NYU School of Medicine
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Department of Surgery
Division of Trauma and Emergency Surgery

Anything You Can Do, I Can Do Meta: An Introduction to Meta-Analysis

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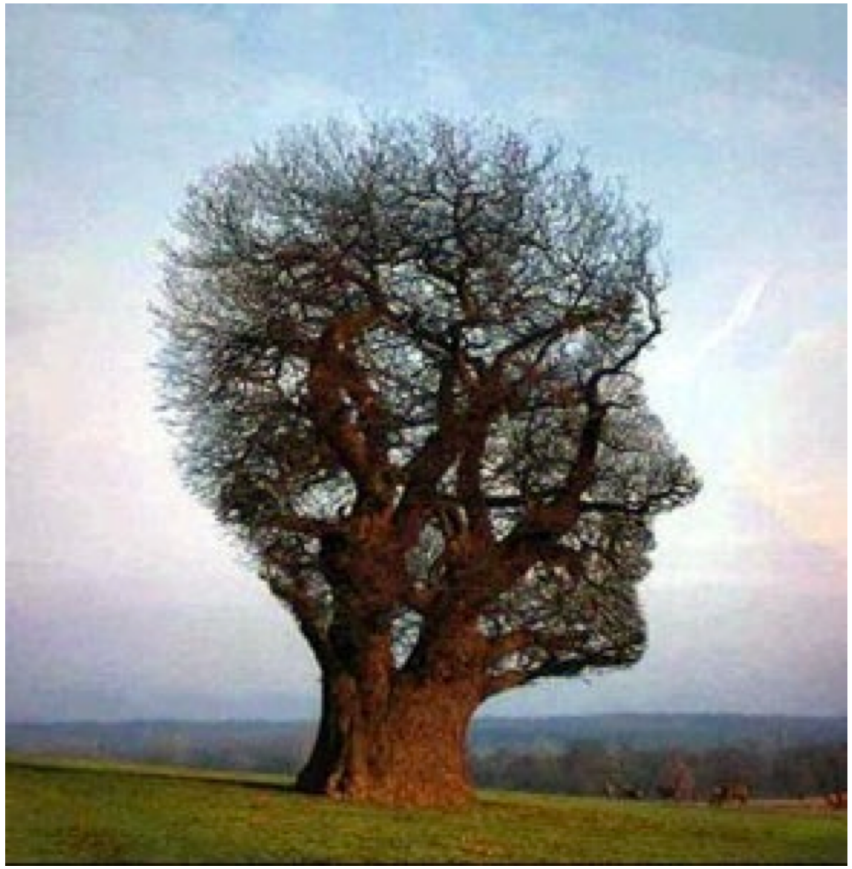
Columbia University Mailman School of Public Health Fall 2017



“If only we knew what we know…”

Caria O’ Dell and Jack Grayson

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Meta-analyses have failed to settle the question of whether violent video games such as *Grand Theft Auto* cause aggression. CATE GILLON/GETTY IMAGES

Jop de Vrieze Science. Sep. 18, 2018

https://www.sciencemag.org/news/2018/09/meta-analyses-were-supposed-end-scientific-debates-often-they-only-cause-more

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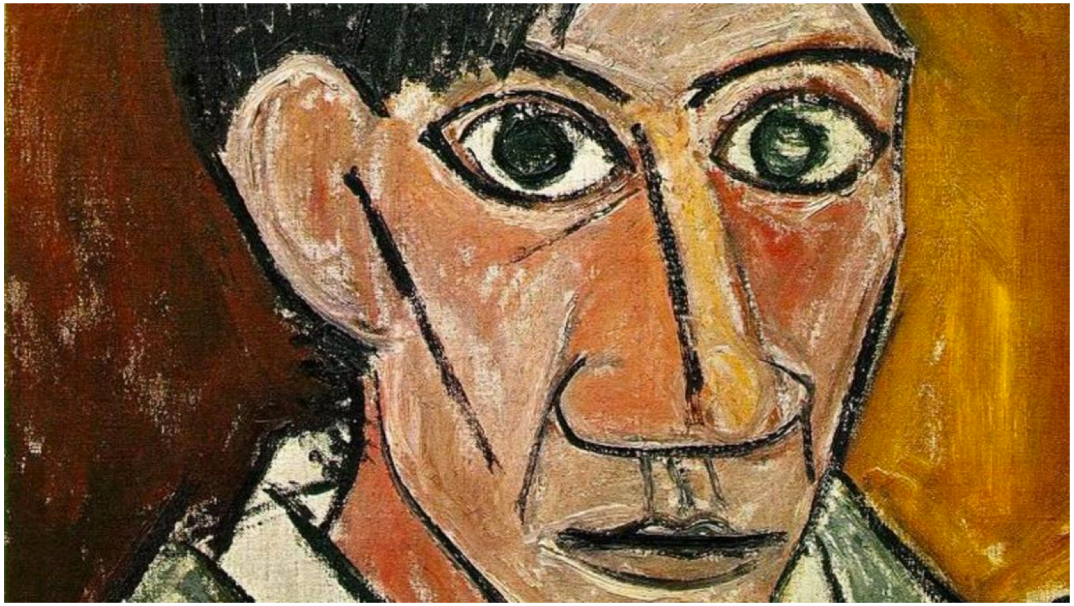
Meta-analyses were supposed to end scientific debates. Often, they only cause more controversy

By **Jop de Vrieze** | Sep. 18, 2018 , 4:15 PM

> **"Scientists have to make several decisions and judgment calls that influence the outcome of a meta-analysis. … Anyone who wants to manipulate has endless possibilities."**
>
> *Jos Kleijnen, Kleijnen Systematic Reviews*

Bushman in producing the 2010 meta-analysis, says she has not lost faith in the method—but she has changed her expectations. "We used to make meta-analyses as objective as possible. Now, we try to make them as transparent as possible," she says. "Anyone who disagrees with a certain decision will have to be able to redo it and see if that has an influence on the results."

“When art critics get together they talk about Form and Structure and Meaning. When artists get together they talk about where you can buy cheap turpentine.”



-Pablo Picasso

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Objectives:

- Define Meta-Analysis
- Understand the Strengths and Limitations of Meta Analysis
- Understand How a Meta Analysis is Conducted
  - Ask a Question
  - Search, Evaluate and Code Studies
  - Statistical Methods to Synthesize Results

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What is meta-analysis?

"A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable"

ASA, 1988

- A set of methods to systematically and reproducibly search, sample and (statistically) synthesize evidence from studies.

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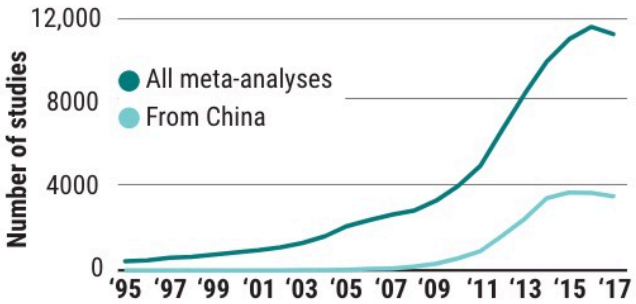
King of the hill?

The votes are in…

Eager for answers

Virtually unknown until the 1990s, meta-analyses have recently become increasingly popular. More than 11,000 were published last year, one-third of them by authors from China.



J. YOU/*SCIENCE*

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The good…

"Meta-analysis clearly has advantages over conventional narrative reviews and carries considerable promise as a tool in clinical research"

Eggers, Davey Smith, 1997

"…now widely accepted as a method of summarizing the results of empirical studies within the behavioral, social and health sciences"

Lipsey and Wilson, 2000

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The bad…

"an exercise in mega-silliness…"

Eyesnack, 1978

"a new bete noire (which represents) the unacceptable face of staticism (and) should be stifled at birth"

Oakes, 1986

"Meta-Analysis, Shmeta-Analysis."

Shapiro 1994

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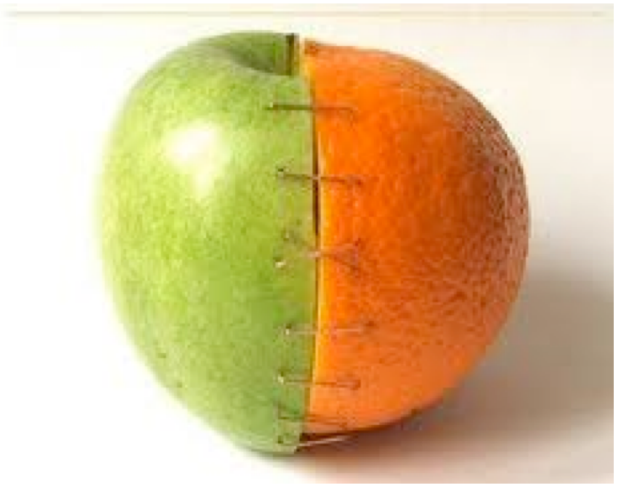
The ugly….



Strengths of Meta-Analysis

- Imposes Discipline
  - Makes process explicit and systematic
  - Organized way of combining a lot of information
  - More differentiated and sophisticated than traditional reviews
- Combining studies increases power
  - Find ‘significant’ results

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Weaknesses of Meta-Analysis

- Heterogeneity – "apples and oranges"
- Biases
  - Missing Studies
    - May differ from published studies (publication bias)
- Quality of Studies ('GIGO')
  - What constitutes quality?
- Requires a lot of effort and substance-area expertise
- Mechanics of statistics may obscure theory
- Best for closed-ended questions

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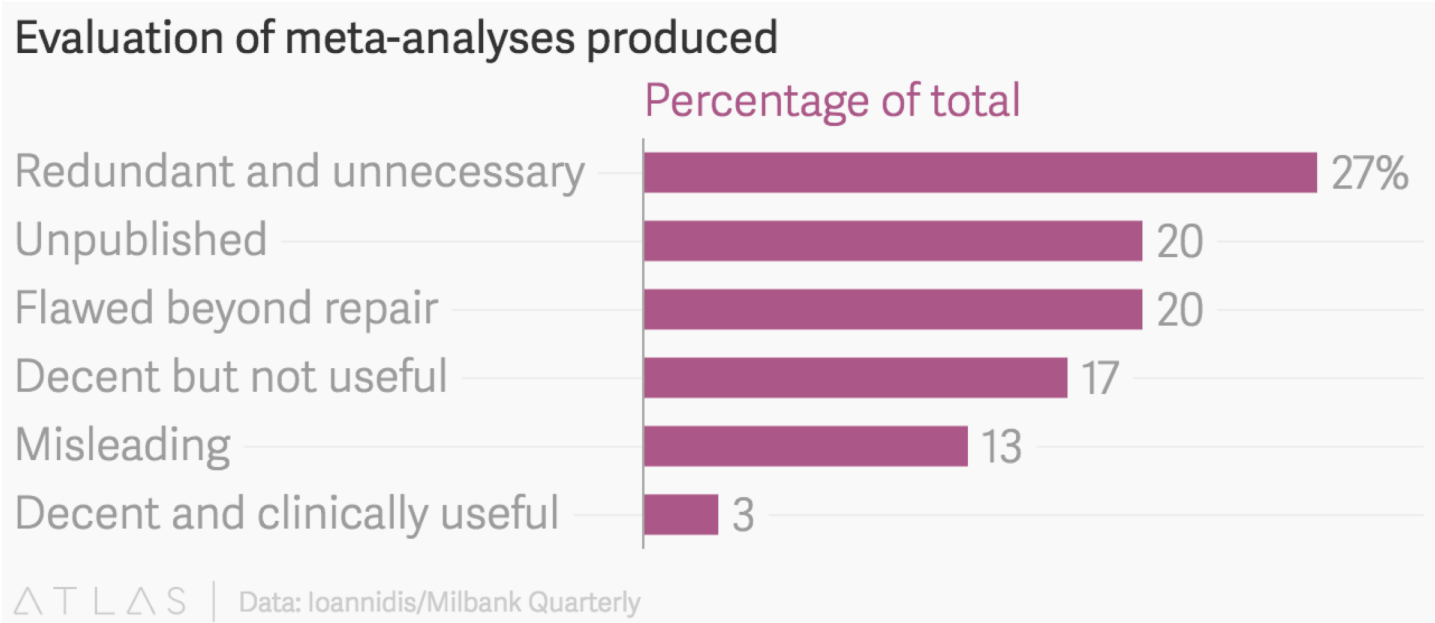
But beware …



… the bete noire still lurks.

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There's a checklist for that

- QUOROM statement (Moher D et al (1999) Lancet 354: 1896-1900) https://journals.plos.org/plosntds/article/file?type=supplementary&id=info:doi/10.1371/journal.pntd.0000381.s002

- PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement http://prisma-statement.org/documents/PRISMA%202009%20checklist.pdf

- MOOSE (Meta-Analysis Of Observational Studies In Epidemiology): http://www.ijo.in/documents/14MOOSE_SS.pdf

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Meta-Analysis: A 12-Step Program

- I. **Specify** Problem
- II. **Search** for and Identify Studies
- III. **Enter** studies into database
- IV. **Select** Studies for Review
- V. **Review** Studies
- VI. Develop Coding **Scheme**
- VII. Abstract / **Code** Studies
- VIII. **Define** Effect Size Statistic
- IX. Transform and **Weight** Effect Sizes
- X. **Assess** Heterogeneity
- XI. **Assess** Bias
- XII. ➔ ➔ ➔ **Synthesize** and Present Results ← ← ←

last and not always appropriate or necessary

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I. Problem Specification

"What are the types and magnitudes of behavioral health disturbances such as depressive symptomotology, post traumatic stress, and somatization seen after terrorist incidents. Do responses vary by variables such as rural vs. urban, developed vs. developing, blast or explosive injuries vs. biological incidents, number injured, and level of publicity. Do terrorist incidents have quantifiable effects on local health care system utilization such as outpatient and emergency department visits, prescription seeking? Are effects sustained and for how long? What social behaviors result from terrorist incidents? Are they adaptive or maladaptive? What community (ecologic) level features are associated with adaptive behaviors?"

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II. Identify Studies

- Has a meta-analysis been done already?
  - PubMed Clinical Queries

- Electronic / Online Resources
  - PubMed, Medline, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine (AMED), PsychINFO, Health and Psychosocial Instruments, ProQuest Digital Dissertation Database, Papers First, Cochrane Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane Controlled Trials Register (CCTR), Sociologic Abstracts and Web of Science
  - Search Terms
    - alcohol*', 'epidem*', 'risk', 'protect*', 'cohort', 'case control', 'longitudinal'

- Hand Search
  - References of electronically identified articles
  - Contact investigators

- ***Ask a Medical Librarian!***

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III. Enter Studies

- **Endnote / Zotero / Bookends/Bib Desk**
  - Search and enter directly through program
  - Remove duplicates
  - Review titles and remove non-relevant studies
  - Review abstracts and remove non-relevant studies
- **Retrieve pdf's**
  - Attach to citation
  - Review full text
  - Divide into main categories

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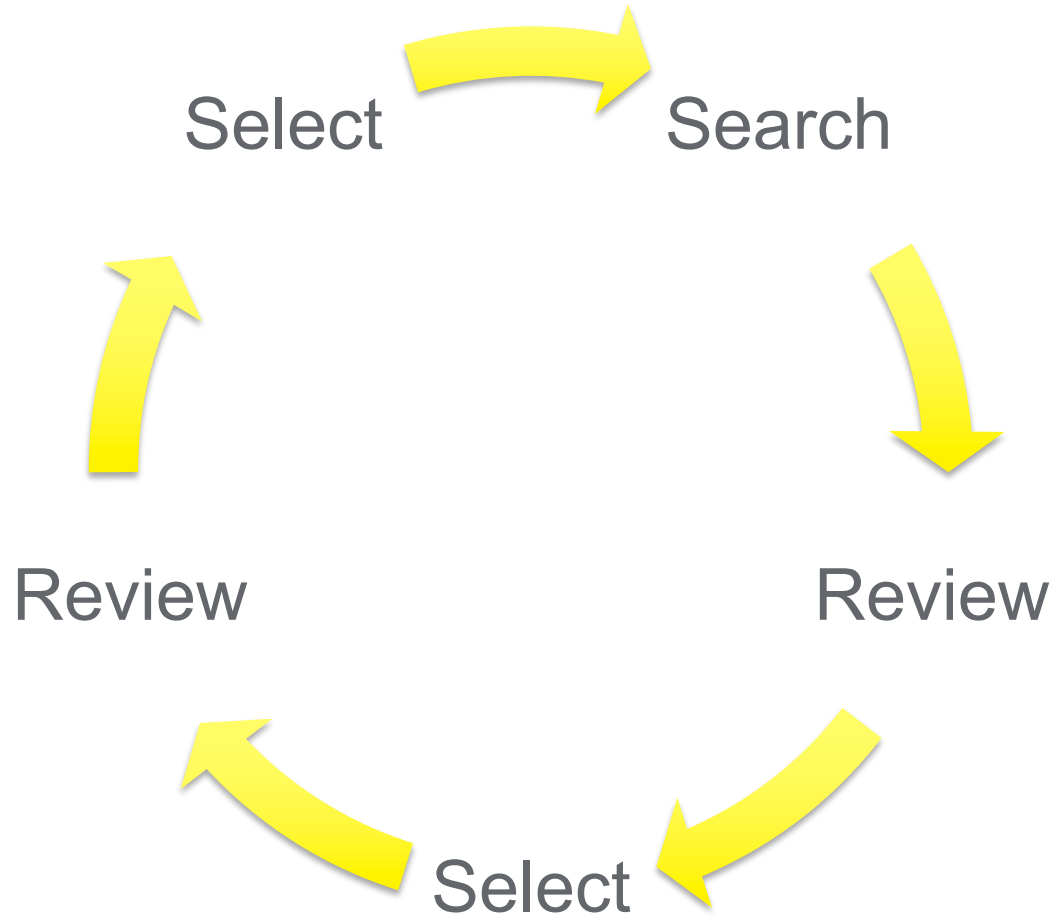
IV. / V. Review and Select Studies



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VI. Develop Coding Scheme

- **"Interviewing" a Study**
  - Identifying information (authors, journal, etc…)
  - Sample size
  - Type of population
  - Type of effect (e.g. odds ratio, prevalence)
  - Results
- **Effect Size / Outcome**
  - Population(s)
  - Methods / Prodecures
  - Designs
  - Variables

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VII. Abstract the Data

- **Meta-analytic data is inherently hierarchical and nested**
  - Multiple outcomes per study
  - Multiple measurement points per outcome
  - Sub-samples per study population
- **Multiple effect sizes per study**
- **Analyses almost always are a subset of coded effect sizes**.
  - Data structure needs to allow for the selection and creation of those subsets
- ***To maintain statistical independence analyses should include only one effect size per study***
  - (or one effect size per sub-sample within a study)

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Example of Relational Data Structure (Multiple Related Flat Files)

Study Level Data File

ID	PubYear	MeanAge	TxStyle
100	92	15.5	2
7049	82	14.5	1

Note that a single record in the file above is "related" to five records in the file to the right

Effect Size Level Data File

ID	ESNum	Outcome Type	TxN	CgN	ES
100	1	1	24	24	-0.39
100	2	1	24	24	0
100	3	1	24	24	0.09
100	4	1	24	24	-1.05
100	5	1	24	24	-0.44
7049	1	2	30	30	0.34
7049	2	4	30	30	0.78
7049	3	1	30	30	0

Practical Meta-Analysis -- Lipsey and Wilson

VIII. The Effect Statistic (ES) – makes meta-analysis possible

- **Comparable**, standardized numeric scale for evidence across disparate studies
- Amenable to calculation of ***standard error***
  - *Allows weighting* of study's contribution to evidence based on sample size
- Different ES's for different kind of outcomes
- Different statistical methods for same ES

Kinds of Effect Statistics

- Proportion
  - Central tendencies
- Standardized mean difference (d)
  - Group contrasts of continuous measures
- Correlation coefficient (r)
  - Linear associations
- Odds-ratio
  - Group contrasts of dichotomous measures

IX. *Transform* and *Weight* ES

- **Transform** the effect statistic
  - magnitude and direction of the effect
  - same scale for all studies
- **Weight** the effect statistic
  - inverse variance gives more 'weight' to larger studies
  - sample size is key (↑n = ↑precision)
  - standard error
    - means, correlations, proportions, odds
      - not well-suited to complex procedures like multivariable or multilevel models

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Why Weight Effect Sizes?

- Studies vary in size.
- ES based on 100 subjects more precise than similar estimate of 10 subjects
  - *Assuming* samples represent the same population of interest.
- So…larger studies should carry more "weight".
- Weighting by the *inverse variance* optimal statistical approach

Synthesizing without weighting can be misleading…

Day care and the risk of being left back a grade ("retained")

Gray 1970	Retained	Total	Risk	*Risk difference*
Daycare	19	36	0.528	*-0.16*
Control	13	19	0.684	

less likely to be left back

+

Schweinhart	Retained	Total	Risk	*Risk difference*
Daycare	6	58	0.1034	*-0.004*
Control	7	65	0.1077	

less likely to be left back

=

Pooled results	Retained	Total	Risk	*Risk difference*
Daycare	25	94	0.266	*+0.03 WRONG!*
Control	20	84	0.238	

more likely to be left back?

(Simpson's Paradox)

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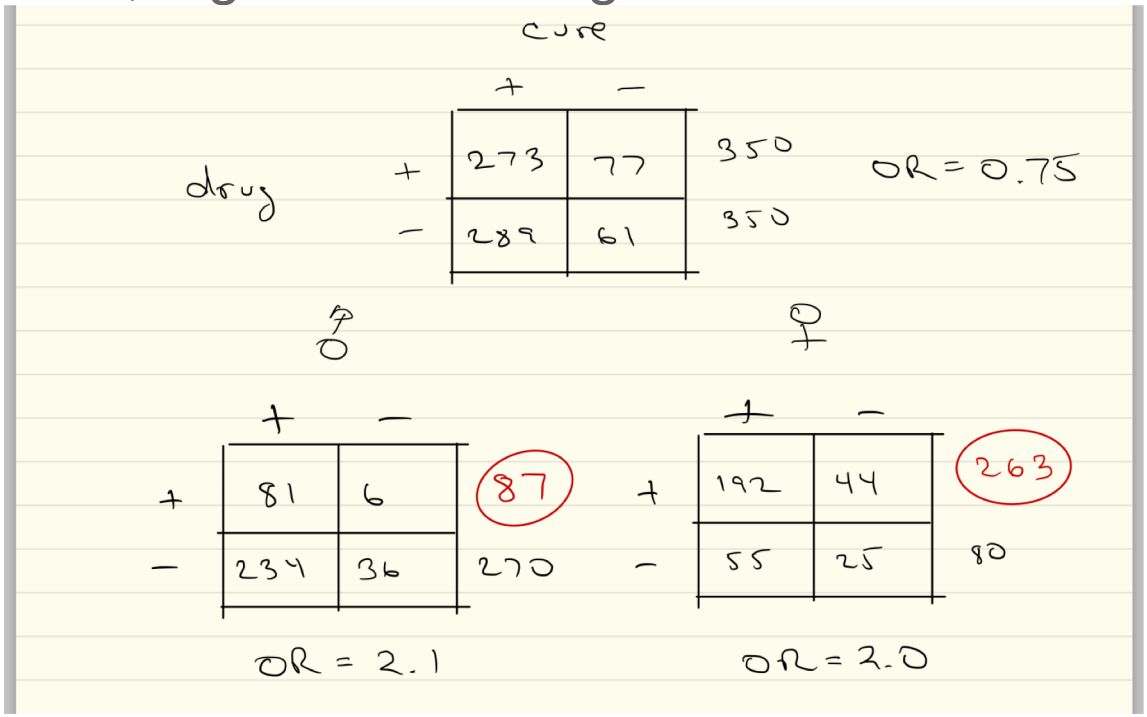
Cochrane Collaborative (http://www.cochrane-net.org/openlearning/HTML/mod12-2.htm)

Simpson's Paradox (Judea Pearl, Causal Inference)

- Statistical association in aggregate (drug cures disease) reversed in subpopulations (drug causes disease)
- Women much more likely to use the drug (263/342 vs 87/257)
- Women much less likely to recover, regardless of drug
- Confounding!
- **Need to stratify and weight!**
- E.g. Mantel Haenszel Odds Ratio



Why weight by inverse variance?

- The standard error (SE) is a direct index of ES precision.
  - influenced by sample size
  - used to create confidence intervals.
- The smaller the SE, the more precise the ES.
- Optimal weights for meta-analysis (Hedges):

$$w = \frac{1}{SE^2}$$

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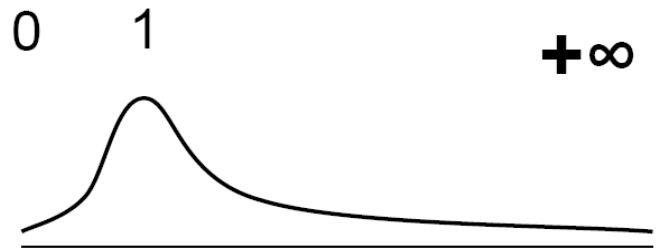
Methods for Dichotomous Effect Sizes

- **Variance-Based Method –log scale**
  - AKA "Inverse Variance Methods"
  - Can be applied to OR's, RR's, RD's
  - Can be applied when don't have complete 2x2 table info
  - Lipsey and Wilson, CMA
- **Mantel-Haenszel –original scale**
  - Long history of experience (vs Peto Method)
  - Statistically optimal
  - Fixed Effects
  - Cochrane, Petitti, R packages
- **DerSimonian and Laird**
  - Random Effects for M-H
  - Cochrane, R packages

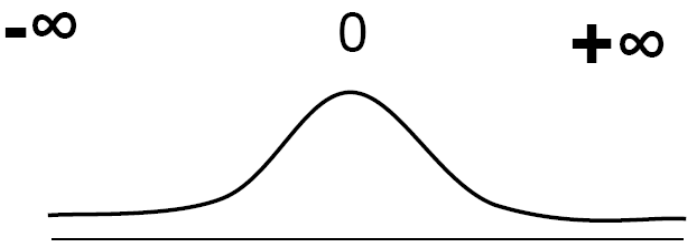
Variance Method for Dichotomous Outcomes

1. **Transform** each effect to the log scale
2. **Weight** each effect by inverse variance
3. Calculate a weighted **mean** effect size
4. Calculate the **standard error** of the weighted mean effect size
5. Calculate a **confidence interval** for the weighted mean effect size

Log transform places OR on continuous scale …



OR



Logit

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… and makes s.e. easier to abstract and weight easier to calculate

- s.e. for a Logit

$$se = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

- Weight for a Logit

$$w = \frac{1}{se^2}$$

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Spreadsheet calculation of a weighted mean odds ratio:

Study	ES	w	w*ES
1	-0.33	11.91	-3.93
2	0.32	28.57	9.14
3	0.39	58.82	22.94
4	0.31	29.41	9.12
5	0.17	13.89	2.36
6	0.64	8.55	5.47
7	-0.33	9.80	-3.24
8	0.15	10.75	1.61
9	-0.02	83.33	-1.67
10	0.00	14.93	0.00
		269.96	41.82

- Enter log of OR (ES) and its inverse variance weight (w)
- Multiply w by ES.
- Sum the columns, w and w*ES.
- Divide the sum of (w*ES) by the sum of (w)
- Convert back by exponentiation

$$\overline{ES} = \frac{\sum (w \times ES)}{\sum w} = \frac{41.82}{269.96} = 0.15$$

Practical Meta-Analysis -- Lipsey and Wilson

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Calculating the Standard Error of the (Mean) Odds Ratio

Study	ES	w	w*ES
1	-0.33	11.91	-3.93
2	0.32	28.57	9.14
3	0.39	58.82	22.94
4	0.31	29.41	9.12
5	0.17	13.89	2.36
6	0.64	8.55	5.47
7	-0.33	9.80	-3.24
8	0.15	10.75	1.61
9	-0.02	83.33	-1.67
10	0.00	14.93	0.00
		269.96	41.82

- **The standard error of the mean is the square root of 1 divided by the sum of the weights.**

$$se_{\overline{ES}} = \sqrt{\frac{1}{\sum w}} = \sqrt{\frac{1}{269.96}} = 0.061$$

Practical Meta-Analysis -- Lipsey and Wilson

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Mean, Standard Error, Z-test and Confidence Intervals for an Odds Ratio Using Variance Method:

Mean ES

$$\overline{ES} = \frac{\sum(w \times ES)}{\sum w} = \frac{41.82}{269.96} = 0.15$$

SE of the Mean ES

$$se_{\overline{ES}} = \sqrt{\frac{1}{\sum w}} = \sqrt{\frac{1}{269.96}} = 0.061$$

Z-test for the Mean ES

$$Z = \frac{\overline{ES}}{se_{\overline{ES}}} = \frac{0.15}{0.061} = 2.46$$

95% Confidence Interval

$$Lower = \overline{ES} - 1.96(se_{\overline{ES}}) = 0.15 - 1.96(.061) = 0.03$$

$$Upper = \overline{ES} + 1.96(se_{\overline{ES}}) = 0.15 + 1.96(.061) = 0.27$$

Practical Meta-Analysis -- Lipsey and Wilson

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The Mantel-Haenszel Method

- Good For Fixed Effects Models
- Better than variance method when rare events and small trials (otherwise similar results)

$$OR_i = (a_i * d_i) / (b_i * c_i)$$

$$OR.var_i = n_i / (b_i * c_i)$$

$$weight_i = 1 / var_i$$

$$OR_{mh} = \sum (w_i * OR_i) / \sum w_i$$

$$RR.var_i = n_i / ((a_i+b_i) * c_i)$$

$$RD.var_i = n_i / n_{1i} * n_{2i}$$

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Mantel-Haenszel 95 % CI

$$\exp(\ln(OR_{mh}) \pm 1.96 * \sqrt{Var[\ln(OR_{mh})]}$$

$$\hat{Var}\left[\ln\left(\hat{OR}_{MH}\right)\right] \cong \frac{\sum_{j=1}^{K} \frac{a_j d_j}{n_j} \cdot \frac{a_j + d_j}{n_j}}{2\left(\sum_{j=1}^{K} \frac{a_j d_j}{n_j}\right)^2} + \frac{\sum_{j=1}^{K} \left(\frac{b_j c_j}{n_j} \cdot \frac{a_j + d_j}{n_j} + \frac{b_j + c_j}{n_j} \cdot \frac{a_j d_j}{n_j} \right)}{2\left(\sum_{j=1}^{K} \frac{a_j d_j}{n_j}\right)\left(\sum_{j=1}^{K} \frac{b_j c_j}{n_j}\right)} + \frac{\sum_{j=1}^{K} \frac{b_j c_j}{n_j} \cdot \frac{b_j + c_j}{n_j}}{2\left(\sum_{j=1}^{K} \frac{b_j c_j}{n_j}\right)^2}$$

Source: Robins J, Breslow N, Greenland S. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol. 1986 Nov;124(5):719-23.

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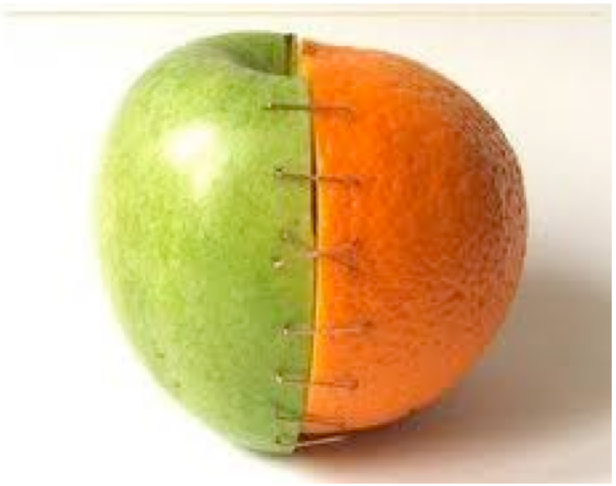
Heterogeneity



Heterogeneity vs. Bias and Confounding

- Studies differ due to selection, bias, confounding, etc… (Observational studies much more so than experimental studies.

- ***There are no statistical methods to account or control for bias and confounding arising from the original studies***

- Some epidemiologists believe *any* summary measure of effect is likely to be misleading. Goal of M-A should be to explore and explain differences, rather than smooth over them.

Fixed Effects vs. Random Effects

- Two *statistical* approaches to calculating the *variance* for the weighted mean effect statistic.

- Fixed Effects
  - Variance of synthesized effect statistic based only on studies included in the analysis

- Random Effects
  - Variance of synthesized effect statistic based on idea that studies included in the analysis are a random *sample* of all possible studies that could have been included
    - "conservative" vs. "abstruse and uninformative"

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Fixed Effects Model

- "What is the effect size based solely on the evidence of the studies included in the meta-analysis?"
- Total variance measured only on basis of within-study variance
- Studies weighted on basis of their inverse variance (sample size)
- Approach recommended by Sir Richard Peto and others.

Random Effects Model

- "What is the average effect size based on the studies included in the meta-analysis *as a sample* of all possible studies?"
- Total variance includes between-study as well as within-study variance
- As between-study variance becomes larger (heterogeneity) dominates, swamps within-study variance and all *studies weighted equally*
  - *collection of separate studies vs. sample from underlying population of studies…*

Fixed Effects vs. Random Effects

- When there is little or no heterogeneity, essentially return the same results
- Random effects models do not ‘control’ for heterogeneity, rather they are assuming a different underlying model.
- Some researchers believe that when there is evidence of heterogeneity, shouldn’t combine studies at all.
- Caution if random effects return meaningfully different results from fixed effects

X. Assessing Heterogeneity

- Test the assumption that all effect sizes are measuring a single, underlying mean.
- Look at effect size CI's. If don't overlap, likely heterogeneity.
- Chi square statistic ("Q test")
  - $Q = \sum w_i (ES_i - meanES)^2$, df = #ES-1
    - Calculating formula: $\sum w_i ES^2 - (\sum w_i ES / \sum w_i)$
  - small p → heterogeneity
    - few studies → low power (set p=0.10)
    - many studies→ statistical significance vs. meaningful heterogeneity ("too much power")

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Q - The Homogeneity Statistic

Study	ES	w	w*ES	w*ES^2
1	-0.33	11.91	-3.93	1.30
2	0.32	28.57	9.14	2.93
3	0.39	58.82	22.94	8.95
4	0.31	29.41	9.12	2.83
5	0.17	13.89	2.36	0.40
6	0.64	8.55	5.47	3.50
7	-0.33	9.80	-3.24	1.07
8	0.15	10.75	1.61	0.24
9	-0.02	83.33	-1.67	0.03
10	0.00	14.93	0.00	0.00
		269.96	41.82	21.24

- **Calculate a new variable that is the ES squared multiplied by the weight.**
- **Sum new variable.**

Calculating Q

$$\sum w = 269.96$$
$$\sum (w \times ES) = 41.82$$
$$\sum (w \times ES^2) = 21.24$$

$$Q = \sum (w \times ES^2) - \frac{\left[\sum (w \times ES)\right]^2}{\sum w} = 21.24 - \frac{41.82^2}{269.96} = 21.24 - 6.48 = 14.76$$

- Calculated Q (14.76) is less than chi square critical value of 16.92
- **fail to reject** the null hypothesis of homogeneity
- Thus, the variability across effect sizes does not exceed what would be expected based on sampling error.

Practical Meta-Analysis --
Analysis -- D.B. Wilson

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I^2

- percentage of variation due to heterogeneity
- (Q-df)/Q*100
  - e.g. (14.76-9)/14.76*100=39%
- How much is too much?
  - 0% to 40%: might not be important;
  - 30% to 60%: may represent moderate heterogeneity
  - 50% to 90%: may represent substantial heterogeneity
  - 75% to 100%: considerable heterogeneity
    - (methods available for 95% CI)

Higgins JPT, Green S.Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 The Cochrane Collaboration, 2008 (MRC Biostatistics Unit Cambridge, UK)

So your studies are heterogeneous…

- There are ‘real’ differences between studies, more than one underlying population mean. ☹
  - Single mean ES not a good measure of the distribution.
  - Model between study differences (ANOVA)
- Or … assume heterogeneity is random ☺
  - → Random Effects Model !

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Random Effect Model

- Additional variance component, based on Q, added to weight

$$w_i = \frac{1}{se_i^2 + \hat{v}_\theta}$$

$$\hat{v}_\theta = \frac{Q_T - k - 1}{\sum w - \left(\frac{\sum w^2}{\sum w} \right)}$$

- Run analysis with random effect weights

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Calculating the Random Effects Variance Component

- The total Q for example data was 14.76
- k is the number of effect sizes (10)
- The sum of w = 269.96
- The sum of w^2 = 12,928.21

$$\hat{v}_\theta = \frac{Q_T - k - 1}{\sum w - \left(\frac{\sum w^2}{\sum w}\right)} = \frac{14.76 - 10 - 1}{269.96 - \frac{12{,}928.21}{269.96}} = \frac{5.76}{269.96 - 47.89} = \underline{0.026}$$

Practical Meta-Analysis -- Lipsey and Wilson

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DerSimonian-Laird Random Effects Model (for M-H approach)

$$\ln \mathrm{OR}_{dl} = \frac{\mathrm{sum}(w_i^* \times \ln \mathrm{OR}_i)}{\mathrm{sum}\ w_i^*}$$

Dersimonian and Laird Summary OR

$$w_i^* = \frac{1}{[D + (1 \div w_i)]}$$

Additional Component "D" to weight

$$D = \frac{[Q - (S - 1)] \times \mathrm{sum}\ w_i}{[(\mathrm{sum}\ w_i)^2 - \mathrm{sum}\ (w_i^2)]} \text{ and D=0 if Q} < \text{S}-1,$$

(S= # studies)

$$Q = \mathrm{sum}\ w_i\ (\ln \mathrm{OR}_i - \ln \mathrm{OR}_{mh})^2$$

$$\mathrm{CI} = e^{\ln\ \mathrm{OR}_{dl} \pm 1.96 \times \sqrt{\mathrm{variance}_i^*}}$$

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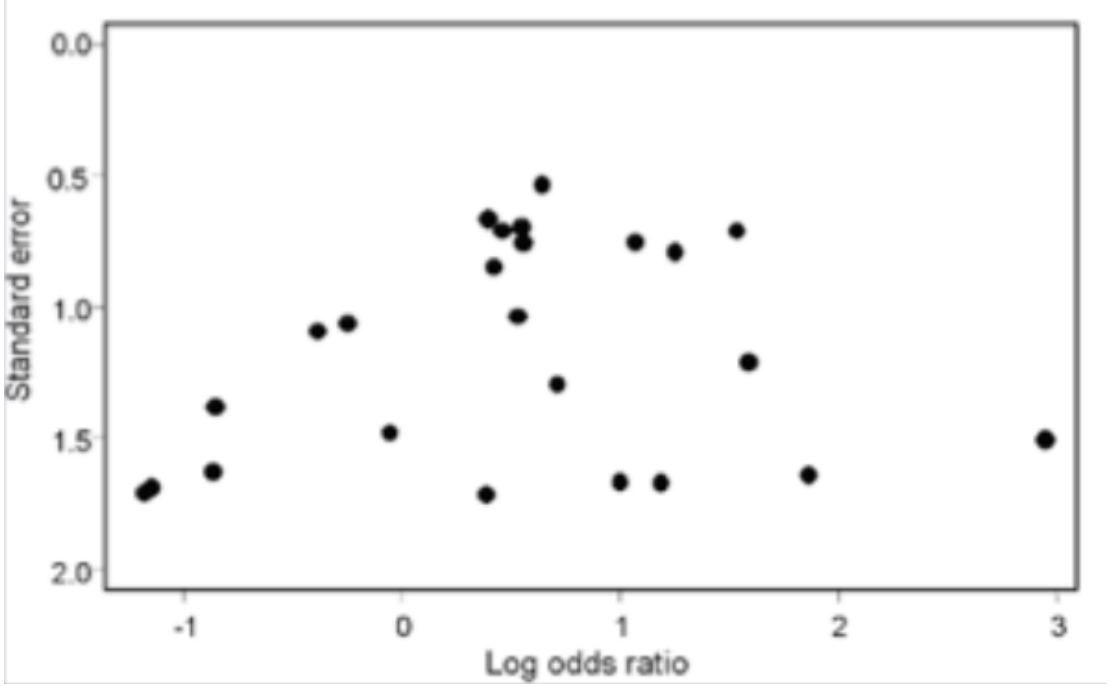
XI. Assessing Bias

- Some biases are peculiar to meta-analysis.
- Positive results are more likely to be…
  - Published (publication bias)
  - Published quickly (time lag bias)
  - Published in English (language bias)
  - Published more than once
  - Be cited by others (citation bias)
- Will be present to some extent in all meta analyses.
- Need to assess *how much* of a problem it is.

Funnel Plots

- Vertical Axis is (inverse) ES precision
- Horizontal Axis is (symmetrical) ES magnitude
- Expect more-precise estimates to cluster together near top of plot and less-precise estimates to fan out near bottom of plot



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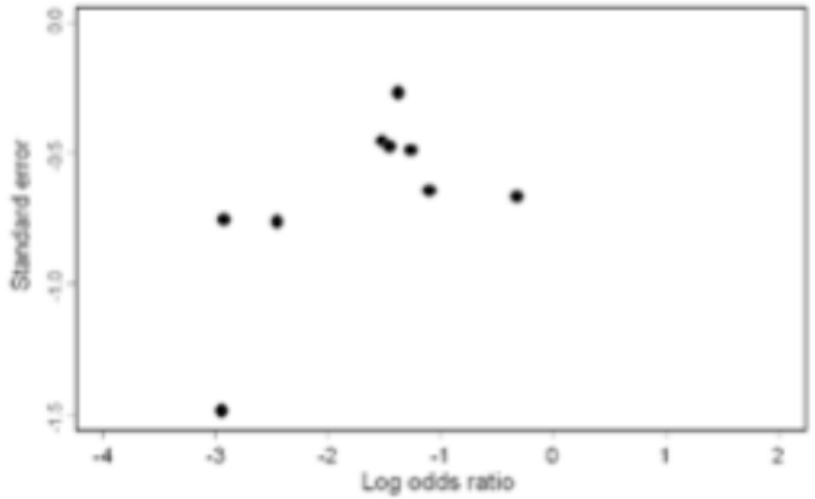
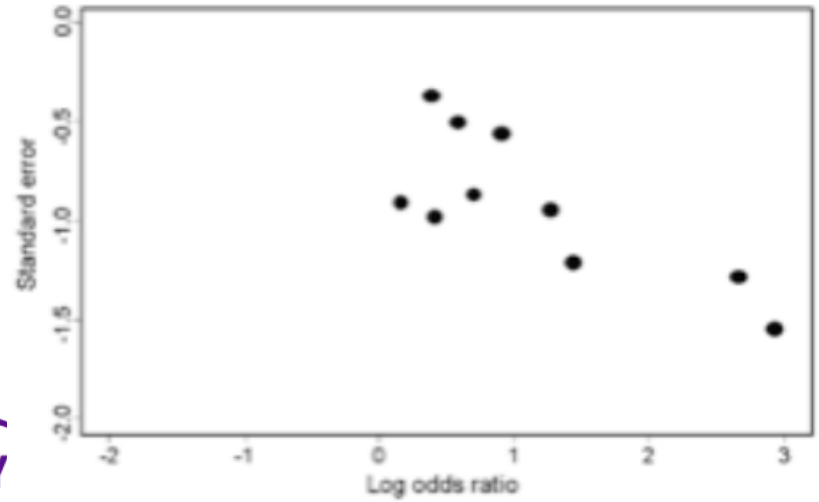
Possible Publication Bias



Outlier from less precise study?



Pattern of less precise studies showing more positive effect.

XII. Summarizing and Presenting Results

- **Searching** - describe information sources, restrictions
- **Selection** - inclusion and exclusion criteria
- **Data Abstraction**
- **Validity Assessment**
- **Study Characteristics** e.g. type of study designs, participants' characteristics
- **Data Synthesis** - effects, method of combining, missing data how heterogeneity assessed agreement on the selection and validity assessment, simple summary results, Funnel plots, Forest plots
- ***See Checklist Criteria (Quorum, PRISMA, MOOSE)***

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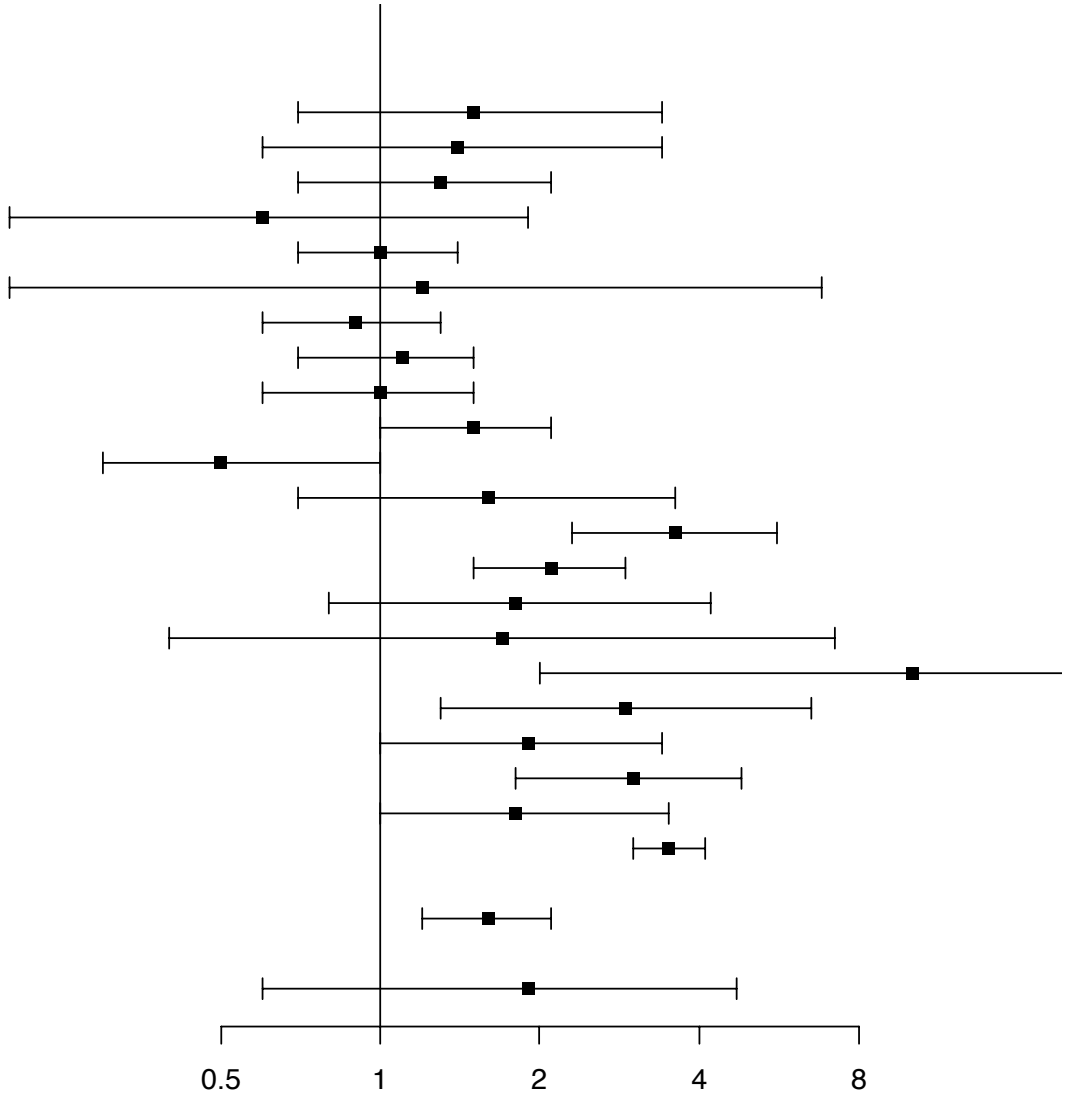
Post Your Code and Data

Forest Plot

STUDY	ESTIMATE
Agran, 1996	1.5 (0.7, 3.4)
Bunn, 2003(b)	1.4 (0.6, 3.4)
Bunn, 2003(c)	1.3 (0.7, 2.1)
Bunn, 2003(d)	0.6 (0.2, 1.9)
Bunn, 2003(e)	1.0 (0.7, 1.4)
Bunn, 2003(f)	1.2 (0.2, 6.8)
Bunn, 2003(g)	0.9 (0.6, 1.3)
Bunn, 2003(i)	1.1 (0.7, 1.5)
Bunn, 2003(j)	1.0 (0.6, 1.5)
Bunn, 2003(k)	1.5 (1.0, 2.1)
Damsere, 2010	0.5 (0.3, 1.0)
Donroe, 2008	1.6 (0.7, 3.6)
Johansson, 2007	3.6 (2.3, 5.6)
Jones,2005	2.1 (1.5, 2.9)
Leden2, 2006	1.8 (0.8, 4.2)
Mueller, 1990	1.7 (0.4, 7.2)
Mutto, 2002	10.1 (2.0, 50.5)
Roberts2, 1995	2.9 (1.3, 6.5)
Shephard, 2010	1.9 (1.0, 3.4)
Stevenson, 1996	3.0 (1.8, 4.8)
Testerm 2004	1.8 (1.0, 3.5)
Wazana, 2000	3.5 (3.0, 4.1)
Synthesis	1.6 (1.2, 2.1)
Predictive	1.9, (0.6, 4.7)



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```
#  FOREST PLOT FULL META

# Table Text

study<-c("   ","Agran, 1996","Bunn, 2003(b)","Bunn, 2003(c)","Bunn, 2003(d)","Bunn, 2003(e)","Bunn, 2003(f)","Bunn, 2003(g)","Bunn, 2003(i)","Bunn,
2003(j)","Bunn, 2003(k)","Damsere, 2010","Donroe, 2008","Johansson, 2007","Jones,2005","Leden2, 2006","Mueller, 1990","Mutto, 2002","Roberts2,
1995","Shephard, 2010","Stevenson, 1996","Testerm 2004","Wazana, 2000","    ","Synthesis","    ","Predictive")

estimate<-c(
"   ",
"1.5  (0.7, 3.4)",
"1.4  (0.6, 3.4)",
"1.3  (0.7, 2.1)",
<snip>
"1.9  (1.0, 3.4)",
"3.0  (1.8, 4.8)",
"1.8  (1.0, 3.5)",
"3.5  (3.0, 4.1)",
"   ",
"1.6  (1.2, 2.1)",
"   ",
"1.9, (0.6, 4.7)")
<snip>

ln.OR<-log(OR)
ln.lci<-log(lci.OR)
ln.uci<-log(uci.OR)


plot(1:27,seq(1,28,len=27), type="n",axes=F,
xlab="                                    Odds Ratio & 95% Cr I ",
ylab=" ",xlim=c(-4.2,2.7))
axis(1, at=c(-.69,0,.69,1.386,2.079),labels=c(0.5, 1, 2, 4, 8), cex=0.3)
abline(v=0)

# column labels
text (-4.2,28,"STUDY", adj=c(0,0), cex=0.6)
text (-2.8,28,"ESTIMATE", adj=c(0,0), cex=0.6)

#loop text
for(i in 1:28) {
text (-4.2,i,study[28-i], adj=c(0,0), cex=0.6)
text (-2.8,i,estimate[28-i], adj=c(0,0), cex=0.6)
}


#loop point estimate ORs for graph
for(i in 1:28)  {
points(ln.OR[i],28-i,pch=15,cex=1)
# loop 95% CI lines
lines(c(ln.lci[i],ln.uci[i]),c(28-i,28-i),lty=1)
# Ends of 95% CI
lines(c(ln.lci [i], ln.lci [i]),c((28-i+.3),(28-i-.3)),lty=1)
lines(c(ln.uci [i], ln.uci [i]),c((28-i+.3),(28-i-.3)),lty=1)
}
```

R Code for Forest Plot

vs.

meta package:

forest(x)

Software

- **Comprehensive Meta-Analysis ($$)**
  - does all calculations for you; user-friendly interface; convenient
  - Little control over approaches, calculations, figures
  - Still need some kind of DBMS
- **MS Access → MS Excel ($)**
  - "easy" interface, wide availability for collaboration
  - Either write all formulas or use ("free") add-on apps, e.g.
    MIX (http://www.mix-for-meta-analysis.info/)
    Lipsey (http://mason.gmu.edu/~dwilsonb/ma.html)
    MetaEasy(http://www.jstatsoft.org/v30/i07)
- **R – rmeta, meta, metaphor (t)**
  - Explicit programming and reproducibility
- **SAS, SPSS, Stata ($$$)**

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But wait … there's more….

- Bayesian meta-analysis
- cumulative meta-analysis
- individual patient data meta-analysis
- network meta-analysis
- prospective meta-analysis
- (Hilda Bastian https://blogs.scientificamerican.com/absolutely-maybe/5-key-things-to-know-about-meta-analysis/)

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Bayesian Meta-Analysis

- Different philosophy
- Statistically combine expectation or uncertainty (prior distribution) with evidence or data (likelihood) to update knowledge

$$\mathbf{p}(\theta|\mathbf{y}) \propto \mathbf{p}(\mathbf{y}|\theta)\mathbf{p}(\theta)$$

- See http://www.injuryepi.org/styled-4/styled-11/code-4/

cumulative meta-analysis

- plot results of first study, then pool it with second, then pool it with third etc, and watch data shift over time
- perform a new meta-analysis each time a new study is published
- https://jamanetwork.com/journals/jama/ae-abstract/398415

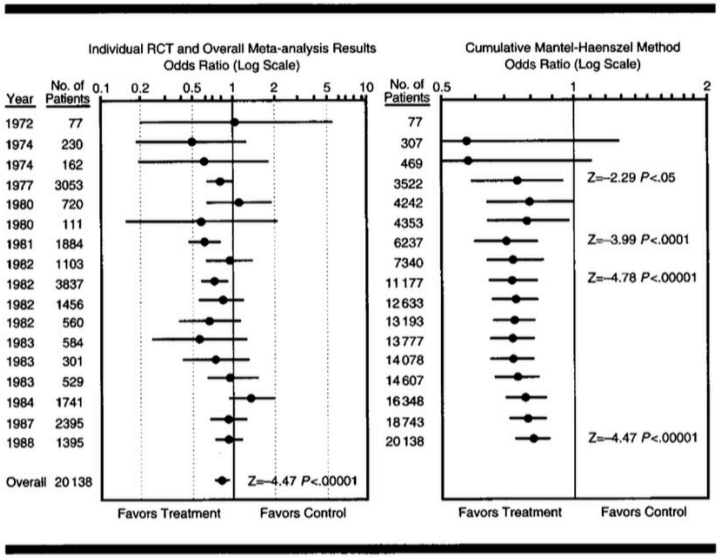

Fig 1.—Results of 17 randomized control trials (RCTs) of the effects of oral β-blockers for secondary prevention of mortality in patients surviving a myocardial infarction presented as two types of meta-analyses. On the left is the traditional one, revealing many trials with nonsignificant results but a highly significant estimate of the pooled results on the bottom of the panel. On the right, the same data are presented as cumulative meta-analyses, illustrating that the updated pooled estimate became statistically significant in 1977 and has remained so up to the present. Note that the scale is changed on the right graph to improve clarity of the confidence intervals.

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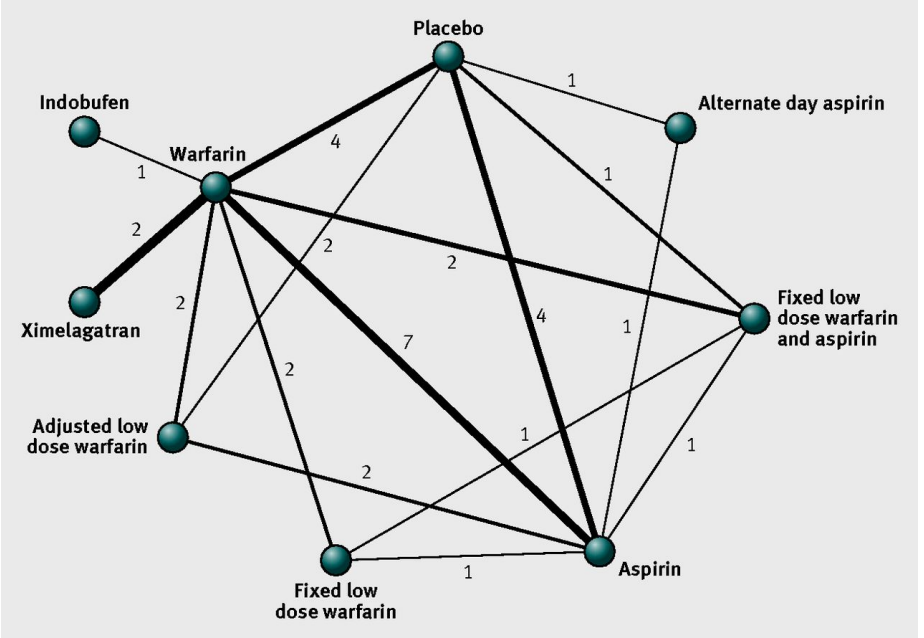
individual patient data meta-analysis

- pool the original patient-level data
  - more precision, more subgroups (gold standard?)
  - results can differ from aggregate (more / different data?)
- statistical approaches
  - 2-stage: calculate aggregates by study, do meta-analysis
  - 1-stage: pool data, multi-level model
- difficult, expensive

network meta-analysis (multiple / mixed treatment ma)

- comparisons not done by the original researchers
  - e.g. over 20 RCTs investigating A fib-related stroke prevention with warfarin, ASA, drugs like pradaxa and lovenox
  - Can look at the trials as a network rather than pair-wise comparisons

Network geometry of well connected network of randomized controlled trials (RCTs) evaluating stroke prevention among populations with atrial fibrillation.



Edward J Mills et al. BMJ 2013;346:bmj.f2914

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prospective meta-analysis

- Cross between multicenter study and MA
- original researchers prospectively agree on how they will pool and meta-analyze their studies
- e.g. NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration
- https://www.ncbi.nlm.nih.gov/pubmed/21235822

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Sources and Resources

- **Lipsey and Wilson. Practical Meta-Analysis. (Sage, 2001)** ***Highly Recommended…***
- **Petitti. Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis. (Oxford, 2000)**
- **Cochrane Collaboration Open Learning Material (http://www.cochrane-net.org/openlearning/HTML/ mod0.htm)**

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Thank you

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