>19</sup>

The first level analysis (within meta-analysis) was as follows: we derived effect sizes (ES) for each trial by dividing the between-group difference in mean values by the pooled standard deviation.<sup>20</sup> A negative ES indicates a beneficial effect of the experimental intervention. If some required data were unavailable, we used approximations as previously described.<sup>21</sup> The data from each trial were obtained from the meta-analyses included in our study. We followed the classification used in the Cochrane reviews to classify the treatment arms as the experimental treatment of interest or as the control group. In the case of studies appearing in more than one review, the study was only considered once in the meta-analysis with the fewer number of overall studies. We then calculated

two pooled effect sizes for each meta-analysis: one corresponding to the pooled effect size from studies having the characteristic of interest (e.g., appropriate influence of funders) and the other for studies that did not (e.g., no or unclear influence of funders). We used standard random-effects meta-analyses to combine ES across trials and calculated the DerSimonian and Laird estimate of the variance to determine heterogeneity between trials.<sup>22,23</sup> Then, for each meta-analysis, we derived the difference between pooled ES estimates from trials with and without the characteristic of interest (e.g., appropriate influence of funders). A negative difference in ES indicates that trials with appropriate influence of funders show a more beneficial effect for the experimental group.

The second level analysis (between meta-analyses) involved pooling the results of the previous analysis to describe the effect of each trial component across all meta-analyses. The effect sizes were also combined at this stage using the DerSimonian and Laird random-effects models<sup>24</sup> to allow for between meta-analysis heterogeneity.

Formal tests of interaction between appropriate influence of funders and estimated treatment benefits were performed separately for each meta-analysis based on Z scores using the estimated difference in ES between trials with and without appropriate influence of funders and the corresponding standard error (SE).

We additionally stratified analyses accompanied by interaction tests according to the pre-specified characteristics as reported by Nuesch et al,<sup>22</sup>: 1) treatment benefit in overall meta-analysis: small [ES greater than -0.5] versus large [ES  $\leq$  to -0.5]; between-trial heterogeneity in overall meta-analysis (low [ $\tau^2 < 0.06$ ] versus high [ $\tau^2 \geq 0.06$ ]), nature of the outcome (subjective or objective) and if the intervention was classified as musculoskeletal or other PT area.

## **RESULTS**

### **Selection and characteristics of meta-analyses and RCTs**

The search identified 3901 Cochrane reviews, with 271 reviews potentially relevant to PT. Of these, 68 reviews included a meta-analysis of at least three studies of PT interventions and used a continuous outcome. We randomly selected 44 meta-analyses but excluded one<sup>25</sup> because it used follow-up data from the same group rather than a control group for comparison (Figure 1). Forty-three meta-analyses including 393 trials and analyzing 44,622 patients contributed to this study. Table 1 summarizes the characteristics of the 43 Cochrane reviews. Briefly, the reviews were published between 2008 and 2011 and included meta-analyses of the effectiveness of PT interventions for musculoskeletal (22 reviews)<sup>26-34</sup>, cardiorespiratory (9 reviews)<sup>35-43</sup>, neurological (6 reviews)<sup>44-50</sup>, and other areas of physical therapy (6 reviews).<sup>50-55</sup> A median number of 6 trials were included in the meta-analyses (interquartile range 5-8). Most trials were parallel group trials (367; 93.4%), single-center studies (298; 76%) and had active control interventions (362; 92%). The most common intervention was exercise (n=282, 71.8%). Supplementary Table S1 (Appendix 1) lists the characteristics of each of the 43 meta-analyses. We analyzed 393 trials included in 43 meta-analyses.

### **Types of sponsorship**

Taking the 393 trials overall, the most common sources of sponsorship for this sample of PT trials were government (n=206, 52.4%) followed by foundation (n=102, 26%), academic (n=44, 11.2%), industry (n=39, 10%), and other types of funding (n=25, 6.36%). Most of the trials presented mixed type of funding having either funding from government, academia, foundation or industry. For example, 281 trials (71.5%) had funding from either government, academia,

foundation, or industry. From these, 261 trials had funding from either government, academia, or foundation only (without involving funding from industry). Trials funded by only one type of funding were less common. A smaller percentage of trials were funded only by government (n=123, 31%), foundation (n=36, 9.2%), academic (n=11, 2.8%), or industry (n=10, 2.5%), or only other type of funding (n=8, 2%). Nineteen trials (4.8%) did not receive any type of funding. The funding was not declared in a high percentage of the trials (n=95, 24%).

The influence of the trial sponsor was assessed as being appropriate in 246 trials (63%) and considered inappropriate/unclear in 147 (37%) of them.

### **Sponsorship bias and treatment effects in PT trials**

Forty meta-analyses including 377 trials and analyzing 43651 patients contributed to the analysis on the influence of sponsorship bias and treatment effects on PT trials. Figure 1 shows the forest plot of the differences in effect sizes between trials with appropriate influence of funders and those with inappropriate influence of funders.

Trials with inappropriate or unclear influence of funders tended to have a larger effect size than those with appropriate influence of funding. Although the difference was not statistically significant, trials with inappropriate influence of funders tended to overestimate the treatment effect (ES= 0.15; 95% CI -0.03; 0.33).

The results of the stratified analyses are displayed in Figure 2. In meta-analyses with a large benefit trials with inappropriate influence of funders tended to overestimate the treatment effects (ES; 0.50 95%CI (0.18, 0.83) vs. 0.01 95%CI -0.19, 0.21). Similarly, meta-analyses with larger heterogeneity between trials in the overall meta-analysis was associated with larger treatment effects than those with lower heterogeneity. The rest of the factors (i.e. type of outcome and

Type of PT area) did not have a significant interaction

## **DISCUSSION**

### **Summary of the findings**

The results of this study showed that most of the trials in the area of physical therapy received government and funding from academic institutions, and only a few of them received industry funding. In addition, reporting of type of sponsorship is poorly reported in the area of physical therapy. Twenty two percent of the trials (n=85) did not clearly reported sponsors. Results of our meta-epidemiological approach suggest that we have moderate evidence to say that trials with inappropriate influence of funders tended to overestimate the treatment effect.

### **Comparison with other studies**

The relationship between funding and biases has been investigated in several medical disciplines. Funding appears to be related to a positive outcome in favor of the pro-industry findings, but in musculoskeletal physical therapy trials, it seems to be limited, taking into account that the source of the finding is still unclear .<sup>56</sup>

The report of funding in clinical trials has become increasingly popular, reasons may include the influence of funding sources in the reporting of research findings and the interpretation of results. This importance is also acknowledged by the CONSORT checklist in which a section for the report of funding is included. The results of this review agree with a previous report in the musculoskeletal area where the majority of the included trials reported being funded.<sup>56</sup> Similarly, the proportion of unfunded trials seems to be stable during the last few years, and better than other areas such dentistry (37 % ,)<sup>8</sup> but there is still a significant percentage (21-22%) of PT trials

in which funding was not mentioned. One explanation for this might be that funding for scientific research in this area is highly competitive and has become difficult to obtain.

Based on the fact that sponsorship may introduce bias, which may distort trial conclusions, more effort needs to be conducted among clinical researchers in PT to disclose the source of funding.

The literature revealed that industry sponsorship might significantly influence clinical outcomes in some disciplines including pharmaceuticals and medical areas.<sup>6,57,58</sup> Less consistent results for this influence are recently found in other areas such as dentistry.<sup>8,9</sup> This study showed that industry sponsorship was the least common source of funding (10%). Although this number is considerably higher than a previous survey (2.4%),<sup>56</sup> the issue of industry funding in PT trials is considerably lower than in other disciplines. This can be explained by the fact that compared to pharmaceutical and medical research, PT studies are less associated with commercial applications, drugs, devices or cost-effectiveness analyses. Thus, in light of this limited evidence, the impact of industry-funded trials for PT research remains unclear.

Since previous research articles lack a sufficient description of the impact of funding sources on treatment effects, the main purpose of this review was to evaluate the influence of sponsorship bias on the treatment effects of RCTs. However, the magnitude of the treatment effect size has been normally paired with the methodological quality of a trial. For example, evidence suggests that design flaws of randomized controlled trials in physical therapy can result in overestimation of the treatment effect size (ES).<sup>16</sup>

This study is the first meta-epidemiological study conducted in PT evaluating the influence of sponsorship bias on treatment effects. As such, our study is not directly comparable to other research in the PT field. As observed in the present study, inappropriate/unclear influence

showed on average a larger effect size than those trials with the appropriate influence of funding. Thus, this is the first study that provides some insights into the influence of sponsorship bias on treatment effects on PT area.

### **Poor reporting of funding**

In our study, we found a poor reporting of funding in physical therapy trials. This is quite common in physical therapy trials and has been reported previously.<sup>56</sup> Specially, it has been seen that the source of funding is poorly reported in PT trials indexed in the PeDRo database.<sup>56</sup> Maas et al., reported that about 38% of the trials did not clearly state the source of funding and thus it was impossible to determine the influence of funders. This percentage was higher than the number found in the current study (22%); although both are considered relatively high. Also, it is possible to speculate that the absence or unclear funding declaration could be due to a real absence of funding for physical therapy trials and not only to a reporting issue.

In addition, our study found that 10% of the trials declared to be funded by industry and Maas et al.,<sup>56</sup> found a smaller percentage (2.4%) of the trials funded by industry. The differences between our study and Maas et al.,<sup>56</sup> could be due to different samples used. They<sup>56</sup> only focused on musculoskeletal PT trials and our study involved different areas of PT.

Looking at these results, it is important to highlight that there is a strong need for PT trials to be transparent regarding the role of funding; thus, the influence of funding and their biases could be accurately evaluated. In addition, since a small percentage of trials in PT is funded by industry, it seems that the role of the industry for funding physiotherapy trials could be much more limited than in medical trials. Having said that, it is still necessary that future research confirm these results in another sample of PT trials.

## **What should be reported regarding sponsorship**

As mentioned above, transparency in the reporting of funding for trials in any discipline is crucial. Hakoum et al.<sup>59</sup> developed guidelines for researchers to report details about funding. They provided a pdf fillable form that researchers should complete at the time of submission of the study for consideration for publication. This form provides details of the involvement of any funding body in the trial in all different stages of trial development and conduct. For example, the form requests information about funding sources, type of funder (internal funding, government, inter-government, private for profit, private not for profit), research phase for which the funding was received, the value of the monetary support, and provision of supplies among others. The use of this form allows transparency in reporting of funding. Researchers in any field and especially in the field of rehabilitation are encouraged to use this guidance. Journal editors should also request this information before considering a paper for publication.

## **Strength and Limitations**

As far as our knowledge, this is the first study that looked more specifically at the description of different types of sponsors and its appropriateness in the area of physical therapy. In addition, this is the first meta-epidemiological study conducted in PT evaluating the influence of sponsorship bias on treatment effects. Therefore, this study provides with novel evidence in this field.

Some of the limitations of this study were that we only analyzed published reports and not actual trials. We did not contact the authors of the trials since contacting authors is time consuming, inconvenient, unpractical, and potentially costly. We decided to follow a pragmatic approach as is commonly performed in the literature. This approach, although widely used, limits



the identification of true bias when study elements are not properly reported by trial authors.

We tried to assemble trials in an area of research (i.e. Physical therapy) to minimize heterogeneity; However, as mentioned by Berkman et al.,<sup>60</sup> meta-epidemiological studies are by nature heterogeneous since they combine results from multiple units of analysis such as patients, trials, and meta-analyses and also several different trials from different specific areas. Therefore, the results of our study are limited by the inherent heterogeneity of the analyzed studies.

In addition, our study analyzed in isolation the influence of sponsorship bias but did not analyze the interaction with other biases. This type of analysis would require a bigger sample size, to provide accurate estimates.

### **Implications for rehabilitation and future directions**

Rehabilitation is a relatively young area of research, when compared to other fields.<sup>61</sup> Due to its focus on functioning, disability, and quality of life and to the need of measurement instruments for these outcomes,<sup>62</sup> research in rehabilitation has concentrated in the last 20 years to produce these tools. However, studies in the field of rehabilitation are steadily growing<sup>63,64</sup> as well as its evidence.<sup>65</sup> Recently the World Health Organization called for more rehabilitation in health services<sup>66,67</sup> due to the increase of disability worldwide<sup>68</sup> Although research in rehabilitation, including physiotherapy, is highly relevant to the challenges faced by modern societies (i.e. aging populations and burden of chronic health conditions) remains less funded than in other fields.<sup>69</sup> The results of our study show that industry sponsorship is relatively low when compared with government or academic funding, and support the need of an expanded governmental funding to support research in this field. As previously reported, PT trials that were funded typically had a higher quality of methodology.<sup>10,56</sup> It has been hypothesized that funding could

facilitate the rigorous conduct of trials by allowing a multidisciplinary research team, having reliable and blinded assessors (when possible), higher sample sizes, and the possibility to be published in higher impact factor journals.<sup>56</sup> Although nowadays obtaining research funding is highly competitive, it is recommended that government agencies expand their programs to fund rehabilitation research and avoid inadequate influence of funders in research reports. In addition, researchers in the field need to clearly report the source of the funding.

## **CONCLUSIONS**

Trials with inappropriate or unclear influence of funders tended to have a larger effect size than those with appropriate influence of funding. Contrarily to other fields, industry funding was relatively small and their influence perhaps less marked. All these results could be explained by the relative youth of the field and/or the absence of clear industry interests. In front of the call for action by the World Health Organization to strengthen rehabilitation in health systems, these results raise the issue of the need of public funding in the field. (3397)

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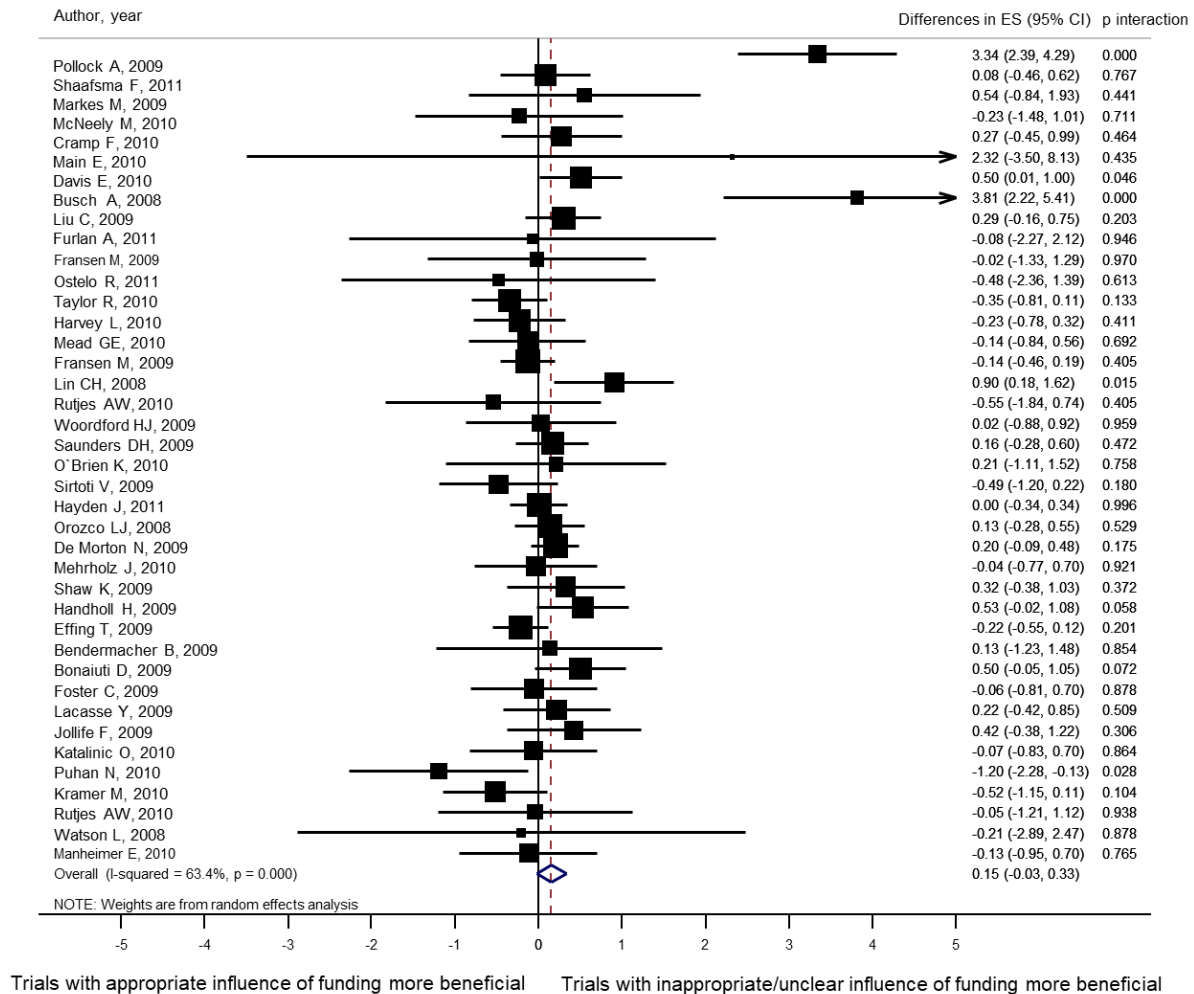
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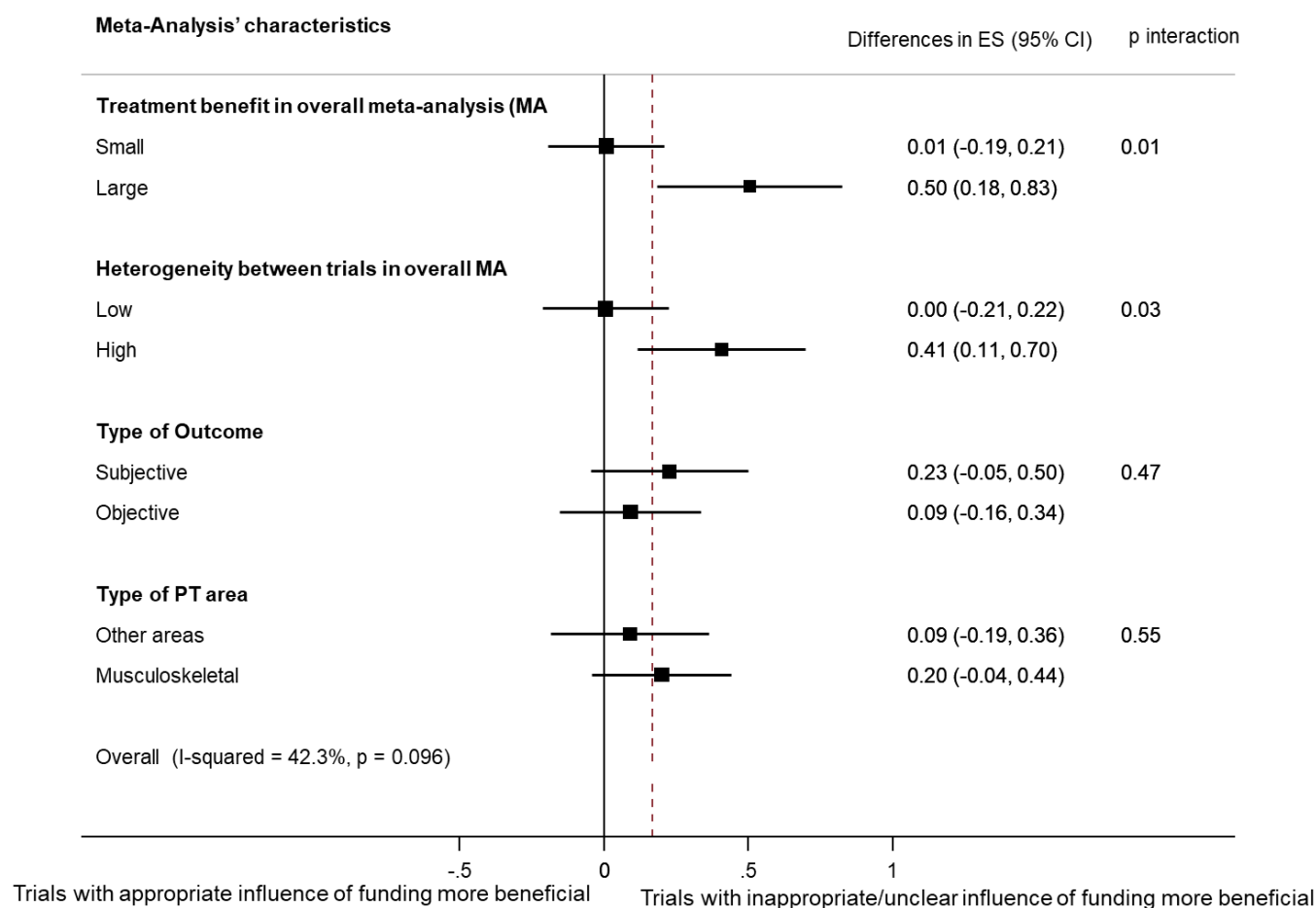
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**Figure 1. Difference in treatment effect size (ES) estimate between trials with appropriate and inappropriate influence of funders. A positive value ( $> 0$ ) across meta-analyses indicates that the inappropriate influence of funders inflates the treatment effect size estimate.**





**Figure 2. Difference in treatment effect size (ES) estimate between trials with appropriate and inappropriate influence of funders stratified by meta-analyses characteristics.**