Assessing bias in osteoarthritis trials included in Cochrane reviews: A meta-epidemiological study

Julie B. Hansen, Carsten B. Juhl, Isabelle Boutron, Peter Tugwell, Elizabeth Ghogomu, Jordi Pardo Pardo, Tamara Rader, George A. Wells, Alain Mayhew, Lara Maxwell, Hans Lund, Henning Bliddal, Robin Christensen, and The Editorial Board of the Cochrane Musculoskeletal Group

Julie Bolvig Hansen

Physiotherapist
Master of Science in Physiotherapy

The Parker Institute, Department of Rheumatology, Copenhagen University Hospitals, Bispebjerg and Frederiksberg, Denmark
Assessing bias in osteoarthritis trials included in Cochrane reviews: A meta-epidemiological study

Julie B. Hansen, Carsten B. Juhl, Isabelle Boutron, Peter Tugwell, Elizabeth Ghogomu, Jordi Pardo Pardo, Tamara Rader, George A. Wells, Elizabeth Ghogomu, Lara Maxwell, Hans Lund, Henning Bliddal, Robin Christensen, and The Editorial Board of the Cochrane Musculoskeletal Group

Julie Bolvig Hansen
Physiotherapist
Master of Science in Physiotherapy

The Parker Institute, Department of Rheumatology, Copenhagen University Hospitals, Bispebjerg and Frederiksberg, Denmark
Main results

- Bias associated with study characteristics such as trials size, blinding of personnel and patients, center status, and funding may lead to exaggeration of intervention effect estimates and increases the between-trial heterogeneity in trials reporting subjectively assessed outcomes.

- Results of OA trials may be affected by other domains (i.e., trial size, center status, and source of funding) than those already included in the Cochrane risk of bias tool.
Main results

• Bias associated with study characteristics such as trials size, blinding of personnel and patients, center status, and funding may lead to exaggeration of intervention effect estimates and increases the between-trial heterogeneity in trials reporting subjectively assessed outcomes.

• Results of osteoarthritis (OA) trials may be affected by other domains (i.e., trial size, center status, and source of funding) than those already included in the Cochrane risk of bias tool.
Introduction

The validity of systematic reviews and meta-analyses is depending on the methodological quality of trials.

Bias in trials can lead to underestimation or overestimation of the true intervention effect (1).

Regardless of tools used to assess risk of bias, the methods for assessing and summarising potential bias and incorporating bias assessments into meta-analyses vary greatly (2;3)

Objective

Our objective was to evaluate the association of estimates of treatment effects with different bias related study characteristics in meta-analyses of interventions used for treating pain in osteoarthritis (OA).
Methods

Eligibility criteria

• Only reviews of randomized or controlled trials in patients with OA
• Patient reported pain outcome
• Compared with sham, placebo, or no intervention control

Data was eligible from the trials, which were included in eligible meta-analyses.

Search in Cochrane Library

Pain estimates were abstracted from overall pain reported in the Cochrane review’s
Bias items

Original Cochrane items

• Sequence generation
• Allocation concealment
• Blinding of participants
• Blinding of personnel
• Incomplete outcome data

New items

• Centre status
• Trials size
• Source of funding
1a. Meta-analysis background information

- Author
- Year and journal of publication
- Type of OA condition
- Type of intervention (NP, P or S)
- Primary pain outcome

1b. Data from meta-analysis

- Mean values ($m_i$ and $m_s$) and standard deviations (SD) were collected from the included meta-analysis
- Number of patients $N_i$ and $N_s$

2. Data from trials

- Author
- Year and journal of publication
- Assessment of bias (Adequate, inadequate, or unclear)
- Trial size
- Centre status
- Funding source

3. Data synthesis

- Treatment effect sizes were expressed as SMD by dividing the mean values available from meta-analyses by the SD’s
- Negative effect size indicated beneficial effect to the intervention (i.e., pain reduction)
Data extraction

1a. Meta-analysis background information
- Author
- Year and journal of publication
- Type of OA condition
- Type of intervention (NP, P or S)
- Primary pain outcome

1b. Data from meta-analysis
- Mean values ($m_i$ and $m_c$) and standard deviations (SD) were collected from the included meta-analysis
- Number of patients $N_i$ and $N_s$

2. Data from trials
- Author
- Year and journal of publication
- Assessment of bias (Adequate, inadequate, or unclear)
- Trial size
- Centre status
- Funding source

3. Data synthesis
- Treatment effect sizes were expressed as SMD by dividing the mean values available from meta-analyses by the SD’s
- Negative effect size indicated beneficial effect to the intervention (i.e., pain reduction)
Data synthesis

1a. Meta-analysis background information
- Author
- Year and journal of publication
- Type of OA condition
- Type of intervention (NP, P or S)
- Primary pain outcome

1b. Data from meta-analysis
- Mean values ($m_i$ and $m_s$) and standard deviations (SD) were collected from the included meta-analysis
- Number of patients $N_i$ and $N_s$

2. Data from trials
- Author
- Year and journal of publication
- Assessment of bias (Adequate, inadequate, or unclear)
- Trial size
- Centre status
- Funding source

3. Data synthesis
- Treatment effect sizes were expressed as SMD by dividing the mean values available from meta-analyses by the SD’s
- Negative effect size indicated beneficial effect to the intervention (i.e., pain reduction)
Methods

• **Meta-epidemiology**: explore the influence of the study characteristics on treatment effect estimates

• The **difference** between the **pooled estimates** from the meta-analyses were **combined** to measure the **variability** in bias estimates, expressed in $\tau^2$

• Random effect models with fixed factor for review and trial characteristics

• The primary outcome domain was **pain - negative effect indicated beneficial effect of experimental intervention**.
Results

Reviews identified and reviewed on basis of title and abstract $M = 78$

Reviews excluded based on title and abstract $M = 41$
- Not RCTs = 1
- Meta-analysis with <2 trials = 1
- No meta-analysis = 1
- No treatment for OA = 35
- Withdrawal = 3

Reviews retrieved for full text review $M^* = 37$

Reviews excluded based on full text review $M^* = 17$
- Not RCTs = 1
- Not sham, placebo, or no-intervention control = 3
- No patient reported outcome = 1
- No meta-analysis from OA overall pain = 8
- Meta-analysis with <2 trials = 3
- Other = 1

Eligible meta-analysis $m = 20$

Trials from meta-analysis $K = 136$

Trials excluded $K = 10$
- Duplicates of same publication = 2
- No full text available = 8

Trials included in meta-epidemiological analysis $k = 126$

Included intervention comparisons $k^* = 140$

Flowchart

$M = $ identified Cochrane Reviews;
$M^* = $ Possible eligible Cochrane reviews;
$m = $ included meta-analysis;
$K = $ Trials from included Cochrane reviews;
$k = $ Trials included in meta-analysis;
$k^* = $ Intervention comparisons.
Results

Overall meta-analysis:
ES = -0.40,
95%CI (-0.46 to -0.34)
I² = 73.3%
Results

Statistical significant difference in effect estimates: between small (<128 participants) and large trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trials*</th>
<th>ES</th>
<th>95% CI</th>
<th>Tau²</th>
<th>Change of Tau² (%)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>140</td>
<td>-0.40</td>
<td>(-0.46 to -0.34)</td>
<td>0.1272</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trial size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>53</td>
<td>-0.31</td>
<td>(-0.43 to -0.19)</td>
<td>0.1082</td>
<td>-14.93</td>
<td>0.003</td>
</tr>
<tr>
<td>Small</td>
<td>87</td>
<td>-0.57</td>
<td>(-0.69 to -0.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

Other factors that could reduce heterogeneity were (prioritised): *Blinding of personnel, Blinding of patients, Centre status, Funding source.*

**Table 2 – Results of the stratified Meta-analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trials*</th>
<th>ES</th>
<th>95% CI</th>
<th>Tau²</th>
<th>Change of Tau² (%)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>140</td>
<td>-0.40</td>
<td>(-0.46 to -0.34)</td>
<td>0.1272</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blinding (Patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>73</td>
<td>-0.33</td>
<td>(-0.44 to -0.21)</td>
<td>0.1137</td>
<td>-10.61</td>
<td>0.004</td>
</tr>
<tr>
<td>Unclear</td>
<td>16</td>
<td>-0.71</td>
<td>(-0.94 to -0.48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>51</td>
<td>-0.61</td>
<td>(-0.81 to -0.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (Personnel)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>87</td>
<td>-0.35</td>
<td>(-0.46 to -0.25)</td>
<td>0.1125</td>
<td>-11.56</td>
<td>0.005</td>
</tr>
<tr>
<td>Unclear</td>
<td>46</td>
<td>-0.65</td>
<td>(-0.80 to -0.50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>7</td>
<td>-0.28</td>
<td>(-0.61 to 0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centre status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi</td>
<td>64</td>
<td>-0.35</td>
<td>(-0.47 to -0.22)</td>
<td>0.1211</td>
<td>-4.80</td>
<td>0.026</td>
</tr>
<tr>
<td>Single</td>
<td>76</td>
<td>-0.56</td>
<td>(-0.69 to -0.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-profit</td>
<td>51</td>
<td>-0.45</td>
<td>(-0.63 to -0.28)</td>
<td>0.1213</td>
<td>-4.64</td>
<td>0.020</td>
</tr>
<tr>
<td>Unclear</td>
<td>40</td>
<td>-0.62</td>
<td>(-0.80 to -0.45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For-profit</td>
<td>49</td>
<td>-0.31</td>
<td>(-0.45 to -0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

Original Cochrane items

- Sequence generation
- Allocation concealment
  - Blinding of participants
  - Blinding of personnel
- Incomplete outcome data

New items

- Centre status
- Trials size
- Source of funding
Discussion

• Strengths and limitations
  – Single reviewer data extraction

• Comparison with other studies
  – Trials size (Nüesch et al 2010)

• Future research
  – Confirmation of these findings
  – Additive effect
Take home message

Results of OA trials may be affected by other domains* than those already included in the Cochrane risk of bias tool.

*i.e., trial size, center status, and source of funding