Combining Results from Multiple Studies: Overview of Systematic Review and Meta-analysis

Department of Anesthesia Research Meeting

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Objectives

• What is a systematic review?
• How is a systematic review different from a narrative review?
• What are the advantages of systematic review?
• What is meta-analysis?
• What are the challenges of meta-analysis?
• Steps of meta-analysis
• Common problems with meta-analyses
• FAQ (Frequently asked questions)
Background

• Bridging the gap between scientific research and policy through systematic synthesis of research findings

• Cochrane advocated creation of readily accessible, rigorous evaluations of research to inform choices by policy makers, professionals, consumers

• The Cochrane Collaboration: http://www.cochrane.org/
  – Founded in 1993 and named after the British epidemiologist, Archie Cochrane
  – Regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews
What is a systematic review?

• **Systematic review**
  
  – An independent rigorous reproducible review of the literature to systematically evaluate the evidence to inform health care, policy-making and consumer decisions
  
  – Any type of review that has been prepared using strategies to avoid bias and that which includes a material and methods section
    

• **Impetus for evidence-based Medicine (EBM)**
  
  – Coined by Gordon Guyatt, McMaster University
  
  – Nominated as one of Medical Milestones 2007: The BMJ's poll to find the greatest medical breakthrough since 1840
    
    • [http://www.bmj.com/cgi/content/full/334/suppl_1/DC4?fbdm](http://www.bmj.com/cgi/content/full/334/suppl_1/DC4?fbdm)
  
Hierarchy of Evidence

(Green SB, Byar DP. Using Observational data from registries to compare treatments: the fallacy of omnimetrics. Statistics in Medicine 1984;3:361-70)
Differences between systematic and narrative reviews


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<th><strong>SYSTEMATIC</strong></th>
<th><strong>NARRATIVE</strong></th>
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<td><strong>QUESTION</strong></td>
<td>Focused</td>
<td>Broad</td>
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<td><strong>SOURCES/SEARCH</strong></td>
<td>Comprehensive; explicit</td>
<td>Usually unspecified; possibly biased</td>
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<tr>
<td><strong>SELECTION</strong></td>
<td>Criterion-based; applied uniformly</td>
<td>Unspecified; possibly biased</td>
</tr>
<tr>
<td><strong>APPRAISAL</strong></td>
<td>Rigorous; reproducible</td>
<td>Variable</td>
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<tr>
<td><strong>SENTHESIS</strong></td>
<td>Quantitative</td>
<td>Usually qualitative</td>
</tr>
<tr>
<td><strong>INFERENCE</strong></td>
<td>Usually evidence-based</td>
<td>Sometimes evidence-based</td>
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Advantages of systematic reviews

• Democratization of the research and its uses:
  – makes research findings more accessible to the general public

• Provides knowledge base for policy makers, practitioners:
  – decision-making on new technologies, development of practice guidelines

• Helps to identify knowledge gaps and prevailing degrees of uncertainty:
  – it is a good learning process
  – provides good source for information for research funders:
    • Identify knowledge gaps to set priorities, avoid unnecessary duplication of past research

• Aids the cumulative development of science:
  – successful research builds on previous efforts
  – helps research community to make sense of the past and plan for future research
  – permits international replication of research and testing of theories
What is Meta-analysis?

*(BMJ 1997;315:1371-1374*)

- **“Meta”**
  - implies something occurring later, more comprehensive
  - "overview"
  - “pooling” of different sources of data

- "Meta-analysis" now included as Medical Subject Heading (MeSH) and publication type within the Medline indexing system of the National Library of Medicine
Definitions of Meta-analysis

- **Definition 1:** Glass GV. Primary, secondary and meta-analysis of research. *Educational Researcher* 1976; 5: 3-8.
  
  Quantitative methods for combining studies have been available since early 1900s. But the term “meta-analysis” was coined after the paper by Glass (1976). Glass defined meta-analysis as “...the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings. It connotes a rigorous alternative to the causal, narrative discussions of research studies which typify our attempts to make sense of a large volume of research literature.”

- **Definitions 2:**
  
  It is a collection of statistical techniques for combining studies

- **Definitions 3:**
  
  A summary and statistical analysis of the results of several studies testing the same relationship. It is part of a Systematic Review.
Number of publications about meta-analysis, 1987-1996 (results from Medline search using text word and medical subject heading "meta-analysis")

Purposes of a meta-analysis

- To summarize a large and complex body of literature on a topic
- To resolve conflicting research reports in the literature
- To clarify or quantify the strengths and weaknesses of studies on a topic
- To document the need for a major clinical trial
- To increase statistical power by combining many smaller studies
- To improve the precision of an estimated treatment effect
- To detect smaller treatment effects that have been reported
- To investigate variations in treatment effects through subgroup (or stratified) analysis or meta-regression
- To investigate or improve the generalizability of known treatment effects
Challenges of Meta-analysis

• Publication bias
  – The tendency to not publish trials that show neutral or negative results

• Posthoc nature of meta-analysis
  – May suffer different types of biases as result of knowing trial results

• Simpson’s paradox
  – Pooling may lead to the reversal of an association between intervention and outcomes as result of other confounding factors

• Combining individual trials into a “composite” trial is viewed by others as combining “apples, oranges, bananas and occasionally, lemons into a single product, the quality of which is difficult to assess”
Formulate the purpose/scope of review

Identify relevant studies

State inclusion/exclusion criteria

Data abstraction and acquisition

Data analysis

Dissemination of results and conclusions

Define scope and research question(s)/hypotheses
Identify PICOT (Population, Intervention(s), Comparator, Outcomes, Time frame)

Have comprehensive search strategies (and document them)

Should be explicit & verifiable

Should be done in duplicate

Explicitly described: Fixed vs random-effects
Effect estimates (95% CI)

Report key findings, discuss how results compare with other works, key limitations and implications
An Example
Thavendiranathan et al. Primary Prevention of Cardiovascular Diseases With Statin Therapy A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2006;166:2307-2313

- **Objective:** To determine the role of statins in primary prevention of cardiovascular events in patients without CVD

- **Inclusion criteria:** Randomized trials of statins compared with controls (placebo, active control, or usual care)

- **Search Databases:** MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), Cochrane Collaboration (CENTRAL, DARE, and CDSR), and the American College of Physicians Journal Club databases

- **Search terms:** keywords related to statins (ie, *HMG-CoA reductase inhibitors, simvastatin, lovastatin, pravastatin, atorvastatin, cerivastatin, fluvastatin*, and *rosuvastatin*), cardiovascular disease (ie, *heart disease, coronary artery disease, myocardial infarction*, and *cerebrovascular disease*), cholesterol (ie, *cholesterol, LDL, HDL*, and *triglycerides*), and study types (ie, *randomized-control-trial, placebo-control-trial*, and *meta-analysis*).

- **Main outcome measure:**
  - Major coronary events (nonfatal myocardial infarction (NFMI) and coronary heart disease (CHD) death)
  - Major cerebrovascular events (fatal and nonfatal strokes)

- **Conclusions:** In patients without CV disease, statin therapy significantly decreases the risk of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality.
1146 Articles Identified in Electronic Searches With Duplicates Removed

1113 Articles Excluded Based on Title or Abstract Review
492 Clinical Outcomes Not Reported as Primary or Secondary End Point
453 Perspectives, Letters to Editors, Editor’s Response, Commentaries, Reviews
103 Subgroup Analysis, Study Rationale of Original Studies, Secondary Prevention Studies
65 Statin Mechanism of Action, Interactions, Comparisons

33 Articles Reviewed in Detail

9 Additional Articles Identified
6 Reference List Search
3 Clinical Trials Books

35 Articles Excluded After Detailed Review
15 Duration <1 Year, <80% Primary Prevention Patients
3 Aggressive vs Moderate Cholesterol Lowering Comparisons
13 Absence of Control Group, Meta-analyses
2 Patients Prescreened for Atherosclerosis
2 Studies in Particular Disease Groups

7 Articles Included in Meta-analysis

Plotted relative risk ratios (RRs) (95% confidence intervals [CIs]) for major coronary events

Common Problems with systematic reviews and meta-analysis

• **Poorly framed research questions**
  – Use PICOT format for framing research questions: **Population, Intervention, Comparator, Outcome, Time frame**

• **No *apriori* identification of factors to explain heterogeneity**
  – No indication of the direction of effect/hypotheses
  – No rationale for hypotheses

• **Decision to explore heterogeneity on the basis of alpha = 0.10**
  – Tests for heterogeneity have low statistical power
  – Analysis to explore heterogeneity needs to be done based on pre-specified variables regardless outcome of heterogeneity tests

• **Inappropriate analyses for exploring heterogeneity**
  – Inappropriate use of subgroup analysis – based tests within groups, not between groups
  – Should be based on meta-regression or between-group comparisons

• **Poor reporting**
  – Meta-analysis of RCTs: The QUOROM Statement
    • *Lancet* 1999; 354: 1896–900
  – Meta-analysis of Observational Studies: The MOOSE Statement
    • JAMA 2000; 283: 2008-12
FAQ about Meta-analysis

- Can one have a systematic review without meta-analysis?
  - Yes, if
    - The studies are too heterogeneous to combine
    - There are no studies to combine
    - There are no reported effect estimates or data

- Can I combine data from a pilot with data from the main study?
  - Yes, provided the sampling frame is the same and so is the methodology

- Can I combine the results of a pilot with the results of another study or in a meta-analysis?
  - Yes, same conditions as above
  - Also depends on whether the main study is reported

- Can I combine the results of internal unpublished studies?
  - Yes, same as above

- Can I combine results of unpublished studies with published studies?
  - Yes, same as above

- Can I combine results of underpowered studies (eg small trials of interventions for rare diseases)?
  - Yes; this requires documenting explicit plans for including results with those of similar trials in a prospective meta-analysis
  - JAMA 2002; 288(3):358-362
FAQ: Discrepancies between meta-analysis and prospective RCTs

- **What if meta-analysis results differ from those of subsequent trials?**
  - LeLorier et al NEJM 1997;337:536-42
    - 2/3 of 12 (out of 19) meta-analyses that had corresponding subsequent large trials (n>1000) had inconsistent findings
      - Kappa stats: 0.35 (95% CI 0.06; 0.64)

- **How can one treat the results of meta-analysis of small trials if the findings differ from those of a large subsequent trial?**
  - Results of meta-analysis can also be misleading
    - Meta-analysis of small trials often suffer from publication bias
    - Small trials are less likely to balance distribution of key baseline prognostic factors between treatment arms – leading to bias
Examples: Discrepancies between meta-analysis of small trials and prospective RCTs

- **Example 1: Trials of ICS (intravenous corticosteroids)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication</th>
<th>Relative Reduction (RR) in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 13 small trials</td>
<td>BMJ 1997;314:1855-9</td>
<td>RR: 9%</td>
</tr>
<tr>
<td>CRASH trial</td>
<td>Lancet 2004;364:1321-8</td>
<td>RR: 18% (ICS: 21.1%, Placebo: 17.9%)</td>
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<td>95% CI: (-26 %, 12 %)</td>
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- **Example 2: Trials of serum albumin concentration in ICU**

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication</th>
<th>Relative Risk (RR) in Mortality</th>
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<tbody>
<tr>
<td>Meta-analysis of 30 small trials</td>
<td>BMJ 1998;317:235-40</td>
<td>RR: 88% higher in albumin group; RD (risk difference) = 6%</td>
</tr>
<tr>
<td>SAFE Study</td>
<td>NEJM 2004;350:2247-56</td>
<td>No difference in mortality</td>
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**MESSAGE:** Meta-analyses of small trials may over- or under-estimate benefits/risks of interventions

Other Issues

• Any discrepancy between meta-analysis of large trials and subsequent large trials?
  – There has been no such examples

• What is cumulative meta-analysis and how is different from ordinary meta-analysis?
  – Repeated performance of meta-analysis whenever a new trial becomes available for inclusion.
  – Such cumulative meta-analysis can retrospectively address the question of “when did we know”?
      – Retrospective cumulative meta-analysis trials of intravenous streptokinase in acute myocardial infarction
        » Shows that a significant beneficial effect (P=0.02) was evident by 1977
        » the combined effect estimate was already both clinically important and highly significant (odds ratio 0.71 (95% confidence interval 0.59 to 0.84), P=0.0001) in 1981
Cumulative meta-analysis of total mortality results from randomised controlled trials of intravenous streptokinase in myocardial infarction


- No of patients randomised
- Odds ratio (95% CI; P value)
- Year of study
- Countries licensing streptokinase (year of licensing)

<table>
<thead>
<tr>
<th>No of patients randomised</th>
<th>Odds ratio (95% CI; P value)</th>
<th>Year of study</th>
<th>Countries licensing streptokinase (year of licensing)</th>
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<tr>
<td>962</td>
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<td>1979</td>
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<td>1986</td>
<td>Mexico, United States, Switzerland (1987)</td>
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* Includes GISSI-1; ** includes ISIS-2
Cumulative meta-analysis of total mortality results from randomised controlled trials of oral β blockers after myocardial infarction. The size of the square reflects the amount of statistical information available at a given point in time (Egger, M. et al. BMJ 1997;315:1371-1374)
Cumulative Meta-analysis

• Key Message:
  – Healthcare professionals are slow in recognizing convincing evidence and adopting it in practice
  – Under such circumstances, it seems unethical to initiate new trials or continue with ongoing trials
Key Messages

• **Systematic reviews of RCTs are useful for informing**
  – Clinical practice
  – Clinical guideline development
  – Policy making decisions
  – The scientific and ethical design of new trials or monitoring of on-going trials

• **Systematic reviews may or may not involve meta-analysis**

• **Pooling data from different studies require caution to minimize bias**
  – Heterogeneity can explored and explained if possible

• **Meta-analysis can**
  – Help resolve uncertainty and disagreements about therapies
  – minimize the chance of false negative results and prevent undue delays in adoption of effective therapies into practice

• **Meta-analysis of large trials is the best way to minimize bias**

• **Results of meta-analysis of small trials may over- or under-estimate benefit/risks of therapies** – caution is needed

• **Examples of (retrospective) cumulative meta-analysis show that healthcare professionals are slow in recognizing convincing evidence and adopting it in practice**
  – There is need to update meta-analysis following completion of new trials as part of requirement for reporting
Further Reading

• Cochrane AL. Effectiveness and Efficiency: Random Reflections on the Health Service. Lond: Nuffield Provincial Hospitals Trust, 1972
• Green SB, Byar DP. Using Observational data from registries to compare treatments: the fallacy of omnimetrics. Statistics in Medicine 1984;3:361-70