Excluding small studies from a systematic review or meta-analysis

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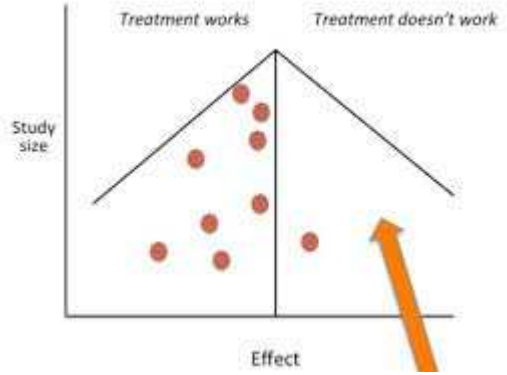

Question

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”

“Medical statistician”

“Biostatistician”

“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

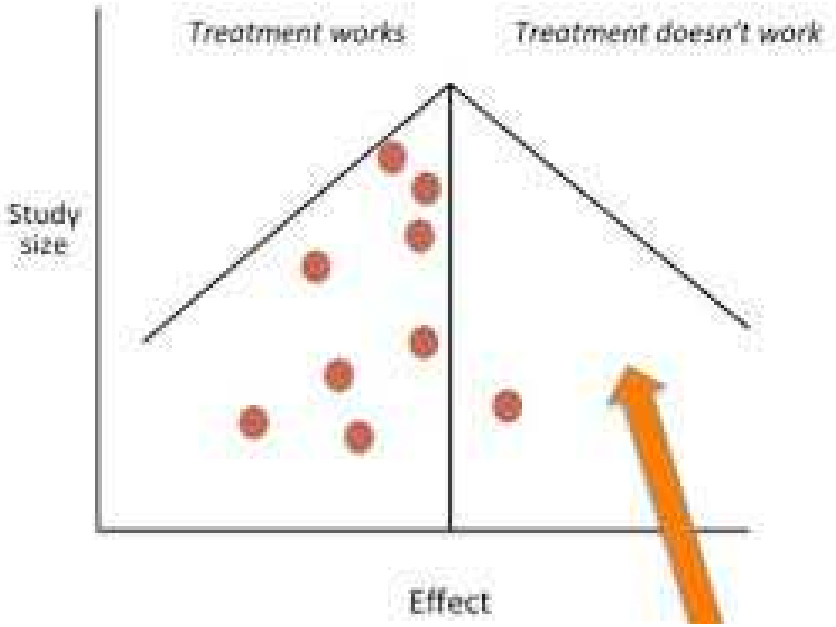
1?

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**

Dechartes et al. 2014

Table 2. Summary of the Average Differences in Treatment Outcomes Between the Meta-ana Expressed as Ratios of Odds Ratios, by Type of Outcome (Subjective vs Objective)

	Subjective (n = 92 [705 RCTs])	
Alternative Strategy	ROR (95% CI)[a]	*P* Value
Single most precise trial	1.13 (1.07-1.19)	<.001
Meta-analysis restricted to the largest trials[b]	1.08 (1.04-1.13)	<.001
Limit meta-analysis	1.17 (1.11-1.22)	<.001
Meta-analysis restricted to trials at low overall risk of bias	0.94 (0.86-1.04)	.23

Abbreviation: ROR, ratio of odds ratios.

[a] An ROR greater than 1 indicates larger treatment outcomes with the meta-analysis of all trials than with the alternative strategy.

[b] The largest trial meta-analysis.

Dechartes et al. 2014

Table 2. Summary of the All Trials and Each Alternative Strategy, Expressed as Ratios of Oc

	sis Outcome		
	Objective (n = 71 [535 RCTs])		
Alternative Strategy	ROR (95% CI)[a]	*P* Value	I^2 (%)
Single most precise trial	1.03 (1.01-1.05)	.002	0
Meta-analysis restricted to	1.03 (1.00-1.06)	.044	0
Limit meta-analysis	1.13 (0.82-1.55)	.46	96
Meta-analysis restricted to of bias	1.03 (1.00-1.06)	.048	23

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

[a] An ROR greater than 1 indi meta-analysis of all trials th

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”