Benefits and Pitfalls of Systematic Reviews and Meta-Analyses

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Definitions –Systematic review–

- A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review.
- Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

PRISMA Statement, Ann Intern Med 2009

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Definitions –Meta-analysis–

- Meta-analysis is a statistical technique used in a systematic review for combining the findings from independent studies .
- Meta-analysis is most often used to assess the clinical effectiveness of healthcare interventions; it does this by combining data from two or more randomised control trials.
- Meta-analysis of trials provides a precise estimate of treatment effect, giving due weight to the size of the different studies included.

Crombie et Davies, 2009 (www.whatisseries.co.uk)

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Definitions –Heterogeneity (inconsistency): I^2 statistic–

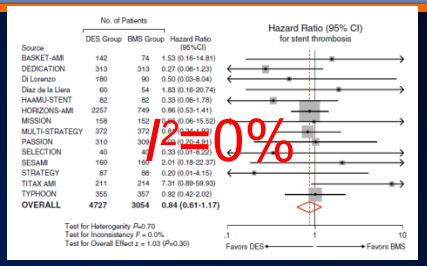
0% No heterogeneity

25% Low heterogeneity

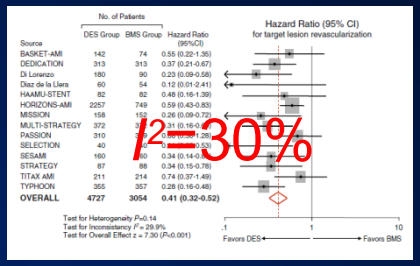
50% Moderate heterogeneity

75% High heterogeneity

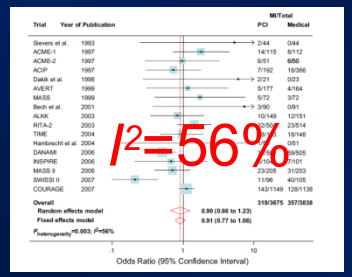
Higgins et al, BMJ 2003



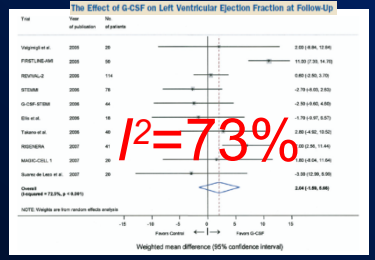
Dibra et al, CRC 2010



Dibra et al, CRC 2010



Schömig et al, JACC 2008



Zohlnhöfer et al, JACC 2008

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Higgins et al, BMJ 2003

Meta-regression is a technique which allows researchers to explore which types of patient-specific factors or study design factors contribute to the heterogeneity.

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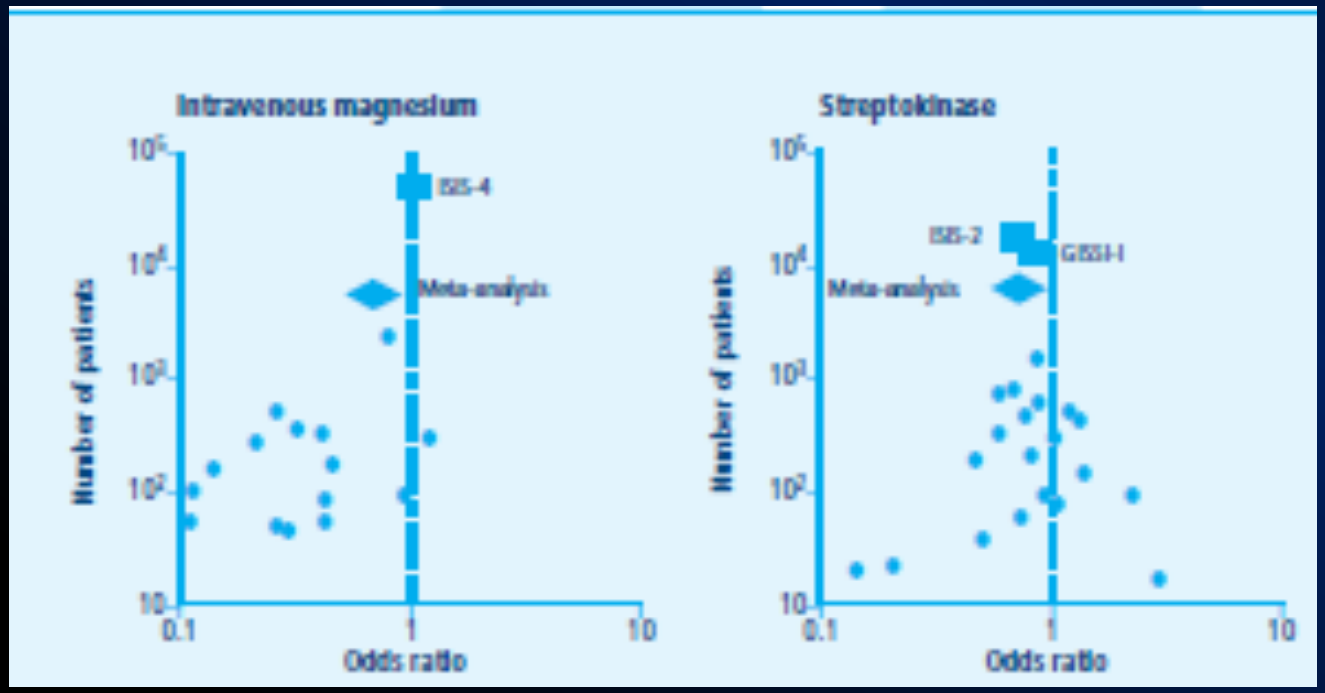
Definitions −Publication bias−

Publication bias is defined as the lesser publication chance of clinical trials with negative findings compared with those that conclude the treatment is effective. One simple qualitative way of assessing publication bias is to examine a funnel plot.



Quantitative assessment

- Egger‘ test
- Peter‘s test

Crombie et Davies, 2009 (www.whatisseries.co.uk)

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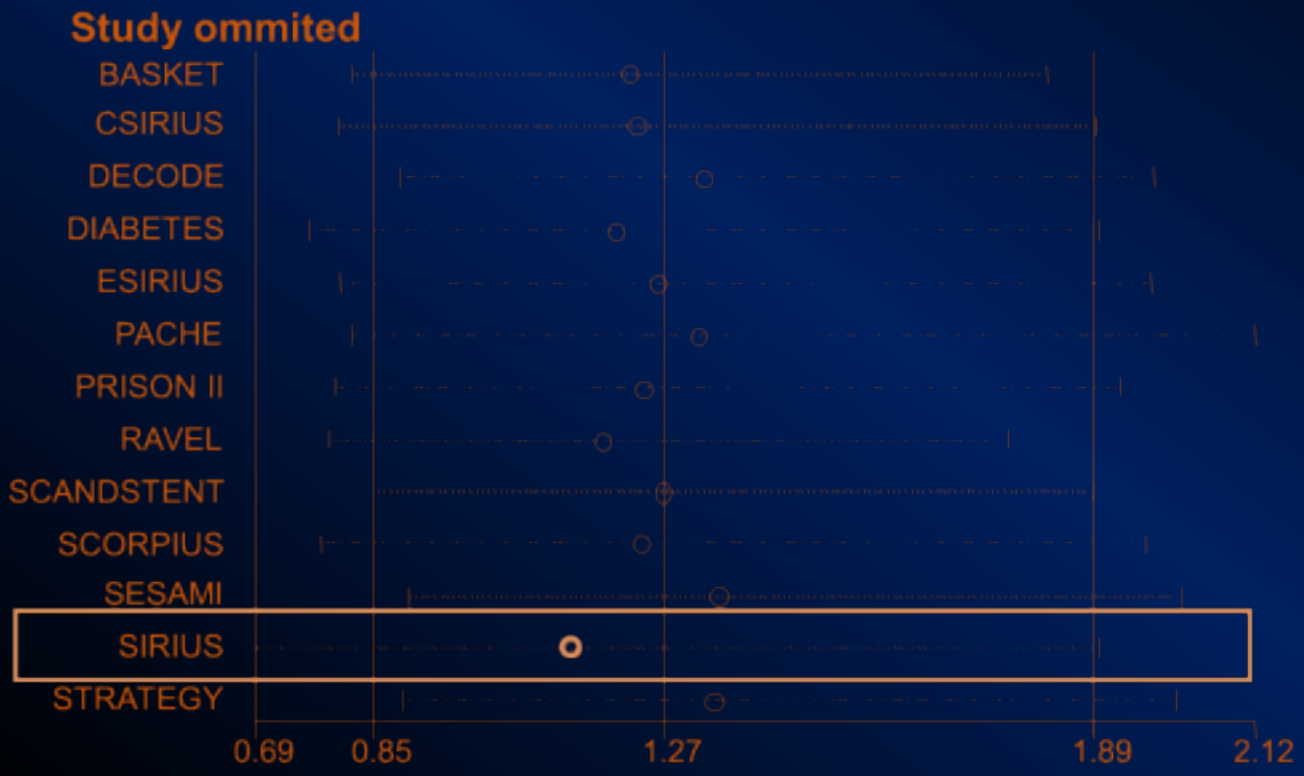
Definitions –Sensitivity analysis–

Sensitivity analysis explores the ways in which the main findings are changed by varying the approach to aggregation. A good sensitivity analysis will explore, among other things, the effect of excluding various categories of studies; for example, unpublished studies or those of poor quality. It may also examine how consistent the results are across various subgroups

Crombie et Davies, 2009 (www.whatisseries.co.uk)

Mortality in DES vs. BMS trials



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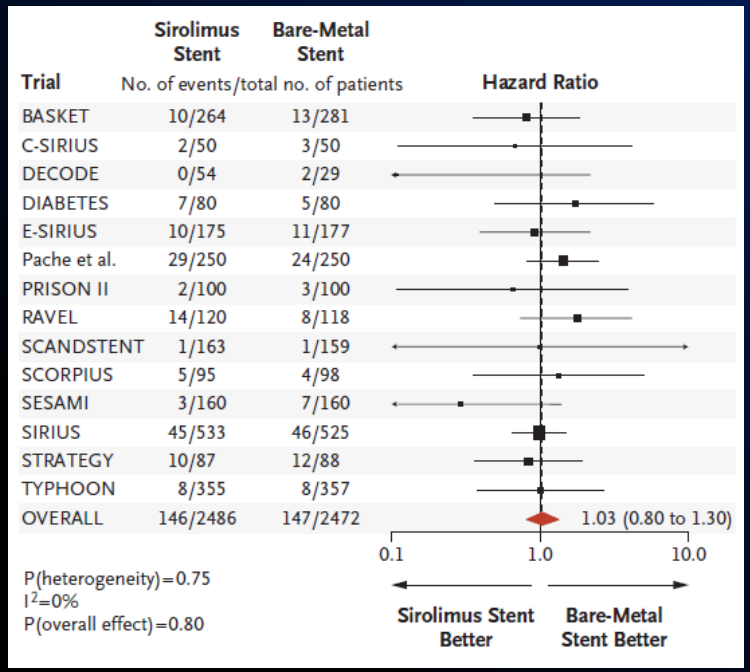
Definitions –Precision–

- Precision of a study is largely dependent on the number of included patients.
- Small study effects can often distort results of meta-analyses. The influence of small trials on estimated treatment effects should be routinely assessed through sensitivity analysis.

Higgins et al, BMJ 2011



Death SES vs. BMS

Overall HR =1.03 (0.80-1.30)

HR (n>238*) =1.01 (0.77-1.32)

*238 is median sample size of the included studies

Kastrati et al, NEJM 2007

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Definitions −External validity−

Extent to which results of trials provide a correct basis for generalisation to other circumstances:

- Patients: age, sex, severity of disease and risk factors, comorbidity
- Treatment regimens: dosage, timing and route of administration, type of treatment within a class of treatments, concomitant treatments
- Settings: level of care (primary to tertiary) and experience and specialisation of care provider
- Modalities of outcomes: type or definition of outcomes and duration of follow up

Jüni et al, BMJ 2001

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Definitions –Internal validity–

Extent to which systematic error (bias) is minimised in clinical trials:

- Selection bias (biased allocation to interventions):
  a) due to inadequate generation of a randomised sequence;
  b) due to inadequate concealment of allocations before assignment.
- Performance bias: due to knowledge of the allocated interventions by participants and personnel during the study.
- Detection bias: due to knowledge of the allocated interventions by outcome assessment.
- Attrition bias: biased occurrence and handling of deviations from protocol and loss to follow up.
- Reporting bias: due to selective outcome reporting.
- Other bias.

Jüni et al, BMJ 2001 & Higgins et al, BMJ 2011

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Benefits of good meta-analyses

- Avoids the danger of unsystematic (or narrative) reviews (wrong impression from unsystematic and non-analytical reading).
- Increases precision, i.e. the power to detect significant differences, especially for rare events and subgroups.

Crombie et Davies, 2009 (www.whatisseries.co.uk)

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Importance of meta-analyses
−Gros levels of evidence−

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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Importance of meta-analyses −More refined levels of evidence−

1a Systematic review of randomized controlled trials (low heterogeneity)

1b Individual RCT (with narrow confidence interval: high precision)

2a Systematic review of cohort studies (no heterogeneity)

2b Individual cohort study

3a Systematic review of case-control studies (no heterogeneity)

3b Individual case-control study

4 Case-series

5 Expert opinion

Phillips et al, Oxford Centre for Evidence-Based Medicine 2001

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Meta-analyses of observational studies are better avoided

Confounding and selection bias often distort the findings from observational studies

There is a danger that meta-analyses of observational data produce very precise but equally spurious results

The statistical combination of data should therefore not be a prominent component of reviews of observational studies

Egger et al, BMJ 1997

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How to perform a good meta-analysis of RCTs

- The validity of the meta-analysis depends on the quality of the systematic review on which it is based.
- Good meta-analyses aim for complete coverage of all relevant studies, assess and report on any kind of potential bias, look for the presence of heterogeneity, and explore the robustness of the main findings using sensitivity analysis

Crombie et Davies, 2009 (www.whatisseries.co.uk)

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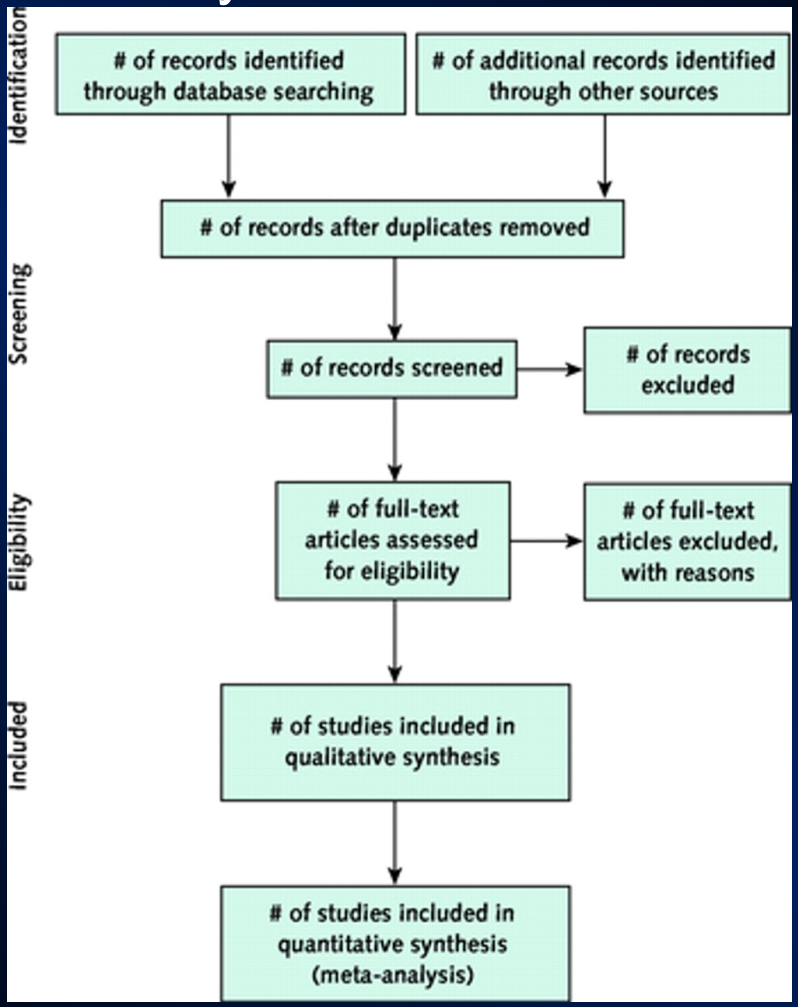
How to perform a good meta-analysis of RCTs

A meta-analysis should be conducted like a scientific experiment and begin with a protocol, which clearly states its aim and methodology

PRISMA Statement, Ann Intern Med 2009

Flow of information through the different phases of a systematic review



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Principles for assessing risk of bias of RCTs

- **Do not use quality scales**
  They tend to combine assessments of aspects of the quality of reporting with aspects of trial conduct, and to assign weights to different items in ways that are difficult to justify.
- **Focus on internal validity**
  It is important to separate assessment of internal validity from that of external validity and precision
- **Perform not only study specific but also outcome specific evaluation of risk of bias**
  The risk of bias may affect differently the reported outcomes (e.g. death vs. MI vs. TLR)

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Principles for assessing risk of bias of RCTs

BMJ 2011;343:d5928 doi: 10.1136/bmj.d5928

RESEARCH METHODS & REPORTING

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials

OPEN ACCESS

Flaws in the design, conduct, analysis, and reporting of randomised trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane Collaboration's tool for assessing risk of bias aims to make the process clearer and more accurate

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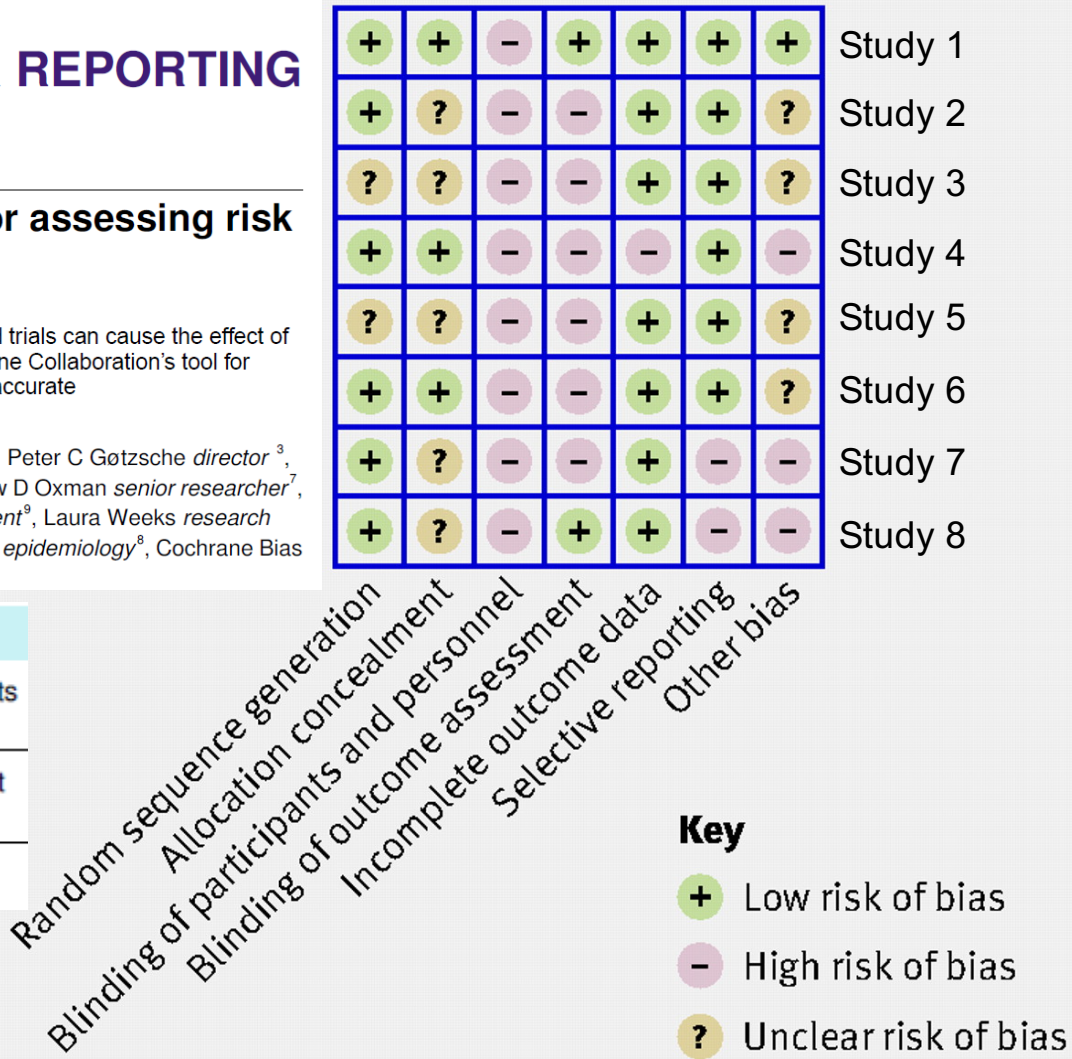
Risk of bias	Interpretation
Low risk of bias	Bias, if present, is unlikely to alter the results seriously
Unclear risk of bias	A risk of bias that raises some doubt about the results
High risk of bias	Bias may alter the results seriously



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