Research Synthesis and meta-analysis: themes

Graham A. Colditz, MD, DrPH
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Today

- Course format
- Goals, competencies
- Overview of themes for the class
Course Format

- Lectures
  » Posted on course page after lectures so that you can review material as needed
  » Lecture notes will include suggested and ‘for additional information’ references
  » References to readings on course page when available electronically – these link through library
- Classroom discussion is encouraged
- Homework assignments (2)
- Project
Office Hours

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  - following each class or by appointment
  - SRMA M19-551
Course Goals

- To give an introduction to the concepts, principles, and methods used in systematic reviews and meta-analyses.

- Non-mathematical focus, though hands on experience with data compilation and analysis are essential component of the course.

- In addition to reference text provide many examples from more recent medical literature – we will work to include examples from your area if possible.

- Gain skills in interpreting SRMA presentation and draw inference from such analysis to inform clinical and public health practices.

- Course builds on past teaching at HSPH:
  - 1994 co-developed course with Fred Mosteller.
  - Evolved and changed to Nan Laird and Cathy Berkey for statistical aspects of course in 1998.
  - Lead instructor through 2002.
  - Model for initial summer course at HSPH (M Stoto instructor).
Course Objectives

- To learn how to use a variety of formal and informal methods for synthesizing clinical, epidemiological, and related information on effectiveness of interventions, diagnostic tests and prognostic markers, and health risks,
- to understand how to use these methods to assess the strength of the evidence in policy development and clinical contexts, and
- to appreciate how research synthesis can contribute to rational policy making in controversial areas.
Competencies

Principles consistent with epidemiology and biostatics competencies for the MPHS (www.mphs.wustl.edu)

Ability to design research synthesis and meta-analysis
  • Define research question
  • Define literature search strategy
  • Conduct literature search and document the process
  • Apply eligibility criteria, data extraction, and data quality scoring
  • Develop data analysis plan
  • Understand and interpret fixed-effects, random-effects, and meta-regression methods and results
  • Recognize heterogeneity and approaches to quantification and reporting of among-study variation
Skills and experience to conduct analysis
• Master data analysis and model fitting in context of meta-analysis
• Quantitatively evaluate publication bias
• Be able to estimate combined results from reports of randomized trials, observational studies, and diagnostic test

Master the core reporting strategies
• Master reporting standards for RCTs and observational data in context of meta-analysis
• Master forest plot, summary tables, and publication bias presentations

Draw inferences from data to inform clinical and public health practices
• Correctly use reasoning for design and methodologies employed
• Present oral and written reports from analyses
• Place inference in context of clinical and public health implications for action and future research
Topics

- Overview – the role and approaches to Systematic Reviews and Meta-Analysis
- CER issues
- Defining research question
- Searching the literature
- Combining data – statistical methods
- Cumulative meta-analysis; meta-regression
- Publication bias
- Heterogeneity
- Data quality
- Software for meta-analysis
- Epidemiologic examples plus examples from ongoing or recent work
- Applying results to policy and practice
- Combining diagnostic test results
- Individual patient data analysis vs. meta-analysis of published results
- Presentations form your own SMRA
Homeworks

1. Define your research question & search strategy
2. Data extraction form and data analysis plan
3. Final paper, write up zeroth draft of manuscript (actually your third memo combining 1 & 2 and adding details per reporting standards)
Student Project: Conduct a SRMA

Project (group of size 1-3):
- Develop a research question (in your area of interest or suggested by an instructor)
- Work on components of SRMA during course
- Submit at end of course

....more in final project handout and guidelines for reporting www.prisma-statement.org, MOOSE-JAMA

SRMA M19-551
Effect of Regional Anesthesia on the Success Rate of External Cephalic Version
A Systematic Review and Meta-Analysis

Katherine R. Goetzinger, MD, Lorie M. Harper, MD, MSCI, Methodius G. Tuuli, MD, MPH,
George A. Macones, MD, MSCE, and Graham A. Colditz, MD, DrPH

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Epidemiology

META-ANALYSIS OF MULTIPLE OUTCOMES
BY REGRESSION WITH RANDOM EFFECTS

C. S. Berkey1,2,3, D. C. Hoaglin2,3, A. Antczak Bouckoms2, F. Mosteller2,4
and G. A. Colditz1,2

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STATISTICS IN MEDICINE Vol. 17, 2537-2550 (1998)

REVIEW ARTICLES
Searching one or two databases was insufficient
for meta-analysis of observational studies
Adina R. Lemeshow1, Robin E. Bham1,*, Jesse A. Berlin1, Michael A. Stoto1,
Graham A. Colditz1,2,4

1Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA
Research synthesis

- systematic
- usually quantitative
- review of published data
- ordinarily addresses a single issue
Synthesis - a long-standing tradition

- identifies areas of agreement
- identifies areas of discrepancy
Exploding number of published studies

● Thousands of journals
● Limited time to read, interpret and synthesize data / results
● Develop expertise in reading research synthesis
● Number of studies continues to increase
  – See Bastian H, Glasziou PP, Chalmers I, 2010
  – Next figures from this piece in PLOS Medicine
Figure 2. The number of published trials, 1950 to 2007. CCTR is the Cochrane Controlled Trials Registry; Haynes filter uses the “narrow” version of the Therapy filter in PubMed:ClinicalQueries; see Text S1.
doi:10.1371/journal.pmed.1000326.g002
Figure 4. The rise in non-systematic reviews, case reports, trials, and systematic reviews, 1950 to 2007 (as identified in MEDLINE). doi:10.1371/journal.pmed.1000326.g004
Meta-analysis and systematic reviews

- Overcome bias that may be induced by traditional reviews
- Avoid authoritative pronouncements
- Guidelines published for conduct of meta-analysis of RCTs and for observational studies
  » PRISMA; MOOSE; STARD, etc
- Used since turn of the 20th century in medicine and public health
What do we know about reviews?

Most reviews do not pass minimum criteria

A study of 158 reviews*
  » Only 2 met all 10 criteria
  » Median was only 1 of 10 criteria met

What are the 10 criteria?

* McAlister Annals of Intern Med 1999
Figure. Percentage of 158 review articles published in 1996 that fulfilled specific methodologic criteria. The numbers on the x axis refer to the first 10 criteria listed in the Appendix Table.
### Appendix Table. Methods Specified in Review Articles Published in 1985–1986 and 1996

<table>
<thead>
<tr>
<th>Criterion</th>
<th>1985–1986 Review Articles (n = 50)*</th>
<th>1996 Review Articles (n = 158)</th>
<th>1996 Meta-Analyses (n = 19)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The review addressed a focused clinical question</td>
<td>40 (80)</td>
<td>54 (34)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>2. The method of locating evidence was described†</td>
<td>1 (2)</td>
<td>44 (28)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>3. Explicit criteria were used to select studies</td>
<td>1 (2)</td>
<td>22 (14)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>4. The methodologic validity or quality of the included studies was assessed</td>
<td>1 (2)</td>
<td>14 (9)</td>
<td>13 (68)</td>
</tr>
<tr>
<td>5. Assessments of studies were reproducible (that is, they were done by</td>
<td>0</td>
<td>18 (11)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>more than one reviewer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Directives for future research initiatives were proposed</td>
<td>21 (42)</td>
<td>61 (39)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>In reviews that included treatment recommendations§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Sources of heterogeneity (clinical or study design) in existing data</td>
<td>Not assessed</td>
<td>15 (14)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>were addressed</td>
<td>3 (6)</td>
<td>23 (21)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>8. Quantitative synthesis of existing data was done</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. The major clinically relevant outcomes (benefits and harms) were</td>
<td>Not assessed</td>
<td>38 (34)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>considered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. The generalizability of existing data was addressed</td>
<td>Not assessed</td>
<td>13 (12)</td>
<td>5 (31)</td>
</tr>
</tbody>
</table>
Benefits of meta-analysis

- increase statistical power
- resolve uncertainty when reports disagree
- improve estimates of effect size
- answer new questions
- improve quality of research
- medical technology evaluation
- more objective summary of literature
Key features - conducting meta-analysis

- develop protocol
- search strategy
- study selection
- methodology - quality assessment
- data extraction
- analysis
- evaluation of heterogeneity
- subgroup and sensitivity analysis
Protocol development

- report should specify protocol development
- the question being asked
- specific subgroups of interest
Search strategy

- defined in sufficient detail that it can be replicated
Where do you look to find studies?
Where do you look to find studies?

- Previous meta-analyses
- Published studies
- Unpublished studies
- Publication bias
Existing systematic reviews

- Search on meta-analysis
- Search Cochrane library
Finding published studies

- Extensive and time consuming
- No easy answers
- Tips
  » Break question into components
  » Use synonyms
  » Check references of articles found
  » Hand searching
Searching cont....

- Use MEDLINE methodologic terms to filter or narrow the search
  - Randomized-controlled-trial in [publication type]
  - Study categories (etiology, prognosis, treatment, diagnosis)
- See appendix C of NHMRC handbook
Unpublished primary studies

- On occasion, unpublished studies may be considered for inclusion in a meta-analysis or systematic review
- They may help interpret publication bias
- Sources may include clinical trials registries
- Contacting experts may help
Publication bias

• Positive studies are more likely to be published than ‘negative’ studies.
• If this assertion is true, then any review of published studies will give a biased summary of the evidence.
  » Studies suggest non-publication is because authors fail to submit, not because journals reject ‘negative’ studies
Does Publication bias affect results?

- Numerous studies of the magnitude of publication bias
- Simes examined efficacy of chemotherapy for ovarian cancer (JCO 1986)
  » 16 pub studies survival ratio = 1.16 (1.06-1.27)
  » 13 unpub, survival ratio = 1.05 (0.98-1.12)
- Methods to examine for publication bias are present but usually require substantial number of studies
Duplicate publication

- Recurring problem
- Often clinical trials have early and later report
- If not identified, then double counting gives undue weight to the duplicate studies and biases the overall assessment
- Use the most recent report (most data)
Study selection

- detailed eligibility criteria
- often human, specific therapy, and specific study design (e.g. randomized controlled trial)
- study design categorized such that analyses can be stratified according to design
- reject log recording omitted studies
Methodologic assessment

- review of trials for eligibility
  » double blind
  » diagnosis meeting standard definition
  » patient group
Data extraction

- methods for extracting data described
  - 2 readers, error checks, etc.
- table summarizing key points of each study
Analysis

- describe approach in detail
- present in clinically meaningful forms
Approaches to combining data
Summarizing outcomes

- Vote counting
- Summary of data - effect size, etc.
  - Effect size expresses the difference between treated and control group mean in units of the standard deviation of measurement
- Simple average
- Weighted average - improves precision of estimate
Simple average

- Equal weights
- Average = \( \frac{d_1 + d_2 + \ldots + d_k}{k} \)
- For \( d_i \), the \( i \)th study has estimated variance \( s^2_i \), and so the estimated variance of \( d \) is:
  \[
  s^2_d = \frac{s^2_1 + s^2_2 + \ldots + s^2_k}{k^2}
  \]
  - Unbiased estimate, but not the most precise
Fixed-effects

- If we assume the studies all estimate the same true difference (risk reduction, etc), we use weights that give the most efficient estimate.
- We are not saying that we believe all the studies estimate exactly the same thing, but rather that the assumption is near enough.
Fixed-effects, cont..

- Weighted average
- Use inverse variance weights
  » This is similar to usual approach in epidemiology for combining 2x2 tables
Random-effects

- Here we suppose there is a universe of many conditions and that a random sample of conditions has been drawn from this universe. We are now estimating the effect from this sample.
  » This is a 2 stage process, we first identify a set of studies from a distribution with mean and variance. We estimate these parameters and then use them for stage 2.
Figure 1  In Stage 1, from the population of studies with mean treatment effect $\mu$ and standard deviation $\sigma_A$, four studies are drawn for illustration (here the population has $\mu = 0, \sigma_A = 1$). These drawings determine the associated unknown true means $\mu_1, \mu_2, \mu_3, \mu_4$. The studies are carried out with varying standard deviations $\sigma_1, \sigma_2, \sigma_3, \sigma_4$ (which may be partly due to different sample sizes) as shown in the Stage 2 diagram. The actual numerical outcomes of the studies are $X_1, X_2, X_3, X_4$. Notice that although $\mu_2 < \mu_4$, it turned out that $X_4 < X_2$ because of sampling variation.
Steps in data analysis & presentation

1. Tabulate summary data
2. Graph data
3. Check for heterogeneity
4. Perform a meta-analysis if heterogeneity is not a major concern
5. If heterogeneity is found, identify factors that can explain it, include consideration of design, quality, and other variables
6. Explore the potential for publication bias
1. Tabulate summary data

- Prepare tables comparing studies with respect to:
  - Year
  - Setting
  - Patients
  - Intervention
  - Comparison
  - Outcome (results)
  - Quality

- Gives a ‘first hand’ feel for the data
- Can make some assessment of quality and heterogeneity
Table I. Prophylactic use of lidocaine after a heart attack: evaluating mortality from prophylactic use of lidocaine in acute myocardial infarction. Source: reference 1

<table>
<thead>
<tr>
<th>Source</th>
<th>Number randomized</th>
<th>Number dead</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lidocaine</td>
<td>Control</td>
</tr>
<tr>
<td>1. Chopra et al.</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>2. Mogensen</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>3. Pitt et al.</td>
<td>107</td>
<td>110</td>
</tr>
<tr>
<td>4. Darby et al.</td>
<td>103</td>
<td>100</td>
</tr>
<tr>
<td>5. Bennett et al</td>
<td>110</td>
<td>106</td>
</tr>
<tr>
<td>6. O’Brien et al.</td>
<td>154</td>
<td>146</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>557</strong></td>
<td><strong>549</strong></td>
</tr>
</tbody>
</table>
2. Graph summary data

- Efficient way of presenting summary results
- Forest plot:
  - Presents the point estimate and CI of each trial
  - Also presents the overall, summary estimate
  - Allows visual appraisal of heterogeneity
- Other graphs:
  - Cumulative meta-analysis
  - Funnel plot for publication bias
Figure 1. Prophylactic lidocaine after a heart attack. The x-axis displays the risk difference, $d_i = \hat{\beta}_{Ti} - \hat{\beta}_{Ci}$, and corresponding 95 per cent confidence intervals $\left( \frac{s_{d_i}^2}{\hat{\beta}_{Ti} n_{Ti}} + \frac{s_{d_i}^2}{\hat{\beta}_{Ci} n_{Ci}} \right)$; the y-axis indicates the study and total sample size.
Staples Compared With Subcuticular Suture for Skin Closure After Cesarean Delivery
A Systematic Review and Meta-Analysis

Methodios G. Tuuli, MD, MPH, Roxane M. Rampersad, MD, Jeanine F. Carbone, MD, David Stamilio, MD, MSCE, George A. Macones, MD, MSCE, and Anthony O. Odibo, MD, MSCE

Fig. 2. Forest plot of the composite outcome of wound complications (separation or infection) in selected studies comparing staples to subcuticular suture for skin closure after cesarean delivery. The pooled odds ratio (OR) is 2.06 (95% confidence interval [CI] 1.43–2.98), with number needed to harm of 16 and 64 excess events per 1000 (95% CI 36–85). $\chi^2$ for heterogeneity=5.79, $P=.327$, $P=13.7\%$.

Cumulative Meta-analysis Plot

Passive smoking and lung cancer review

4. Perform meta-analysis

- Decide what data to combine
- Data types:
  - Continuous
  - Dichotomous
- Examples of measures that can be combined:
  - Risk ratio
  - Odds ratio
  - Risk difference
  - Effect size (Z statistic; standardized mean difference)
  - P-values
  - Correlation coefficient (R)
  - Sensitivity & Specificity of a diagnostic test
Table III. Study summaries for the lidocaine example. T denotes treatment group, C denotes control group, \( q_i = 1 - p_i \); \( n_{Ti} \) and \( n_{Ci} \) denote the total number of treated and control patients, respectively; and \( a, b, c, \) and \( d \) denote the number of observations in each of the cells defined by the treatment (lidocaine or control) and outcome (dead or alive) table. The confidence intervals for the relative risk and odds ratio are computed on the logarithmic scale and transformed back to the original scale.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk difference</th>
<th>Relative risk</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D = P_T - P_C )</td>
<td>( R = P_T / P_C )</td>
<td>( \Omega = \frac{P_T(1-P_T)}{P_C(1-P_C)} )</td>
<td></td>
</tr>
<tr>
<td>( d_i = \hat{p}<em>{Ti} - \hat{p}</em>{Ci} )</td>
<td>( r_i = \frac{\hat{p}<em>{Ti}}{\hat{p}</em>{Ci}} )</td>
<td>( \omega_i = \frac{\hat{p}<em>{Ti}q</em>{Ci}}{\hat{p}<em>{Ti}q</em>{Ti}} )</td>
<td></td>
</tr>
<tr>
<td>Standard error ( s_{d_i} = \sqrt{\left( \frac{p_{Ti}q_{Ti}}{n_{Ti}} + \frac{p_{Ci}q_{Ci}}{n_{Ci}} \right)} )</td>
<td>( s_{\log(r_i)} = \sqrt{\left( \frac{q_{Ti}}{n_{Ti}p_{Ti}} + \frac{q_{Ci}}{n_{Ci}p_{Ci}} \right)} )</td>
<td>( s_{\log(\omega_i)} = \sqrt{\left( \frac{1}{n_a} + \frac{1}{n_b} + \frac{1}{n_c} + \frac{1}{n_d} \right)} )</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>( d_i ) (%)</th>
<th>95% CI</th>
<th>( r_i )</th>
<th>95% CI</th>
<th>( \omega_i )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>2.8</td>
<td>(-5.5, 11.1)</td>
<td>2.2</td>
<td>(0.2, 23.4)</td>
<td>2.3</td>
<td>(0.2, 26.1)</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>0.0</td>
<td>(-12.0, 12.0)</td>
<td>1.0</td>
<td>(0.3, 3.8)</td>
<td>1.0</td>
<td>(0.2, 4.3)</td>
</tr>
<tr>
<td>3</td>
<td>217</td>
<td>2.0</td>
<td>(-3.6, 7.6)</td>
<td>1.5</td>
<td>(0.5, 5.3)</td>
<td>1.6</td>
<td>(0.4, 5.7)</td>
</tr>
<tr>
<td>4</td>
<td>213</td>
<td>1.8</td>
<td>(-4.7, 8.3)</td>
<td>1.4</td>
<td>(0.4, 4.1)</td>
<td>1.4</td>
<td>(0.4, 4.5)</td>
</tr>
<tr>
<td>5</td>
<td>216</td>
<td>3.5</td>
<td>(-2.0, 9.1)</td>
<td>2.2</td>
<td>(0.6, 8.5)</td>
<td>2.3</td>
<td>(0.6, 9.3)</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>4.4</td>
<td>(-0.5, 9.3)</td>
<td>2.6</td>
<td>(0.8, 8.0)</td>
<td>2.7</td>
<td>(0.8, 8.8)</td>
</tr>
</tbody>
</table>
Is there heterogeneity?

How will we know?
Cochran’s Q

- This is a chi-squared statistics with k-1 degrees of freedom
- \( Q = \sum w_i (y_i - y_w)^2 \)
- \( Q \) also allows us to estimate the among study variance \( \sigma_A^2 \)
- Include the estimate of among study variance in the weights
- \( W_i = \frac{1}{(\sigma_A^2 + s_i^2)} \)

Cochran WG, Biometrics 1954
Comparing models

- If we use the fixed-effects assumptions, then to the degree that it is false, we will report better precision than we are justified in using.
- When the data reveal homogeneity, the random-effects model degenerates to the fixed effects model. The random-effects model gives back the fixed-effects model when the situation deserves it.
5. Identify factors that can explain heterogeneity

- If heterogeneity is found, use these approaches to identify factors that can explain it:
  - Graphical methods
  - Subgroup analysis
  - Sensitivity analysis
  - Meta-regression

- Of all these approaches, subgroup analysis is easily done and interpreted
5. Identify sources of Heterogeneity among results

- situation in which differences in study outcomes are not readily accounted for by sampling variation within studies
- it should be assessed and reported
- when substantial heterogeneity is identified exploratory analyses should describe factors that account for the it
Subgroup analysis

- special care in reporting and interpretation is required
- a priori vs. post hoc analysis
Sensitivity analysis

- assess the robustness of the findings from the meta-analysis
- may repeat analysis omitting studies with lowest quality, the earliest studies, or some other subset such as trimming the extreme 10 percent of studies from each end of the distribution of results
Sources of heterogeneity

- Design
  - Degree of control
    - RCT vs. nonrandom comparison, nonconcurrent control, etc.
    - type of control
      - CHD and HRT: Hospital vs. community control
  - Action: Initial a priori stratification by design is useful
Sources of heterogeneity - cont

- Study quality
  » Studies of exercise and heart disease
    – see example Berlin and Colditz, AJE

- Degree and or type of exposure
  » Studies of exercise and CHD
  » Asbestos and GI cancer
Approaches to combining data

- Heterogeneity (H) is expected
- Do not test for it - low power test of H
- Expect H and estimate the among study variance
- Report the among study variance
- Report change in among study variance as potential explanations for H are included in the analysis
Approaches cont..

- A null results in a test for heterogeneity does not rule out heterogeneity
  - for example, 20 studies, $Q = 18$. This leaves plenty of variation still to be explained.
What to do...

- Report among study variance
- Stratify
- Graphical display
- Regression
  » Remember the principles of good regression practices
    - don't over interpret exploratory analysis
    - use robust techniques
What not to do

• Omit outliers because they are outliers
• “The results are homogeneous after we discard the studies that disagree with what the rest of the studies say”
  – but which are the outliers?
• Trock et al. (JNCI 1990, 82:650-61)
  – Removed studies “giving least support to the association” and the results were no longer heterogeneous
Heterogeneity - conclusions

- Heterogeneity is common. But many authors fail to report it, discuss it, explore its sources, etc.
- Analysis of H should be performed but interpreted cautiously, as with any exploratory analysis
- Exploring H can lead to new insights
conclusions cont..

- Exploring H can help plan future studies
- Excluding outliers because they are outliers is BAD
- Trimming and other good regression practices apply to MA
- Identify sources of H that will be explored in advance - when preparing protocol for MA
An example - streptokinase

- Stampfer et al. combined data on streptokinase and death among patients in 8 RCTs reported through 1979
- 2.7 deaths prevented per 100 patients
- 95% CI -6.3 to +0.9
- substantial heterogeneity
streptokinase cont..

- each trial reported mean time from onset of symptoms to therapy
- earlier treatment should be more beneficial
- include duration of symptoms as a covariate in meta-analysis regression
- 5.3 deaths prevented per 100 patients treated within 12 hours of onset of chest pain 95% CI (-10 to -1)
by explaining the source of heterogeneity among trials’ results we arrive at a more clinically relevant estimate of treatment benefit

analysis across studies addressed an issue that could not be answered in the early small studies of efficacy of streptokinase
6. Explore publication bias

- Studies with significant results are more likely
  - to be published
  - to be published in English
  - to be cited by others
  - to produce multiple publications

- Including only published studies can introduce publication bias

- Most reviews do not look for publication bias

- Methods for detecting publication bias:
  - Graphical: funnel plot asymmetry
  - Tests: Egger test, Rosenthal’s Fail-safe N
Does the meta-analysis inform your clinical practice?

- many meta-analyses may not report all these details
- even if all details are reported, the reader must still make judgment regarding application to reader’s practice
Factors that may influence judgment

- Are your patients similar to those in studies?
  - is age similar
  - is underlying disease similar
  - can treatment be administered as effectively in clinic as in research studies

- when heterogeneity among study results is substantial, does a sound explanation exist to account for it, does it relate to your patients?
Interpretation and application go beyond guidelines

- sharpness of question
- potential sources of bias to distort the evidence
- generalizability of results to other clinical settings
- even with estimate of efficacy, application to individual patients still requires weighing risks and benefits of therapy given the underlying disease and its complications
EBM (quick & dirty)

Steps
1. Ask Question
2. Search
3. Appraise
4. Apply

- Time: 90 seconds
- < 20 articles
- This patient survives!

Systematic Review

Steps
1. Ask Question
2. Search ++++ x 2
3. Appraise x 2
4. Synthesize
5. Apply

- Time: 6 months, team
- < 2,000 articles
- This patient is dead

Find a systematic review!! (and appraise it FAST)

From Glasziou
Pros and cons of systematic reviews

- Advantages
  - Larger numbers & power
  - Robustness across PICOs

- Disadvantages
  - May conclude small biases are real effects