Treatment effect in meta-analyses: comparison of different strategies for analysis

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Which trials to combine: a persistent dilemma

Meta-analysis

- Inclusion of all trials
  - More precise but some trials could be biased
  - Systematic error

- Restriction to trials at low risk of bias
  - Lower risk of bias but potentially imprecise
  - Random error
Incorporation of risk of bias assessment into meta-analyses

• What is recommended\(^1\)
  • To restrict the primary meta-analysis to trials at low risk of bias
  • To present meta-analyses stratified according to risk of bias

• Less recommended option:
  • To present meta-analysis of all trials while providing a summary of the risk of bias across trials

• What is actually done\(^2\)
  • Cross sectional review
  • 200 SRs published in Jan-March 2012 (100 Cochrane SRs)
  • 11% incorporated the risk of bias assessment into the analysis
    • Sensitivity analysis with exclusion of trials at high or unclear risk of bias

\(^1\) Higgins et al. *BMJ*. 2011
\(^2\) Hopewell et al. *BMJ open*. 2013
Influence of trial sample size on treatment effect within meta-analyses

- Not only « small » trials
- Stronger effects in small to moderate-sized trials may not reflect the true treatment effect
- Should meta-analyses be restricted to the largest trials?
  - 4th quarter of sample size within MAs
  - « Largest » trial

Dechartres et al. *BMJ*. 2013
Interest of recent methods for correcting « small study effect »

- Regression-based methods
  - Described by Rücker et al.\(^1,2\) and Moreno et al.\(^3\)

- « Limit » meta-analysis method
  - Predicted treatment effect for an infinite precision trial (variance or standard error=0)
  - By extrapolation of the regression line (treatment effect \(\sim\) variance or standard error)

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1 Rücker al. *Biostatistics*. 2011
2 Rücker et al. *Biom J*. 2011
Objectives

• To compare treatment effects obtained from all available evidence (meta-analysis of all trials) to:

• “Best evidence” strategy related to trial sample size and precision:
  • Trial with the most precise treatment effect
  • Meta-analysis restricted to the largest trials (Quarter 4 with 25% of the largest trials)
  • « Limit » meta-analysis method¹

• “Best evidence” strategy related to risk of bias:
  • Meta-analysis restricted to trials at low risk of bias

¹ Rücker et al. Biostatistics. 2011
Data sources

- Combination of data from 2 collections of meta-analyses used for previous meta-epidemiological studies\(^1,^2\):
  - 48 MAs (421 RCTs) for the 1\(^{\text{st}}\) collection
    - Published in high-impact factor journals in 2008 and 2010
    - Minimum number of trials: 3
  - 45 MAs (314 RCTs) for the 2\(^{\text{nd}}\) collection
    - Cochrane reviews published in 2011
    - Minimum number of trials: 4
  - Binary outcomes

\(^1\) Dechartres et al. *Ann Intern Med.* 2011

\(^2\) Dechartres et al. *BMJ.* 2013
Data extraction

- General characteristics and results
- Assessment of risk of bias by domains
  - From individual RCT reports (1\textsuperscript{st} collection)
  - From Cochrane reviews (2\textsuperscript{nd} collection)
- Overall risk of bias for a trial

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Interpretation</th>
<th>Within a trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk of bias</td>
<td>Bias, if present, is unlikely to alter the results seriously</td>
<td>Low risk of bias for all key domains</td>
</tr>
<tr>
<td>Unclear risk of bias</td>
<td>A risk of bias that raises some doubt about the results</td>
<td>Low or unclear risk of bias for all key domains</td>
</tr>
<tr>
<td>High risk of bias</td>
<td>Bias may alter the results seriously</td>
<td>High risk of bias for one or more key domains</td>
</tr>
</tbody>
</table>

**Key domains:**
- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data

Higgins et al. *BMJ*. 2011
Analysis

• Treatment effect expressed as Odds ratios (ORs)

• Meta-analyses performed with DerSimonian and Laird random-effects model
  • All trials
  • Trials at low overall risk of bias
  • Largest trials (Quarter 4 with 25% of the largest trials)

• « Limit » meta-analysis method (Rücker et al.¹)
  • Expected limit estimate

• Stratification: Objective versus subjective outcomes

¹ Rücker et al. *Biostatistics*. 2011
Classification of outcomes

- **Objective outcomes:**
  - All-cause mortality
  - Other objectively assessed
    - Pregnancy, live births, laboratory outcomes
  - Objectively measured but potentially influenced by clinicians or patients' judgement
    - Hospitalizations, total dropouts or withdrawals, cesarean section, operative or assisted delivery, additional treatments administered

- **Subjective outcomes:**
  - Clinician-assessed outcomes, symptoms, pain, mental-health outcomes, cause-specific mortality

Characteristics of the 93 meta-analyses

• Nb of trials per meta-analysis:
  • Median 7 (range 3 to 30)

• Treatment effect: 0.10 (0.03-0.35) to 1.59 (1.15-2.20)
  • 48 MAs: statistically significant benefit for the experimental arm
  • 1 MA: statistically significant benefit for the control arm
  • 44 MAs: no statistical difference between experimental and control arms

• Overall risk of bias
  • 47 MAs included at least 1 trial at low overall risk of bias
  • 24 MAs included only 1 trial at low overall risk of bias
Classification of outcomes

- 43 (46%): objective outcome
  - 31: all-cause mortality
  - 7: other objectively assessed
  - 5: objectively measured but potentially influenced by clinician or patient judgement

- 50 (54%): subjective outcome
Comparison of treatment effect between the overall MA and the most precise trial

Objective outcomes

Subjective outcomes
Comparison of treatment effect between the overall MA and MA restricted to trials with the largest sample size (4th quarter)
Comparison of treatment effect between the overall MA and the « limit » MA method.
In summary

- Treatment effect is frequently larger in the meta-analysis of all trials than in the:
  - Most precise trial
  - Meta-analysis restricted to trials with the largest sample size (4th quarter)
  - « Limit » meta-analysis

- Our results suggest a difference between objective and subjective outcomes
Comparison of treatment effect between the overall MA and MA restricted to trials with low risk of bias

27/43 (63%) MAs with an objective outcome have at least 1 trial at low risk of bias

20/50 (40%) MAs with a subjective outcome have at least 1 trial at low risk of bias
Treatment effect according to risk of bias within each meta-analysis

Objective outcomes

Subjective outcomes

Legend:
- Green: Low overall risk of bias
- Red: High/unclear overall risk of bias
In summary

- Low number of meta-analyses with at least one trial at low overall risk of bias

- No evidence of larger treatment effect in the MA of all trials than in the MA restricted to trials at low risk of bias

- Results of meta-epidemiological studies suggested larger treatment effect estimates in trials at high or unclear risk of bias compared to those at low risk domain by domain
  - No meta-epidemiological study compared treatment effect according to overall risk of bias
Meta-epidemiological analysis: treatment effect by overall risk of bias

### Objective outcomes

#### ROR (95% CI) % Weight

- 0.76 (0.30, 1.92) 2.30
- 1.73 (0.49, 6.13) 1.24
- 1.32 (0.45, 3.86) 1.72
- 1.18 (0.69, 2.00) 6.73
- 0.55 (0.13, 2.25) 1.00
- 0.72 (0.37, 1.41) 4.32
- 1.38 (0.33, 5.80) 0.97
- 0.91 (0.38, 2.20) 2.52
- 0.51 (0.12, 2.18) 0.95
- 0.62 (0.13, 2.88) 0.84
- 0.70 (0.37, 1.33) 4.61
- 1.32 (1.01, 1.72) 23.07
- 0.32 (0.01, 13.74) 0.14
- 0.81 (0.51, 1.32) 8.76
- 0.21 (0.06, 0.73) 1.33
- 4.62 (0.16, 131.37) 0.18
- 1.38 (0.24, 8.07) 0.64
- 0.81 (0.36, 1.80) 3.09
- 0.50 (0.18, 1.38) 1.88
- 4.76 (0.19, 117.07) 0.20
- 0.59 (0.20, 1.71) 1.73
- 1.10 (0.69, 1.76) 8.53
- 1.22 (0.91, 1.62) 20.49
- 1.02 (0.88, 1.17) 2.75

Overall (I-squared = 3.4%, p = 0.415)

Weights are from random effects analysis

- High/unclear risk trials show larger effect
- Low risk trials show larger effect

### Subjective outcomes

#### ROR (95% CI) % Weight

- 0.86 (0.58, 1.28) 12.06
- 1.04 (0.18, 6.12) 0.59
- 0.59 (0.03, 9.86) 0.23
- 1.04 (0.67, 1.60) 9.81
- 1.06 (0.70, 1.60) 10.86
- 1.02 (0.71, 1.46) 14.11
- 0.74 (0.16, 3.45) 0.78
- 1.03 (0.29, 3.59) 1.19
- 0.72 (0.30, 1.69) 2.53
- 2.40 (0.21, 27.65) 0.31
- 0.99 (0.70, 1.41) 15.30
- 0.81 (0.34, 1.93) 2.49
- 1.32 (0.90, 1.95) 12.46
- 0.83 (0.14, 5.01) 0.57
- 2.29 (1.07, 4.88) 3.24
- 1.44 (0.66, 3.13) 3.08
- 0.90 (0.44, 1.87) 3.49
- 1.23 (0.68, 2.22) 5.37
- 0.77 (0.16, 3.65) 0.77
- 3.92 (0.80, 19.12) 0.74

Overall (I-squared = 0.0%, p = 0.874)

Weights are from random effects analysis

- High/unclear risk trials show larger effect
- Low risk trials show larger effect
Conclusions

• In a sample of meta-analyses, we compared meta-analyses of:
  • All available evidence
  • Best-evidence
    • Largest trials (Quarter 4), most precise trial, limit MA
    • Trials at low risk of bias

• Frequently larger treatment effect in the MA of all trials than in the « limit » meta-analysis, most precise trial or Quarter 4
  • More marked for subjective outcomes
  • Consistent results for the 3 comparisons
Conclusions: assessing trial overall risk of bias

• No difference of treatment effect according to overall risk of bias

• Difference of treatment effect domain by domain?

• Current definition of overall risk of bias
  • Same risk of bias for trials with 1 domain at high/unclear risk and all key domains at high/unclear risk of bias
  • Does not take into account potential interactions between domains

• Assessing risk of bias: « The why is easy, the how is a challenge »¹
  • Difficult to understand bias and their impact on treatment effect

¹ Hrobjartsson et al. Cochrane Database Syst Rev. 2013
Thank you for your attention

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Limit MA versus most precise trial
Modifications of conclusions

• Out of 48 meta-analyses showing statistically significant outcomes in favor of the experimental arm when including all trials
  • No difference in 11 (23%) meta-analyses using one of the alternative strategies for analysis

• None of the 47 meta-analyses without significant differences became statistically significant using one of the alternative strategies for analysis
Comparison of treatment effect according to risk of bias assessment

- Cross sectional study
- 163 trials in child health
- Effects sizes combined under DerSimonian and Laird random effects model
- Results:
  - Lower treatment effect in trials with low risk of bias trials than in those with high or unclear risk of bias

Hartling et al. *BMJ*. 2009
Appearances can be misleading

- Same analysis using our data
- Comparison of treatment effect between low and high or unclear risk of bias without taking into account meta-analysis stratification
- DerSimonian and Laird random effects model