Cochrane Methodology Annual Training
Assessing Risk Of Bias In Cochrane Systematic Reviews
Loughborough UK, March 2012

Publication and other reporting biases; funnel plots and asymmetry tests

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Outline

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

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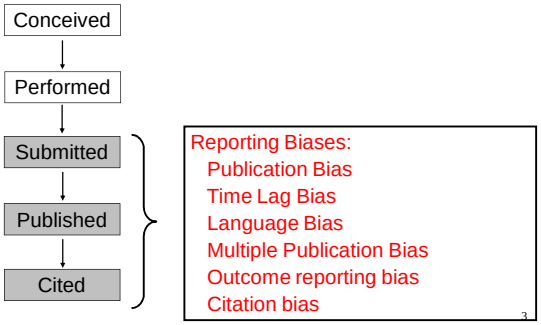
Sources of bias in the production and dissemination of evidence



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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(unpublished)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)

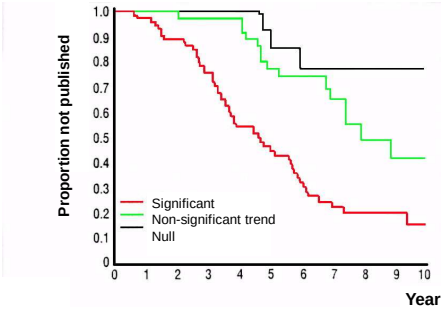
Type of reporting bias	Definition
Publication bias	The *publication* or *non-publication* of research findings, depending on the nature and direction of the results
Time lag bias	The *rapid* or *delayed* publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The *multiple* or *singular* publication of research findings, depending on the nature and direction of the results
Location bias	The publication of research findings in journals with different *ease of access* or *levels of indexing* in standard databases, depending on the nature and direction of results.
Citation bias	The *citation* or *non-citation* of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings *in a particular language*, depending on the nature and direction of the results
Outcome reporting bias	The *selective reporting* of some outcomes but not others, depending on the nature and direction of the results[5]

Identification and follow-up of studies submitted to ethics committees

Ethics committee	Identification	Follow-up	% Published
JHU-PH	1980	1988	66
JHU-MED	1980	1988	81
COREC	1984-87	1990	73
Royal Alfred	1979-88	1992	59

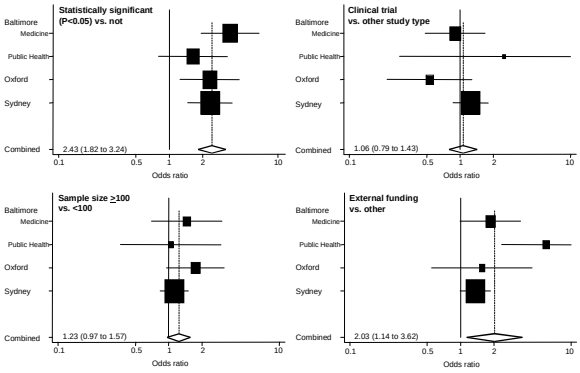
JHU_PH: Johns Hopkins, Public Health
JHU-MED: Johns Hopkins, Medical School
COREC: Central Oxford Research Ethics Committee
Royal Alfred Hospital Sydney

Publication bias



Proportion of clinical trials not published, by result
Stern and Simes, *BMJ 1997*

Predictors of publication



Source of funding

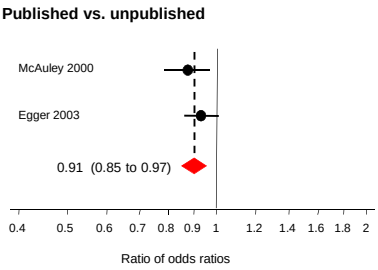
- **Industry-supported trials are less likely to be published or presented**

  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



How to prevent bias:

Trial registration

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 unanswerable." Editors of the *BMJ* and *Lancet* made this statement in 1999. Five years of industry resistance, government impotence, and public confusion followed. Medical journals persisted with noble intentions and wise words but were themselves 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 *BMJ* also considered asking for compulsory registration, but it seemed to us that trial registries were too diverse, disorganised, and easily disregarded to insist on registration before submission.

BMJ 2004;329:637–8

- **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"

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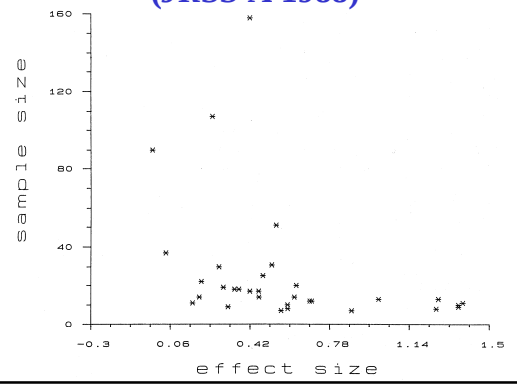
Funnel plots

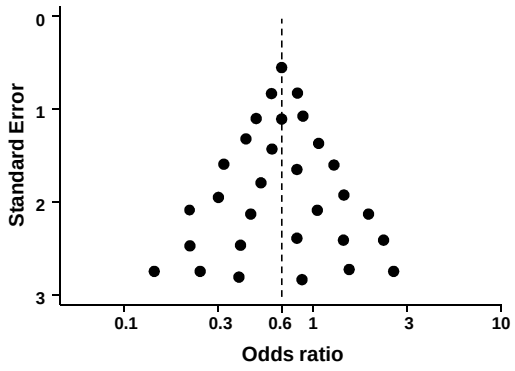
- If all studies come from a single underlying population, this graph should look like a funnel, with the effect sizes homing in on the true underlying value as n increases. [If there is publication bias] there should be a bite out of the funnel."

Light RJ, Pillemer DB. Summing up. The science of reviewing research. *Harvard University Press*, 1984.

Funnel plot from Begg and Berlin (*JRSS* A 1988)



Funnel plot: no evidence of bias



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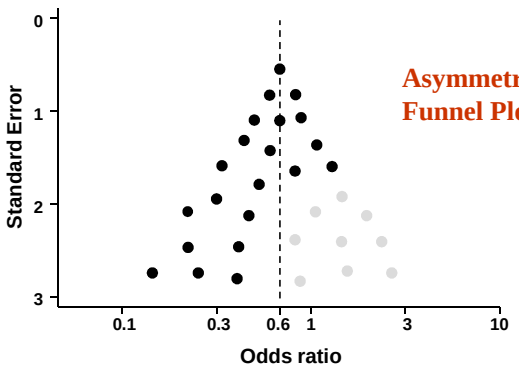
Reporting bias present



Asymmetrical Funnel Plot

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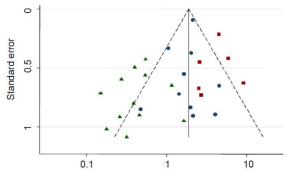
Possible reasons for funnel plot asymmetry

(Adapted from Egger et al. *BMJ* 1997)

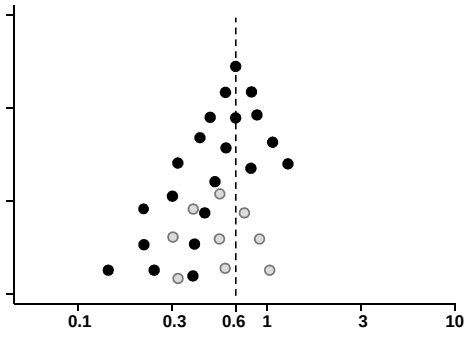
1. Heterogeneity
   - Size of effect differs according to study size
   - Poor methodological quality leading to spuriously inflated effects in smaller studies
2. Reporting biases
   - Publication bias
   - Selective outcome reporting
3. Artefact
4. Chance

Asymmetry due to heterogeneity



Source: Sterne JAC, Sutton AJ, Ioannidis JPA et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;342:d4002 doi: 10.1136/bmj.d4002

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

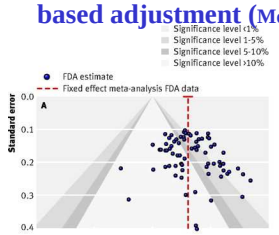
Small study effects need not result from bias

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)



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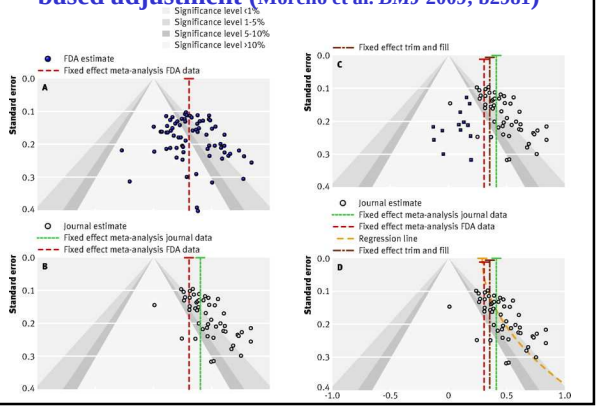


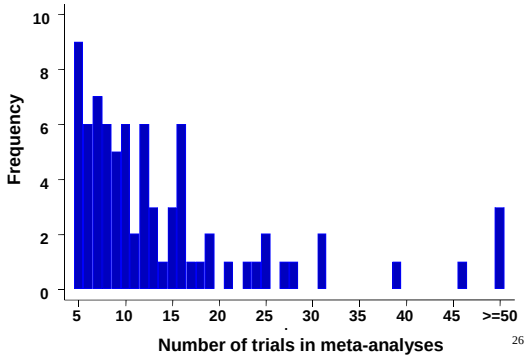
Statistical tests for funnel plot asymmetry

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

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



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)

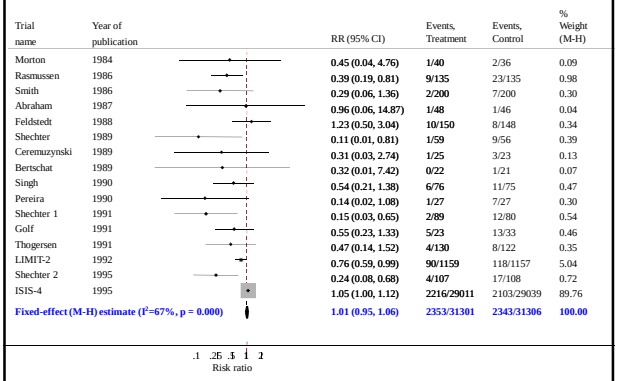
- For continuous outcomes with intervention effects measured as mean differences:
  - Use the test proposed by Egger et al. (1997) to test for funnel plot asymmetry
- For binary outcomes with intervention effects measured as odds ratios:
  - The tests proposed by Harbord et al. (2006) and Peters et al. (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 $w_i = \frac{1}{v_i}$
- **Random-effects meta-analysis:**
  - treatment effect varies between studies
  - weights

$$w_i^* = \frac{1}{v_i + \hat{\tau}^2}$$

Comparing fixed and random-effects estimates



Comparing fixed and random-effects estimates

- 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.

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Final note on random-effects meta-analysis

- 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.
  - disadvantage of random-effects analysis?
- *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

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RESEARCH METHODS & REPORTING

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

Jonathan A C Sterne,[1] Alex J Sutton,[2] John P A Ioannidis,[3] Norma Terrin,[4] David R Jones,[2] Joseph Lau,[4] James Carpenter,[5] Gerta Rücker,[6] Roger M Harbord,[1] Christopher H Schmid,[4] Jennifer Tetzlaff,[7] Jonathan J Deeks,[8] Jaime Peters,[9] Petra Macaskill,[10] Guido Schwarzer,[6] Sue Duval,[11] Douglas G Altman,[12] David Moher,[7] Julian P T Higgins[13]

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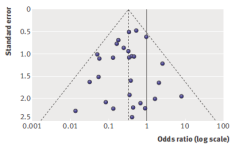
[5]Medical Statistics Unit, London School of Hygiene and Tropical

Funnel plots, and tests for funnel plot symmetry, have been widely used to examine bias in the results of meta-analyses. Funnel plot asymmetry should not be equated with publication bias, because it has a number of other possible causes. This article describes how to interpret funnel plot asymmetry, recommends appropriate tests, and explains the implications for choice of meta-analysis model



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

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