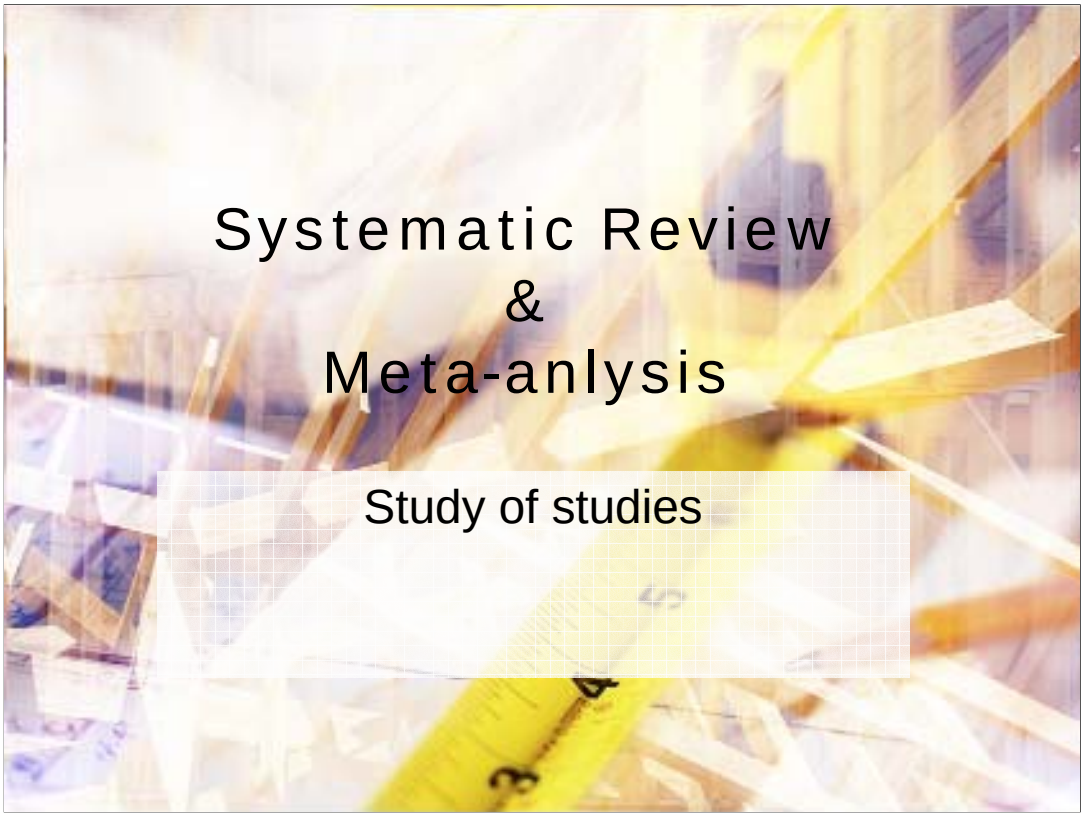


Systematic means standardized and critically appraised to minimize bias and systemic error

Review mean search, summarize and synthesis of literature

Meta Gr.: after, beyond, over

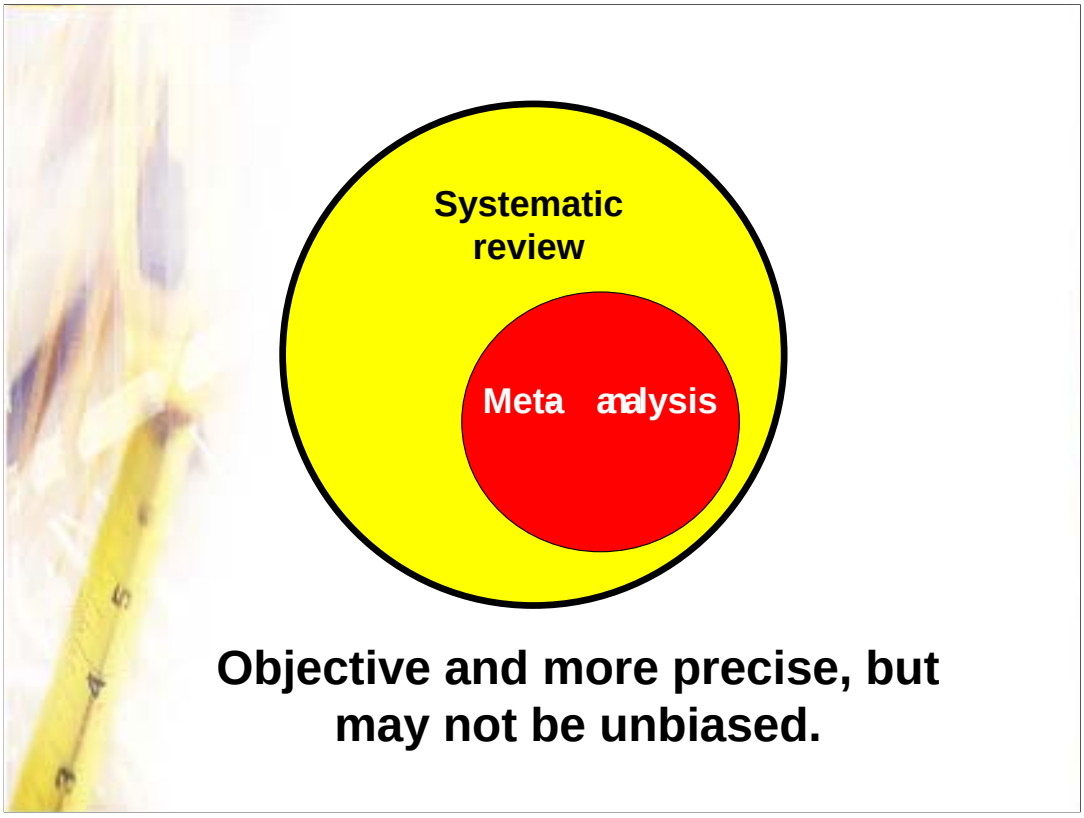
SRs is a process

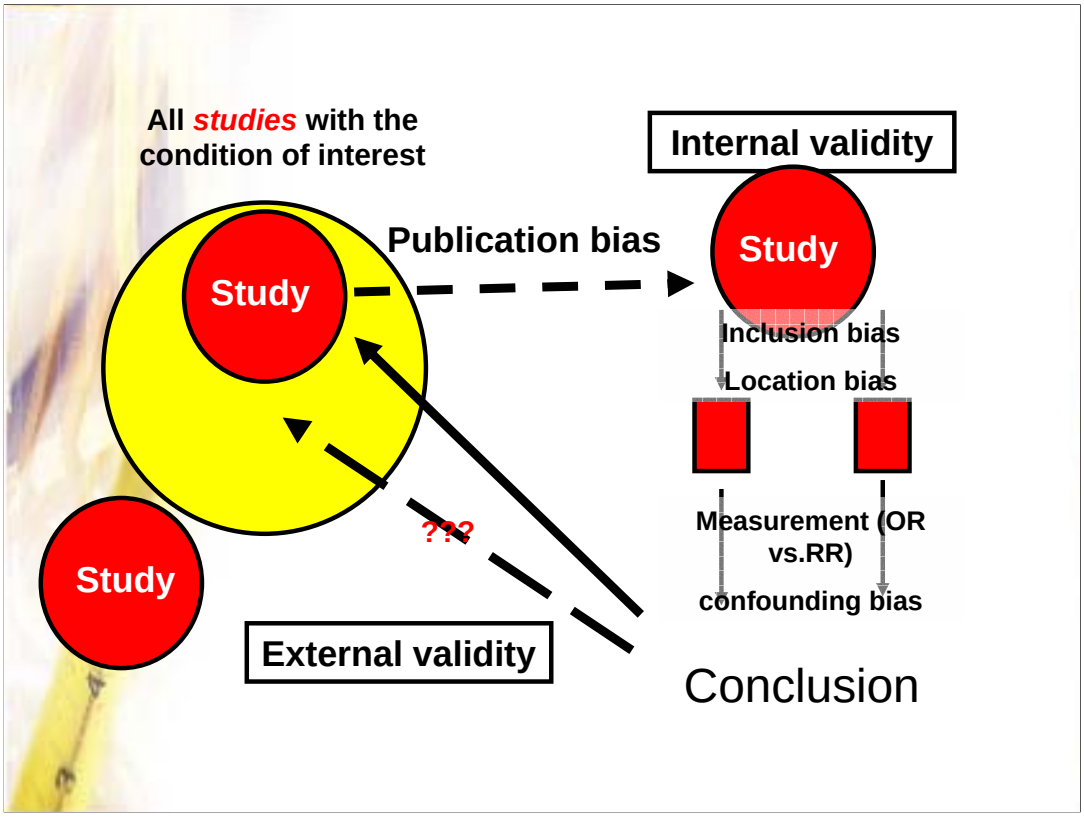
Meta-analysis is a statistical procedure to combine/aggregate results from several studies, epidemiological study of results.

Historically, the first published meta-analysis was in 1904. It was done by the famous statistician Karl Pearson who reporting the preventive effect of serum inoculations against enteric fever. The rationale put forward by Pearson for pooling studies is still one of the main reasons for undertaking meta-analysis today: “Many of the groups…are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved.”

It is interesting to know that the first meta-analysis assessing the effect of a therapueutic intervention was the evaluation of the treatment effect of the placebo.

BMJ 1997;315:1971-1374


Systematic review
Meta analysis
Objective and more precise, but may not be unbiased.



In the strict sense, publication bias is not sampling bias but is an 'unintended' selection bias.

Definition

Inclusion of a trial in SR/MA because of preferential publication of trial due to the direction of treatment effect and sample size (i.e. other than chance)

Reporting Bias in MA

1. Publication bias – negative result are less likely to be published, or even it is published it is published late, especially if it is funded by the pharmaceutical industry. Anticipated rejection leads to selective submission of papers.
2. Location bias
    - English language bias – negative results are more likely to be published in non-English journal
    - Citation bias – when reference lists are searched, negative trials are quoted less frequently and are therefore more likely to be missed in the search for relevant trials. Moreover, different peer-reviewed journal has different no. of citation. (NEJM vs. Annals of Internal Medicine)
    - Database bias – trials with statistically significant results are more likely to be published in an indexed journal whereas trials with null results are published in non-indexed journals.*
    - Multiple publication bias – results of "positive" trials, large trials, multi-centered trials are sometimes reported more than once, increasing the probability that they will be located for MA. (more likely to be selected, duplicated data will cause overestimation of effect size)
    - Outcome reporting bias

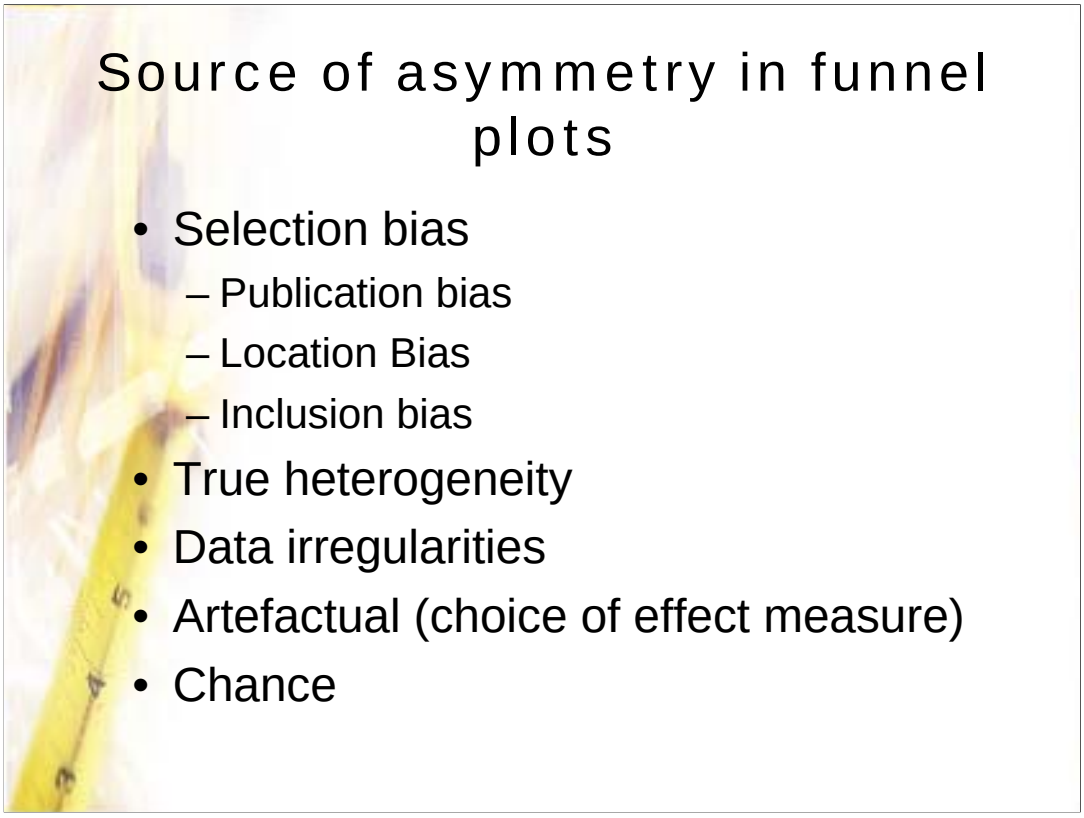
        Negative data make the investigator less willing to provide data, this is a problem in unpublished trials or trials published only as conference abstracts.
3. Inclusion bias

    Usually MA is conducted by investigator familiar with the area under the study, the criteria can be influenced by his knowledge of the results of the set of potential studies.

    For example, some MA of trials of cholesterol lowering treatment have excluded certain studies on the grounds that the treatment used seem to have had an adverse effect independent of cholesterol lowering itself.

*Only about 30journals indexed in Medline is published in India, despite the fact that India is the developing country with the largest research output and medical research is published in English.

BMJ 316: 61



What is funnel plot?

Funnel plot is scatter plots of treatment effects estimated from individual studies (horizontal axis) against some measure of study size (vertical axis)

This is a graphical test for any type of bias that is associated with sample size – the strongest confounding factor in MA.

It is funnel in shape because precision of effect estimation is inversely proportional to the sample size

Precision in estimating the underlying treatment effect increases as a study's sample size increases, effect estimates from small studies scatter more widely at the bottom of the graph.

In the absence of bias, the plot should resembles a symmetrical inverted funnel

Forest plot

trying to see the woods and the trees

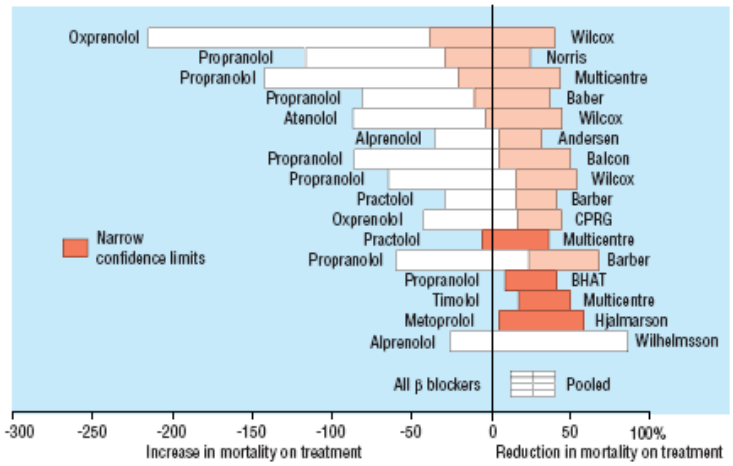


Fig 1 First use of forest plot for meta-analysis of effect of β blockers on mortality[3]
(reproduced with permission from Physicians World/Thomson Healthcare, Secaucus, NJ)

BMJ 322:1479

Forest plots show the information from the individual studies that went into the meta-analysis at a glance

They show the amount of variation between the studies and an estimate of the overall result

Origin of forest plots:

The origin of forest plots goes back at least to the 1970s. Freiman et al displayed the results of several studies with horizontal lines showing the confidence interval for each study and a mark to show the point estimate. This study was not a meta-analysis, and the results of the individual studies were therefore not combined into an overall result.2 In 1982, Lewis and Ellis produced a similar plot but this time for a meta-analysis, and they put the overall effect on the bottom of the plot (fig 1).3 However, smaller studies, with less precise estimates of effect, had larger confidence intervals and, perversely, were the most noticeable on the plots.

Means of focusing attention on the larger, more precise, studies were sought. Replacement of the mark with a square whose size was proportional to the precision of the estimate may have been first suggested by Stephen Evans at a Royal Statistical Society medical section meeting at the London School of Hygiene and Tropical Medicine in 1983 (S Evans, personal communication). He based the idea on modified box plots.4 Ideas such as radial plots were also proposed.5 6

The first meta-analyses to include squares of different sizes to show the positions of the point estimates were probably those produced by the Clinical Trial Service Unit in Oxford in the 1998 overview of the prevention of vascular disease by antiplatelet therapy.7 The area of each square was proportional to the weight that the individual study contributed to the meta-analysis.

Why a forest plot is being called a forest plot?

The plot was not called a "forest plot" in print for some time, and the origins of this title are obscured by history and myth. At the September 1990 meeting of the breast cancer overview, Richard Peto jokingly mentioned that the plot was named after the breast cancer researcher Pat Forrest, and, at times, the name has been spelt "forrest plot." However, the phrase actually originates from the idea that the typical plot appears as a forest of lines. A contender for the first use of the name "forest plot" in print is a review of nursing interventions for pain that was published in 1996.9 An abstract at the Cochrane colloquium later that year also used this name.10 We would welcome suggestions of precedents to these uses or any other versions of this brief history of the plot.

Funnel plot

Publication is not a random process

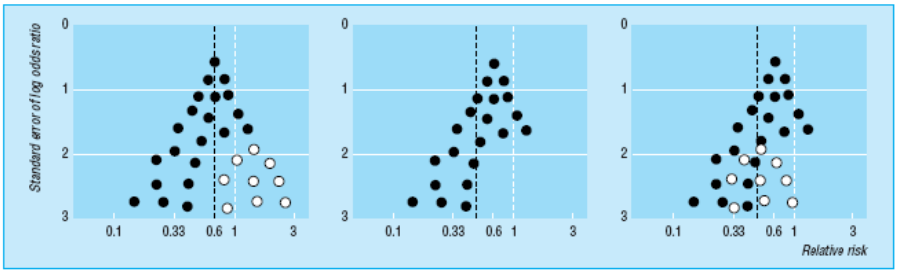


Fig 1 Hypothetical funnel plots: left, symmetrical plot in absence of bias (open circles are smaller studies showing no beneficial effects); centre, asymmetrical plot in presence of publication bias (smaller studies showing no beneficial effects are missing); right, asymmetrical plot in presence of bias due to low methodological quality of smaller studies (open circles are small studies of inadequate quality whose results are biased towards larger effects). Solid line is pooled odds ratio and dotted line is null effect (1). Pooled odds ratios exaggerate treatment effects in presence of bias

BMJ 2001;323:101-5

Reporting bias for example, because smaller studies showing no statistically significant beneficial effect of the treatment (open circles in fig 1 (left)) remain unpublished leads to an asymmetrical appearance with a gap in the bottom right of the funnel plot (fig 1 (centre)). In this situation the combined effect from meta-analysis overestimates the treatment's effect. 14 15 Smaller studies are, on average, conducted and analysed with less methodological rigour than larger ones, so that asymmetry may also result from the overestimation of treatment effects in smaller studies of lower methodological quality (fig 1 (right)).

Choice of axis in Funnel plot

Axis / measure	Advantages and disadvantages	Recommendations
Vertical axis		
Standard error	Funnel shape with straight 95% confidence lines. Emphasis of the plot is on smaller studies where bias is more likely. Axis has to be inverted to place the largest trials at the top of the graph.	The best choice in most cases
Precision (1/SE)	Plot is not funnel shaped; 95% confidence lines are curved. Emphasis of the plot is on larger studies; smaller studies are compressed at the bottom.	An option in studies which focus on a comparison of meta-analyses of small trials with subsequent large trials
Variance (SE^2)	Plot is not funnel shaped; 95% confidence lines are curved. Emphasis of the plot is on smaller studies where bias is more likely.	Not recommended
Inverse variance (1/variance)	Plot is not funnel shaped; 95% confidence lines are curved. Emphasis of plot is on larger studies, smaller studies are compressed at the bottom.	An option in studies which focus on a comparison of meta-analyses of small trials with subsequent large trials, but precision would usually be better.
Sample size or log sample size	Expected shape of plot in absence of bias is unpredictable.	Invalid choice
Horizontal axis		
Log odds ratio	Scale is not constrained and plots have the same shape whether the outcome is defined as occurrence or non-occurrence of the disease. Odds ratios may be misinterpreted as risk ratios.	The best choice in most cases
Log risk ratio	Readily understood measure. Scale is naturally constrained so that heterogeneity may be introduced if the event rate is high.	Valid choice in many cases but not recommended if the event rate is high. Can give different conclusions depending on outcome definition.
Risk difference	Readily understood measure. Often associated with increased heterogeneity which may result in funnel plot asymmetry which is not apparent when ratio measures are used.	Not recommended in most cases

Journal of clinical epidemiology vol 54, 10:1046-1055

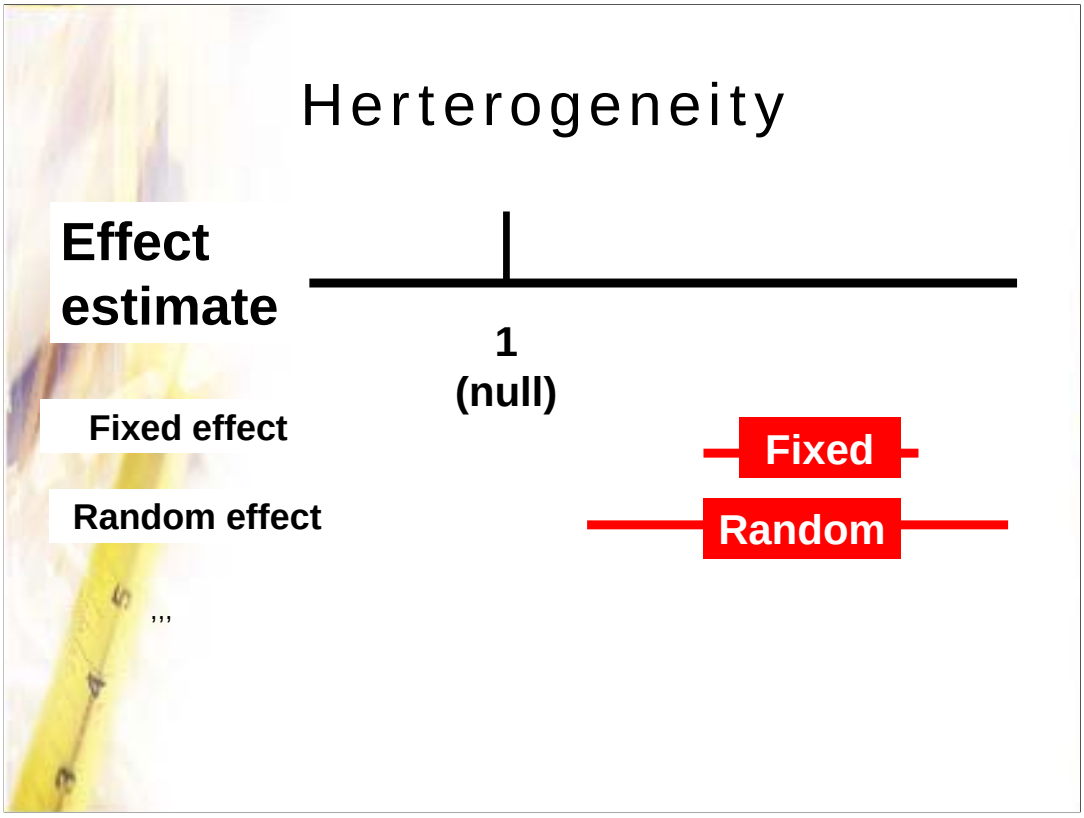
Heterogeneity

	Small trial	Large trial
methodology	poor	Better
Patient / event rate	High risk patient, high event rate	Low, medium and high risk patient
Intensity of intervention	Lower	higher
Fu	Shorter	Longer
Publication	Not/non-English	Multiple

What is heterogeneity?

Inclusion of trials with different effect size (true heterogeneity) or methodological quality (data irregularities)

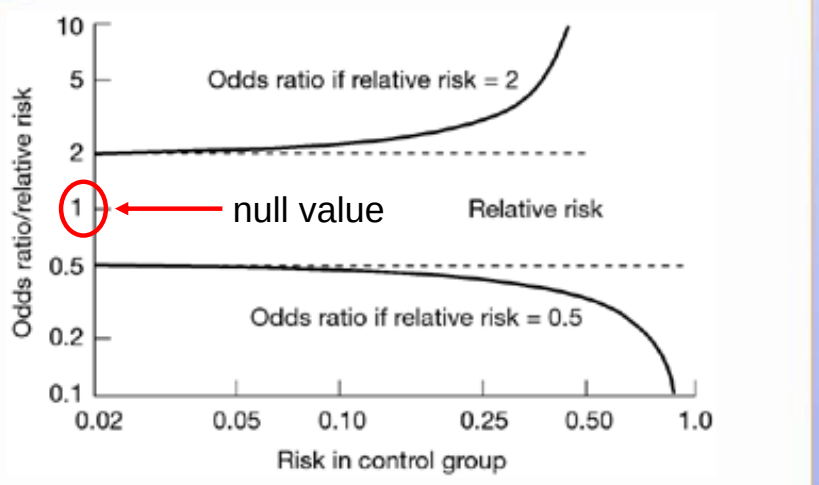
Heterogeneity is important because size of effect differs according to study size.



Fixed effects models assume variability is exclusively due to random variation. Therefore, if all the studies were infinitely large, they would give identical results.

Random effect model assumes a different underlying effect for each study and takes this into consideration as an additional source of variation, which leads to somewhat wider CI.

Choice of effect meausres



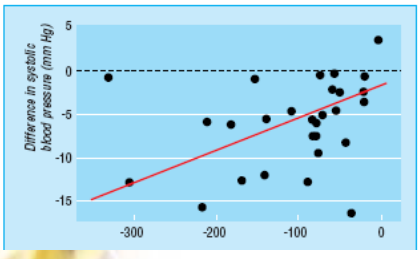
Oxford textbook of public health P.661

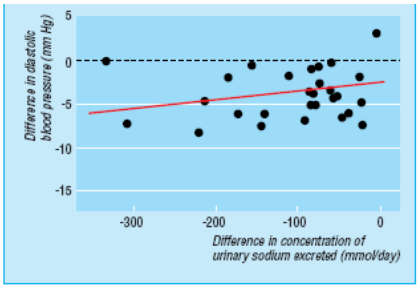
Odds ratio over estimate the relative reduction/increase in risk if event rate is high. This can lead to funnel plot asymmetry if the smaller trials were consistently conducted in patients at higher risk.

Similarly, if events accrue at a constant rate, relative risks will move towards unity with increasing length of follow up, which more likely to happen in large trials.

The range that relative risk can take therefore depends on the baseline event rate. This could obviously cause problems if we were performing a meta-analysis of relative risks in trials with greatly different event rates. Odds ratios also possess a symmetrical property: if you reverse the outcomes in the analysis and look at good outcomes rather than bad, the relationships will have reciprocal odds ratios. This again is not true for relative risks.

Scatter plot of treatment effect vs adherence

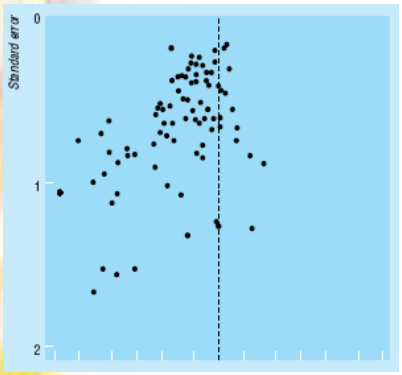




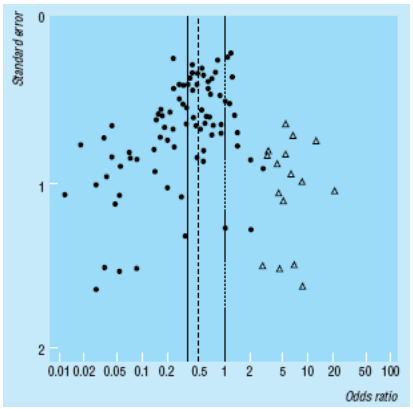
- Non-zero intercept indicates bias or a treatment effect that is not mediated through the treatment
- This is independent of study size

If patients' adherence to an effective treatment varies across trials this should result in corresponding variation in treatment effects. Scatter plots of treatment effect against adherence should be compatible with there being no treatment effect at 0% adherence, and so a simple regression line should intercept the vertical axis at zero treatment effect. If a scatter plot indicates a treatment effect even when no patients adhere to treatment then bias is a possible explanation. Such plots provide an analysis that is independent of study size.

Trim and fill method



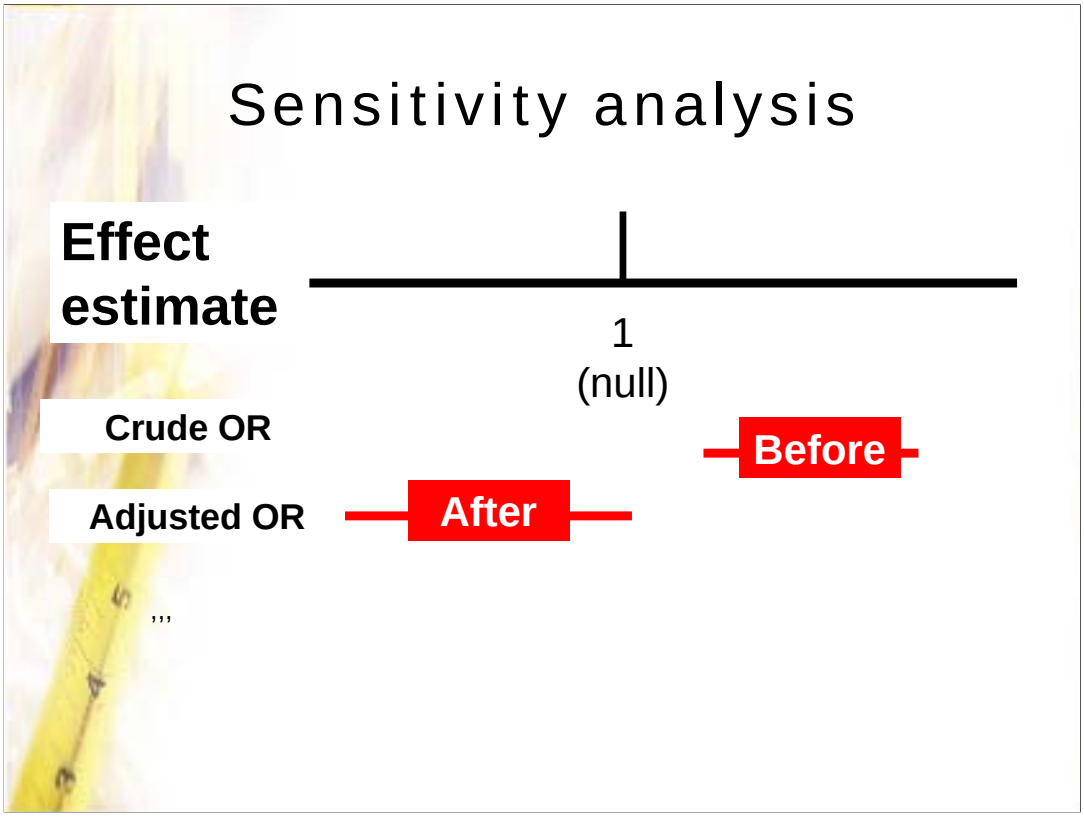
Trimmed



Filled

Duval and Tweedie have proposed “trim and fill”; a method based on adding studies to a funnel plot so that it becomes symmetrical.30–32 Smaller studies are omitted until the funnel plot is symmetrical (trimming). The trimmed funnel plot is used to estimate the true “centre” of the funnel, and then the omitted studies and their missing “counterparts” around the centre are replaced (filling). This provides an estimate of the number of missing studies and an adjusted treatment effect, including the “filled” studies.

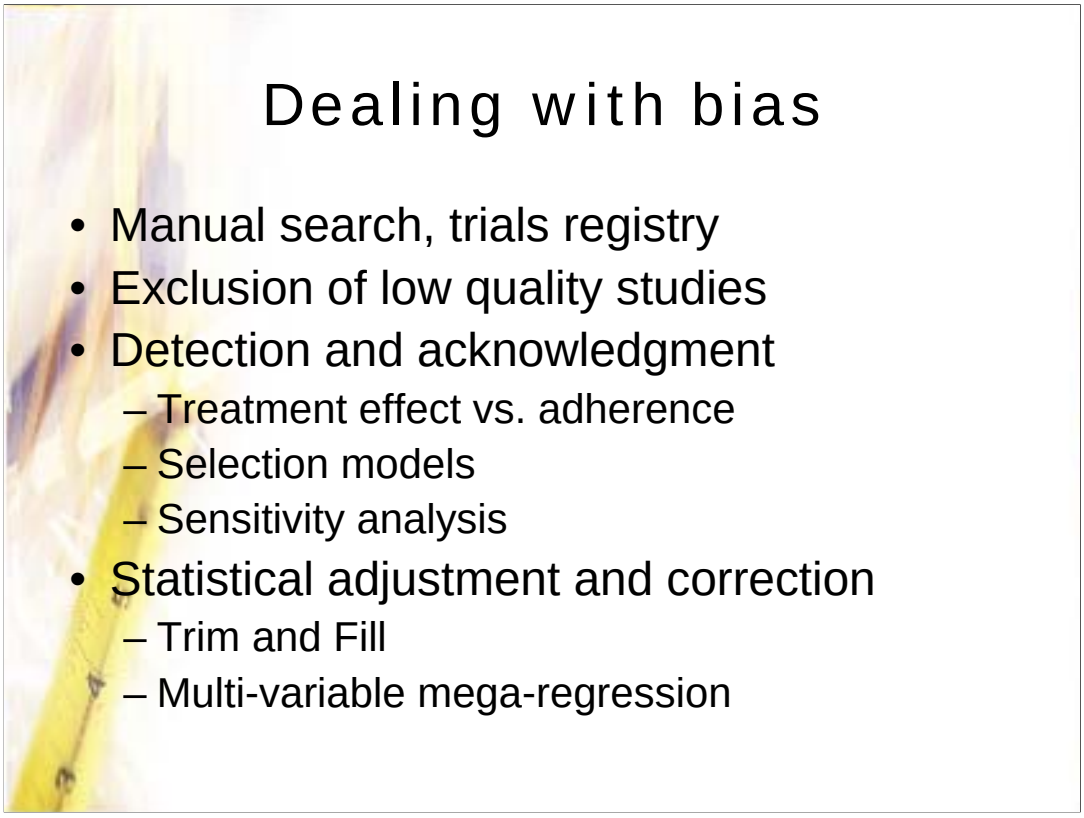
However, simulation studies have found that the trim and fill method detects “missing” studies in a substantial proportion of meta-analyses, even in the absence of bias. Thus there is a danger that in many meta-analyses application of the method could mean adding and adjusting for non-existent studies in response to funnel plot asymmetry arising from nothing more than random variation.



Sensitivity analysis

robustness of the findings (effect estimates) to different assumption about the effect of bias.

1. Statistical model
2. Methodology quality – exclusion of trials which has poor quality (no allocation concealment, non-double blind, short fu)
3. Sample size – exclusion of trials with small sample size or small event rate
4. Intensity of intervention – exclusion of trials that were stopped early



1. Selection models

   Model the selection process based on the assumption that the study's p value affects its probability of publication. Moreover, it also attempted to estimate the treatment effects corrected for the estimated publication bias.

   The method is complex and need large no. of studies so that a sufficient range of p values is included.

2. Statistical methods to detect funnel plot asymmetry

   a) Rank correlation method to examine the association between the effect estimates and their variance or standard errors

   b) Linear regression approach – weighted regression of treatment effect on its standard error, with weights inversely proportional to the variance of effect size.

   The regression model is more sensitive but the sensitivity of both method is generally low in MA based on less than 20 trials.

3. Mutlivariable metaregression model

   1. Overfitting of the regression model with covariates in small sample size may lead to spurious claims of association
   2. Cannot adjust confounding factors other than the chosen covariates
   3. Aggregation bias or "ecological fallacy"

      The characteristics of the patients in each trials has been averaged

Ideally…

Researcher should consider including only controlled trials with proper randomization of patients that report on all initially included patients according to the intention to treat principle and with an objective, preferably blinded, outcome assessment.

Similarly

Resarcher should consider including all conducted trials with proper randomization of patients that report on all initially included patients according to the intention to treat principle and with an objective, preferably blinded, outcome assessment.