

Introduction to systematic review and meta-analysis

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Outline

- 1. What is systematic review and meta-analysis?
- 2. How to appraise systematic review?
- 3. How to do systematic review and meta-analysis?

What is systematic review?

- A literature review focused on a single question which tries to **identify**, **appraise**, **select** and **synthesize** all high quality research evidence relevant to that question.
- Regarded as the highest level of medical evidence in the hierarchy of evidence level.

What is systematic review?

- A summary of healthcare research that uses **explicit methods** to perform a thorough literature search and **critical appraisal** of individual studies to identify valid and applicable evidence.
- Often, but not always, uses **meta-analyses** to combine these valid studies.

What is meta-analysis?

- A **quantitative** overview that not only statistically combines and summarizes the results of all relevant studies, but also explores sources of heterogeneity between studies.
- It is about making order of scientific chaos and making sense of information.

Differences between narrative and systematic review

	Narrative review	Systematic review
Question	Often broad	Often focused
Sources and search	Usually not specified, potentially biased	Comprehensive sources, explicit search strategy
Selection	Usually not specified, potentially biased	Criterion-based selection uniformly applied
Appraisal	Variable	Rigorous, criterion-based
Synthesis	Often qualitative	Often quantitative
Inference	Sometimes evidence-based	Always evidence-based

Why do we need systematic review?

- Information explosion with increasingly unmanageable amounts.
 - >2,000,000 articles published in 20,000 medical journals annually.
 - Large amounts of information can be assimilated quickly by looking at SR.
- Single studies rarely provide definitive answers to clinical questions.
 - SR of multiple studies increase **trustworthiness** if results consistent.
- Results from individual studies often conflicting.
 - SR can **resolve uncertainty** when individual studies disagree.
 - SR can investigate sources of **heterogeneity**.
- Explicit and systematic methods used in SR limit bias and improves **reliability and accuracy** of conclusions.
- SR increases **statistical power** and precision of estimates of treatment effects and exposure risk.
- SR can address questions in specific **subgroups** that individual studies may not have examined.
- SR identifies information gaps and generate new hypotheses for future research.
- SR provides **high level evidence** to guide healthcare policy decisions.

What are the limitations of systematic review?

- Retrospective re-analysis of prior studies
 - Affected by the quality of original studies (garbage in, garbage out).
 - Detailed information on individual studies are often unavailable for analyses.
- Heterogeneity among studies may preclude valid and reliable conclusions
- Reporting/publication bias
- Potential for selection bias – subjectivity
 - Inter-observer variations
- May lose important information of individual studies after pooling the results
- Cannot replace large, well-designed randomized controlled trials

How to appraise systematic review?

- 3 major questions for all critical appraisal:
 - Is the study (systematic review) valid?
 - What are the results?
 - Are the results applicable locally?
- 10 components.

Is the systematic review valid?

- 1. Did the review ask a clearly-focused question?
 - *Consider if the question is focused in terms of:*
 - *the population studied*
 - *the intervention given or the exposure*
 - *the outcomes considered*

Is the systematic review valid?

- 2. Did the review include the right types of studies?
 - *Consider if the included studies*
 - *address the review questions*
 - *have an appropriate study design, e.g.,*
 - *RCTs for intervention*
 - *cohort or case-control studies for risk factors and etiology*
 - *cohort studies for prognosis and outcome*
 - *cross-sectional studies for diagnostic tools*

Is the systematic review valid?

- 3. Did the reviewers try to identify all relevant studies?
 - Consider
 - *which databases were used*
 - *if there was follow-up from reference lists*
 - *if the reviewers searched for unpublished studies*
 - *if the reviewers search for non-English language studies*
 - *if the reviewers contacted experts or other sources for potential studies, e.g., pharmaceutical companies, conference proceedings*

Is the systematic review valid?

- 4. Did the reviewers assess the quality of the included studies?
 - *Consider*
 - *if a clear, pre-determined strategy was used to determine which studies were included and how included studies were appraised*
 - *whether >1 assessor was involved, with reproducible assessments*

Is the systematic review valid?

- 5. If the results of the studies have been combined, was it reasonable to do so?
 - *Consider whether*
 - *the results of each study are clearly displayed*
 - *the results were similar from study to study*
 - *look for tests of heterogeneity*
 - *the reasons for any variations in results (heterogeneity) are discussed*

What are the results?

- 6. How are the results presented and what is the main result?
 - *Consider*
 - *how the results are expressed (e.g., odds ratio, relative risk, risk difference, standardized mean difference, NNT, etc.)*
 - *how large this size of result is and how meaningful it is*

What are the results?

- 7. How precise are these results?
 - Consider:
 - *if a confidence interval were reported*
 - *If the confidence interval indicates a significant result*
 - *if a p-value is reported*
 - *Lack of evidence of association ≠ evidence of no association*

Are the results applicable locally?

- 8. Can the results be applied to the local population?
 - Consider whether
 - *the population sample covered by the review could be different from your population in ways that would produce different results*
 - *local setting differs much from that of the review*
 - *the intervention can be provided in the local setting*
 - *the intervention is acceptable to local patients*
 - *the intervention is affordable by local community*

Are the results applicable locally?

- 9. **Were all important outcomes considered?**
 - *Consider outcomes from the point of view of the*
 - *Individual*
 - *policy makers and professionals*
 - *family/carers*
 - *wider community*

Are the results applicable locally?

- 10. Should policy or practice change as a result of the evidence contained in the review?
 - *Consider*
 - *whether benefit reported outweighs harm and/or cost.*
 - *If this information is not reported can it be filled in from elsewhere?*

How to do systematic review?

- 1. Understand the principles and standards.
- 2. Study examples.
 - One of the best sources of examples is Cochrane Database of Systematic Review (CDSR)
- 3. **Practice** yourselves.
 - One of the best ways is to join Cochrane Collaboration
 - Manage the largest database of systematic review
- Conducting systematic review is not very difficult!
- Interest and time are the most important.

Cochrane Reviews

- One of the best sources of review.
 - Can be searched by Pubmed/Medline
 - Full texts can be assessed through HKU Library on-line.
- “Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review”
BMJ 2006;333:782
 - Compared with industry supported reviews and reviews with undeclared support, Cochrane reviews had more often considered the potential for bias in the review, e.g., by describing the method of allocation concealment and describing excluded patients or studies.

Cochrane Reviews

- “Assessment of methodological quality of primary studies by systematic reviews: results of the metaquality cross sectional study” BMJ 2005;330:1053
 - Cochrane reviews fared better than systematic reviews published in paper based journals in terms of assessment of methodological quality of primary studies.

Cochrane Collaboration

- Developed in 1993 in response to the call of a British epidemiologist (Archie Cochrane) for up-to-date, systematic reviews of all relevant randomized controlled trials of health care.
- An international non-profit, independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare.
- It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence from clinical trials and other studies of interventions.
- >27,000 volunteers in >100 countries

Cochrane Collaboration

- Consists of
 - 1 or more Cochrane Centers in each participating country to coordinate activities
 - 1 Steering Group to set policies
 - 52 Review Groups in various specialties to develop reviews, e.g., Pregnancy and childbirth group, gynaecological cancer group, menstrual disorder and subfertility group, fertility regulation group, etc
 - 14 Methods Groups to provide advice and support on methodological issues
 - 13 Fields/Networks to identify health issues of importance to specific populations
 - 1 Consumer Network to ensure that the perspective and needs of consumers are incorporated into Cochrane systematic reviews.
- Interested person can join a Review Group by **registering a title**.
- However, scope of systematic reviews is limited to interventions.
 - No reviews of risk factors, diagnosis or prognosis

Cochrane Review

- Essential contents
 - Title:
 - target disease + treatment +/- population +/- outcome
 - Synopsis
 - plain language summary for layperson
 - Abstract
 - Text of review
 - Background
 - Objectives
 - Criteria for selecting studies
 - types of studies, participants, interventions, outcomes
 - Search strategies
 - Methods of the review
 - Descriptions of studies
 - Methodological qualities of included studies
 - Results
 - Discussion
 - Authors conclusions
 - implications for practice, implications for research

Cochrane Review

- Essential contents
 - References
 - Included studies
 - Excluded studies
 - Studies awaiting assessments
 - Ongoing studies
 - Other references
 - Tables
 - Characteristics of included studies
 - Characteristics of excluded studies
 - Characteristics of ongoing studies
 - Additional tables
 - Graphs
 - Forest plots
 - Additional graphs, e.g., funnel plots

Methods of systematic review

- Methods of the review should be pre-specified and laid down in a **protocol**
- Development of the review should follow the protocol.
- The protocol should not be amended without good reason.
- At least 2 reviewers is required for the whole review process.
- Set objectives to answer a specific answerable question.

Methods of systematic review

- Set criteria for selecting studies:
 - Specify types of studies, types of population, types of interventions and types of outcomes.
 - Usually only RCTs included to ensure high quality of evidence.
 - If <2 RCTs, can consider non-randomized controlled clinical trials (CCTs)
 - Should not specify quality criteria.
 - Should exclude multiple publications of same cohort of patients.

Methods of systematic review

- Formulate search strategies
 - Specify electronic databases: usually include PubMed, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (**CENTRAL**).
 - Specify other searches: search references, hand search, search conference proceedings/abstracts, personal contact with companies/experts for published or unpublished studies, etc.
 - Specify search words for Medline and other databases.

Search strategy

- **Highly sensitive search for RCTs in MEDLINE:**
 - 1. randomized controlled trial.pt
 - 2. controlled clinical trial.pt
 - 3. randomized controlled trials/
 - 4. random allocation/
 - 5. double blind method/
 - 6. single blind method/
 - 7. or/1-6
 - 8. (ANIMALS not HUMANS).sh
 - 9. 7 not 8
 - 10. clinical trial.pt
 - 11. exp clinical trials/
 - 12. (clin\$ adj25 trial\$).ti,ab
 - 13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab
 - 14. placebos/placebo\$.ti,ab
 - 15. random\$.ti,ab
 - 16. research design/
 - 17. or/10-16
 - 18. 17 not 8
 - 19. 18 not 9
 - 20. 9 or 19

Search strategy

- **Highly sensitive search for pre-eclampsia in MEDLINE:**
 - 1. pregnan\$
 - 2. exp PREGNANCY/
 - 3. exp PREGNANCY COMPLICATIONS/
 - 4. exp HYPERTENSION/
 - 5. hypertens\$
 - 6. blood press\$
 - 7. (1 or 2 or 3) and (4 or 5 or 6)
 - 8. PIH
 - 9. toxaemi\$ near pregnan\$
 - 10. toxemi\$ near pregnan\$
 - 11. exp PRE-ECLAMPSIA/
 - 12. pre-eclamp\$
 - 13. preeclamp\$
 - 14. pre next eclamp\$
 - 15. or/7-14

Assessment of studies

- Select studies according to selection criteria, independently by 2 reviewers
- Exclude studies if not fulfill inclusion criteria
- Extract trial data for each trial into data extraction form
 - Study methods, design, randomization method, allocation concealment, blinding method
 - Participants: inclusion/exclusion criteria, number in each group, age and gender distribution, diagnosis, co-morbidities, comparability of groups at baseline, etc
 - Treatment details of all groups
 - Follow-up data: duration of FU, loss to FU with reasons
 - Outcomes
 - Dichotomous: event frequencies, number of patients available for each group
 - Continuous: mean, standard deviation for each group
 - Methods of analyses, intention-to-treat or not, statistical techniques

Assessment of studies

- Assess **quality** of included studies, independently by 2 reviewers, with respect to:
 - **Selection bias:**
 - Was allocation of patients to treatment and control groups truly randomised?
 - Was randomisation concealed?
 - **Performance bias:**
 - Were patients in the comparison groups treated differently apart from the study treatments?
 - **Attrition bias:**
 - Were there systematic differences between the comparison groups in the loss of participants from the study?
 - Was the extent of incomplete data likely to alter conclusion?
 - Were analyses by intention-to-treat?
 - **Detection bias:**
 - Were those assessing outcomes of the intervention blinded to the assigned intervention?
 - Were there systematic differences between the comparison groups in evaluation of outcomes?
 - **Reporting bias:**
 - Were there selective reporting of results?
- Determine the risk of bias
 - Low risk of bias: all the validity criteria met.
 - Moderate risk of bias: one or more validity criteria partly met but none are not met.
 - High risk of bias: one or more criteria not met.

Data analysis

- Handling of missing data

- The authors of included studies should be contacted to supply missing data whenever possible.
- Missing data and drop-outs should be assessed for each included study, and the extent to which the results/conclusions of the review could be altered by the missing data should be assessed and discussed.
- If >30% of patient data were missing, the study data should not be used as they are too prone to bias.
- Consider imputing missing values where appropriate.
- Statistical techniques are available to estimate missing standard deviations from p values, confidence intervals, etc.
 - Sometimes missing standard deviations need to be borrowed from data generated in other studies.

Data analysis

- Summary of data

- Dichotomous outcomes:

- Relative risk (**RR**) or odds ratio (**OR**) or risk difference (**RD**) estimations with 95% CI can be used
 - Number needed to treat (**NNT**) with 95% CI may be calculated.

- Continuous outcomes:

- Mean difference (**MD**) or standardized mean difference (**SMD**) estimations with 95% CI can be used.

Heterogeneity

- Difference between studies: clinical or statistical
- Investigation of heterogeneity
 - **Clinical heterogeneity**
 - Assessed by comparing the distribution of important participant factors (age, underlying disease subtypes, specifics of treatments), and trial factors (randomization concealment, blinding of study participants, losses to follow-up) between trials.
 - **Statistical heterogeneity**
 - Assessed by examining I^2 , a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather than sampling error.
 - **Chi-squared** test of homogeneity may be used to determine the strength of evidence that heterogeneity was genuine.
- If significant heterogeneity is present, trials should be explored to investigate for possible explanations.
- Sensitivity analyses excluding outlying results may be performed.

Data analysis

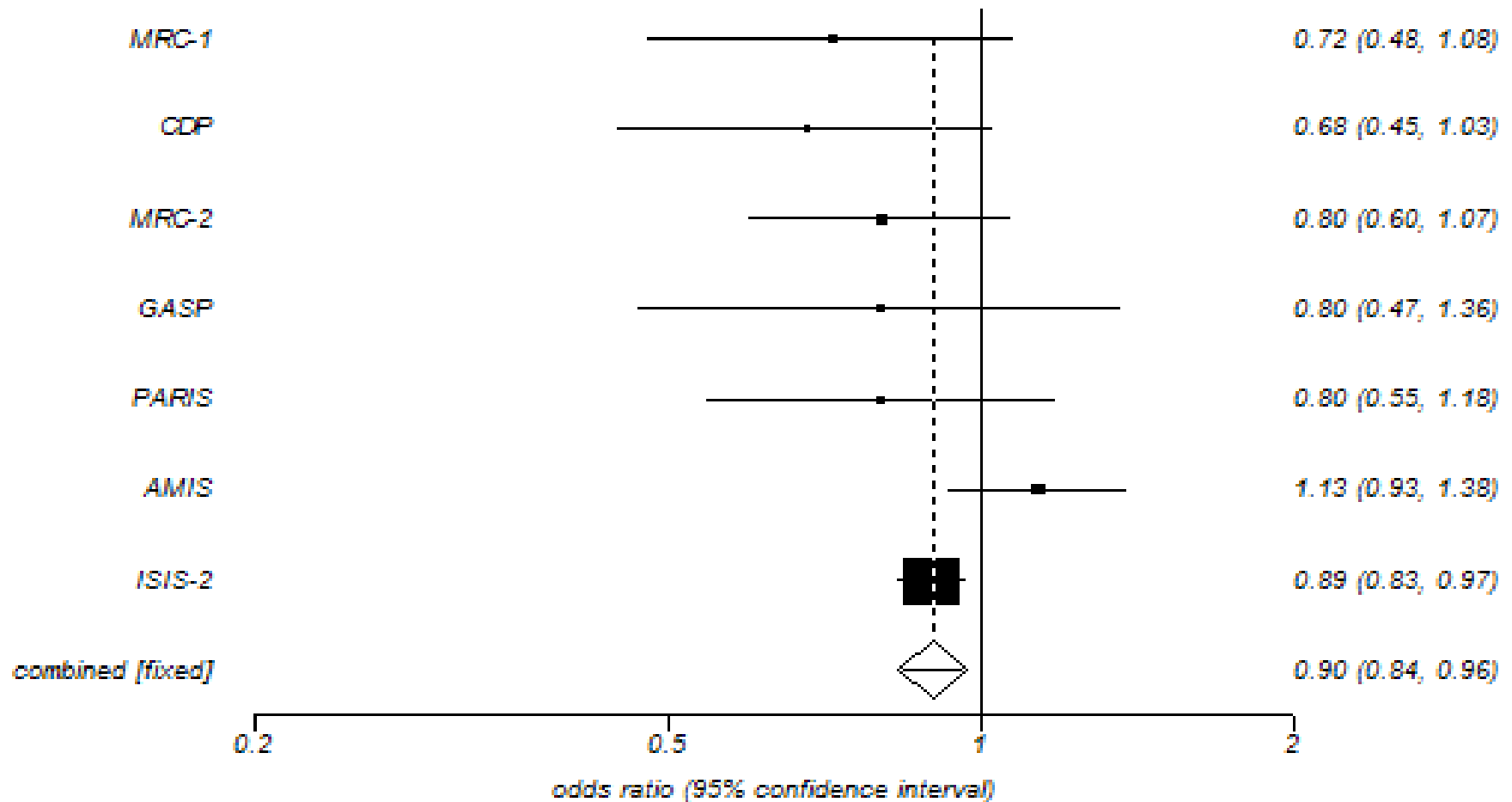
- Synthesis of results by meta-analysis:
 - Where the interventions are the same or similar enough without significant heterogeneity
 - Overall treatment effect is calculated as a **weighted average** of the summary statistics
 - Weights are inverse of variance or other statistics directly related to sample size or inversely related to dispersion to reflect the relative contribution to amount and certainty of information
 - Data from all included studies cannot be considered and combined as if they were from a single trial – **Simpson's paradox**.

Data analysis

- 2 statistical models: **fixed effects model** or **random effects model**
 - Fixed effects model: What is the best estimate of the treatment effect?
 - Random effects model: What is the average treatment effect?
 - Fixed effects model usually preferred.
 - If no significant statistical heterogeneity is present, use a fixed effects model.
 - If there is unexplained heterogeneity, consider a random effects model.
 - Random effects model should not be used to overcome or explain away heterogeneity
- Meta-analysis can be done by RevMan software provided by Cochrane collaboration – free to download
 - **Forest plots** will be produced

Forest plot

Odds ratio meta-analysis plot [fixed effects]



Data analysis

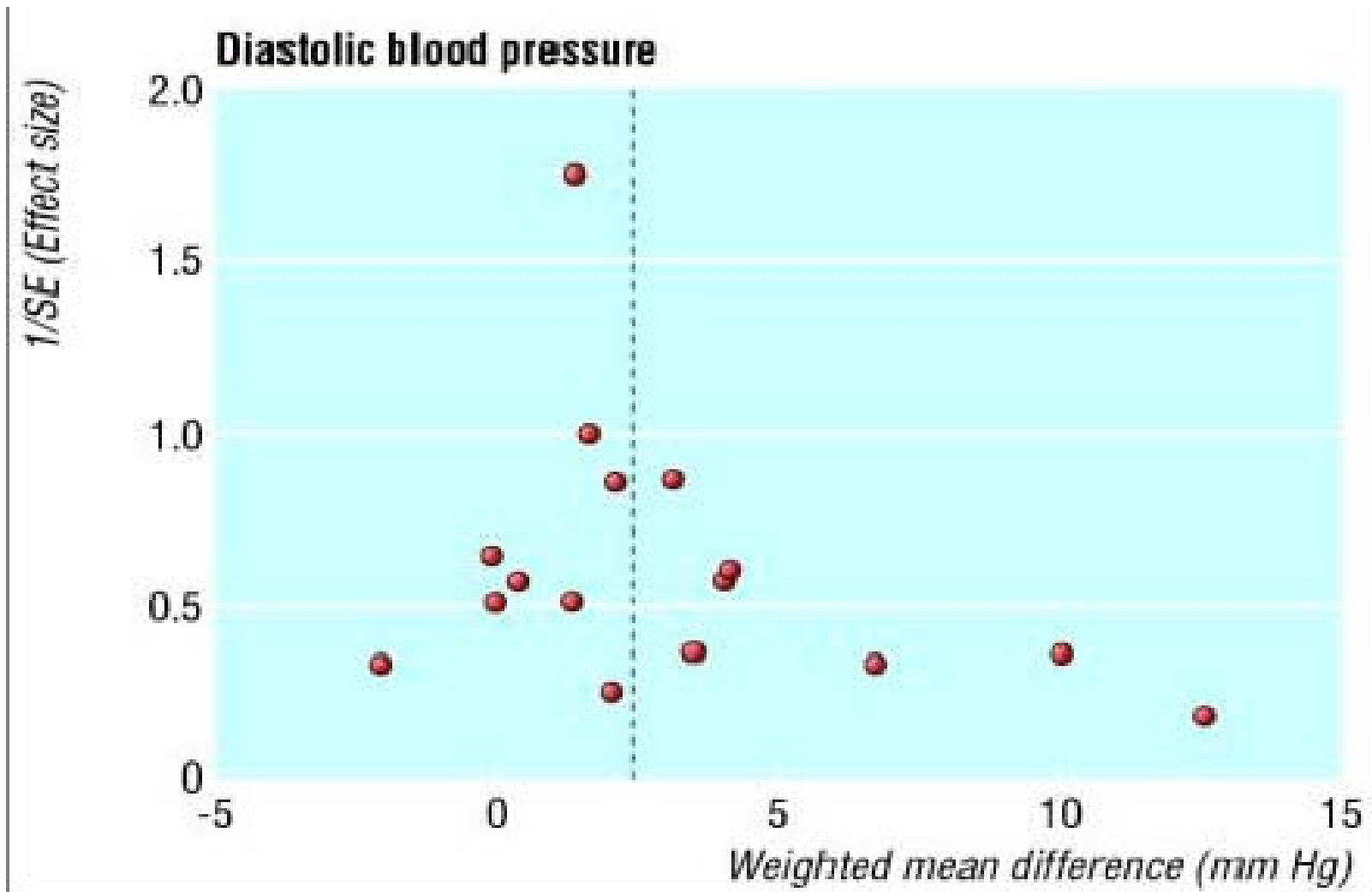
	Fixed effects model	Random effects model
Assumption	Effect size consistent across study	Studies represent a random sample from the population
Variation	Within studies	Within and between studies
Confidence interval	Narrower	Wider
Heterogeneity	Not allowed	Allowed
Inference	Within the studies Best estimate of treatment effect	More generalizable Average treatment effect
Statistical methods	Mantel-Haenszel, Peto, inverse variance	DerSimonian-Laird

Both models produce the same result if there is no heterogeneity.

Data analysis

- Assessment of publication bias
 - Funnel plots
 - Plots of estimated treatment effect sizes against their standard error if sufficient studies (>5) are found.
 - Asymmetry could be due to publication bias, but could also be due to a relationship between trial size and effect size, poor methodological quality of smaller studies, different choices of summary statistics, different underlying risks, or other types of biases.
 - In the event that a relationship is found, clinical diversity of the studies should be examined.

Funnel plot



Data analysis

- **Subgroup analyses**

- Analyze treatment effects in different subgroups
- Problems:
 - Observational in nature
 - Not derived from randomized comparisons.
 - Prone to bias
 - Inflate both type 1 and type 2 errors
- Should be limited in number.
- Should be **pre-specified** in protocol.
- Should be limited to clinically important sub-groups only.
- Possible difference in treatment effects of subgroups should be highly relevant and biologically plausible.

Data analysis

- **Sensitivity analysis**

- Repeat analysis for primary outcome excluding one or more trials with
 - Poor quality
 - Outlying results
- Repeat analysis using different assumptions on outcome data
 - worse and best case scenarios for missing data
 - different imputations of individual outcome data or summary statistics (standard deviations, correlations, etc.)
- Aim to evaluate whether the result and conclusion is robust or sensitive to changes in the study inclusion or missing data.

Discussion part

- Interpretation of results
 - Magnitude of treatment effects
 - Precision of treatment effects
 - Clinical significance
- Limitations of included studies and the systematic review
 - Risk of bias (internal validity)
- Adverse effects of interventions
 - Usually not adequately addressed by RCTs
 - Other sources, e.g., phase 4 surveillance
- Cost-benefit analyses

Conclusion part

- Implications for **practice**
 - Intervention recommended?
 - For which types of patients?
 - Under which circumstances?
 - Uncertainties
- Implications for **research**
 - Gaps of knowledge
 - Recommend future directions
 - Types of studies to perform, types of patients, types of interventions, types of outcomes to study
 - Types of pitfalls to avoid

Resources for learning SR

- **Cochrane handbook (>600 A-4 sized pages, 22 chapters)**
 - Freely available from
 - www.cochrane.org/training/cochrane-handbook
- **Cochrane Collaboration open learning materials**
 - www.cochrane.org/resources/openlearning/index.htm
- **Meta-analysis software**
 - RevMan
 - Free download from
 - www.ims.cochrane.org/revman
- **Training seminars/workshops**
 - Information from
 - www.cochrane.org/events/w-shops/all
 - Coming workshops
 - Systematic Review Protocol Development and Analysis Workshop- Vellore, India
 - 31 May – 4 Jun 2010
 - Developing a Protocol and Introduction to Analysis Workshop- Melbourne, Australia
 - 7-8 Jun 2010
 - Introduction to Meta-analysis Workshop- Glasgow, UK
 - 9 Jun 2010