

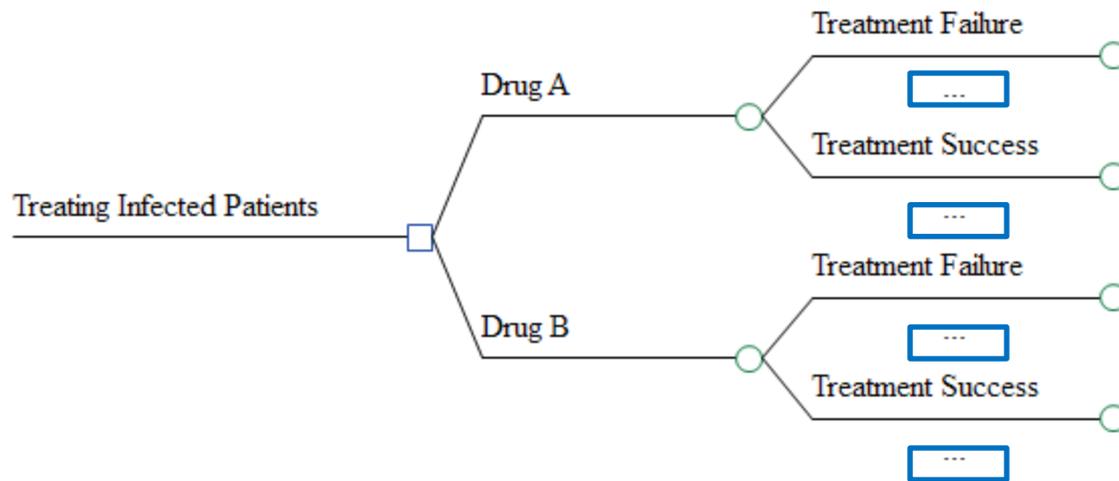
Evidence Synthesis for Decision Modeling: Meta-Analysis

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June 11, 2014

Probabilities in a Decision Model

- You have a model, now you need inputs for your transition probabilities



Cost-Effectiveness Inputs

Variables	Estimate	Range	Distribution	Data source*	Reference
Surgical clipping					
Procedure-related death	1.8%	1.2-2.5%	Beta	Meta-analysis	4, 18
Permanent moderate to severe disability	2.8%	2.2-3.5%	Beta	Meta-analysis	4, 18
Permanent mild disability	2.8%	2.2-3.5%	Beta	Meta-analysis	4, 18
Regrowth rate after clipping/year	0.4%	0.3-0.5%	Uniform	Cohort study	20, 21, 23
Endovascular coiling					
Procedure-related death	0.6%	0.2-1.0%	Beta	Meta-analysis	4, 19
Permanent moderate to severe disability	2.2%	1.3-3.4%	Beta	Meta-analysis	4, 19
Permanent mild disability	4.8%	3.4-6.5%	Beta	Meta-analysis	4, 19
Reopening					
First year after coiling	14%	11-17%	Uniform	Cohort study	24, 25
Second year after coiling	5%	3-7%	Uniform	Cohort study	24, 25
Third year after coiling	2%	1-3%	Uniform	Cohort study	24, 25
De novo aneurysms					
De novo aneurysm formation/year	0.5%	0.3-0.8%	Beta	Cohort study	21, 22, 26
Risk of rupture de novo/year	0.9%	0.7-1.0%	Beta	Meta-analysis	17
SAH					
Death before reaching the hospital	12%	11-14%	Beta	Meta-analysis	1
Case fatality (at 1 yr)	35%	25-45%	Beta	Meta-analysis	2, 3
Moderate to severe disability	9%	7-11%	Beta	Meta-analysis	2, 3
Mild disability	15%	13-17%	Beta	Meta-analysis	2, 3

Ways to derive model inputs

- Transforming existing data inputs
 - Creating data inputs: synthesizing available data
 - Meta-Analysis
 - Mixed Treatment Comparisons
 - Meta Regression
-

Meta-Analysis

- Multiple studies have evaluated the question of interest
 - Create a single pooled estimate from these multiple studies
 - Premise: the pooled estimate based on multiple studies will be higher quality than the estimate provided by a single study
-

Multiple Studies Published

Which to select?

The screenshot shows a PubMed search results page. The search query is ("Ascorbic Acid"[Mesh]) AND "Common Cold"[Mesh]. The page displays 66 results, with the first three shown. Each result includes a checkbox, a title, authors, journal, date, volume, issue, pages, PMID, and a link to related citations.

PubMed ("Ascorbic Acid"[Mesh]) AND "Common Cold"[Mesh]

RSS Save search Advanced

Display Settings: Summary, 20 per page, Sorted by Recently Added Send to:

Results: 1 to 20 of 66 << First < Prev Page 1 of 4 Next > Last >>

Filters activated: Clinical Trial. [Clear all](#) to show 247 items.

[Effect of vitamin C on common cold: randomized controlled trial.](#)

1. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S.
Eur J Clin Nutr. 2006 Jan;60(1):9-17.
PMID: 16118650 [PubMed - indexed for MEDLINE]
[Related citations](#)

[Evaluation of the efficacy of a combined formulation \(Grippostad-C\) in the therapy of symptoms of common cold: a randomized, double-blind, multicenter trial.](#)

2. Koytchev R, Vlahov V, Bacratheva N, Giesel B, Gawronska-Szklarz B, Wojcicki J, Mrozikiewicz A, van der Meer M, Alken RG.
Int J Clin Pharmacol Ther. 2003 Mar;41(3):114-25.
PMID: 12665160 [PubMed - indexed for MEDLINE]
[Related citations](#)

[Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey.](#)

3. Van Straten M, Josling P.
Adv Ther. 2002 May-Jun;19(3):151-9.
PMID: 12201356 [PubMed - indexed for MEDLINE]
[Related citations](#)

Answer: All that are relevant to your research question! Then (you may be able to) synthesize into a single pooled estimate

From: Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis

JAMA. 2012;308(10):1024-1033. doi:10.1001/2012.jama.11374

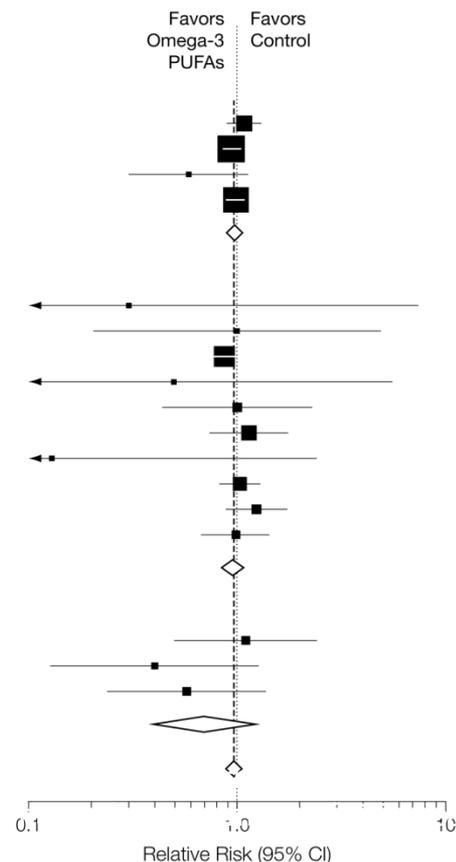
Raw Data

Summary Stats

Forest Plot

Study Weights

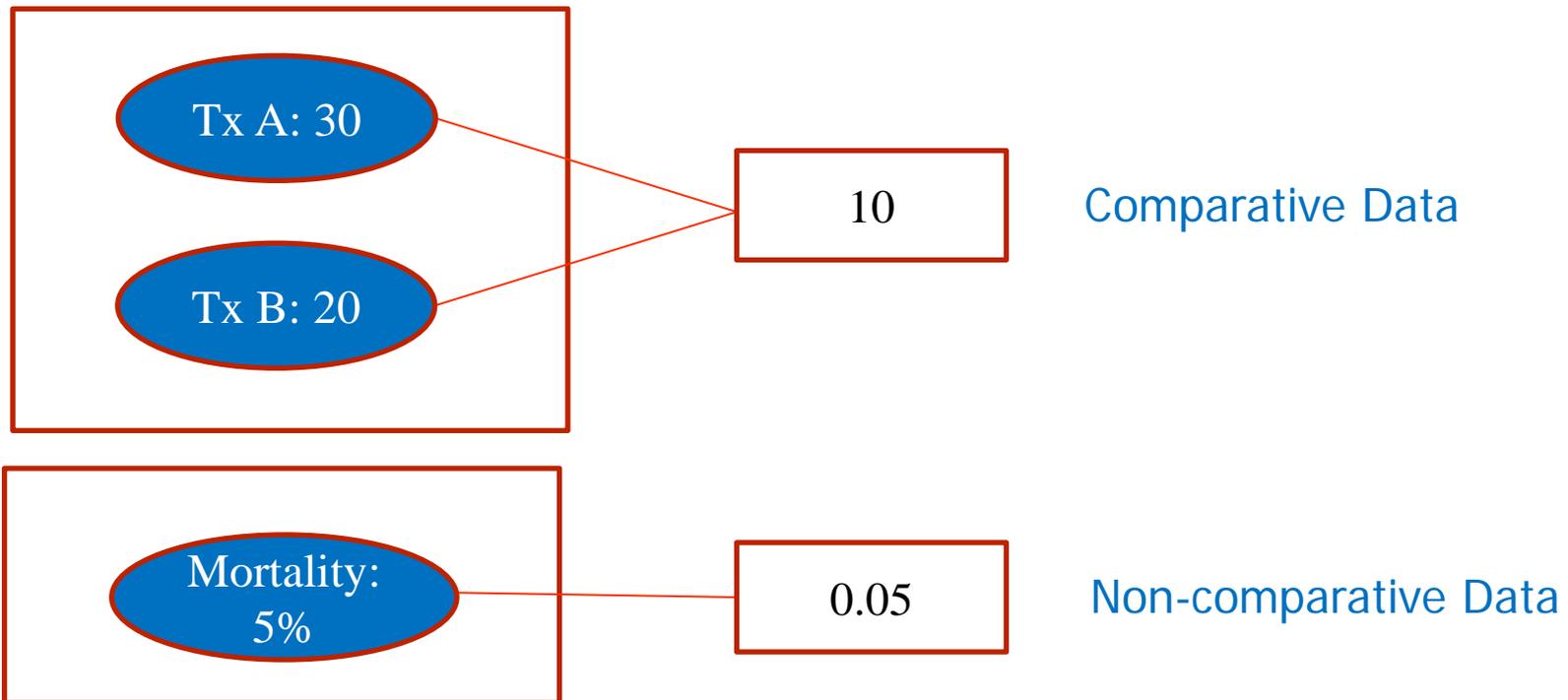
	No. of Events		No. of Participants		RR (95% CI)	Weight, %
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control		
Mixed prevention						
Yokoyama et al, ³ 2007	286	265	9326	9319	1.08 (0.91-1.27)	10.00
Tavazzi et al, ² 2008	955	1014	3494	3481	0.94 (0.87-1.01)	28.99
Einvik et al, ³⁷ 2010	14	24	282	281	0.58 (0.31-1.10)	0.80
ORIGIN, ⁵ 2012	951	964	6281	6255	0.98 (0.90-1.07)	26.23
Subtotal: $I^2 = 38.9\%$, $P = .18$	2206	2267	19383	19336	0.97 (0.90-1.05)	66.02
Secondary prevention						
Sacks et al, ²⁷ 1995	0	1	31	28	0.30 (0.01-7.13)	0.03
Leng et al, ²⁶ 1998	3	3	60	60	1.00 (0.21-4.76)	0.13
Marchioli et al, ¹ 1999	472	545	5666	5658	0.86 (0.77-0.97)	16.80
von Schacky et al, ²⁵ 1999	1	2	112	111	0.50 (0.05-5.39)	0.06
Nilsen et al, ²⁴ 2001	11	11	150	150	1.00 (0.45-2.24)	0.50
Svensson et al, ³² 2006	34	30	103	103	1.13 (0.75-1.70)	1.91
Garbagnati et al, ³⁸ 2009	0	3	20	18	0.13 (0.01-2.34)	0.04
Kromhout et al, ⁴ 2010	186	184	2404	2433	1.02 (0.84-1.24)	7.45
Rauch et al, ³⁶ 2010	88	70	1919	1885	1.23 (0.91-1.68)	3.28
Galan et al, ²⁹ 2010	58	59	1253	1248	0.98 (0.69-1.39)	2.51
Subtotal: $I^2 = 1.5\%$, $P = .43$	853	908	11718	11694	0.95 (0.86-1.04)	32.71
ICD						
Leaf et al, ³⁴ 2005	13	12	200	202	1.09 (0.51-2.34)	0.56
Raatt et al, ³³ 2005	4	10	100	100	0.40 (0.13-1.23)	0.26
Brouwer et al, ³⁵ 2006	8	14	273	273	0.57 (0.24-1.34)	0.45
Subtotal: $I^2 = 19.9\%$, $P = .29$	25	36	573	575	0.69 (0.39-1.23)	1.27
Overall: $I^2 = 11.7\%$, $P = .32$	3084	3211	31274	31605	0.92 (0.91-1.02)	100.00



Meta-Analysis:

Step 1: Study-specific estimate

- Step 1: a summary statistic is calculated for each study



Meta-Analysis:

Step 2: Weight the study-specific estimate

- Step 2: Summary statistic for study is (almost always) weighted
 - Can weight each study in a different ways
 - Inverse-variance method is often used
 - Smaller variance (larger) studies get more weight
 - Quality weights: Cochrane recommends against their use
-

Meta-Analysis:

Step 3: Create a single pooled estimate

- Step 3: Individual weighted estimates are then averaged to create a pooled point estimate
 - Meta-analysis is the computation of a **weighted mean** estimate
 - of means
 - of probabilities
 - of ORs
 - of RRs
 - etc.
-

Meta-Analysis:

Step 4: Calculate variance around the pooled estimate

Step 4: Calculation of variation around pooled point estimate

Meta-analysis is the computation of a (**weighted**) **mean** estimate along with an estimate of variation around this mean

What meta-analysis does NOT do

- Does NOT combine 2 by 2 tables from each study to construct an overall 2 by 2 table, and then calculate summary statistics

	Exposed	Unexposed
Disease	15	20
No Disease	4	1

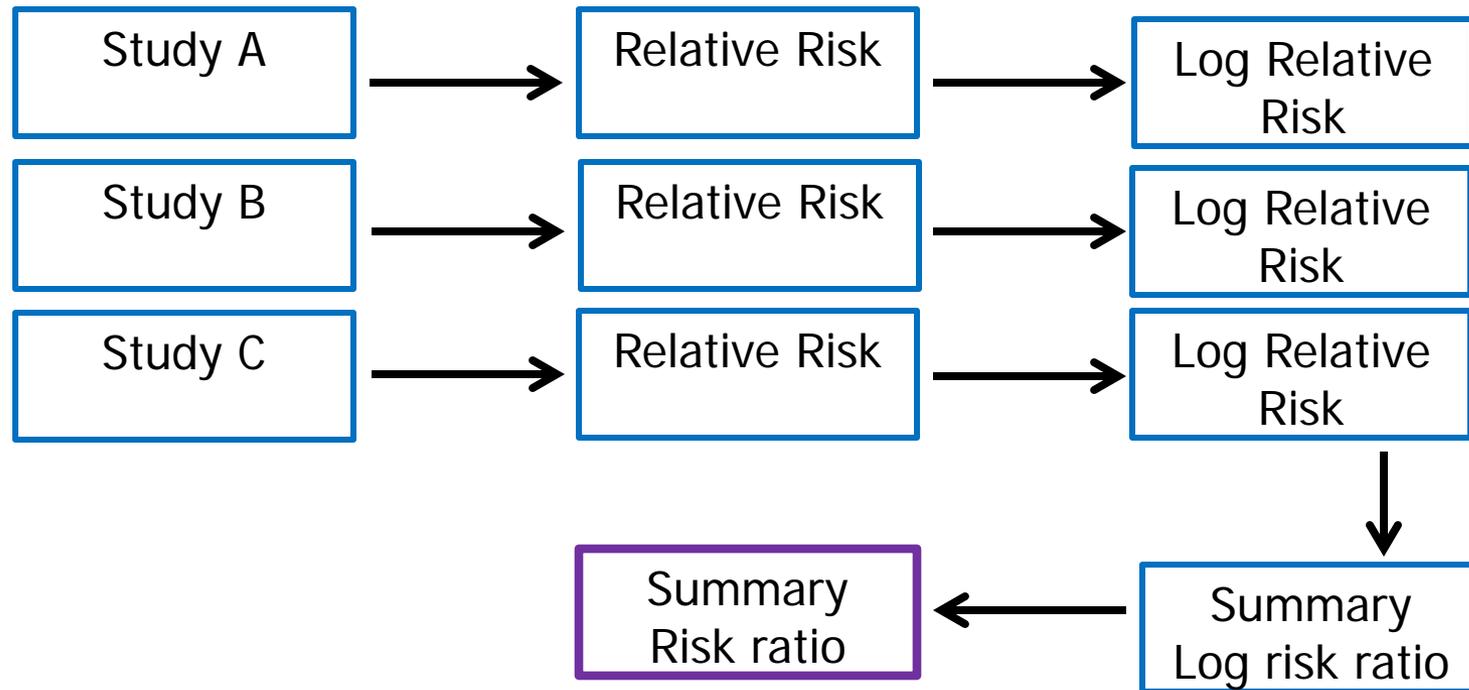
	Exposed	Unexposed
Disease	30	6
No Disease	12	4

	Exposed	Unexposed
Disease	45	26
No Disease	16	5

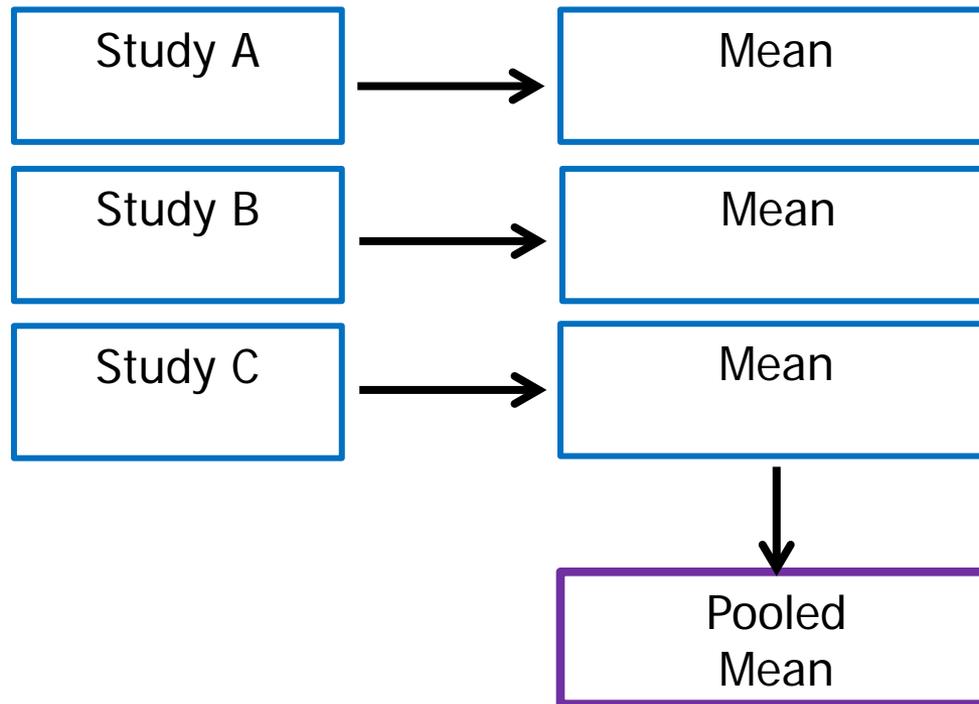


$$RR = 1.05$$

Creating a pooled estimate (RR)

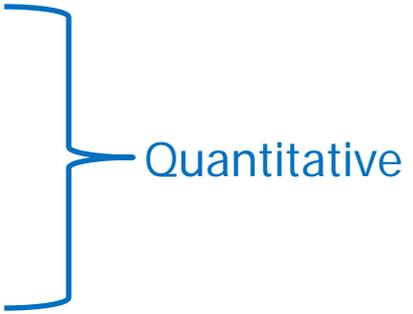


Creating a pooled estimate, Mean



Steps in a Meta-Analysis

1. Systematic Literature Search
2. Title + Abstract Review
3. Data Extraction of Selected Studies
4. Separate OS and RCTs
5. Convert all outcomes to the same scale
6. Evaluate heterogeneity of Selected Studies
7. Conduct Meta-Analysis



Quantitative

1. Systematic Literature Search

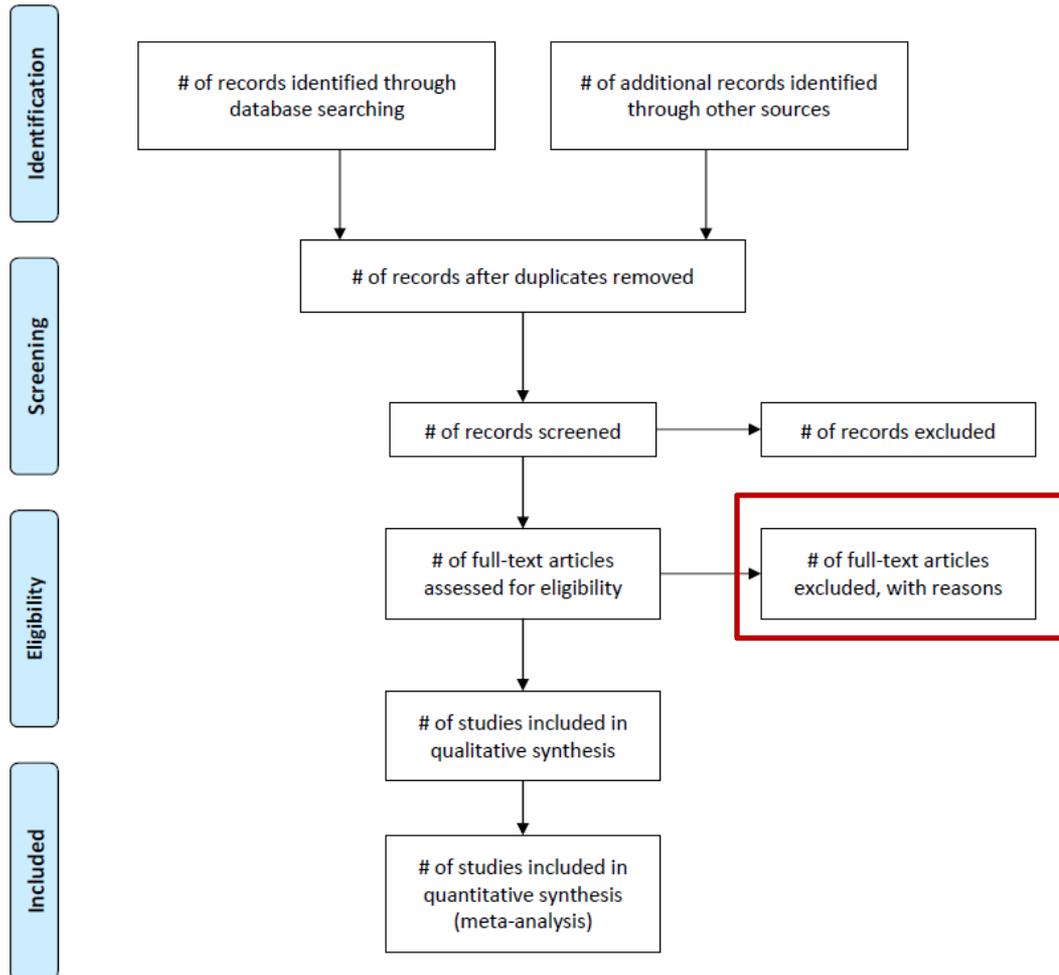
- Determine inclusion and exclusion criteria *a priori*
 - Database search
 - Save your MeSH/other search strings
 - Search reference sections of articles you keep
 - Search www.clinicaltrials.gov for RCTs

 - Gray literature
 - Not peer-reviewed
-

2. Title + Abstract Review

1. Read through all titles, discard those that are irrelevant
 2. Read through all abstracts, discard those that are irrelevant
 3. Full-text review of remaining studies,
 - Discarding those that are irrelevant
 - Keep track of WHY you discarded studies for which you did a full-text review
 - Example: “High risk” on Cochrane Risk of Bias tool
 4. Create a PRISMA diagram
-

PRISMA diagram



3. Data Extraction of Selected Studies

- PRISMA template: <http://www.prisma-statement.org/2.1.2%20-%20PRISMA%202009%20Checklist.pdf>
 - Your own template
 - Author, Year
 - Journal
 - Study Design (RCT, OS, Case-control, etc)
 - Treatment Arm 1
 - If medication, add a column for dosage
 - Treatment Arm x
 - If medication, add a column for dosage
 - Sample size, Arm 1
 - Sample size, Arm x
 - Important Demographic characteristics (% female, mean age, mean BMI, etc)
 - Follow-up time (3 months, 12 months, etc)
 - Measurement of outcome (OR, RR, probability, means, median, etc)
 - Measurement of variation (SD, SE, variance, IQR, range, etc)
 - ITT, Per Protocol results, or both
 - Value of outcome, Treatment Arm 1
 - Value of outcome, Treatment Arm x
 - Value of variation, Treatment Arm 1
 - Value of variation, Treatment Arm x
-

Good research practices, Data Extraction

- All categorical variables should be recorded in the same way
 - RCT ≠ Randomized Controlled Trial
 - Test your template with a small number of studies, revise the template as needed.
 - Data extraction can be tricky – rushing will cause many headaches down the road
-

4. Separating out OS and RCTs



Questions

- Why separate out RCTs and Observational Studies?
- Why conduct a meta-analysis on an Observational Study?

4. Separating out OS and RCTs

- Observational Studies have systematic differences between groups, RCTs do not
 - Relative effect is extracted from each study
 - RCTs: may not be generalizable to the population that is in your cost-effectiveness analysis
-

5. Converting outcomes to the same scale

- All outcomes should be in the same scale (binary for a decision model)
 - May require the involvement of a PhD statistician – point estimate and variation
- OR and RR
 - work in the log scale
- Continuous data
 - work in standardized means if data are not all reported on the same scale
- Risk Difference
 - work in absolute scale

6. Evaluate Heterogeneity of Selected Studies

- This step is critical! If data are too sparse, of low quality, or studies are too heterogeneous – you cannot continue to a meta-analysis and must end at a systematic literature review!
 - Informal
 - Review completed data extraction template
 - Formal
 - Statistical tests
 - Graphical assessments
-

Informal Assessment of Heterogeneity

- Evaluate:
 - Differences in study population
 - Differences in length of follow-up
 - Differences in way outcomes are measured
 - Differences in intervention
-

Formal Assessment of Heterogeneity

- There will almost always be some difference in the effect sizes from different studies
 - Homogeneity: Difference in effect size due to random variation (sampling error)
 - Heterogeneity: Difference in effect sizes exceeds that which can be expected from sampling error alone
 - Can exist when effect sizes are in different directions, or when magnitude of effect sizes differs
-

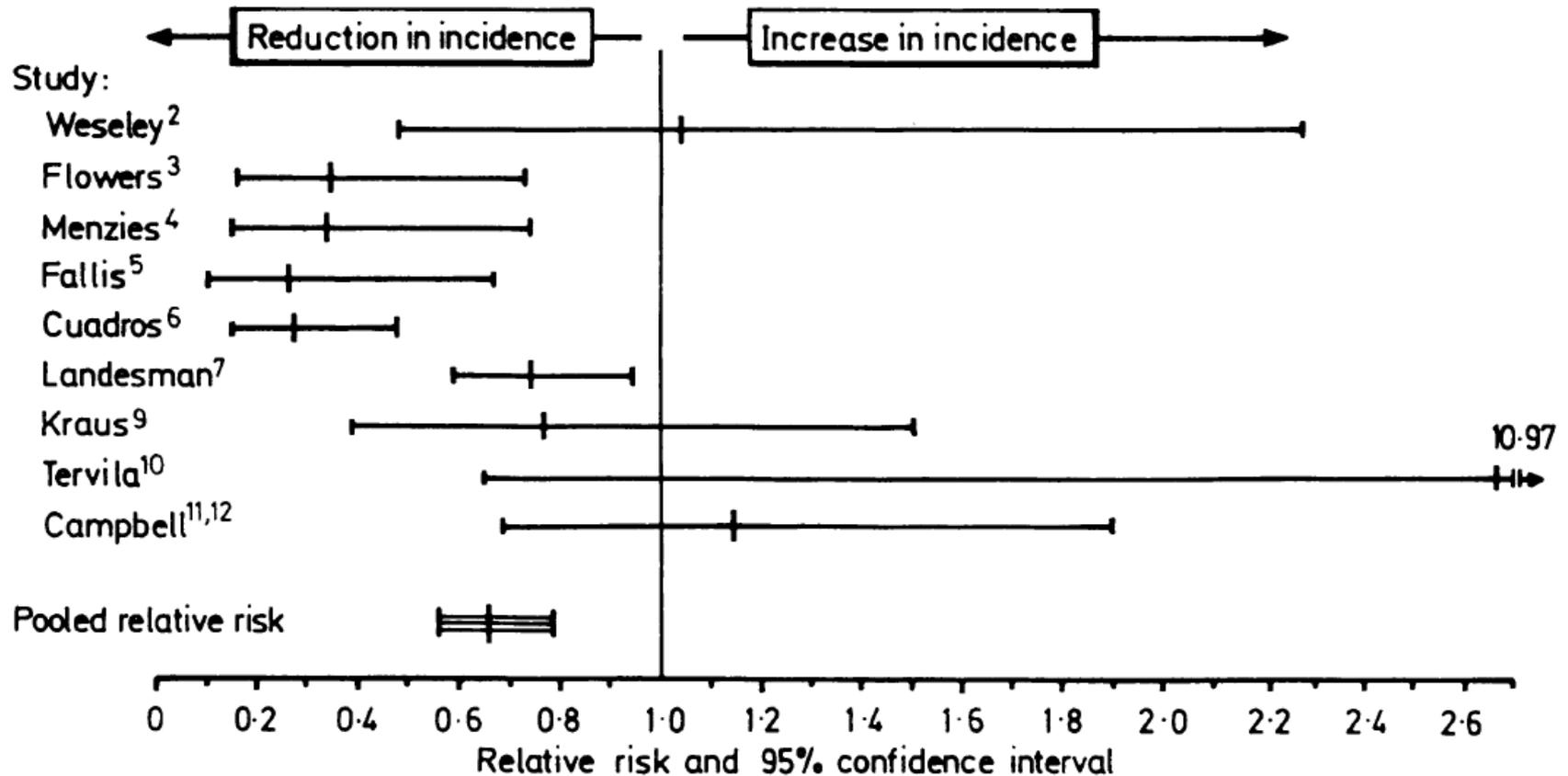
Formal Assessment of Heterogeneity: Statistical Tests:

- Cochran's Q: tests null hypothesis that true treatment effects are the same in all the studies
 - H1: at least one effect differs from the rest
 - Problem: power to detect heterogeneity is low when you have ≤ 10 studies)
 - You can have heterogeneity but fail to reject null hypothesis
 - Recommend using $p < 0.10$ as significance level
 - Conversely, if you have studies with large sample sizes, you can reject the null hypothesis even when effect sizes do not differ much
 - **So, don't put a lot of stock in the Q statistic**
-

Formal Assessment of Heterogeneity: Statistical Tests

- I-squared:
 - Tells you percentage of total variation across studies that is due to heterogeneity (rather than chance)
 - Reflects the extent of overlap in CIs
 - Uses the Q statistic
 - Rough guide to interpreting the I^2 statistic
 - 0-25%: low heterogeneity
 - 25-50%: moderate heterogeneity
 - 50-75%: high heterogeneity
 - Also look at the confidence intervals around the I^2 statistic
-

Formal Assessment of Heterogeneity: Forest Plots



Formal Assessment of Heterogeneity: Forest Plots

- Consistent effect sizes
 - focus on pooled estimate
- Variations in effect sizes
 - can report pooled estimate, but note the true effect could be higher or lower
- Substantial variations in effect sizes
 - focus on variation rather than pooled effect

Summary: heterogeneity

- Do an informal assessment: examine your data extraction table
- Formal assessment: forest plots, I^2

If you have heterogeneity

- Excluding studies is frowned upon!
 - You have to have an excellent reason to do so
 - Test excluding these studies in sensitivity analyses
 - Analyze groups of studies (grouping should be determined a priori)
 - Using random effects models (more on this later)
 - Conduct a meta-regression
 - No clear guidelines exist for how much heterogeneity “sinks the ship”
-

Recap

1. Conducted a systematic literature search
 2. Completed title and abstract review
 3. Extracted data from selected studies
 4. Separated RCTs from OS
 5. Converted all outcomes to the same scale
 6. Evaluated heterogeneity of studies
 - No heterogeneity, or Heterogeneity will be handled (subgroup, random-effects analysis, meta-regression)
-

7. Conducting Meta-Analysis

- a. Determine fixed versus random effects
- b. Decide how to pool your studies



Fixed vs. Random-Effects

	Fixed Effects	Random Effects
Assumes	Variance among studies is due to sampling error There is some fixed underlying true effect.	Variance among studies is due to both sampling error and because true effect could vary from study to study (e.g., because of different participants, different ways intervention was administered, etc.)
Variance	Within-study	Within-study and between-study (τ^2)
CIs	Narrower	Wider
Inference	The true effect is X	The mean of the effects is X
Small Studies	Are less precise, given less weight	Given more weight than in a FE analysis

Random Effects Distribution

- Random effects are often more suitable -- there are almost always differences between studies
 - *But, random effects are not always more conservative!*
 - If small studies are systematically different than large studies then increasing weight of smaller studies by doing a RE analysis will overestimate treatment effect.
-

Pooling studies

Pooling Option	Use when you have
Mantel-Haenszel	OR no 0 cells, RR, risk difference
Peto method	OR, 0 cells
Inverse-variance (FE)	Continuous Data, low heterogeneity
DerSimonian and Laird (Inverse Variance with RE)	Continuous Data, low heterogeneity, multiple studies
Knapp-Hartung (RE)	Continuous Data, heterogeneity, 6 or more studies
Profile Likelihood (RE)	Continuous Data, heterogeneity, suspect asymmetry in distribution of tau-squared
Bayesian approach (RE)	Continuous Data, heterogeneity, sparse data and/or few studies

Greenland S, Salvan A. (1990). Bias in the one-step method for pooling study results. *Stat. Med.* **9**: 247-52.

Fleiss JL. (1993). The statistical bias of meta-analysis. *Stat Methods Med Res* **2**:121-45.

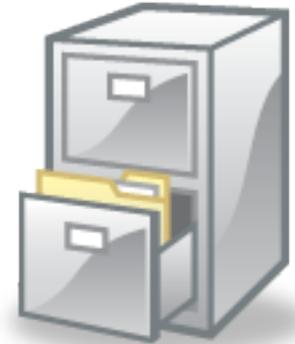
Fleiss JL. (1981). *Statistical Methods for Rates and Proportions*. 2nd ed. New York: Wiley.

Cornell JE, Mulrow CD, Localio R, et al. Random-Effects Meta-analysis of Inconsistent Effects: A Time for Change. *Ann Intern Med.* 2014;160:267-270.

Problems with DerSimonian and Laird and inverse-variance

- Shuster, Statistics in Medicine 2010
 - Raised problems with inverse-variance and DerSimonian and Laird
 - The inverse-variance/DerSimonian and Laird approaches assume that the point estimate and the variance are INDEPENDENT
 - Binomial distribution, variance is not independent of the point estimate [variance = $(p*q)/n$]
- Cornell et al., Annals of Internal Medicine 2014
 - Assumes that we have estimated between-study variance exactly → narrow CIs, low p-value
- Is the default weighting method in RevMan (used by Cochrane Collaboration)

Publication Bias



- Studies with significant results are more likely to be published
 - Meta-analysis will overestimate effect

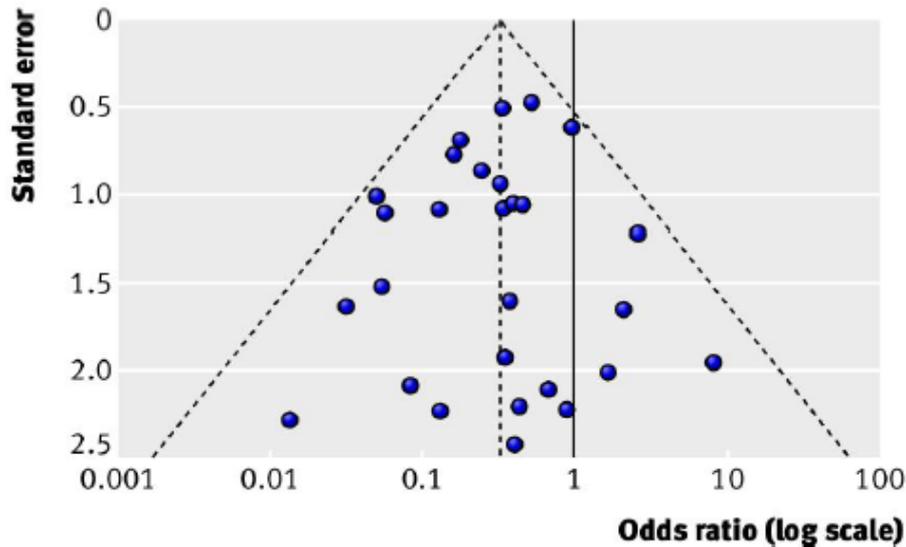
 - Larger studies more likely to be published
 - If results of smaller studies are systematically different from larger studies:
 - Random effects will be more problematic
 - gives greater weight to smaller studies than fixed effects do
-

Assessing Publication Bias

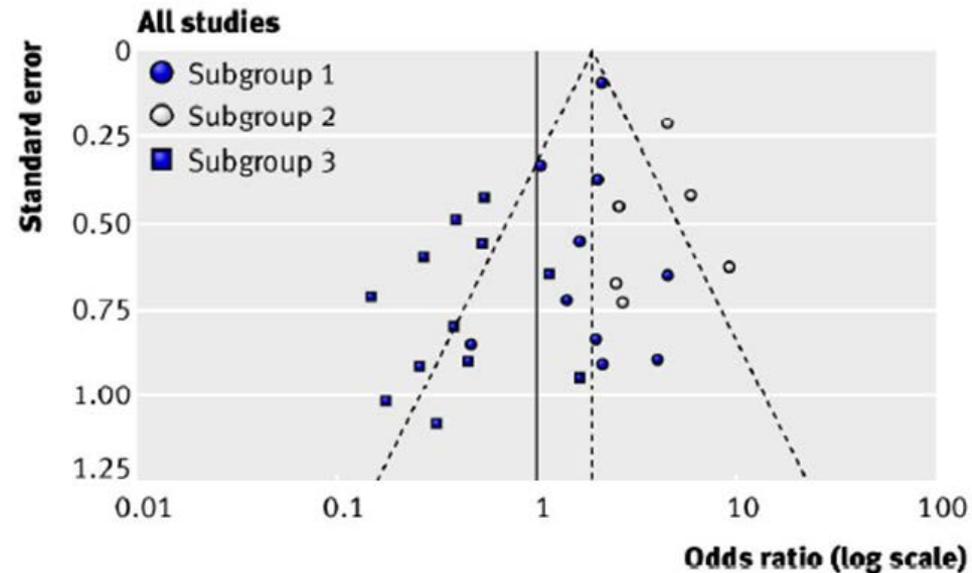
- Funnel plots
 - Asymmetry is problematic
 - Unless quality of studies varies with size
 - Publication bias can still exist even if there is symmetry

Funnel Plots for Publication Bias

Symmetric Funnel Plot



Asymmetric Funnel Plot



Funnel Plot Asymmetry

- Large sample sizes – easier to find significant effects
- Asymmetric funnel plot: heterogeneity, or quality varies with size
- Don't just look at the funnel plot – evaluate it in context of the other info you have about the studies, such as quality of study or heterogeneity of intervention
- Note: For a funnel plot to be useful, have to have studies with various sizes.

What do to with Publication Bias

- Cumulative meta-analysis, ordered by precision
- Glesser and Olkin: estimate the number of missing studies
- Weighted distribution theory-based selection methods
- Trim-and-Fill method
- Copas and Li method

Sutton AJ, Abrams KR. Publication Bias. In: *Methods for Meta-Analysis in Medical Research*. West Sussex, England: John Wiley & Sons, Ltd; 2000: 109-132.

Meta-Analysis and CEA

REVIEW

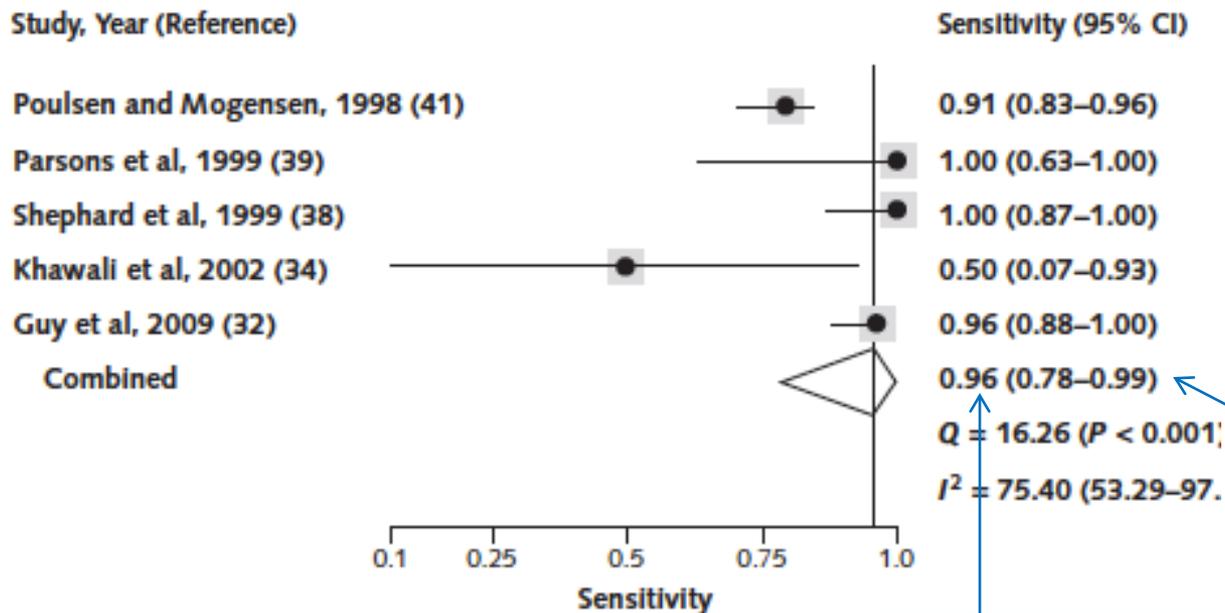
Annals of Internal Medicine

Diagnostic Accuracy of Point-of-Care Tests for Detecting Albuminuria

A Systematic Review and Meta-analysis

Malcolm P. McTaggart, PhD; Ronald G. Newall, PhD; Jennifer A. Hirst, MSc; Clare R. Bankhead, DPhil; Edmund J. Lamb, PhD; Nia W. Roberts, MSc(Econ); and Christopher P. Price, PhD

Figure 4. Forest plots for the quantitative test.



CI for CEA sensitivity analyses

Point estimate – input in CEA

Software Programs

- STATA
- SAS
- R
- RevMan (Cochrane)
- CMA
- OpenBugs/WinBugs

Be careful with plug-and-chug software!

ADVANCED TOPICS

Advanced Topics

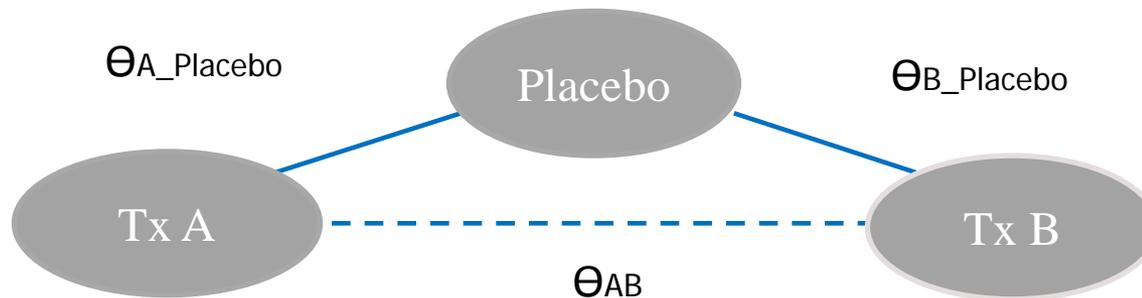
- Meta-Regression
- Mixed Treatment Comparisons
- Individual-Patient Data (IPD) Meta-Analysis

Meta-regression

- Regression: adjust for differences at a patient-level
 - Meta-Regression: adjust for differences at a study-level
 - Not recommended when # of studies is small
 - Regression: at least 10 events per covariate
 - Meta-regression: no established rule
-

Mixed Treatment Comparisons

- Statistical method for estimating the relative treatment effect of interest using a network of evidence



$$(\Theta_{AB}) = (\Theta_{A_Placebo}) - (\Theta_{B_Placebo})$$

$$\text{Var} (\Theta_{AB}) = \text{Var} (\Theta_{A_Placebo}) + \text{Var} (\Theta_{B_Placebo})$$

Individual-Patient Data Meta-Analysis

- “Regular” meta-analysis uses the summary statistic from each study
 - 8 studies = 8 data inputs
- IPD meta-analysis uses the individual patient data from each study
 - 8 studies with 50 patients each = 400 data inputs

SUMMARY

Summary

- Meta-analysis: single pooled estimate + variance from (usually) weighting and combining individual effects from multiple studies
 - Requires a systematic literature review
 - Considerations:
 - Assessment of study heterogeneity
 - Fixed versus random effects
 - How to pool individual studies
 - Publication bias
-

Further Reading

- Borenstein M, Hedges LV. *Introduction to Meta-Analysis*. West Sussex, United Kingdom: John Wiley & Sons Ltd; 2009.
 - Sutton AJ, Abrams KR. *Methods for Meta-Analysis in Medical Research*. West Sussex, England: John Wiley & Sons, Ltd; 2000.
 - Higgins JPT, Green S (editors) *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration, 2011. Available from <http://handbook.cochrane.org/>
-

REFERENCE EQUATIONS

Inverse Variance (fixed effects)

- Pooled treatment effect:

$$\bar{T}_{\cdot} = \frac{\sum w_i T_i}{\sum w_i}$$

- Weight:

$$w_i = \frac{1}{v_i}$$

- Variance

$$\text{var}(\bar{T}_{\cdot}) = \frac{1}{\sum w_i}$$

Inverse Variance with random effects

(DerSimonian and Laird, Knapp-Hartung,
Profile likelihood, Bayesian)

- Pooled treatment effect is calculated in the same way as the fixed effect analysis
- However, the weight now includes the within-study variance and between-studies variance.
- The four approaches differ in their calculation of tau-squared (the between studies variance)

$$\bar{T}_{\cdot RND} = \frac{\sum w_i^* T_i}{\sum w_i^*}$$

$$w_i^* = \frac{1}{[(1/w_i) + (\tau^2)]}$$

$$var(\bar{T}_{\cdot RND}) = \frac{1}{\sum w_i^*}$$

Mantel-Haenszel (OR, RR, RD no 0 cells)

$$\bar{T}_{MH(OR)} = \frac{\sum \frac{a_i d_i}{n_i}}{\sum \frac{b_i c_i}{n_i}}$$

$$\bar{T}_{MH(OR)} = \frac{\left[\left(\frac{67 \times 86}{309} \right) + \dots + \left(\frac{117 \times 3}{188} \right) \right]}{\left[\left(\frac{87 \times 69}{309} \right) + \dots + \left(\frac{12 \times 56}{188} \right) \right]} = 0.95$$

Peto Method (OR)

- Also for odds ratios
- Is a modification of the Mantel-Haenszel method, but can be used when you have cells with 0 values

$$\bar{T}_{PETO(OR)} = e^{\left[\frac{\sum(O_i - E_i)}{\sum v_i} \right]}$$

Questions?