Excluding small studies from a systematic review or meta-analysis

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Question

Is it ever acceptable to exclude studies from a systematic review and meta-analysis solely on the basis of sample size?
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Case study 1 – Diagnostic Test Accuracy Review

• A study team wishes to exclude any study that has less than 100 participants at the abstract stage for the following reasons

  1. Resources are not available to complete the review within a realistic timeframe given rapid policy developments in the area

  2. In very small studies there exists a high possibility of selection bias
Case study 2 – Intervention Review

- A Cochrane Review currently containing 80 trials is due for an update
  
  1. CRG has issued guidelines on how reviews could be kept manageable?

  2. One suggestion was to limit review to studies with >40 participants
    - Rationale: reviews could become so unwieldy they will become difficult to understand

  3. Argued that smaller studies are often of poor quality
Why we should not exclude studies based on sample size

1. How small is small: Where to draw the line?
2. Defeats main premise underlying meta-analyses
3. Reduces the potential to explore heterogeneity
4. May lose information on important sub-groups of patients
The Statisticians point of view!

“Statistician”

“Biostatistician”

“Medical statistician”

“Epidemiologist”
Message to the Cochrane Statistical Methods Group

• Are there occasions where it would be acceptable to exclude studies from a Cochrane review or meta-analysis for the following reasons?

1) Smaller studies are associated with a higher risk of bias
2) For practical reasons
The verdict

Those in favour of excluding small studies

Those against excluding small studies
The verdict

Those in favour of excluding small studies
0

Those against excluding small studies
26
The verdict

Those in favour of excluding small studies

1?

Those against excluding small studies

25?
Main theme 1: Small study effects

- Publication bias: Small “negative” studies less likely to get published
Main theme 1: Small study effects

• Publication bias: Small “negative” studies less likely to get published

• Problem made worse by fact that in random effects meta-analyses small and large studies weighted equally
Main theme 1: Small study effects

• Many tests available to test for and correct funnel plot asymmetry
  • But need 10 studies to assess funnel plot symmetry

• Other possibilities
  – Analyse only the largest study(s)
  – Cumulative meta-analysis

*Dechartes et al. JAMA 2014;312:623-630*

• 163 meta-analyses of RCTs published in either the Cochrane library or leading medical journals (top 10 in category) between 2008 and 2013
Table 2. Summary of the Average Differences in Treatment Outcomes Between the Meta-analysis and Single Most Precise Trial, Expressed as Ratios of Odds Ratios, by Type of Outcome (Subjective vs Objective)

<table>
<thead>
<tr>
<th>Alternative Strategy</th>
<th>Subjective (n = 92 [705 RCTs])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROR (95% CI)</td>
</tr>
<tr>
<td>Single most precise trial</td>
<td>1.13 (1.07-1.19)</td>
</tr>
<tr>
<td>Meta-analysis restricted to the largest trials&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.08 (1.04-1.13)</td>
</tr>
<tr>
<td>Limit meta-analysis</td>
<td>1.17 (1.11-1.22)</td>
</tr>
<tr>
<td>Meta-analysis restricted to trials at low overall risk of bias</td>
<td>0.94 (0.86-1.04)</td>
</tr>
</tbody>
</table>

Abbreviation: ROR, ratio of odds ratios.

<sup>a</sup> An ROR greater than 1 indicates larger treatment outcomes with the meta-analysis of all trials than with the alternative strategy.

<sup>b</sup> The largest trial meta-analysis.
Table 2. Summary of the All Trials and Each Alternative Strategy, Expressed as Ratios of Oc

<table>
<thead>
<tr>
<th>Alternative Strategy</th>
<th>Objective (n = 71 [535 RCTs])</th>
<th>ROR (95% CI)</th>
<th>P Value</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single most precise trial</td>
<td></td>
<td>1.03 (1.01-1.05)</td>
<td>.002</td>
<td>0</td>
</tr>
<tr>
<td>Meta-analysis restricted to</td>
<td></td>
<td>1.03 (1.00-1.06)</td>
<td>.044</td>
<td>0</td>
</tr>
<tr>
<td>Limit meta-analysis</td>
<td></td>
<td>1.13 (0.82-1.55)</td>
<td>.46</td>
<td>96</td>
</tr>
<tr>
<td>Meta-analysis restricted to of bias</td>
<td></td>
<td>1.03 (1.00-1.06)</td>
<td>.048</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviation: ROR, ratio of ed as those in quarter 4 of sample size within each

*An ROR greater than 1 indicates meta-analysis of all trials that...
Main theme 2: The relationship between study size and study quality

- Second reason why including small studies could inflate the magnitude of an odds ratio
- Advice is to restrict meta-analyses to studies with low risk of bias in a sensitivity analyses
  - Only 11% of systematic reviews do so!
- But can sample size be used as a surrogate for assessing risk of bias?
  - 3 respondents favoured keeping these separate
Main theme 3: practicality

• 1 respondent involved in review where <50 people per treatment group excluded
  – IPD review (time and effort)
  – Rare outcome so small trials will contribute little information
  – Overhead in negotiating collaboration, etc.
  – Small studies have less impact in meta-analysis
Summary

• Beware fixation with sample size: determinants of precision
  – Sample size
  – Outcome frequency
  – Exposure distribution (or allocation ratio)
  – Covariate adjustment

• Consider exclusion of small studies in sensitivity analyses as well as those with high RoB (but keep concepts separate)

➢ Future Research

• Relationship between study size and study quality
• Explore scenarios where small study exclusions could be feasible
  – e.g. rapid reviews (Turner et al. PLoS One 8(3):e59202)
“Cochrane Statistician”

“Clinical trialist”

“Evidence based medicine guru”