Evidence Synthesis for Decision Modeling:
Part 1: Preparing for Meta-Analysis

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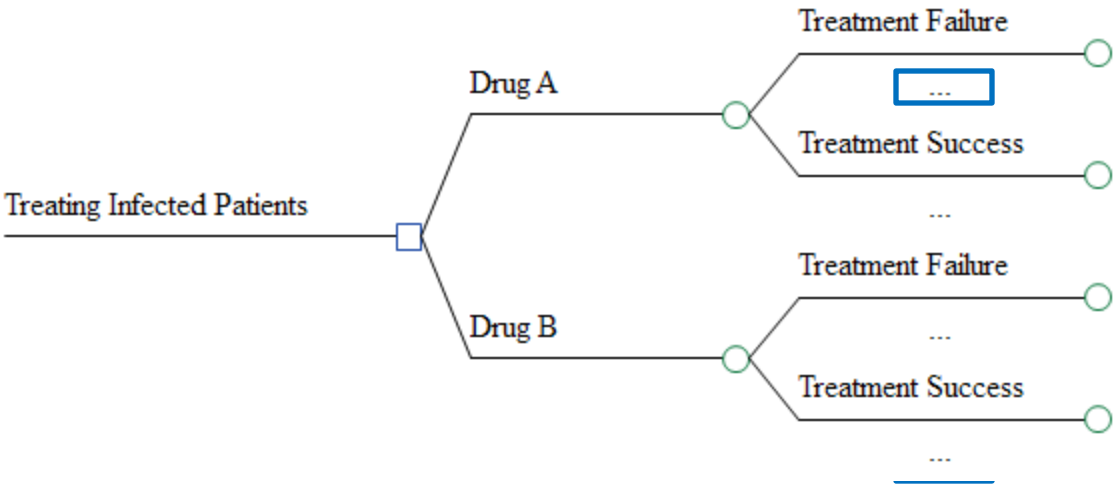
Probabilities in a Decision Model

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



Cost-Effectiveness Inputs

Table 1 Transition probabilities, utilities, and costs used in the Markov model

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

Greving et all., Cost-effectiveness of preventive treatment of intracranial aneurysms: New data and uncertainties. Neurology 2009; 73: 258.

Ways to derive model inputs

- Transforming existing data inputs

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

Poll

- What is your experience with meta-analyses?

1) Have conducted many
2) Have conducted one
3) Looking to conduct one
4) Looking for general information

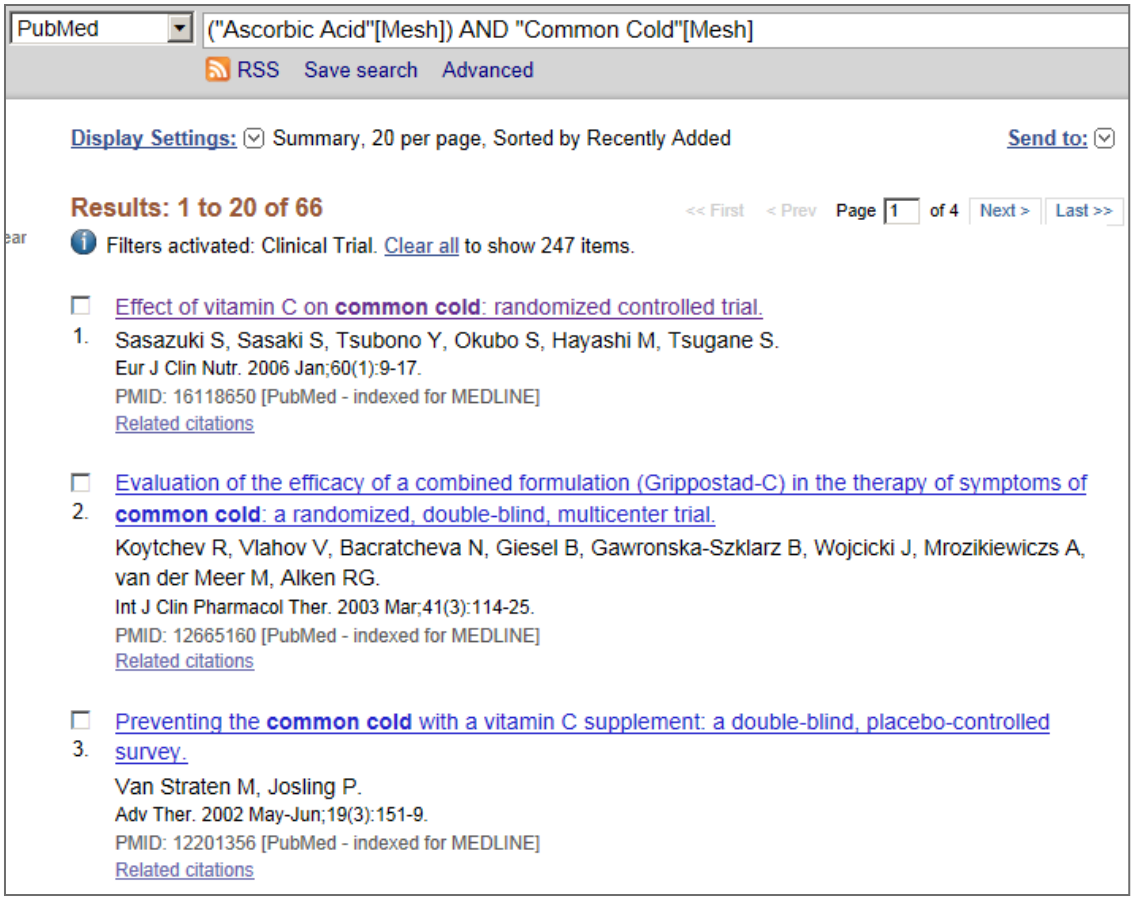
Meta-Analysis

- 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?



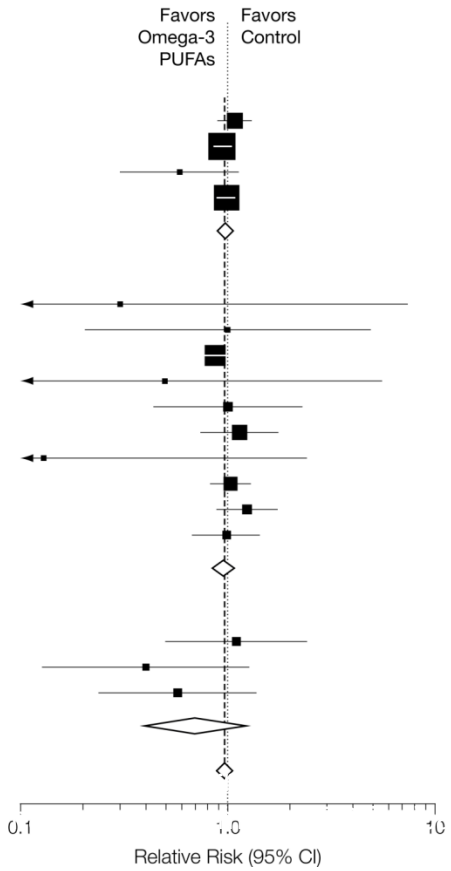
Answer: All that are relevant to your research question! Then (you may be able to) synthesize into a single pooled estimate

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			
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control	RR (95% CI)	Weight, %
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
Raitt 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**	**31674**	**31605**	**0.96 (0.91-1.02)**	100.00



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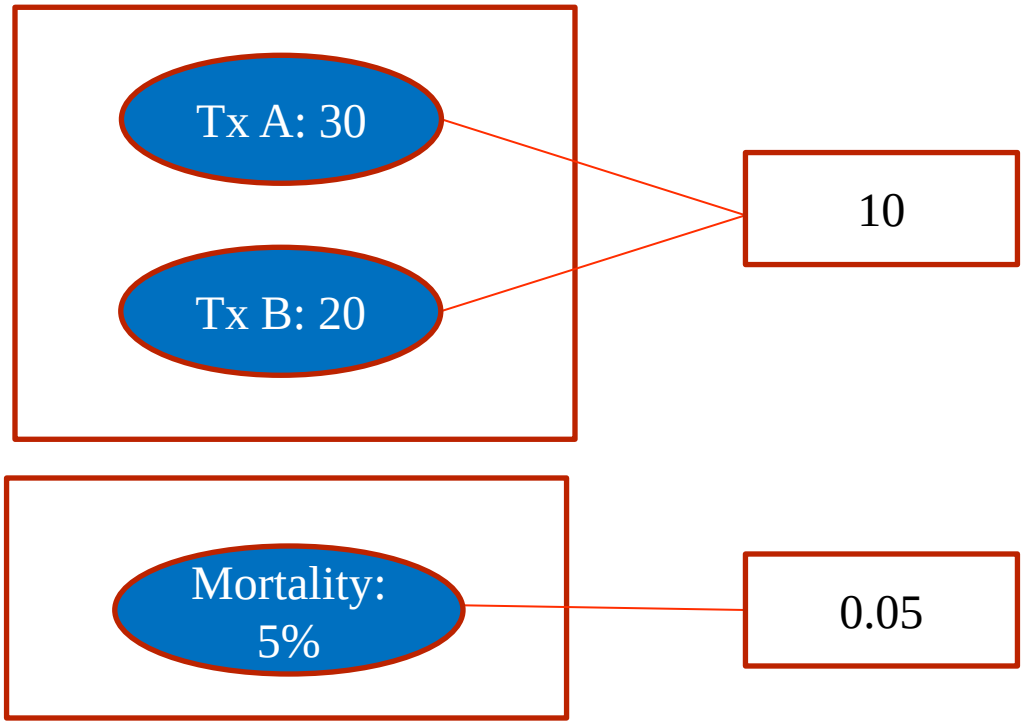
Meta-Analysis: Step 1: Study-specific estimate

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



Comparative Data

If you want to use the input in a decision model, you need to produce non-comparative data from your meta analysis

Non-comparative Data

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

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

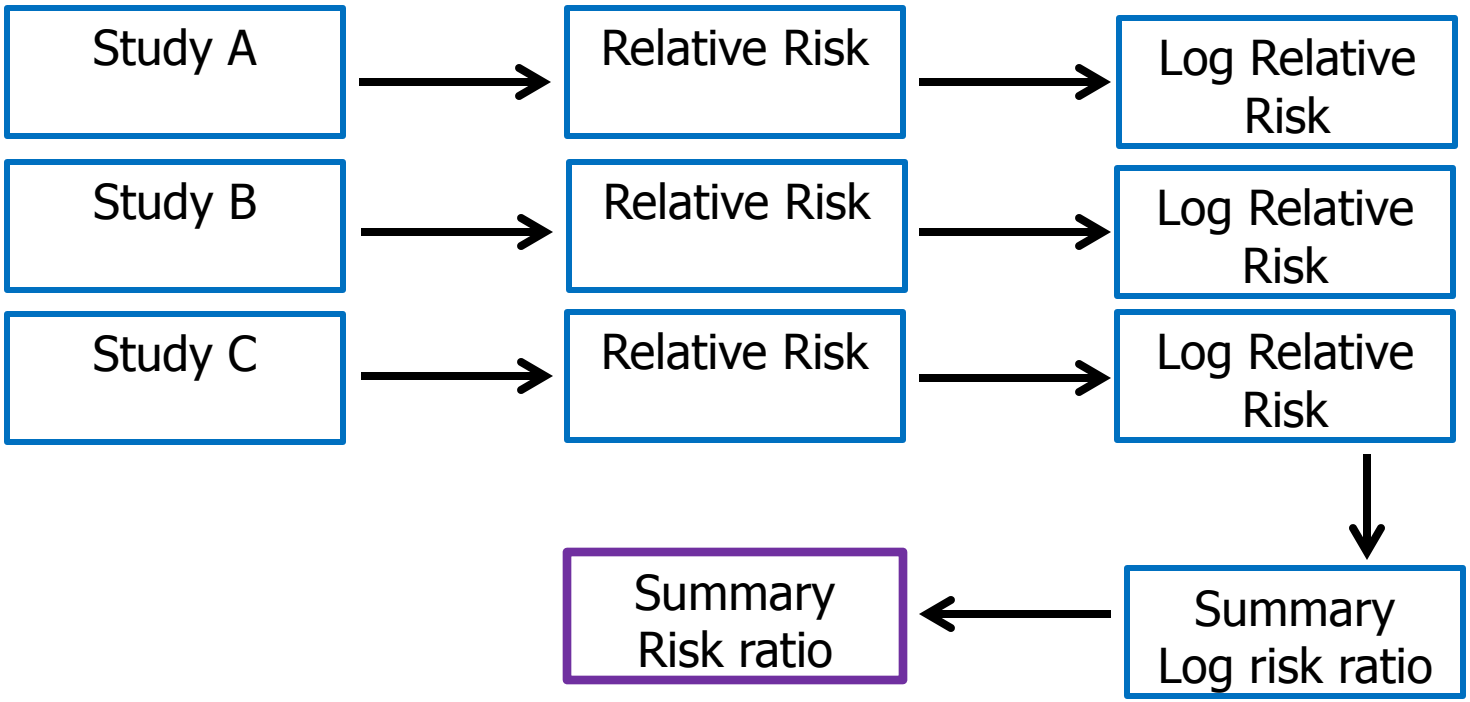
	Exposed	Unexposed
Disease	15	20
No Disease	4	1

	Exposed	Unexposed
Disease	30	6
No Disease	12	4

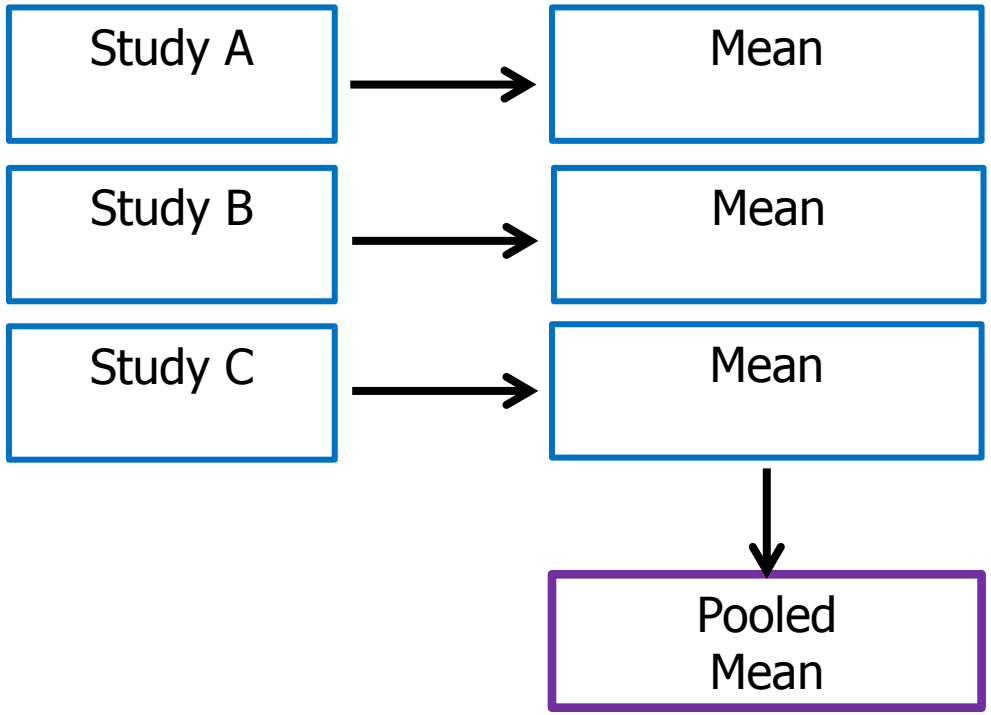
	Exposed	Unexposed
Disease	45	26
No Disease	16	5

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

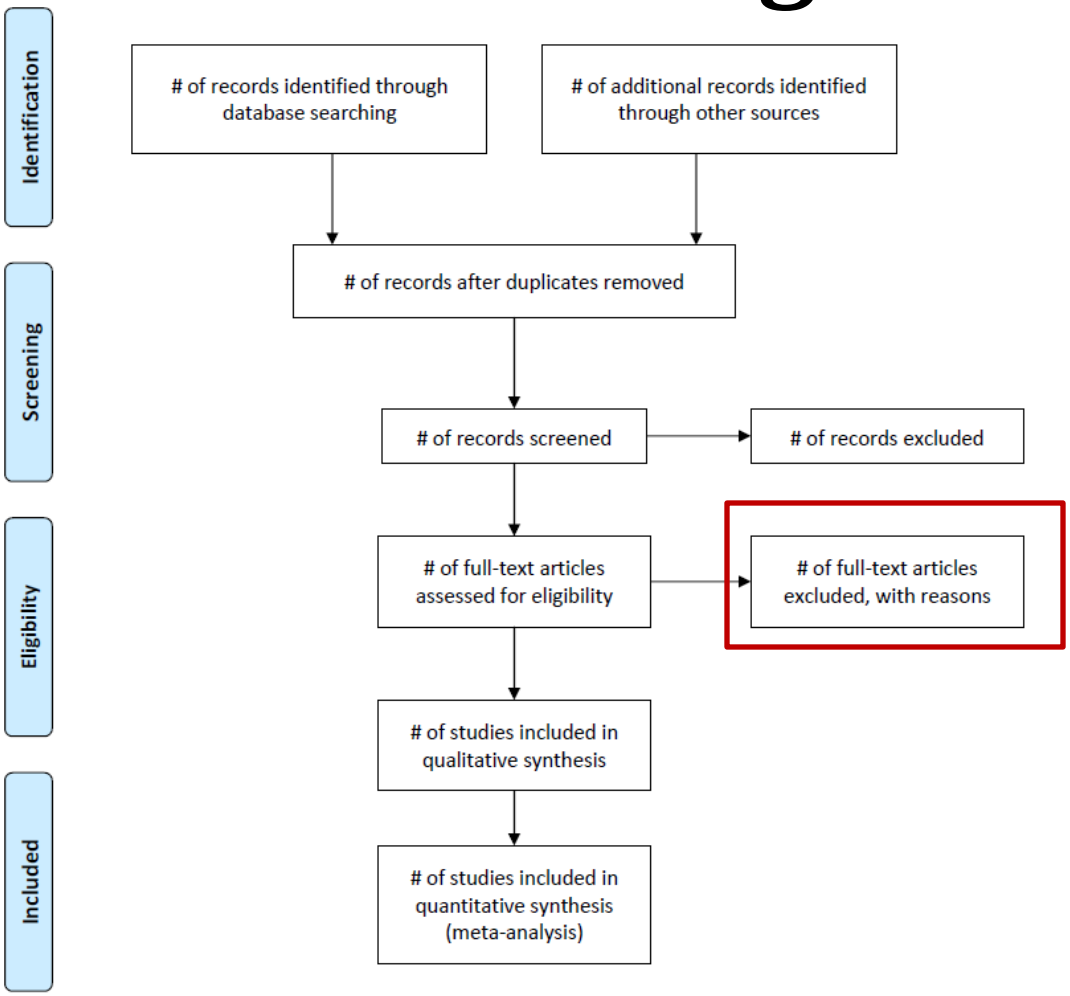
1. Read through all titles, discard those that are irrelevant

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



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

3. Data Extraction of Selected Studies

- PRISMA template: http://www.prisma-statement.org/
- Your own template:
  - Author, Year
  - Journal
  - Study Design (RCT, OS, Case-control, etc)
  - Treatment Arm 1 (if a medication, add a column for dosage)
  - Treatment Arm x (if a 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
  - Risk of Bias within study

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

Risk of Bias

- Cochrane Collaboration recommends qualitatively evaluating risk of bias
  - Within trial
  - Across trials

Within Trial Bias

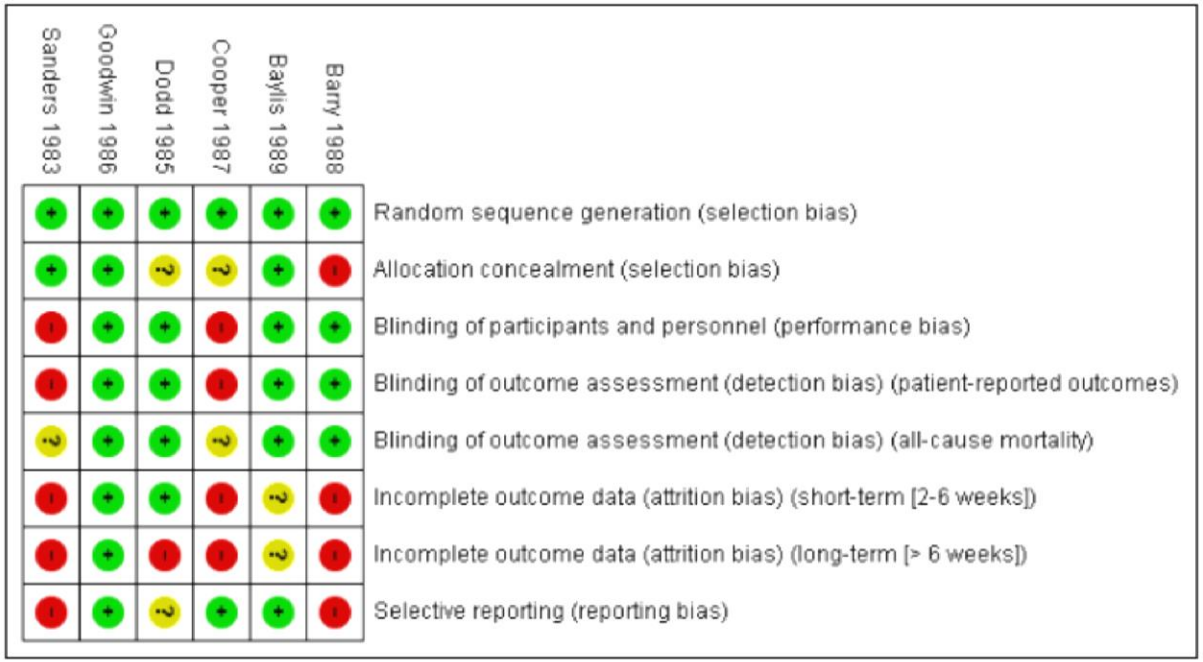
- Selection Bias
- Performance Bias
- Detection Bias
- Attrition Bias
- Reporting Bias
- Other

Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement
Selection bias.	
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Performance bias.	
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Detection bias.	
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
Attrition bias.	
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Reporting bias.	
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
Other bias.	
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.

Across Trial Bias

Figure 8.6.c: Example of a 'Risk of bias summary' figure



Poll: RCTs and Observational studies

- Should both RCTs and Observational studies be included in the same meta analysis?

  a. Yes
  b. Yes, but you should do sub-group analysis on each separately
  c. No, they should be separated

4. Separating out OS and RCTs

- Observational Studies have systematic differences between groups, RCTs do not
  - This is a problem if the 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 measured using the same statistic
  - May require the involvement of a PhD statistician – point estimate and variation

- Binary Data: 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

Borenstein M, Hedges LV. Converting Among Effect Sizes. In: *Introduction to Meta-Analysis*. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2009: 45-49.

Why the log scale?

- To maintain symmetry in the analysis
- Example:

  Study 1: Risk of event is 2x in Group A than it is for Group B

  Study 2: Risk of event is ½ for Group A than for Group B.

  - If studies have equal weights, they should negate each other
  - However, if using RR, Study 1 would have an RR of 2.0, Study 2 would have an RR of 0.5
    - This yields mean RR of 1.25 (not 1.0)

  - In the log scale, the 2 estimates are 0.693 and -0.693

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 your 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:

- Cochrane'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

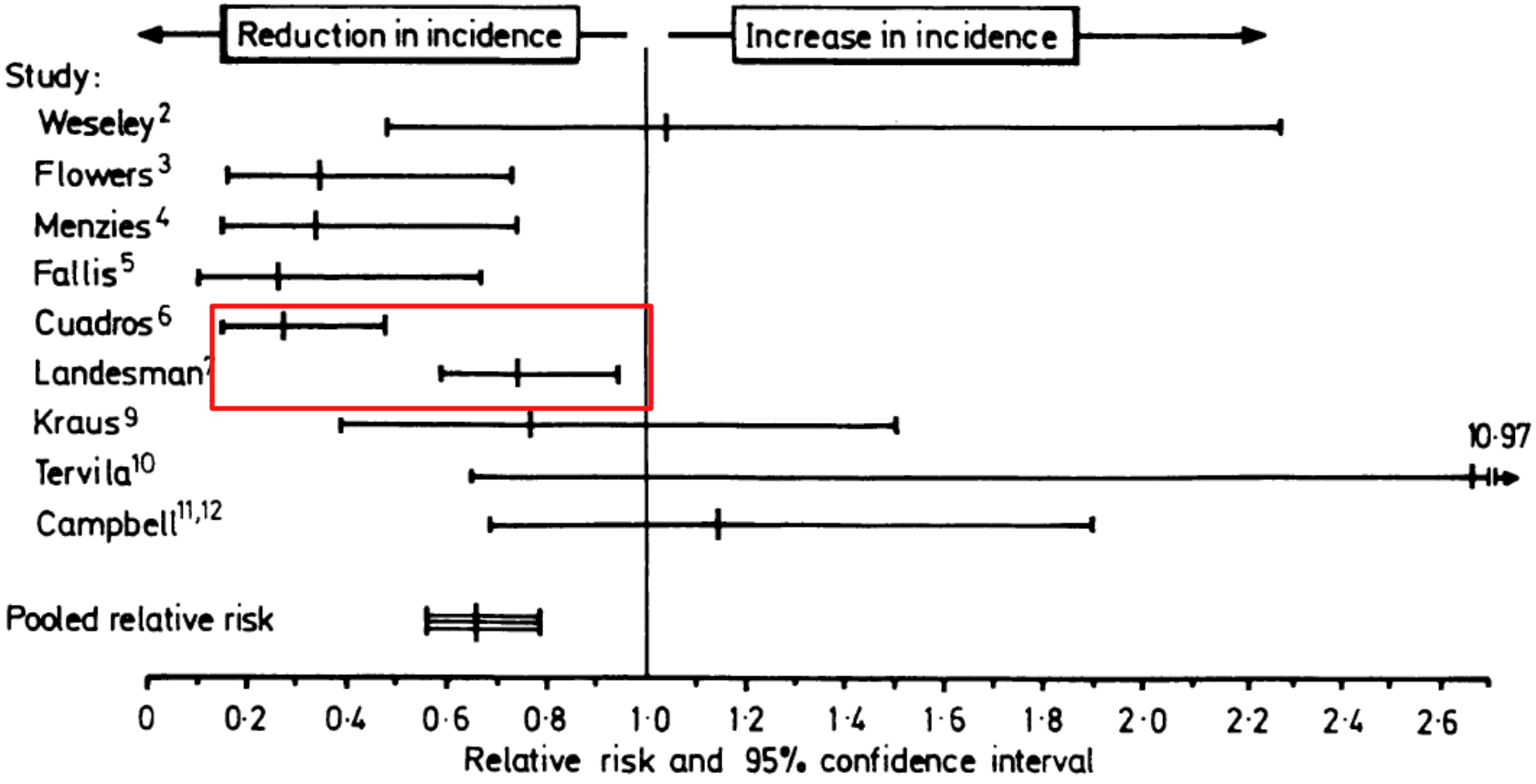
- Problem: power to detect heterogeneity is low when you have ≤ 10 studies)
  - You can have heterogeneity but fail to reject null hypothesis
    - Recommend using $p < 0.10$ as significance level
  - Conversely, if you have studies with large sample sizes, you can reject the null hypothesis even when 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



Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. Br Med J (Clin Res Ed). 1985 Jan 5;290(6461):17-23.

Moving forward with 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

Next Lecture:

March 28, 2018

SUMMARY

Summary

- Meta-analysis: single pooled estimate + variance from (usually) weighting and combining individual effects from multiple studies

- Considerations:
  - Systematic literature review
  - Consistent data extraction of studies
  - Proper assessment (handling) of heterogeneity

- Too much heterogeneity → do not conduct the meta-analysis, stop at literature review.

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 Researc*h. 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/

Questions?

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