Evidence Synthesis for Decision Modeling:

Part 2: Meta-Analysis

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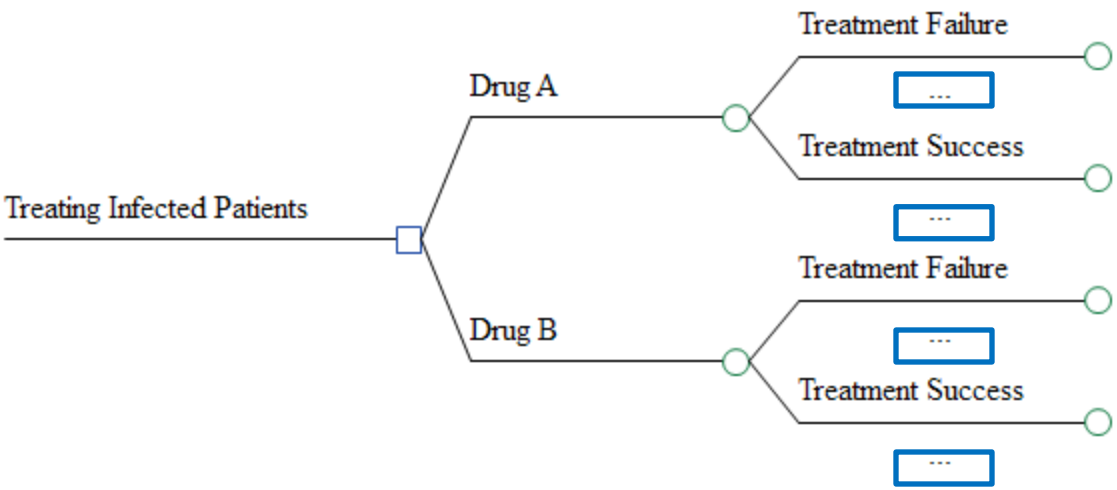
Probabilities in a Decision Model

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



Ways to derive model inputs

- Transforming existing data inputs

- Creating data inputs: synthesizing available data
  - Meta-Analysis
    - Individual Patient 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

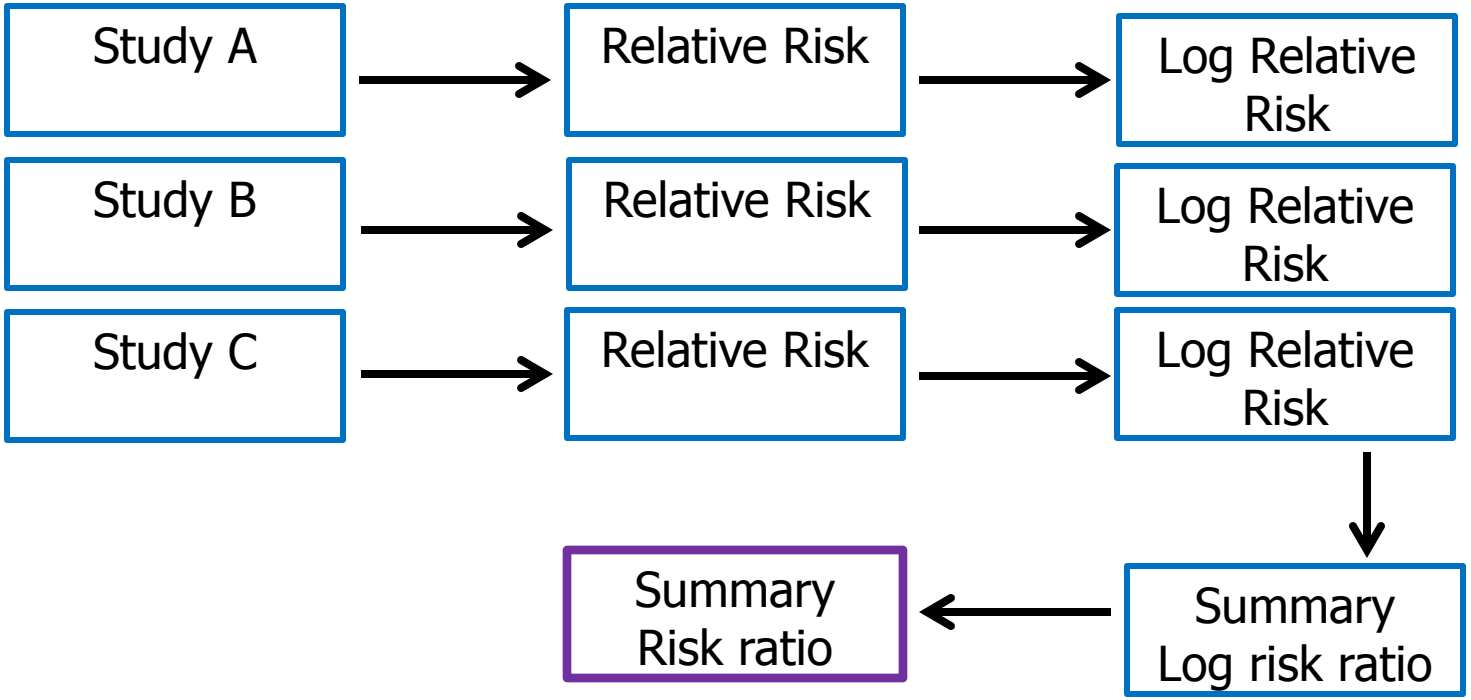
- Premise: the pooled estimate based on multiple studies will be higher quality than the estimate provided by a single study

Steps in a Meta-Analysis:

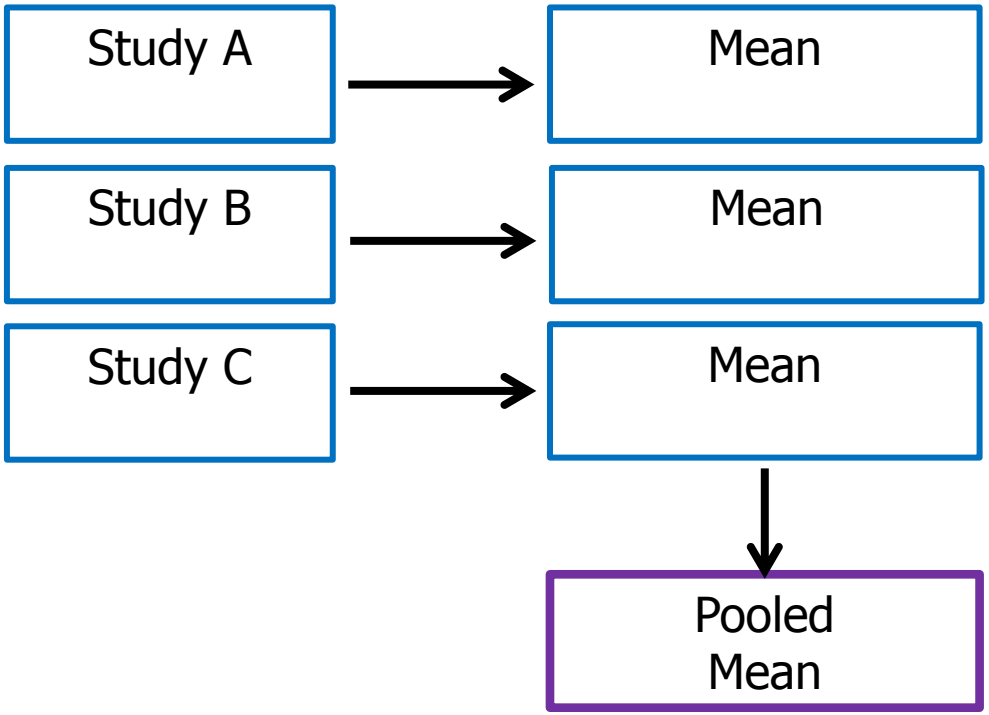
- Step 1: A summary statistic is calculated for each study
- Step 2: Weight the summary-statistic (conventionally)
- Step 3: Average the individual weighted estimates from each study to create a pooled point estimate
- Step 4: Calculation of variation around pooled point estimate

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

Creating a pooled estimate (RR)



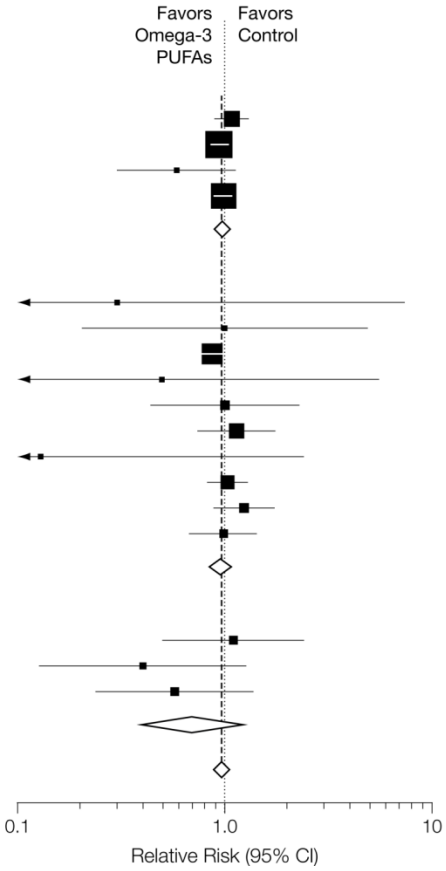
Creating a pooled estimate, Mean



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

	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**	**19 383**	**19 336**	**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**	**11 718**	**11 694**	**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**	**31 674**	**31 605**	**0.96 (0.91-1.02)**	100.00



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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**

Poll

- How do you proceed if you have identified heterogeneity amongst your studies?
  1. Do not continue
  2. Exclude studies that cause heterogeneity and conduct a meta analysis on the remaining studies
  3. Run a meta-regression

7. Conducting Meta-Analysis

4 steps, each implemented in the software

2 decisions:

a) fixed versus random effects

b) 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 bias the treatment effect.

Random Effects Distribution

- Width describes the degree of heterogeneity.
  - The distribution is usually assumed to be normal
- When heterogeneity is present, the confidence interval for the random-effects pooled estimate will be greater than that for a fixed-effects pooled estimate.
- Random effects pooled estimate will only estimate the average treatment effect if the biases are symmetrically distributed

Pooling studies

Pooling Option	Use when you have
Inverse-variance (FE)	Binary data if you have the 2x2 table, Continuous data, low heterogeneity
DerSimonian and Laird (RE)	Binary data if you have the 2x2 table, Continuous data, low heterogeneity, multiple studies
Hartung-Knapp-Sidik-Jonkman (HKSJ method)	Continuous data, heterogeneity, small number of studies (be careful when < 6 studies and they have very unequal sample size)
Profile Likelihood (RE)	Continuous data, heterogeneity, asymmetry in distribution of tau-squared
Bayesian approach (RE)	Binary or Continuous data, heterogeneity, sparse data and/or few studies
Mantel-Haenszel	OR no 0 cells, RR, risk difference
Peto method	OR, 0 cells

Pooling studies, references

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.

IntHout J, Ioannidis JPA, Born GF. (2014) The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Medical Research Methodology* 14:25.

EQUATIONS

Inverse Variance (fixed effects)

- Pooled treatment effect:

$$\bar{T}. = \frac{\sum w_i T_i}{\sum w_i}$$

- Weight:

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

- Variance

$$var(\bar{T}.) = \frac{1}{\sum w_i}$$

Inverse Variance with random effects

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

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

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

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

Within-study variance

Between-studies variance

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

Tau-squared

- Variance of the true effect sizes

- Cannot compute this directly – we estimate if from the observed effects

Problems with DerSimonian and Laird and inverse-variance

- Shuster, Statistics in Medicine 2010
  - 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
  - DerSimonian and Laird method assumes we have estimated between-study variance exactly → narrow CIs, low p-value

- Is the default weighting method in RevMan (used by Cochrane Collaboration)

Pooling studies: Publication Bias

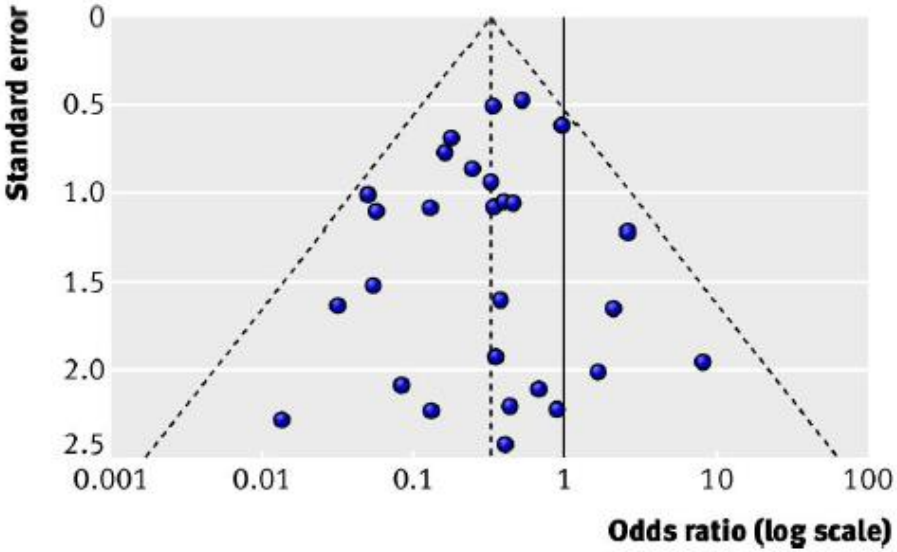
- Studies in the analysis are systematically different from all the studies that should have been included
- Studies with sig. results more likely to be published
  - Meta-analysis will overestimate effect
- Larger studies more likely to be published
  - If results of smaller studies are systematically different from larger studies:
    - Random effects will be more problematic
      - gives greater weight to smaller studies (compared with fixed effects

Assessing Publication Bias

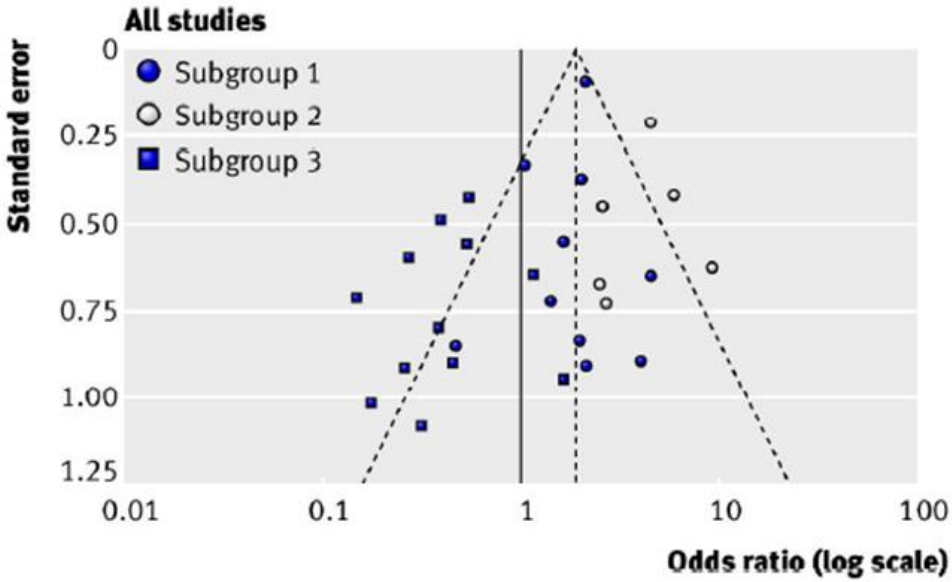
- Funnel plots
  - Asymmetry is problematic
    - Unless quality of studies varies with size
  - Publication bias can still exist even if there is symmetry

Funnel Plots for Publication Bias

Symmetric Funnel Plot



Asymmetric Funnel Plot



Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011 Jul 22;343:d4002.

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 other info you have about studies, such as quality of study or heterogeneity of intervention
- For a funnel plot to be useful, have to have studies with various sizes.
- Failure to find asymmetry does not mean there is no publication bias

What do to with Publication Bias

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

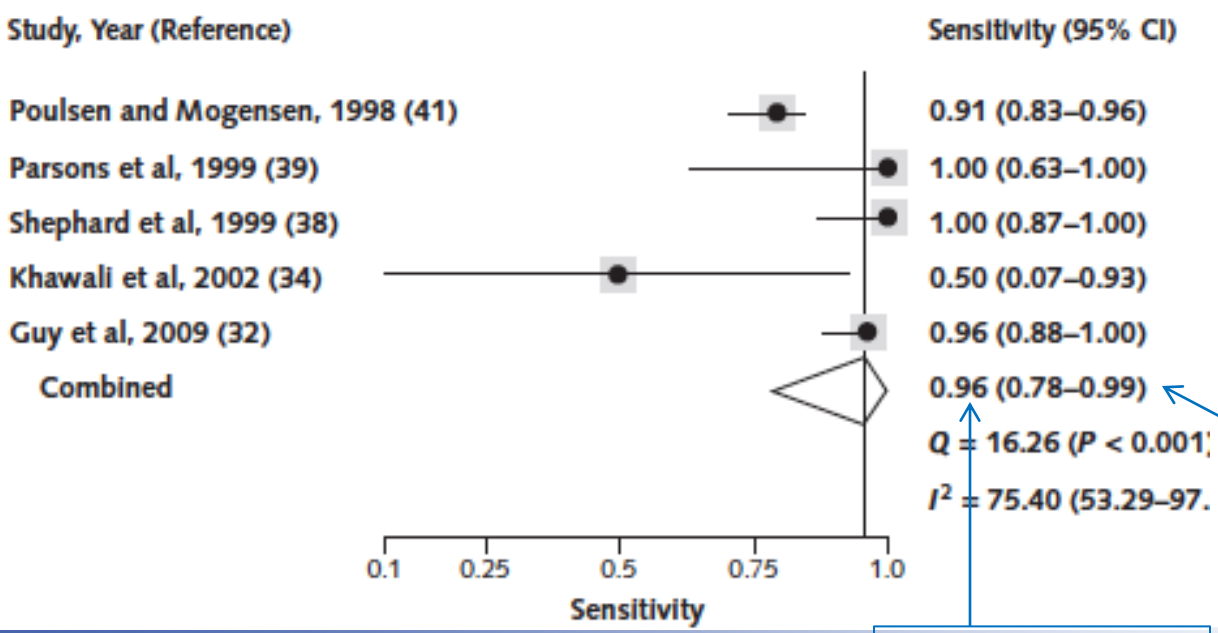
REVIEW | Annals of Internal Medicine

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

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

Individual-Patient Data Meta-Analysis

- "Regular" meta-analysis uses the <u>summary</u> 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

Advantages of IPD Meta Analysis

- Conduct analyses of your interest
  - different summary statistics, different follow-up time, time-to-event analysis, impute missing data

- NOTE: IPD versus conventional meta-analysis could produce different results
  - (e.g., differences in handling of missing data)

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: rule of thumb at least 10 events per covariate
  - Meta-regression: no established rule

- Caveat: subject to the “ecological” fallacy

Fixed vs. Random Effects, Meta-Regression

- Fixed Study-level effects assumes:
  - *All* variation between studies' outcomes can be accounted for by the covariates in the regression model
  - Studies that have the same values for all covariates share the same population effect
  - H0: Effect size is the same for all values of the covariate
- Random Study-level effects assumes:
  - Covariates explain *part* of variation between studies' outcomes
  - Studies that have the same value for all covariates share a distribution of effects
  - H0: Mean effect size is the same for all values of the covariate

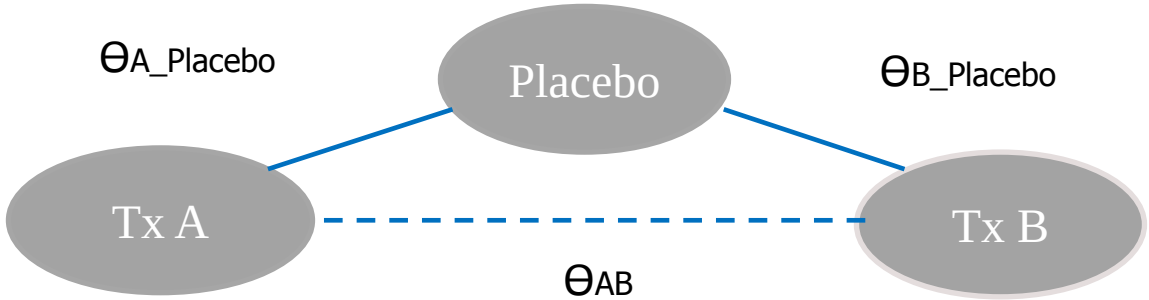
Multiple treatments

- Meta regression works well when all of your studies are evaluating the same intervention(s) of interest
  - Drug A versus placebo

- Most of the time, for a CEA, you are interested in the effect of one intervention versus another
- Studies may not have directly evaluated these interventions
  - Drug A versus placebo
  - Drug B versus placebo

Mixed Treatment Comparisons (Network Meta Analysis)

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



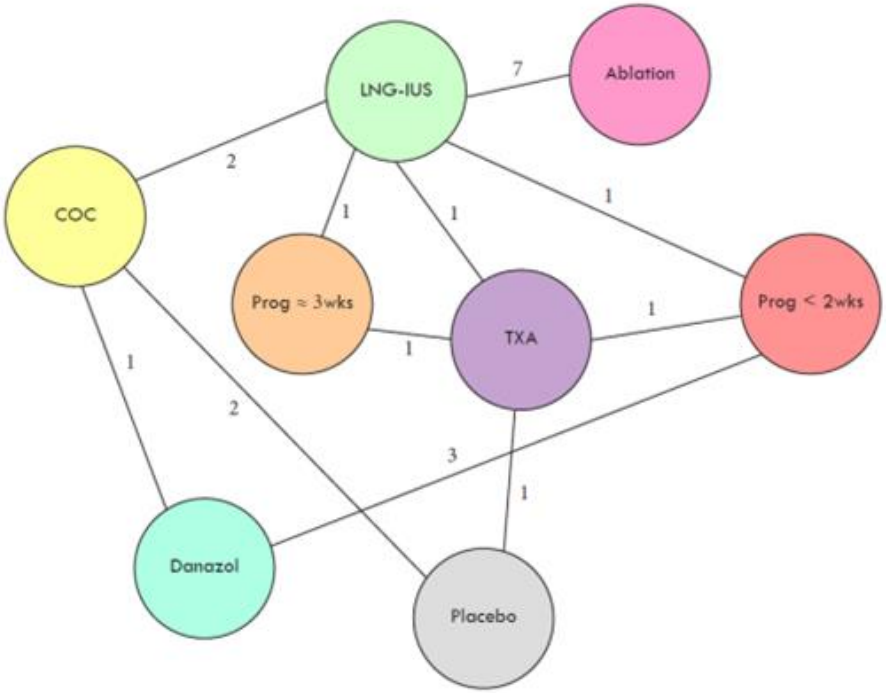
$$(\Theta_{AB}) = (\Theta_{A_Placebo}) - (\Theta_{B_Placebo})$$

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

Mixed Treatment Comparisons

- Advanced topic; do not proceed without consulting a statistician
  - Provide information about your network

Figure 1. Evidence network of RCTs for MBL in HMB



SUMMARY

Meta-Analysis Summary

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

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7. Conduct Meta-Analysis

Considerations, quantitative pooling (step 7)

1. <u>Decide whether to use FE or RE</u>
   - Fixed Effects
     - Assume: universe of studies
     - Inference: the true effect is Θ
   - Random Effects
     - Assume: sample from universe of studies
     - Inference: the mean of the true effect is Θ
2. <u>Decide how to pool the studies</u>

   Y = Binary (OR, RR): Mantel-Haenszel, Peto

   Y = Continuous: IV, D&L, K-H, PL, Bayesian

Summary

- Meta-Analysis
  - Individual Patient Data Meta-Analysis
  - ➢ Use when studies evaluated your intervention(s) of interest

- Mixed Treatment Comparisons
  - ➢ Use when your interventions have not been evaluated in a head-to-head trial

- Meta-regression can be used with Meta-analyses or Mixed Treatment Comparisons analyses

- <u>Meta-analyses and MTCs themselves are observational studies</u>
  - – People are not randomly assigned to studies; they are randomly assigned to treatments within studies.

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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