Evidence Synthesis for Decision Modeling:
Part 2: Meta-Analysis

Risha Gidwani, DrPH
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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

Study A -> Mean

Study B -> Mean

Study C -> Mean

Mean -> Pooled Mean
Error bars indicate 95% CIs of the relative risk (RR) estimates. The size of the squares correspond to the study weight in the random-effects meta-analysis. Diamonds represent the meta-analysis summary effect estimate. ICD indicates implantable cardioverter-defibrillator; PUFAs, polyunsaturated fatty acids.

**Figure Legend:**

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


<table>
<thead>
<tr>
<th>Study</th>
<th>Omega-3 PUFAs</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixed prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yokoyama et al,3 2007</td>
<td>286</td>
<td>265</td>
<td>1.08 (0.91-1.27)</td>
<td>10.00</td>
</tr>
<tr>
<td>Tavazzi et al,2 2008</td>
<td>955</td>
<td>1014</td>
<td>0.94 (0.87-1.01)</td>
<td>28.99</td>
</tr>
<tr>
<td>Eirikvik et al,37 2010</td>
<td>14</td>
<td>24</td>
<td>0.58 (0.31-1.10)</td>
<td>0.80</td>
</tr>
<tr>
<td>ORIGIN,3 2012</td>
<td>951</td>
<td>964</td>
<td>0.98 (0.90-1.07)</td>
<td>26.23</td>
</tr>
<tr>
<td>Subtotal: $I^2 = 38.9%, P = .18$</td>
<td>2206</td>
<td>2267</td>
<td>0.97 (0.90-1.05)</td>
<td>66.02</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacks et al,22 1995</td>
<td>0</td>
<td>1</td>
<td>0.30 (0.01-7.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Lang et al,26 1998</td>
<td>3</td>
<td>3</td>
<td>1.00 (0.21-4.76)</td>
<td>0.13</td>
</tr>
<tr>
<td>Marchiol et al,1 1999</td>
<td>472</td>
<td>545</td>
<td>0.86 (0.77-0.97)</td>
<td>16.80</td>
</tr>
<tr>
<td>von Schacky et al,25 1999</td>
<td>1</td>
<td>2</td>
<td>0.50 (0.05-5.39)</td>
<td>0.06</td>
</tr>
<tr>
<td>Nilsen et al,23 2001</td>
<td>11</td>
<td>11</td>
<td>1.00 (0.45-2.24)</td>
<td>0.50</td>
</tr>
<tr>
<td>Sverrisson et al,36 2006</td>
<td>34</td>
<td>30</td>
<td>1.13 (0.75-1.70)</td>
<td>1.91</td>
</tr>
<tr>
<td>Garagnoni et al,33 2009</td>
<td>0</td>
<td>3</td>
<td>0.13 (0.01-3.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Kronholz et al,4 2010</td>
<td>186</td>
<td>184</td>
<td>1.02 (0.84-1.24)</td>
<td>7.45</td>
</tr>
<tr>
<td>Rauch et al,39 2010</td>
<td>88</td>
<td>70</td>
<td>1.23 (0.91-1.68)</td>
<td>3.28</td>
</tr>
<tr>
<td>Galet et al,31 2010</td>
<td>58</td>
<td>59</td>
<td>0.90 (0.69-1.29)</td>
<td>2.51</td>
</tr>
<tr>
<td>Subtotal: $I^2 = 1.3%, P = .43$</td>
<td>853</td>
<td>908</td>
<td>0.95 (0.86-1.04)</td>
<td>32.71</td>
</tr>
<tr>
<td><strong>ICD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaf et al,34 2005</td>
<td>13</td>
<td>12</td>
<td>1.09 (0.51-2.34)</td>
<td>0.56</td>
</tr>
<tr>
<td>Pratt et al,33 2005</td>
<td>4</td>
<td>10</td>
<td>0.40 (0.13-1.23)</td>
<td>0.26</td>
</tr>
<tr>
<td>Brouwer et al,35 2006</td>
<td>8</td>
<td>14</td>
<td>0.57 (0.24-1.34)</td>
<td>0.45</td>
</tr>
<tr>
<td>Subtotal: $I^2 = 19.9%, P = .29$</td>
<td>25</td>
<td>36</td>
<td>0.69 (0.39-1.23)</td>
<td>1.27</td>
</tr>
<tr>
<td>Overall: $I^2 = 11.7%, P = .32$</td>
<td>3084</td>
<td>3211</td>
<td>0.96 (0.91-1.02)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Fixed Effects</th>
<th>Random Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumes</td>
<td><strong>Variance among studies is due to sampling error</strong>&lt;br&gt;There is some fixed underlying true effect.</td>
<td><strong>Variance among studies is due to both sampling error and because true effect could vary from study to study</strong> (e.g., because of different participants, different ways intervention was administered, etc.)</td>
</tr>
<tr>
<td>Variance</td>
<td>Within-study</td>
<td>Within-study and between-study ($\tau^2$)</td>
</tr>
<tr>
<td>CIs</td>
<td>Narrower</td>
<td>Wider</td>
</tr>
<tr>
<td>Inference</td>
<td>The true effect is X</td>
<td>The mean of the effects is X</td>
</tr>
<tr>
<td>Small Studies</td>
<td>Are less precise, given less weight</td>
<td>Given more weight than in a FE analysis</td>
</tr>
</tbody>
</table>

**Fixed Effects**

- Assumes: Variance among studies is due to sampling error. There is some fixed underlying true effect.

**Random Effects**

- Assumes: 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 and between-study ($\tau^2$)

- Inference: The true effect 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

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


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 between-studies variance.
  - The four approaches differ in their calculation of between-studies variance (tau-squared)

\[
\tilde{T}_{RND} = \frac{\sum w_i^* T_i}{\sum w_i^*}
\]

\[
\text{Within-study variance: } w_i^* = \frac{1}{\left(\frac{1}{w_i} + (\tau^2)\right)}
\]

\[
\text{Between-studies variance: } \text{var}(\tilde{T}_{RND}) = \frac{1}{\sum w_i^*}
\]
Tau-squared

- Variance of the true effect sizes

- Cannot compute this directly – we estimate it 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 \( \text{variance} = \frac{(p\times q)}{n} \)

- 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

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

Meta-Analysis and CEA

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.

Study, Year (Reference)  
Poulsen and Mogensen, 1998 (41)  
Parsons et al, 1999 (39)  
Shephard et al, 1999 (38)  
Khawali et al, 2002 (34)  
Guy et al, 2009 (32)  
Combined

Sensitivity (95% CI)
- 0.91 (0.83–0.96)
- 1.00 (0.63–1.00)
- 1.00 (0.87–1.00)
- 0.50 (0.07–0.93)
- 0.96 (0.88–1.00)
- 0.96 (0.78–0.99)

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

- 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 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
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

\[
\begin{align*}
(\Theta_{AB}) &= (\Theta_{A\_Placebo}) - (\Theta_{B\_Placebo}) \\
\text{Var} (\Theta_{AB}) &= \text{Var} (\Theta_{A\_Placebo}) + \text{Var} (\Theta_{B\_Placebo})
\end{align*}
\]
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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Considerations, quantitative pooling (step 7)

1. Decide whether to use FE or RE
   - Fixed Effects
     - Assume: universe of studies
     - Inference: the true effect is $\Theta$
   - Random Effects
     - Assume: sample from universe of studies
     - Inference: the mean of the true effect is $\Theta$

2. Decide how to pool the studies
   - $Y =$ 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

- **Meta-analyses and MTCs themselves are observational studies**
  - 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.


Questions?

rishagidwani@va.gov