Outline

- Sources of bias in the dissemination of evidence
- Graphical and statistical methods to examine reporting biases

Sources of bias in the production and dissemination of evidence

- Publication bias
- Time lag bias
- Language bias
- Multiple publication bias
- Outcome reporting bias
- Citation bias

The dissemination of evidence ...

unavailable (unpublished)
available in principle (e.g. thesis, obscure journal)
easily available (Medline-indexed)
actively disseminated (e.g. reprint from drug company)

Identification and follow-up of studies submitted to ethics committees

<table>
<thead>
<tr>
<th>Ethics committee</th>
<th>Identification</th>
<th>Follow-up</th>
<th>% Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHU-PH</td>
<td>1980</td>
<td>1988</td>
<td>66</td>
</tr>
<tr>
<td>JHU-MED</td>
<td>1980</td>
<td>1988</td>
<td>81</td>
</tr>
<tr>
<td>COREC</td>
<td>1984-87</td>
<td>1990</td>
<td>73</td>
</tr>
<tr>
<td>Royal Alfred</td>
<td>1979-88</td>
<td>1992</td>
<td>59</td>
</tr>
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</table>

JHU_PH: Johns Hopkins, Public Health
JHU-MED: Johns Hopkins, Medical School
COREC: Central Oxford Research Ethics Committee
Royal Alfred Hospital Sydney
Source of funding

- Industry-supported trials are less likely to be published or presented
  Easterbrook, Lancet 1991
- Of 107 trials published in 1984:
  - 89% of the industry-supported trials compared to
  - 61% of the trials supported by other means favoured the new therapy
  Davidson. J Gen Intern Med. 1986

Impact of publication bias

Published vs. unpublished

McKeeley 2000

Egger 2003

0.91 (0.85 to 0.97)

Ratio of odds ratios

BMJ, 18 Sept 2004

Compulsory registration of clinical trials

Will be a requirement before submission to the BMJ from July 2005

- “The case for registering all clinical trials - first advanced a decade ago - is now unassailable.” Editors of the BMJ and
  Medical journals persisted with noble intentions and wise words but were in part resistant, impotent, and confused about how to enforce registration.
  Some journals, including the BMJ, tried an amnesty for unpublished trials, with little success.
  The case for registering all clinical trials was unanswerable. Editors of the BMJ and
  Medical journals persisted with noble intentions and wise words but were in part resistant, impotent, and confused about how to enforce registration.
  Some journals, including the BMJ, tried an amnesty for unpublished trials, with little success.
  The case for registering all clinical trials was unanswerable.

- In September 2004 a number of major general medical journals announced that they will no longer publish trials that were not registered at inception
  - “By suppressing negative findings and exaggerating positive ones, by downplaying harms and talking up benefits, healthcare decisions are based on incomplete data and ultimately harm the patients.”
Funnel plots

- If all studies come from a single underlying population, this graph should look like a funnel, with the effect sizes homing in on the true underlying value as n increases. [If there is publication bias] there should be a bite out of the funnel.”


Funnel plot from Begg and Berlin (JRSS A 1988)

Funnel plot: no evidence of bias

Possible reasons for funnel plot asymmetry
(Adapted from Egger et al. BMJ 1997)

1. Heterogeneity
   - Size of effect differs according to study size
   - Poor methodological quality leading to spuriously inflated effects in smaller studies
2. Reporting biases
   - Publication bias
   - Selective outcome reporting
3. Artefact
4. Chance
Asymmetry due to heterogeneity


Bias because of poor quality of small trials

Bias because of poor quality of small trials

Bias because of poor quality of small trials

Bias because of poor quality of small trials

“Small study effect”

- a tendency for smaller trials in a meta-analysis to show greater treatment effects than the larger trials

Small study effects need not result from bias

Sterne et al. Journal of Clinical Epidemiology 2000

Identifying small-study effects

• Assess each outcome separately
• Methods available:
  • funnel plots
  • statistical tests
  • sensitivity analysis

Contour-enhanced funnel plots and regression-based adjustment (Moreno et al. BMJ 2009; b2981)
Statistical tests for funnel plot asymmetry

Egger et al. (BMJ 1997; 315: 629-634) – equivalent to a weighted regression of treatment effect on its s.e.
  – Citation classic (over 3000 citations so far…) but there are statistical problems
  • Harbord et al. (Statistics in Medicine 2006) – modified version of the Egger test
    – Avoids the statistical problems, unless there is substantial between-study heterogeneity
  • Peters et al. (JAMA 2006; 295: 676) – regress treatment effect on inverse of sample size
  • Rücker et al. (Statistics in Medicine 2008; 27: 746-763)
    – Test based on arcsine transformation

Recommendations on testing for funnel plot asymmetry (1)

• Only use tests when there are 10 or more studies
• Don’t test when studies are all of similar sizes
• Interpret results in the light of visual inspection of the funnel plot
• When there is evidence of small study effects, publication bias should be considered as one of a number of explanations
• Remember that tests have low power (they cannot usually exclude publication bias)

Recommendations on testing for funnel plot asymmetry (2)

• For continuous outcomes with intervention effects measured as mean differences:
  – Use the test proposed by Egger et al. (1997) to test for funnel plot asymmetry
• For binary outcomes with intervention effects measured as odds ratios:
  – The tests proposed by Harbord et al. (2006) and Peters et al. (2006) may be used unless there is substantial between-study heterogeneity
  – The test proposed by Rücker et al. (2008) works when there is substantial between-study heterogeneity, but its interpretation is more difficult
  – Specify testing strategy in advance if possible

Comparing fixed and random-effects estimates

• **Meta-analysis:** calculate a summary effect estimate which is a weighted average of the estimated treatment effects from individual studies
• **Fixed-effect meta-analysis:**
  – assume treatment effect is the same in each study
  – weights $w_i = \frac{1}{\mu_i}$
• **Random-effects meta-analysis:**
  – treatment effect varies between studies
  – weights $w_i = \frac{1}{\mu_i + \hat{\tau}^2}$

Most meta-analyses are based on a small number of trials

<table>
<thead>
<tr>
<th>Number of trials in meta-analyses</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1.0</td>
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<tr>
<td>10</td>
<td>2.0</td>
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<tr>
<td>20</td>
<td>4.0</td>
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<td>30</td>
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<td>50</td>
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<td>&gt;50</td>
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Comparing fixed and random-effects estimates

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year of publication</th>
<th>RR (95% CI)</th>
<th>Events Treatment</th>
<th>Events Control</th>
<th>% Weight (M-H)</th>
<th>Events Treatment</th>
<th>Events Control</th>
<th>% Weight (M-H)</th>
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<tbody>
<tr>
<td>Munchen</td>
<td>1981</td>
<td>0.17 (0.14, 0.21)</td>
<td>3/176</td>
<td>2/197</td>
<td>0.08</td>
<td>0.57 (0.14, 2.18)</td>
<td>1/44</td>
<td>0.29 (0.06, 1.36)</td>
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<tr>
<td>Heidelberg</td>
<td>1986</td>
<td>0.47 (0.14, 1.52)</td>
<td>1/235</td>
<td>1/240</td>
<td>0.10</td>
<td>0.54 (0.21, 1.38)</td>
<td>1/16</td>
<td>0.54 (0.21, 1.38)</td>
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<td>Kiel</td>
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<td>0.99 (0.64, 1.57)</td>
<td>1/148</td>
<td>1/148</td>
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<td>Marburg</td>
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<td>1/137</td>
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<td>0.16 (0.09, 0.28)</td>
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<td>1/42</td>
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<td>The Hague</td>
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<td>Vrije U.</td>
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<td>1/68</td>
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<td>0.13 (0.07, 0.25)</td>
<td>1/68</td>
<td>0.10</td>
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<tr>
<td>Leiden</td>
<td>1995</td>
<td>0.16 (0.09, 0.31)</td>
<td>1/57</td>
<td>1/57</td>
<td>0.10</td>
<td>0.16 (0.09, 0.31)</td>
<td>1/57</td>
<td>0.10</td>
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<tr>
<td>Leiden</td>
<td>1996</td>
<td>0.15 (0.08, 0.29)</td>
<td>1/51</td>
<td>1/51</td>
<td>0.10</td>
<td>0.15 (0.08, 0.29)</td>
<td>1/51</td>
<td>0.10</td>
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<tr>
<td>Leiden</td>
<td>1997</td>
<td>0.14 (0.07, 0.27)</td>
<td>1/48</td>
<td>1/48</td>
<td>0.10</td>
<td>0.14 (0.07, 0.27)</td>
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<td>1/45</td>
<td>1/45</td>
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<td>0.14 (0.07, 0.26)</td>
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<td>0.14 (0.07, 0.28)</td>
<td>1/45</td>
<td>1/45</td>
<td>0.10</td>
<td>0.14 (0.07, 0.28)</td>
<td>1/45</td>
<td>0.10</td>
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<tr>
<td>Leiden</td>
<td>2000</td>
<td>0.14 (0.07, 0.27)</td>
<td>1/45</td>
<td>1/45</td>
<td>0.10</td>
<td>0.14 (0.07, 0.27)</td>
<td>1/45</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Fixed-effect M-H estimate (F test): p = 0.090

<table>
<thead>
<tr>
<th>M-H (Fixed)</th>
<th>Random Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.09 (0.83, 1.49)</td>
<td>2.545/2.938</td>
</tr>
<tr>
<td>2.545/2.938</td>
<td>10.89</td>
</tr>
</tbody>
</table>

Red color
When authors are concerned about small-study effects and there is evidence of between-study heterogeneity ($I^2 > 0$), then compare the fixed- and random-effects estimates of the treatment effect.

If the estimates are similar then small study effects have little effect on the treatment effect estimate.

If the random-effects estimate is more beneficial, then consider whether it is reasonable to conclude that the treatment was more effective in the smaller studies. If the larger studies are those conducted with more methodological rigour, or in circumstances typical of the use of the intervention in practice, consider reporting meta-analyses restricted to the larger, more rigorous studies.

Formal statistical comparisons of the fixed and random-effects estimates are not possible. It is still possible for small study effects to bias the results of a meta-analysis in which there is no evidence of heterogeneity.

Comparing fixed and random-effects estimates

Random-effects meta-analysis weights studies more equally than fixed-effect analysis.

If random- and fixed-effects summary estimates differ, then the average estimate from smaller studies differs from the average of the large ones: may indicate bias.

Explanations for heterogeneity may provide useful insights, and may have implications for clinical practice

But we should be very cautious about an approach which adjusts for heterogeneity without explaining it.

Final note on random-effects meta-analysis

What does this mean for my review?

Prevention

- a comprehensive search of multiple sources
- grey literature, non-English literature, handsearching
- trials registries

Diagnosis

- consider looking for small-study effects
- sensitivity analysis to identify possible impact
- publication bias is not the only explanation

There is no (simple) cure

- explore any observed small-study effects
- comment on the likelihood of reporting biases

RESEARCH METHODS & REPORTING

Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials

BMJ 2011;343:d4002 doi: 10.1136/bmj.d4002