

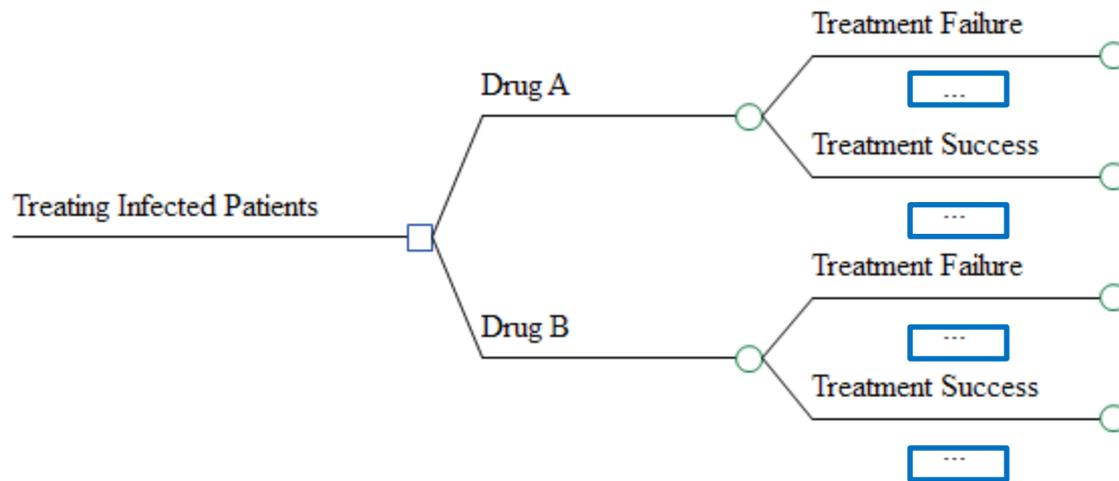
# **Evidence Synthesis for Decision Modeling: Part 1: Preparing for Meta-Analysis**

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# Probabilities in a Decision Model

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



# Cost-Effectiveness Inputs

Variables	Estimate	Range	Distribution	Data source*	Reference
<b>Surgical clipping</b>					
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
<b>Endovascular coiling</b>					
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
<b>Reopening</b>					
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
<b>De novo aneurysms</b>					
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
<b>SAH</b>					
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
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# 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
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# 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 listed. Each result includes a checkbox, a title, authors, journal, year, 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

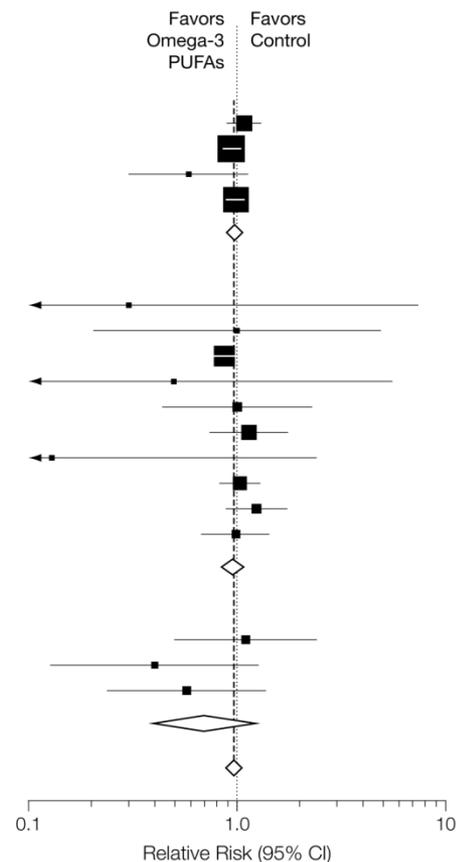
## Raw Data

## Summary Stats

## Forest Plot

## Study Weights

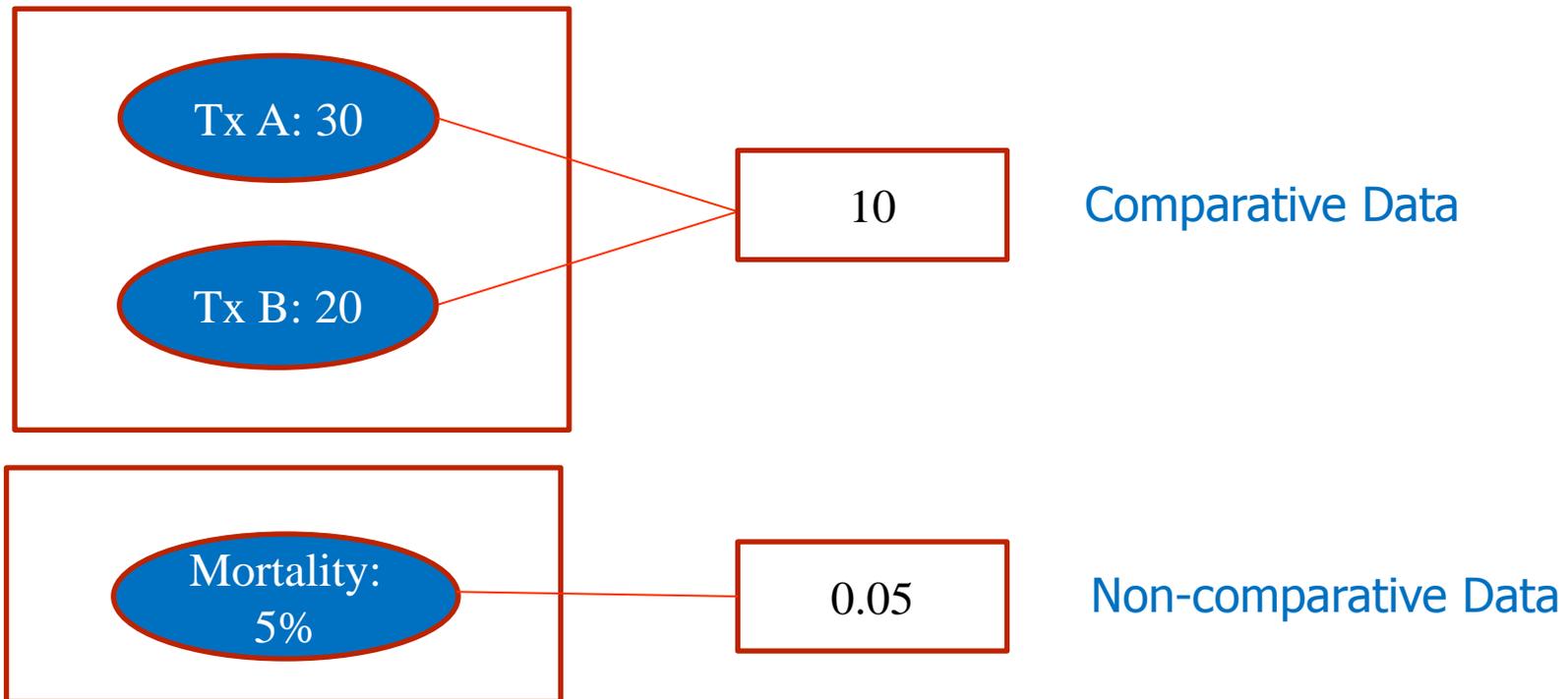
	No. of Events		No. of Participants		RR (95% CI)	Weight, %
	Omega-3 PUFAs	Control	Omega-3 PUFAs	Control		
<b>Mixed prevention</b>						
Yokoyama et al, <sup>3</sup> 2007	286	265	9326	9319	1.08 (0.91-1.27)	10.00
Tavazzi et al, <sup>2</sup> 2008	955	1014	3494	3481	0.94 (0.87-1.01)	28.99
Einvik et al, <sup>37</sup> 2010	14	24	282	281	0.58 (0.31-1.10)	0.80
ORIGIN, <sup>5</sup> 2012	951	964	6281	6255	0.98 (0.90-1.07)	26.23
<b>Subtotal: <math>I^2 = 38.9\%</math>, <math>P = .18</math></b>	<b>2206</b>	<b>2267</b>	<b>19383</b>	<b>19336</b>	<b>0.97 (0.90-1.05)</b>	<b>66.02</b>
<b>Secondary prevention</b>						
Sacks et al, <sup>27</sup> 1995	0	1	31	28	0.30 (0.01-7.13)	0.03
Leng et al, <sup>26</sup> 1998	3	3	60	60	1.00 (0.21-4.76)	0.13
Marchioli et al, <sup>1</sup> 1999	472	545	5666	5658	0.86 (0.77-0.97)	16.80
von Schacky et al, <sup>25</sup> 1999	1	2	112	111	0.50 (0.05-5.39)	0.06
Nilsen et al, <sup>24</sup> 2001	11	11	150	150	1.00 (0.45-2.24)	0.50
Svensson et al, <sup>32</sup> 2006	34	30	103	103	1.13 (0.75-1.70)	1.91
Garbagnati et al, <sup>38</sup> 2009	0	3	20	18	0.13 (0.01-2.34)	0.04
Kromhout et al, <sup>4</sup> 2010	186	184	2404	2433	1.02 (0.84-1.24)	7.45
Rauch et al, <sup>36</sup> 2010	88	70	1919	1885	1.23 (0.91-1.68)	3.28
Galan et al, <sup>29</sup> 2010	58	59	1253	1248	0.98 (0.69-1.39)	2.51
<b>Subtotal: <math>I^2 = 1.5\%</math>, <math>P = .43</math></b>	<b>853</b>	<b>908</b>	<b>11718</b>	<b>11694</b>	<b>0.95 (0.86-1.04)</b>	<b>32.71</b>
<b>ICD</b>						
Leaf et al, <sup>34</sup> 2005	13	12	200	202	1.09 (0.51-2.34)	0.56
Raitt et al, <sup>33</sup> 2005	4	10	100	100	0.40 (0.13-1.23)	0.26
Brouwer et al, <sup>35</sup> 2006	8	14	273	273	0.57 (0.24-1.34)	0.45
<b>Subtotal: <math>I^2 = 19.9\%</math>, <math>P = .29</math></b>	<b>25</b>	<b>36</b>	<b>573</b>	<b>575</b>	<b>0.69 (0.39-1.23)</b>	<b>1.27</b>
<b>Overall: <math>I^2 = 11.7\%</math>, <math>P = .32</math></b>	<b>3084</b>	<b>3211</b>	<b>31674</b>	<b>31605</b>	<b>0.96 (0.91-1.02)</b>	<b>100.00</b>



# 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

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

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# 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

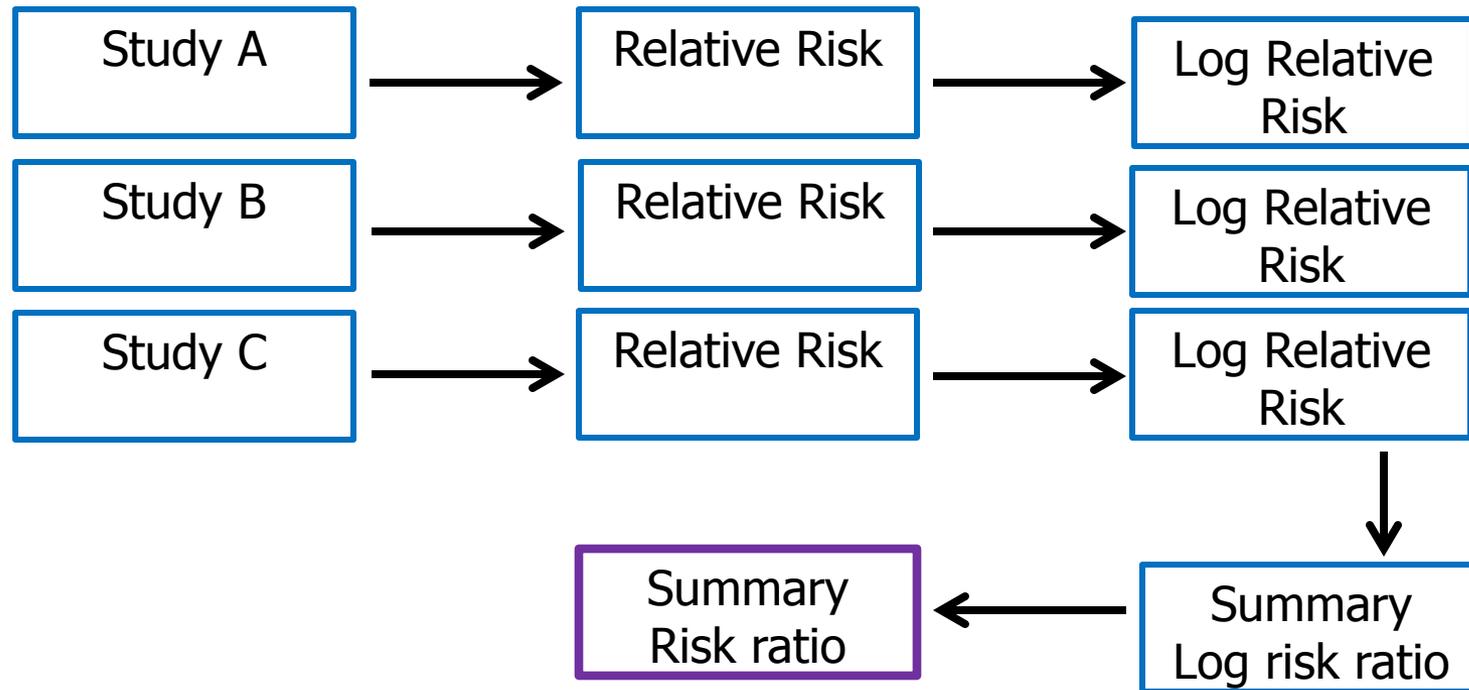
	Exposed	Unexposed
Disease	30	6
No Disease	12	4

	Exposed	Unexposed
Disease	45	26
No Disease	16	5

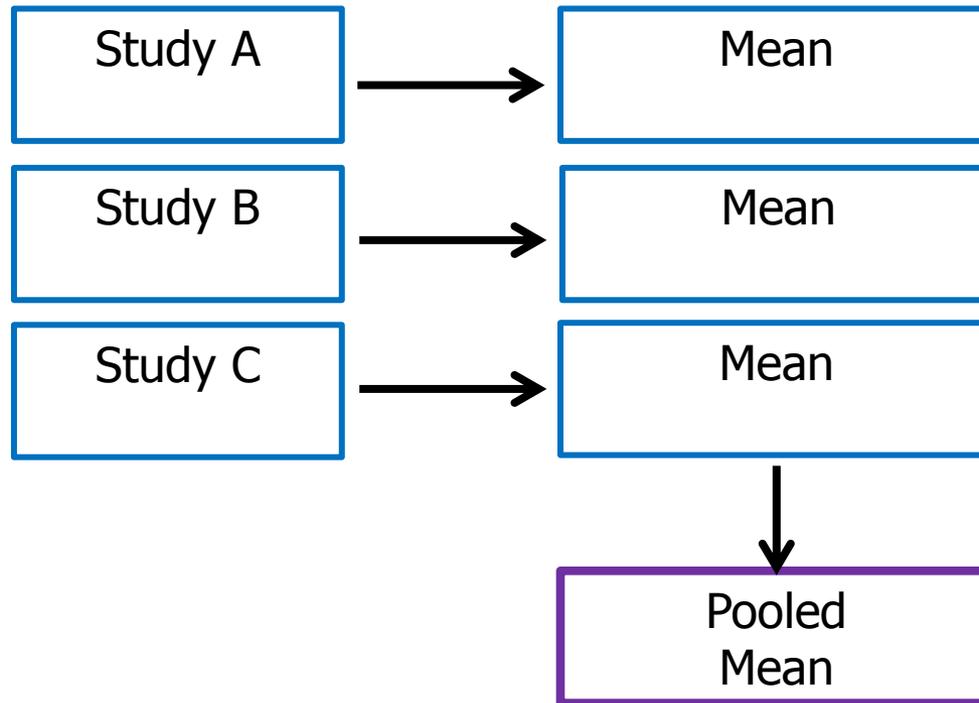


$$RR = 1.05$$

# Creating a pooled estimate (RR)

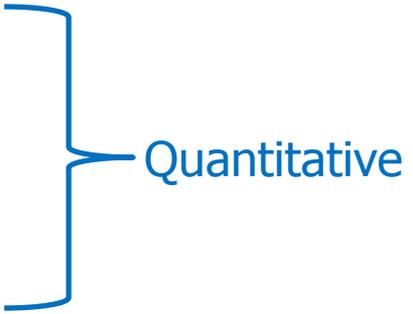


# Creating a pooled estimate, Mean



# 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

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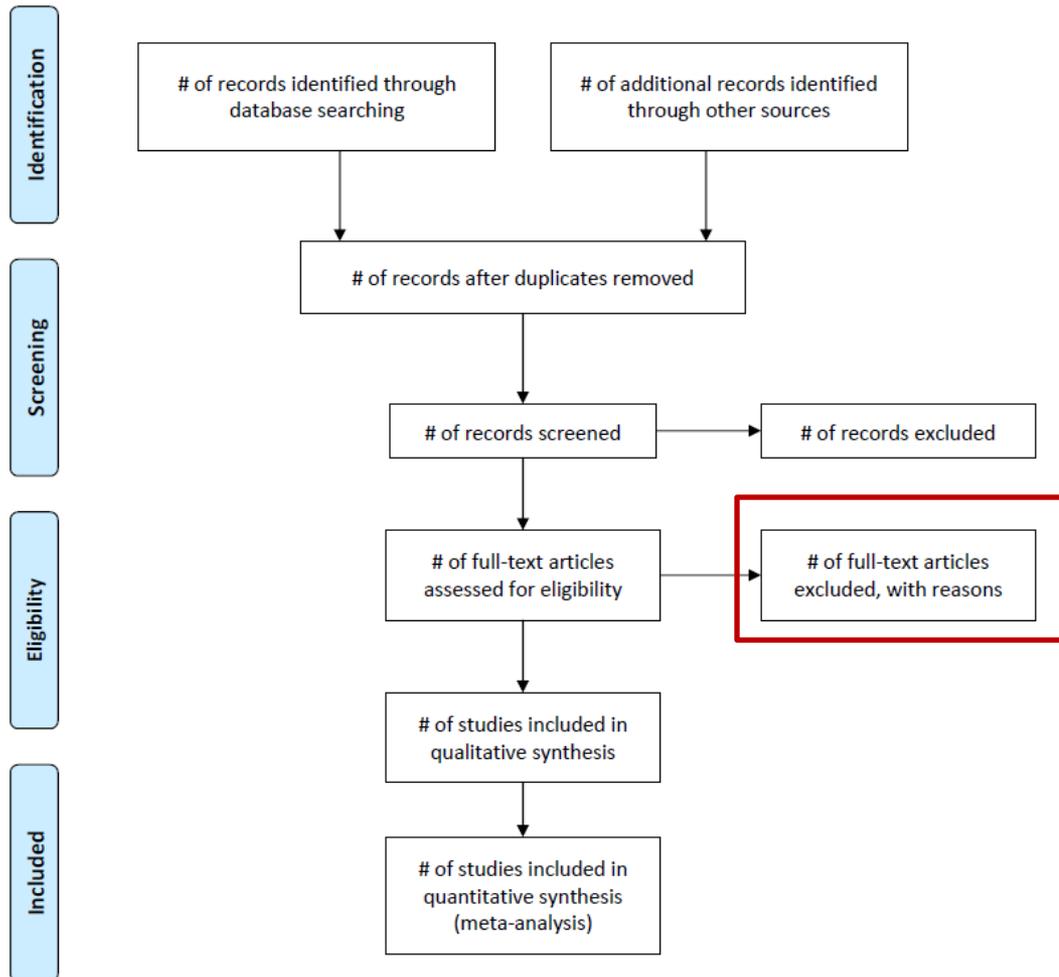
# 1. Systematic Literature Search

- 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](http://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
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# PRISMA diagram



# 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 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
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# 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

# 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  $\frac{1}{2}$  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 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
-

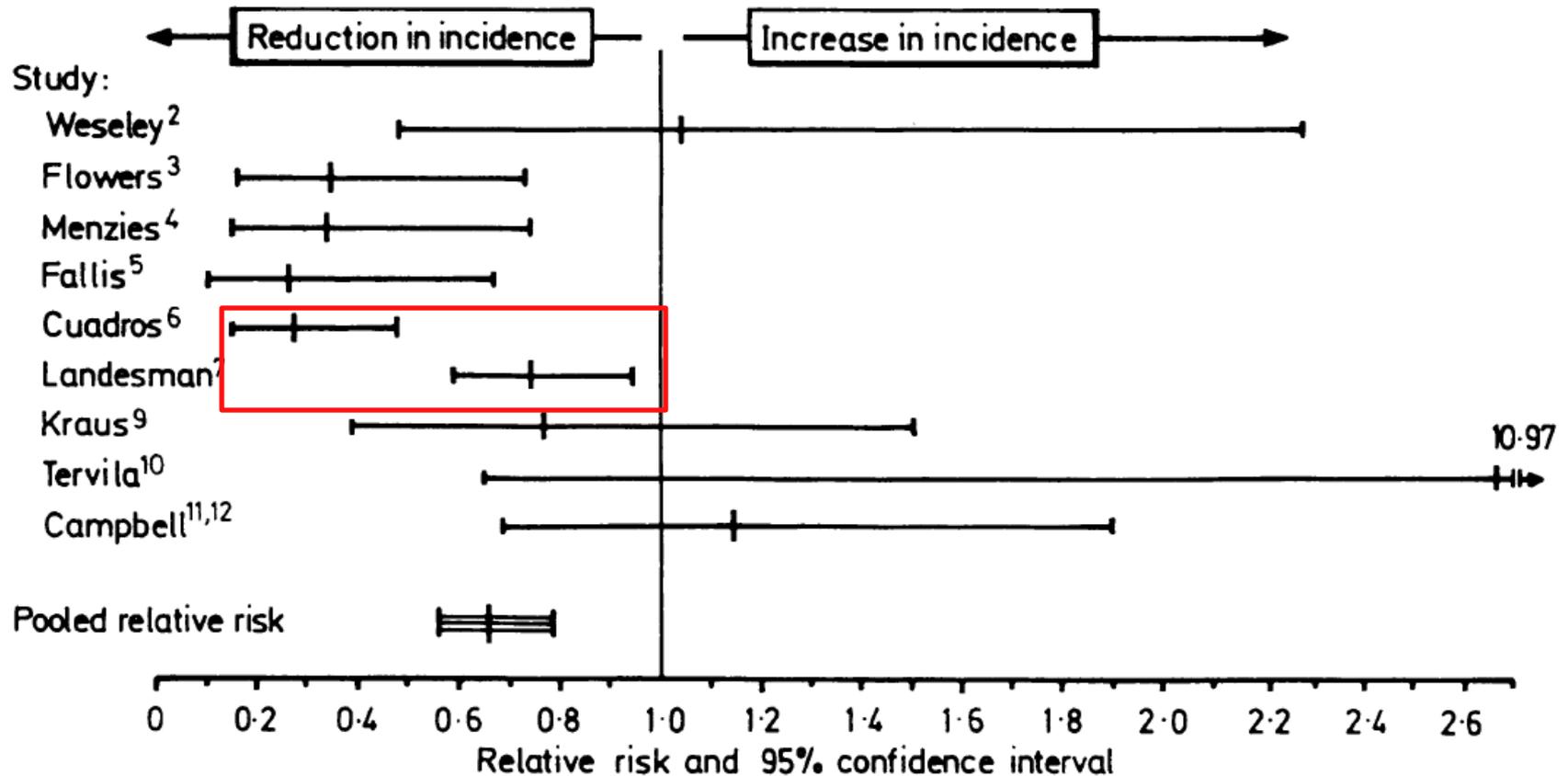
# Formal Assessment of Heterogeneity: Statistical Tests:

- 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  $\leq 10$  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**
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# 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



# 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 23, 2016*

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# SUMMARY

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# 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 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/>
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# Questions?

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