Session II: Heterogeneity in Meta-Analysis

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IBC Short Course
Florence, 6 July 2014

Plan of the Session

The aim of this session is to:

- introduce random effects model and sources of heterogeneity, and its consequences;
- discuss how to detect heterogeneity;
- introduce statistical methods which attempt to allow for heterogeneity (e.g. subgroup analysis and meta-regression), and
- illustrate with examples.

At the end of this session the objectives are that you should

- understand the sources, and potential consequences of heterogeneity;
- understand, and be able to perform subgroup analysis and meta-regression, and
- be able to summarise the results for a clinical audience.

Random effects model

DerSimonian and Laird (1986); Fleiss (1993):

\( \hat{\theta}_i \overset{iid}{\sim} N(\theta, \sigma_k^2) \)

- \( \hat{\theta}_i \) observed treatment effect in study \( i \)
- \( \theta_k \) true mean in study \( i \), \( \sigma_k \) standard error in study \( i \)
- True study means \( \theta_k \) vary randomly around a fixed global mean \( \theta \) with a between-study (heterogeneity) variance \( \tau^2 \):

\( \theta_k \overset{iid}{\sim} N(\theta, \tau^2) \)

Alternative notation

\( \hat{\theta}_k = \theta + \sqrt{\sigma_k^2 + \tau^2} \epsilon_k, \quad \epsilon_k \overset{iid}{\sim} N(0, 1) \)

- Two variance components: \( \sigma_k^2 \) within-study sampling variance, \( \tau^2 \) between-study (heterogeneity) variance
Random Effects Model – Graphical Presentation

Study 1
Study 2
Study 3
Study 4
Study 5

Odds ratio

Inverse variance weighting (both models)

- Pooled effect estimate: Weighted mean of the study estimates
  \[
  \hat{\theta} = \frac{\sum w_k \hat{\theta}_k}{\sum w_k}
  \]

- Weights in fixed effect model:
  \[
  w_k = \frac{1}{\hat{\sigma}_k^2}
  \]

- Weights in random effects model:
  \[
  w_k = \frac{1}{\hat{\sigma}_k^2 + \tau^2}
  \]

- Large heterogeneity ⇒ Weights tend to be more similar ⇒ Smaller studies get larger weights

Comparison of Random and Fixed Effect Model

- Random effects model: Effects vary randomly around a global mean
  - Exchangeability: Effects are assumed to be exchangeable a-priori (Higgins et al., 2009)
    - Study-treatment interactions (contrasts) interpreted as a random sample from a ‘population of potential treatment effects’ (Senn, 2000, 2010)
  - Confidence intervals for random effects model at least as wide as those for fixed effect model
  - In addition, Higgins et al. (2009) proposed a prediction interval that gives a range of effects of future studies

- Fixed effect model
  - Special case of random effects model for \( \tau^2 = 0 \)
    ⇒ Often no difference in pooled estimates since often \( \tau^2 \approx 0 \)
Sources of Heterogeneity

Principal sources of heterogeneity in meta-analysis:

- **Clinical baseline heterogeneity** between patients from different studies (e.g. baseline characteristics); not necessarily reflected on outcome measurement scale
- **Heterogeneity from other sources**, e.g. design-related heterogeneity
- **Heterogeneity reporting and related bias**, e.g. selective publication of small studies if they show an effect
- **Statistical heterogeneity** quantified on the outcome measurement scale (may or may not be clinically relevant and may or may not be statistically significant)
  - Random effects modelling, subgroup analysis, meta-regression

Example: Amiodarone for Conversion of Atrial Fibrillation

Letelier et al. (2003), Arch Intern Med:

- 21 randomised or quasi-randomised controlled trials
- Patients with atrial fibrillation (AF) of any etiology and duration
- Amiodarone compared with placebo, digoxin, CCB, or no treatment
- Primary outcome: conversion to sinus rhythm within 4 weeks (binary outcome)

```r
> amio <- read.table(file="Amiodarone.csv", header=TRUE, sep = ",", + quote="\"", dec=".", fill = TRUE)
> names(amio)
[1] "Study" "afduration" "RR" "LL" "UL" "N"
> amio$logRR <- log(amio$RR)
> # Recalculation of standard errors
> amio$SE <- (log(amio$UL)-log(amio$LL))/2/1.96
> m1 <- metagen(logRR, SE, data=amio, sm="RR", studlab=Study)
```

### Explaining heterogeneity in meta-analysis

- **Random effects model**
  - Adjusts for unexplained heterogeneity (via wider confidence interval)
  - Does not explain heterogeneity
- **Subgroup analysis**
  - Use categorical variable (with limited number of possible values) to define subgroups – ideally pre-specified variable
  - Explains heterogeneity well if large variation exists between subgroup means and little variation within subgroups
  - Examples:
    - High risk vs low risk patients
    - High quality vs low quality studies
- **Meta-regression**
  - Extension of subgroup analysis by allowing for continuous variables
  - Example: Geographical latitude as effect modifier for efficacy of vaccine in tuberculosis prevention (Colditz et al., 1994)
  - Risk of ecological bias if continuous variable measured on study-level (e.g. mean age) (Higgins and Thompson, 2004)
Amiodarone example – Inverse Variance Method

```r
> print(summary(m1), digits=2)
```

Number of studies combined: k=21

<table>
<thead>
<tr>
<th>RR</th>
<th>95%-CI</th>
<th>z</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>1.45 [1.35; 1.56]</td>
<td>9.93</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1.53 [1.32; 1.76]</td>
<td>5.77</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Quantifying heterogeneity:

<table>
<thead>
<tr>
<th>tau^2</th>
<th>H [95% CI]</th>
<th>I^2 [%] [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0581</td>
<td>1.71 [1.36; 2.15]</td>
<td>65.8% [45.8%; 78.4%]</td>
</tr>
</tbody>
</table>

Test of heterogeneity:

<table>
<thead>
<tr>
<th>Q</th>
<th>d.f.</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>58.46</td>
<td>20</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Details on meta-analytical method:

- Inverse variance method
- DerSimonian-Laird estimator for tau^2

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Amiodarone example – Subgroup Analysis

A priori specified subgroup analyses:

1. Mean duration of the current AF episode (≤ 48 vs > 48 hours)
2. Mean left atrial size (< 45 vs ≥ 45 mm)
3. Proportion of patients with underlying cardiovascular disease (< 50% vs ≥ 50%)
4. Type of control treatment (placebo or no treatment vs digoxin vs CCB)
5. Amiodarone regimen (single vs continuous oral or intravenous dosage)
6. Time to outcome measurement (< 12 vs ≥ 12 hours)

```r
> m2 <- update(m1, byvar=afduration, print.byvar=FALSE)
> m3 <- update(m1, byvar=afduration, print.byvar=FALSE, tau.common=TRUE)
```

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Amiodarone example – Forest plot with subgroups

```r
> forest(m2, leftcols="studlab", xlim=c(0.05, 20),
+ hetstat=FALSE, overall=FALSE, col.by="darkblue")
```

<table>
<thead>
<tr>
<th>Study</th>
<th>AF Duration &lt;= 48h</th>
<th>AF Duration &gt; 48h</th>
<th>Fixed effect model</th>
<th>Random effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowan 1986</td>
<td>1.11 [0.78; 1.58]</td>
<td>4.33 [2.79; 6.73]</td>
<td>1.11 [0.78; 1.58]</td>
<td>4.33 [2.79; 6.73]</td>
</tr>
<tr>
<td>Noc 1990</td>
<td>1.00 [0.77; 1.27]</td>
<td>1.36 [1.00; 1.86]</td>
<td>1.00 [0.77; 1.27]</td>
<td>1.36 [1.00; 1.86]</td>
</tr>
<tr>
<td>Capucci 1992</td>
<td>0.77 [0.37; 1.61]</td>
<td>1.15 [0.91; 1.45]</td>
<td>0.77 [0.37; 1.61]</td>
<td>1.15 [0.91; 1.45]</td>
</tr>
<tr>
<td>Cochrane 1994</td>
<td>1.15 [0.91; 1.45]</td>
<td>1.29 [0.97; 1.72]</td>
<td>1.15 [0.91; 1.45]</td>
<td>1.29 [0.97; 1.72]</td>
</tr>
<tr>
<td>Hsu 1995</td>
<td>1.33 [0.71; 2.48]</td>
<td>1.53 [0.71; 2.48]</td>
<td>1.33 [0.71; 2.48]</td>
<td>1.53 [0.71; 2.48]</td>
</tr>
<tr>
<td>Kontopanakis 1993</td>
<td>1.05 [0.69; 1.60]</td>
<td>1.13 [0.64; 1.92]</td>
<td>1.05 [0.69; 1.60]</td>
<td>1.13 [0.64; 1.92]</td>
</tr>
<tr>
<td>Dorian 1994</td>
<td>1.42 [0.86; 1.68]</td>
<td>1.32 [0.86; 1.68]</td>
<td>1.42 [0.86; 1.68]</td>
<td>1.32 [0.86; 1.68]</td>
</tr>
<tr>
<td>Garth 1996</td>
<td>1.26 [0.83; 1.94]</td>
<td>1.13 [0.74; 1.73]</td>
<td>1.26 [0.83; 1.94]</td>
<td>1.13 [0.74; 1.73]</td>
</tr>
<tr>
<td>Kontopanakis 1998</td>
<td>1.41 [0.75; 2.64]</td>
<td>1.12 [0.62; 1.99]</td>
<td>1.41 [0.75; 2.64]</td>
<td>1.12 [0.62; 1.99]</td>
</tr>
<tr>
<td>Bellard 1999</td>
<td>1.46 [0.99; 2.16]</td>
<td>1.17 [0.76; 1.80]</td>
<td>1.46 [0.99; 2.16]</td>
<td>1.17 [0.76; 1.80]</td>
</tr>
<tr>
<td>Kobylanski 1999</td>
<td>1.43 [1.14; 1.79]</td>
<td>2.04 [1.55; 2.66]</td>
<td>1.43 [1.14; 1.79]</td>
<td>2.04 [1.55; 2.66]</td>
</tr>
<tr>
<td>Cubicci 2000</td>
<td>2.45 [1.49; 4.02]</td>
<td>1.70 [1.03; 2.85]</td>
<td>2.45 [1.49; 4.02]</td>
<td>1.70 [1.03; 2.85]</td>
</tr>
<tr>
<td>Vardas 2000</td>
<td>2.01 [1.55; 2.60]</td>
<td>1.32 [0.96; 1.82]</td>
<td>2.01 [1.55; 2.60]</td>
<td>1.32 [0.96; 1.82]</td>
</tr>
<tr>
<td>Cybulski 2001</td>
<td>1.40 [1.03; 1.86]</td>
<td>1.40 [1.03; 1.86]</td>
<td>1.40 [1.03; 1.86]</td>
<td>1.40 [1.03; 1.86]</td>
</tr>
</tbody>
</table>

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**Notation for Subgroup Analysis (like Analysis of Variance)**

- p subgroups of studies (s = 1, ..., p)
  - Within subgroup s, K_s studies (k = 1, ..., K_s)
  - K = \( \sum_{s=1}^{p} K_s \) total number of studies over all subgroups
- Weighted mean estimate for subgroup s (s = 1, ..., p):
  \[ \hat{\theta}_s = \frac{\sum_{k=1}^{K_s} w_{sk} \hat{\theta}_{sk}}{\sum_{k=1}^{K_s} w_{sk}} \]
- Weight w_{sk} is the inverse variance of study k in subgroup s
- Denominator is the subgroup weight W_s = \( \sum_{k=1}^{K_s} w_{sk} \)
- Global mean
  \[ \hat{\theta} = \frac{\sum_{s=1}^{p} \sum_{k=1}^{K_s} w_{sk} \hat{\theta}_{sk}}{\sum_{s=1}^{p} \sum_{k=1}^{K_s} w_{sk}} \]
Heterogeneity in Meta-Analysis

**Heterogeneity Statistics**

- Between-groups heterogeneity statistic $Q_B$:
  \[ Q_B = \sum_{s=1}^{p} W_s (\hat{\theta}_s - \hat{\theta})^2 \]

- Under homogeneity between subgroups, $Q_B$ follows a $\chi^2$-distribution with $p - 1$ degrees of freedom

- Within-group heterogeneity statistic $Q_W$:
  \[ Q_W = \sum_{s=1}^{p} \sum_{k=1}^{K_s} w_{sk} (\hat{\theta}_{sk} - \hat{\theta}_s)^2 \]

- Under homogeneity within all subgroups, $Q_W$ follows a $\chi^2$-distribution with $K - p$ degrees of freedom

**Partition of $Q$ (in Fixed Effect Model)**

- $Q_W$ can be partitioned into subgroup-specific parts $Q_{Ws}$ by
  \[ Q_W = \sum_{s=1}^{p} Q_{Ws}, \]
  each with $K_s - 1$ degrees of freedom

- $Q_W$ has $\sum_{s=1}^{p} (K_s - 1) = \sum_{s=1}^{p} K_s - p = K - p$ degrees of freedom

- $Q_{Ws}$ measures the extent of heterogeneity attributed to subgroup $s$

- In total, we have
  \[ Q = Q_B + Q_W \]
  with $(p - 1) + (K - p) = K - 1$ degrees of freedom

(Cooper et al., 2009)

**Amiodarone example – Partition of $Q$**

```r
> print(summary(m2, comb.random=FALSE), digits=2)
*** Output truncated ***
```

Test of heterogeneity:

<table>
<thead>
<tr>
<th>Q d.f.</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>58.46</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Results for subgroups (fixed effect model):

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>k</th>
<th>RR</th>
<th>95%-CI</th>
<th>Q</th>
<th>$\hat{\tau}^2$</th>
<th>I^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF Duration &lt;= 48h</td>
<td>16</td>
<td>1.40</td>
<td>[1.30; 1.51]</td>
<td>30.58</td>
<td>0.0243</td>
<td>60.9%</td>
</tr>
<tr>
<td>AF Duration &gt; 48h</td>
<td>5</td>
<td>4.33</td>
<td>[2.79; 6.73]</td>
<td>3.46</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Test for subgroup differences (fixed effect model):

<table>
<thead>
<tr>
<th>Q d.f.</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between groups</td>
<td>24.42</td>
</tr>
<tr>
<td>Within groups</td>
<td>34.04</td>
</tr>
</tbody>
</table>

**Amiodarone example: AF subgroup results**

- Fixed effect model ($Q_B = 24.42, df = 1, p < 0.0001$):
  \[ Q_W = 34.04, df = 19, p = 0.018 \]

- Random effects model ($Q_B = 23.69, df = 1, p < 0.0001$):

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>k</th>
<th>RR</th>
<th>95%-CI</th>
<th>Q</th>
<th>$\hat{\tau}^2$</th>
<th>I^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF Duration &lt;= 48h</td>
<td>16</td>
<td>1.40</td>
<td>[1.25; 1.57]</td>
<td>30.58</td>
<td>0.0243</td>
<td>50.9%</td>
</tr>
<tr>
<td>AF Duration &gt; 48h</td>
<td>5</td>
<td>4.33</td>
<td>[2.71; 6.96]</td>
<td>3.46</td>
<td>0.023</td>
<td>0%</td>
</tr>
</tbody>
</table>

  Random effects model with common $\tau^2$ ($Q_B = 20.92, df = 1, p < 0.0001$):

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>k</th>
<th>RR</th>
<th>95%-CI</th>
<th>Q</th>
<th>$\hat{\tau}^2$</th>
<th>I^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF Duration &lt;= 48h</td>
<td>16</td>
<td>1.40</td>
<td>[1.25; 1.57]</td>
<td>30.58</td>
<td>0.0230</td>
<td>50.9%</td>
</tr>
<tr>
<td>AF Duration &gt; 48h</td>
<td>5</td>
<td>4.33</td>
<td>[2.71; 6.96]</td>
<td>3.46</td>
<td>0.0230</td>
<td>0%</td>
</tr>
</tbody>
</table>
Meta-Regression

Fixed effect meta-regression:
\[
\hat{\theta}_k = \theta + \beta x_k + \sigma_k \epsilon_k, \quad \epsilon_k \sim N(0, 1), \quad k = 1, \ldots, K
\]

Random effects meta-regression:
\[
\hat{\theta}_k = \theta + \beta x_k + u_k + \sigma_k \epsilon_k, \quad \epsilon_k \sim N(0, 1); \quad u_k \sim N(0, \tau^2)
\]

with covariate \(x_k\) and regression parameter \(\beta\)

Meta-regression of AF duration in amiodarone example:
- \(x_k = 1\) if AF duration > 48 hours
- \(x_k = 0\) if AF duration \(\leq 48\) hours

Example: Vaccine for the prevention of tuberculosis

Colditz et al. (1994), JAMA:
- Efficacy of vaccine for the prevention of tuberculosis
- 13 prospective trials

Amiodarone example – Meta-regression

```r
> mr2 <- metareg(m2)
> print(mr2)
```

Mixed-Effects Model (k = 21; tau^2 estimator: DL)

\*\*\* Output truncated \*\*\*

Test for Residual Heterogeneity:
QE(df = 19) = 34.0399, p-val = 0.0182

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 20.9197, p-val < .0001

Model Results:

<table>
<thead>
<tr>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>intrcpt</td>
<td>0.3353</td>
<td>0.0671</td>
<td>&lt;.0001</td>
<td>0.2234</td>
</tr>
<tr>
<td>AF Duration &gt; 48h</td>
<td>1.1330</td>
<td>0.2477</td>
<td>4.5738</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

- Risk Ratio (AF \(\leq 48\) hours): \(\exp(\hat{\theta}) = \exp(0.3353) = 1.40\)
- Risk Ratio (AF > 48 hours): \(\exp(\hat{\theta} + \hat{\beta}) = \exp(0.3353 + 1.1330) = 4.34\)

```r
> data(dat.colditz1994, package="metafor")
> m4 <- metabin(tpos, tpos+tneg, cpos, cpos+cneg, data=dat.colditz1994, studlab=paste(author, year))
> forest(m4, rightcols=c("effect", "ci"), print.pval.Q=FALSE, + label.left="Vaccine better", label.right="Vaccine worse")
```
### Vaccination example – Forest plot

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%−CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronsen 1948</td>
<td>4</td>
<td>123</td>
<td>11</td>
<td>0.41</td>
<td>[0.13; 1.26]</td>
</tr>
<tr>
<td>Ferguson &amp; Simes 1949</td>
<td>6</td>
<td>306</td>
<td>20</td>
<td>0.20</td>
<td>[0.09; 0.49]</td>
</tr>
<tr>
<td>Rosenthal et al 1960</td>
<td>3</td>
<td>231</td>
<td>11</td>
<td>0.26</td>
<td>[0.07; 0.92]</td>
</tr>
<tr>
<td>Hart &amp; Sutherland 1977</td>
<td>62</td>
<td>13598</td>
<td>248</td>
<td>0.24</td>
<td>[0.16; 0.31]</td>
</tr>
<tr>
<td>Frimodt-Moller et al 1973</td>
<td>33</td>
<td>5069</td>
<td>47</td>
<td>0.80</td>
<td>[0.62; 1.25]</td>
</tr>
<tr>
<td>Stein &amp; Aronsen 1953</td>
<td>180</td>
<td>1541</td>
<td>372</td>
<td>0.46</td>
<td>[0.39; 0.54]</td>
</tr>
<tr>
<td>Vandiver et al 1973</td>
<td>8</td>
<td>2545</td>
<td>10</td>
<td>0.20</td>
<td>[0.08; 0.50]</td>
</tr>
<tr>
<td>TPT Madras 1980</td>
<td>505</td>
<td>80391</td>
<td>499</td>
<td>1.01</td>
<td>[0.89; 1.14]</td>
</tr>
<tr>
<td>Coetzee &amp; Berjak 1968</td>
<td>29</td>
<td>7499</td>
<td>45</td>
<td>0.63</td>
<td>[0.39; 1.00]</td>
</tr>
<tr>
<td>Rosenthal et al 1961</td>
<td>17</td>
<td>1716</td>
<td>65</td>
<td>0.25</td>
<td>[0.15; 0.43]</td>
</tr>
<tr>
<td>Comstock et al 1974</td>
<td>186</td>
<td>50634</td>
<td>141</td>
<td>0.71</td>
<td>[0.57; 0.89]</td>
</tr>
<tr>
<td>Comstock &amp; Webster 1969</td>
<td>5</td>
<td>2498</td>
<td>3</td>
<td>1.56</td>
<td>[0.37; 6.53]</td>
</tr>
<tr>
<td>Comstock et al 1976</td>
<td>27</td>
<td>16913</td>
<td>29</td>
<td>0.98</td>
<td>[0.58; 1.66]</td>
</tr>
</tbody>
</table>

### Vaccination example – Forest plot (Sorted by Latitude)

<table>
<thead>
<tr>
<th>Study</th>
<th>Latitude</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%−CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frimodt-Moller et al 1973</td>
<td>13</td>
<td>0.80</td>
<td>[0.52; 1.25]</td>
<td></td>
</tr>
<tr>
<td>TPT Madras 1980</td>
<td>13</td>
<td>1.01</td>
<td>[0.89; 1.14]</td>
<td></td>
</tr>
<tr>
<td>Comstock et al 1974</td>
<td>18</td>
<td>0.71</td>
<td>[0.57; 0.89]</td>
<td></td>
</tr>
<tr>
<td>Vandiver et al 1973</td>
<td>19</td>
<td>0.20</td>
<td>[0.08; 0.50]</td>
<td></td>
</tr>
<tr>
<td>Coetzee &amp; Berjak 1968</td>
<td>27</td>
<td>0.63</td>
<td>[0.39; 1.00]</td>
<td></td>
</tr>
<tr>
<td>Comstock &amp; Webster 1969</td>
<td>33</td>
<td>1.56</td>
<td>[0.37; 6.53]</td>
<td></td>
</tr>
<tr>
<td>Comstock et al 1976</td>
<td>33</td>
<td>0.98</td>
<td>[0.58; 1.66]</td>
<td></td>
</tr>
<tr>
<td>Rosenthal et al 1960</td>
<td>42</td>
<td>0.25</td>
<td>[0.07; 0.92]</td>
<td></td>
</tr>
<tr>
<td>Stein &amp; Aronsen 1953</td>
<td>44</td>
<td>0.41</td>
<td>[0.13; 1.26]</td>
<td></td>
</tr>
<tr>
<td>Hart &amp; Sutherland 1977</td>
<td>52</td>
<td>0.24</td>
<td>[0.18; 0.31]</td>
<td></td>
</tr>
<tr>
<td>Ferguson &amp; Simes 1949</td>
<td>55</td>
<td>0.20</td>
<td>[0.09; 0.49]</td>
<td></td>
</tr>
</tbody>
</table>

### Example: Vaccine for the prevention of tuberculosis

Colditz et al. (1994), JAMA:

- Efficacy of vaccine for the prevention of tuberculosis
- 13 prospective trials
- Random effects meta-regression

Variables considered in meta-regression:

- Absolute geographical latitude (i.e. distance from the equator)
- Study validity score
- Mean age at vaccination
- Study design
- Year of publication
- Year trial began
- Follow-up time (in years)

### Vaccination example – Meta-Regression

Random effects meta-regression:

$$\hat{\theta}_k = \theta + \beta x_k + u_k + \sigma_k e_k, \quad e_k \overset{i.i.d.}{\sim} N(0, 1), \quad u_k \overset{i.i.d.}{\sim} N(0, \tau^2)$$

where covariate $x_k$ is the absolute geographical latitude

Results:

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.2595</td>
<td>0.2323</td>
<td>1.12</td>
</tr>
<tr>
<td>Latitude</td>
<td>$\hat{\beta} = -0.0292$</td>
<td>0.0067</td>
<td>-4.34</td>
</tr>
</tbody>
</table>

$$\tau^2 = 0.0633$$ (estimated according to DerSimonian and Laird (1986))

Parameter $\beta$ is a log risk ratio

1 R command: `mr4 <- metareg(m4, ablat)`
Vaccination example – Bubble plot

> bubble(mr4, lwd=2, col.line="blue")

Caveats with Meta-Regression and Subgroup Analysis

Thompson and Higgins (2002); Higgins and Thompson (2004):
- Visual presentation of relationship essential
- Often meta-regression does not explain all observed heterogeneity
  ⇒ Meta-regression should be based on random effects model
- Risk of spurious findings from meta-regression/subgroup analysis
  - Avoid meta-regression if there are less than five studies
  - Limit the number of covariates used in meta-regression
  - Use only pre-specified characteristics; avoid ‘data-dredging’
- Be careful to interpret the coefficient estimates correctly. E.g. if the outcome is the (log) odds ratio, they are (log) odds ratios of odds ratios.

Summary

- Understanding and – as far as possible – explaining heterogeneity is important if we are to have confidence in the results of our meta-analysis.
- Decomposition of the heterogeneity statistic, $Q$, helps pinpoint the causes.
- Subgroup analyses and meta-regression can help explain heterogeneity, but really need to be pre-specified;
- If heterogeneity is present then the random effects model should be used instead of the fixed effects model – principally because of the larger standard error, which reflects the heterogeneity.
- However, if there is a contextually important difference between the fixed and random effect estimates, this may indicate that smaller studies are systematically different, and further investigation is needed – see the next session.
References


