Introduction to Meta-analysis

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IHS Evidence Synthesis Group
What is meta-analysis?

“The combination of data or results from a collection of studies which address a common scientific question”

Glass 1977

‘Meta’ means ‘after’ or ‘beyond’
A Quantitative Systematic Review Question

Systematic reviews can designed to address a variety of questions:

- What is the treatment effectiveness of medication X
  - QUANTITATIVE

- What are the barriers and facilitators to the implementation of a training programme for midwives to implement X
  - QUALITATIVE

(A typology of reviews: an analysis of 14 review types and associated methodologies. Grant M, Booth A. Health Information and Libraries Journal, 26, pp.91–108)
What are you estimating?

You are trying to estimate a statistic for a specific population, such as a treatment effect, risk of a complication, the sensitivity and specificity of a diagnostic test, a correlation between two continuous variables.
The Sample

The sample in a randomised controlled trial consists of patients.

The sample in a meta-analysis consists of studies.

There is a population of studies that have been conducted, with varying populations, interventions, outcomes and biases. Some are published in journals, others languish in PhD theses or as conference abstracts.

The sample of studies should be as representative of the available evidence as possible. The best available evidence should be sought. This requires a systematic approach to identify the evidence, and consequently meta-analyses are often conducted as part of systematic reviews of the literature.
Similarity of study characteristics?

Same population: if there are several published studies investigating the same population, then incorporating all studies will
- increase the sample size, the amount of evidence
- have the advantage of including studies demonstrating the reproducibility of the experiment

Different population: clinical studies may use specific populations in order to maximise the outcome prevalence and therefore allow a lower sample size, or because it is a convenient population for the clinical researchers. Including studies of slightly different, but related populations may allow generalisation to a slightly broader population, and with more evidence.
Benefits of meta-analysis?

- Increase in precision: less uncertainty around the estimate of the outcome
- Extra power: more likely to reject a hypothesis if it is in fact false
- Estimate heterogeneity: variation in true effects
Meta-analysis: a statistical method

Meta-analysis is a statistical method that synthesises the results from individual studies to estimate the statistic of interest.

What are the data that may be used in a meta-analysis?
Mean, Standard deviation and Standard error

The mean (average) is the sum of the sample values divided by the sample size

A standard deviation describes the variation in a population

The effect estimate (mean difference) is the difference in the mean values of the intervention and control arms of a study

A standard error describes the uncertainty in the estimate of the mean or in the mean difference
## Deriving study summary statistics: continuous data

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>2.8</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>4.1</td>
</tr>
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<td>3.5</td>
<td>3.8</td>
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<td>2.4</td>
<td>3.4</td>
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<tr>
<td>3.2</td>
<td>5</td>
</tr>
<tr>
<td>2.6</td>
<td>3.2</td>
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</table>

<table>
<thead>
<tr>
<th>N</th>
<th>8</th>
<th>8</th>
<th>8</th>
<th>8</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>2.9375</td>
<td>3.95</td>
<td>Mean</td>
<td>3.1125</td>
</tr>
<tr>
<td>SD</td>
<td>0.6346</td>
<td>0.5904</td>
<td>SD</td>
<td>0.4853</td>
</tr>
</tbody>
</table>
Deriving summary study summary statistics

• Study 1
  • \( \text{Mean difference} = 3.95 - 2.94 = 1.01 \)
  • \( SE(\text{difference}) = \sqrt{\frac{SD_1^2}{N_1} + \frac{SD_2^2}{N_2}} = 0.31 \)
  • 95\% CI: (1.01-0.31*1.96) to (1.01+0.31*1.96) = 0.41 to 1.61

• Study 2
  • \( \text{Mean difference} = 3.95 - 3.11 = 0.84 \)
  • \( SE(\text{difference}) = \sqrt{\frac{SD_1^2}{N_1} + \frac{SD_2^2}{N_2}} = 0.22 \)
  • 95\% CI: (1.01-0.22*1.96) to (1.01+0.22*1.96) = 0.41 to 1.27
What is meta-analysis?

<table>
<thead>
<tr>
<th>Study</th>
<th>NT</th>
<th>MeanT</th>
<th>SDT</th>
<th>NC</th>
<th>MeanC</th>
<th>SDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>4.87</td>
<td>0.97</td>
<td>75</td>
<td>5.03</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>6.85</td>
<td>0.97</td>
<td>135</td>
<td>7.12</td>
<td>0.74</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>8.04</td>
<td>0.97</td>
<td>90</td>
<td>8.08</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7.47</td>
<td>1.15</td>
<td>40</td>
<td>7.54</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Mean difference (95% CI):

-0.16 (-0.43 to 0.11)
-0.27 (-0.47 to -0.07)
-0.04 (-0.29 to 0.21)
-0.07 (-0.51 to 0.37)

Summary
-0.17 (-0.29 to -0.04)
Forest plots

Point estimate

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>175</td>
</tr>
<tr>
<td>B</td>
<td>290</td>
</tr>
<tr>
<td>C</td>
<td>190</td>
</tr>
<tr>
<td>D</td>
<td>90</td>
</tr>
</tbody>
</table>

Pooled result

Mean difference

-1 -0.5 0 0.5 1

Favours intervention  Favours control

Line of no effect

95% Confidence Interval

Weight of trial

Effect estimate

95% Confidence Interval

Meta-analysis estimate
Greater precision

The confidence interval of the pooled estimate is narrower than the confidence intervals of the individual studies.
Combining studies: inverse variance

<table>
<thead>
<tr>
<th>Study</th>
<th>NT</th>
<th>MeanT</th>
<th>SDT</th>
<th>NC</th>
<th>MeanC</th>
<th>SDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>4.77</td>
<td>0.84</td>
<td>75</td>
<td>4.96</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>6.75</td>
<td>0.99</td>
<td>135</td>
<td>7.06</td>
<td>0.85</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>7.72</td>
<td>0.92</td>
<td>90</td>
<td>8.01</td>
<td>0.83</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7.36</td>
<td>0.91</td>
<td>40</td>
<td>7.47</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Possible study weights | Summary effect estimate
---|---
Equal | $-0.225$
Trial sample size | $-0.253$
Inverse variance | $-0.242$

Inverse variance: $\frac{1}{\text{var}} = \frac{1}{SE_{MD}^2}$

MD: mean difference; difference in mean effects between trial arms
Study weights: inverse variance

In an inverse variance meta-analysis, the weight given to each study is the inverse of the variance of the intervention effect in each study.

\[
\text{Inverse variance} = \frac{1}{\text{var}} = \frac{1}{\text{SE}_{IE}^2}
\]

var: variance
SE: standard error
IE: intervention effect, e.g. difference in mean pain scores between trial arms
Fixed-effect meta-analysis

Study weights

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Total Mean</th>
<th>SD</th>
<th>Control Total Mean</th>
<th>SD</th>
<th>Mean difference</th>
<th>MD</th>
<th>95%-CI</th>
<th>W(fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>4.77</td>
<td>0.84</td>
<td>75</td>
<td>4.96</td>
<td>0.70</td>
<td>-0.19</td>
<td>[-0.42; 0.04]</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>6.75</td>
<td>0.99</td>
<td>135</td>
<td>7.06</td>
<td>0.85</td>
<td>-0.31</td>
<td>[-0.52; -0.10]</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>7.72</td>
<td>0.92</td>
<td>90</td>
<td>8.01</td>
<td>0.83</td>
<td>-0.29</td>
<td>[-0.54; -0.04]</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7.36</td>
<td>0.91</td>
<td>40</td>
<td>7.47</td>
<td>0.65</td>
<td>-0.11</td>
<td>[-0.43; 0.21]</td>
</tr>
</tbody>
</table>

Fixed effect model 405 340

Heterogeneity: I-squared=0%, tau-squared=0, p=0.7402
## Variables and Outcomes

<table>
<thead>
<tr>
<th>Variable type</th>
<th>Example variable</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Pain</td>
<td>Mean difference</td>
</tr>
<tr>
<td>Dichotomous (Binary)</td>
<td>Heart attack</td>
<td>Risk ratio/odds ratio</td>
</tr>
<tr>
<td>Time-to-event</td>
<td>Time to death</td>
<td>Hazard ratio</td>
</tr>
</tbody>
</table>
Dichotomous (binary) outcomes: 2-by-2 table

<table>
<thead>
<tr>
<th></th>
<th>Event</th>
<th>No event</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>a=10</td>
<td>b=40</td>
<td>NT=50</td>
</tr>
<tr>
<td>Control</td>
<td>c=20</td>
<td>d=30</td>
<td>NC=50</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>N=100</td>
</tr>
</tbody>
</table>

The risk of an event in the treatment group is \( \frac{a}{a+b} = \frac{10}{50} = 0.2 \)

The risk of an event in the control group is \( \frac{c}{c+d} = \frac{20}{50} = 0.4 \)
Equal effects = 1 for a ratio

• When the risk of the outcome is the same in both treatment arms

\[
RR = 1
\]

• When the odds of the outcome is the same in both treatment arms

\[
OR = 1
\]
Further reading- binary outcomes


  http://ebm.bmj.com/content/ebmed/1/6/164.full.pdf


- Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ. 2014;348:f7450.
  http://www.bmj.com/content/348/bmj.f7450.full.print
Meta-analysis process for binary data

<table>
<thead>
<tr>
<th>Study</th>
<th>eT</th>
<th>NT</th>
<th>eC</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>240</td>
<td>40</td>
<td>240</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>224</td>
<td>36</td>
<td>240</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>280</td>
<td>35</td>
<td>264</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>224</td>
<td>28</td>
<td>208</td>
</tr>
</tbody>
</table>

\[
\text{LN(RR)} (95\% \text{ CI}): -0.30 (-0.53 \text{ to } -0.06)
\]

RR (95\% CI): 0.74 (0.59 to 0.94)

NNT??
Fixed effect meta-analysis on RR scale

Although meta-analysis is conducted on the log scale, all the data and results are presented on a scale such as risk ratio or odds ratio.
Zero events: inverse-variance and Mantel-Haenszel method

- Add $\frac{1}{2}$ to every cell of a 2x2 table (Revman automatically does this)
Clinical heterogeneity (diversity)

Clinical heterogeneity is variation in patient, intervention and outcome characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Follow up time point</th>
<th>Mean difference in pain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>45</td>
<td>4 weeks</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>70</td>
<td>4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>65</td>
<td>1 week</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>60</td>
<td>3 weeks</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Statistical heterogeneity

Low statistical heterogeneity

High statistical heterogeneity
Clinical & Statistical heterogeneity

Clinical heterogeneity (variation, diversity) is variation between studies in patient, intervention and outcome characteristics.

Statistical heterogeneity is greater variation in study effects than would be expected due to chance (sampling error).

Clinical heterogeneity may result in statistical heterogeneity where clinical variation affects the intervention effect.

Sometimes, clinical heterogeneity is referred to as clinical variation and statistical heterogeneity as simply heterogeneity.
Fixed and random effects meta-analysis

• A fixed effect meta-analysis assumes that there is one true intervention effect. Variation between studies is purely due to chance.

• A random-effects meta-analysis does not assume that there is one true effect.

- Because of clinical heterogeneity, it assumes that the true intervention effect varies from one study to the next, and these effects are random samples from a normal distribution.

- Hence, the pooled estimate is the average effect from the PICO characteristics of the included studies
Random-effects meta-analysis

Variation in intervention effects greater than chance
Some confidence intervals don’t even overlap
When to conduct meta-analysis

• A meta-analysis is a statistical technique used to answer a question specified in the protocol of a systematic review

• If the question is relevant, the inclusion criteria are relevant, and a meta-analysis is planned to estimate a statistic then conduct the meta-analysis

• Any meta-analyses of subgroups should be stated in the protocol

• The presence of statistical heterogeneity is not a reason to abandon a meta-analysis; it affects how you interpret the results and the conclusions you draw
Limitations of meta-analysis

• If the included studies are poor quality, the summary result will also be poor. The uncertainty associated with the potential bias in the included studies will not be captured in the confidence interval of the summary estimate.

• The value of a meta-analysis depends on the identification of the relevant studies from the systematic review of the literature. A biased search or the omission of the most important studies will mean that the result is biased. If there is significant publication bias in a field then even a systematic review may not identify all relevant data.
Useful resources

• Cochrane Handbook, Chapter 9: Analysing data and undertaking meta-analyses (free):
  http://handbook.cochrane.org/chapter_9/9_analysing_data_and_undertaking_meta_analyses.htm

• Revman 5 software (free):
  http://tech.cochrane.org/revman/download


• Meta PDF document for r (free):
  https://cran.r-project.org/web/packages/meta/meta.pdf
Recommended reading:

• A good introduction to meta-analysis can be found in a series of six short education articles published in the BMJ during 1997-98, which are as relevant today as they were in 1997 and the Cochrane Handbook for systematic reviews of interventions which was updated much more recently (2011). These BMJ articles form much of the book: "Systematic reviews in health care: meta-analysis in context, 2nd Edition" by Egger M, Davey Smith G, and Altman DG (BMJ Publishing Group 2001). The Cochrane Handbook and the first two BMJ articles provide a general overview:


Additional reading:


