Meta-analysis & Systematic Review: An Introduction

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META-ANALYSIS

• A statistical analysis of results from separate studies, examining sources of differences in results among studies, and leading to a quantitative summary of the results if the results are judged sufficiently similar to support such synthesis.

Dictionary of epidemiology, 2nd edition
Systematic Review

- The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.

- Meta-analysis may be, but is not necessarily, used as part of this process.

Dictionary of epidemiology, 2nd edition
Cochrane Reviews

• These are systematic reviews of primary research in health care and health policy.

• They investigate the effects of interventions for prevention, treatment and rehabilitation.

• They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting.

http://www.cochrane.org/cochrane-reviews
All reviews (Overviews)

- Meta-analysis
- Individual patient data meta-analysis
- Traditional or Non-systematic reviews
- Systematic Reviews
Hallmarks of a good systematic review

• A clearly formulated question
• A thorough search for all the existing primary research on a topic that meets certain criteria
• Assessment of the primary studies using stringent guidelines
• Establish whether or not there is conclusive evidence about a specific treatment.

http://www.cochrane.org/cochrane-reviews
WHEN to do a meta-analysis?

• When more than one study has estimated an effect

• When there are no differences in the study characteristics (patients, interventions) that may affect outcome, so that combining data will produce a clinically useful and meaningful result

• When the outcome has been measured in similar ways

• When the data are available (beware when only some data are available)

• REMEMBER, you do not need to statistically pool results to include a systematic review
The QUOROM (Quality Of Reporting Of Meta-analyses) Statement

<table>
<thead>
<tr>
<th>Heading</th>
<th>Subheading</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
<td>Identify the report as a meta-analysis [or systematic review] of RCTs²⁶</td>
</tr>
<tr>
<td>Abstract</td>
<td></td>
<td>Use a structured format²⁷</td>
</tr>
<tr>
<td></td>
<td><strong>Describe</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Objectives</strong></td>
<td>The clinical question explicitly</td>
</tr>
<tr>
<td></td>
<td><strong>Data sources</strong></td>
<td>The databases (ie, list) and other information sources</td>
</tr>
<tr>
<td>Review methods</td>
<td></td>
<td>The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication</td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td>Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses</td>
</tr>
<tr>
<td>Conclusion</td>
<td></td>
<td>The main results</td>
</tr>
</tbody>
</table>
Steps in a meta-analysis

- Define comparisons (interventions)
- Decide on appropriate study results (outcomes) for each comparison
- Select an appropriate summary statistic for each comparison
- Weight studies
- Pool results (Data synthesis/meta-analysis)
- Assess the similarity of study results within each comparison (homogeneity)
- Consider the reliability of the summaries
Defining comparisons

- Clinically meaningful comparisons
- Specific interventions or generic ones
- Drug A vs Drug B
Combining results

- For example:
  - 6 controlled trials studying the effect of hypothermia on death rates in head injured patients
- How can we summarise the effect of hypothermia across these trials?
Summary statistic for each study

• Calculate a single summary statistic to represent the effect found in each study
• For binary data
  – Ratio of risks (risk ratio; relative risk)
  – Difference in risks (risk difference)
  – Ratio of odds (odds ratio)
• For continuous data
  – Difference between means
For example

- 6 studies, hypothermia following head injury vs. no hypothermia; relative risks of death (95% CI)
  - 1.0  (0.08, 11.93)
  - 0.96 (0.44, 2.10)
  - 0.67 (0.24, 1.83)
  - 0.45 (0.21, 0.96)
  - 0.97 (0.44, 2.13)
  - 1.08 (0.27, 4.37)
Weighting studies

- More weight to the studies which give us more information
  - More participants
  - More events
  - Lower variance

- Weight is proportional to inverse variance
For example

<table>
<thead>
<tr>
<th></th>
<th>Deaths on hypothermia</th>
<th>Deaths on control</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifton 1992</td>
<td>1/5</td>
<td>1/5</td>
<td>2.4</td>
</tr>
<tr>
<td>Clifton 1993</td>
<td>8/23</td>
<td>8/22</td>
<td>20.0</td>
</tr>
<tr>
<td>Hirayama 1994</td>
<td>4/12</td>
<td>5/10</td>
<td>13.4</td>
</tr>
<tr>
<td>Jiang 1996</td>
<td>6/23</td>
<td>14/24</td>
<td>33.5</td>
</tr>
<tr>
<td>Marion 1997</td>
<td>9/39</td>
<td>10/42</td>
<td>23.6</td>
</tr>
<tr>
<td>Meissner 1998</td>
<td>3/12</td>
<td>3/13</td>
<td>7.1</td>
</tr>
</tbody>
</table>
Algorithm of statistical choices available to systematic reviewers.
Displaying results graphically

- forest plots
  - Commonly used
### Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 3 Neurological Death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favours Surgery+WBRT</th>
<th>Favours WBRT alone</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mintz</td>
<td>12/43</td>
<td></td>
<td>27.4 %</td>
<td>0.52   [ 0.22, 1.27 ]</td>
<td></td>
</tr>
<tr>
<td>Patchell</td>
<td>11/22</td>
<td></td>
<td>33.7 %</td>
<td>0.57   [ 0.26, 1.27 ]</td>
<td></td>
</tr>
<tr>
<td>Vecht</td>
<td>10/30</td>
<td></td>
<td>39.0 %</td>
<td>0.96   [ 0.46, 2.02 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (all)</strong></td>
<td>95</td>
<td></td>
<td>100.0 %</td>
<td>0.68   [ 0.43, 1.09 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total over (Favours WBRT alone) 95, 60.0%

Test for overall effect: Z = 1.61 (P = 0.11)

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**Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death.**

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 3 Neurological Death

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<td>9/22</td>
<td>10/30</td>
<td></td>
<td>39.0%</td>
<td>0.96 [0.46, 2.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>95</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.68 [0.43, 1.09]</strong></td>
</tr>
</tbody>
</table>

For each study there is an id (first author and date of publication)

The data for each trial are here, divided into the experimental and control groups

This is the % weight given to this study in the pooled analysis

Each study is given a blob, placed where the data measure the effect.

- The size of the blob is proportional to the % weight
- The horizontal line is called a confidence interval and is a measure of how we think the result of this study might vary with the play of chance.
- The wider the horizontal line is, the less confident we are of the observed effect.
The vertical line in the middle is where the treatment and control have the same effect - there is no difference between the two.

At the bottom there’s a horizontal line. This is the scale measuring the treatment effect. Here the outcome is death and towards the left the scale is less than one, meaning the treatment has made death less likely.

Take care to read what the labels say - things to the left do not always mean the treatment is better than the control.

The pooled analysis is given a diamond shape where the widest bit in the middle is located at the calculated best guess (point estimate), and the horizontal width is the confidence interval.

**Note on interpretation**
If the confidence interval crosses the line of no effect, this is equivalent to saying that we have found no statistically significant difference in the effects of the two interventions.

**Analysis 01.01: Comparison 01 All nursing intervention vs control trials, grouped by intensity of intervention, Outcome 01 Smoking cessation at longest follow-up**

**Review:** Nursing interventions for smoking cessation

**Comparison:** 01 All nursing intervention vs control trials, grouped by intensity of intervention

**Outcome:** 01 Smoking cessation at longest follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 High intensity intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen 1996</td>
<td>9/14</td>
<td>6/11</td>
<td></td>
<td>0.7</td>
<td>1.48 [0.30, 7.16]</td>
</tr>
<tr>
<td>Bolman 2002</td>
<td>103/334</td>
<td>110/401</td>
<td></td>
<td>1.66</td>
<td>1.18 [0.86, 1.62]</td>
</tr>
<tr>
<td>Casey 2000</td>
<td>24/147</td>
<td>24/139</td>
<td></td>
<td>2.8</td>
<td>1.37 [1.00, 1.91]</td>
</tr>
<tr>
<td>Dennis 1997</td>
<td>16/37</td>
<td>16/37</td>
<td></td>
<td>1.8</td>
<td>2.78 [1.91, 4.15]</td>
</tr>
<tr>
<td>Curry 2003</td>
<td>4/156</td>
<td>3/147</td>
<td></td>
<td>0.8</td>
<td>1.26 [0.28, 5.63]</td>
</tr>
<tr>
<td>DeBusk 1994</td>
<td>92/131</td>
<td>64/121</td>
<td></td>
<td>6.6</td>
<td>2.08 [1.25, 3.46]</td>
</tr>
<tr>
<td>Hollis 1993</td>
<td>79/197</td>
<td>15/710</td>
<td></td>
<td>7.8</td>
<td>1.33 [1.09, 2.77]</td>
</tr>
<tr>
<td>Lancaster 1999</td>
<td>8/249</td>
<td>10/248</td>
<td></td>
<td>0.9</td>
<td>0.79 [0.31, 2.03]</td>
</tr>
<tr>
<td>Lewis 1998</td>
<td>4/62</td>
<td>3/61</td>
<td></td>
<td>0.7</td>
<td>1.33 [0.29, 6.07]</td>
</tr>
<tr>
<td><strong>Miller 1997</strong></td>
<td>245/1000</td>
<td>191/942</td>
<td></td>
<td>37.3</td>
<td>1.34 [1.03, 1.58]</td>
</tr>
<tr>
<td>Rice 1994</td>
<td>21/207</td>
<td>16/48</td>
<td></td>
<td>2.3</td>
<td>0.19 [0.08, 0.46]</td>
</tr>
<tr>
<td>Rigotti 1994</td>
<td>12/44</td>
<td>12/43</td>
<td></td>
<td>2.4</td>
<td>0.46 [0.14, 1.20]</td>
</tr>
<tr>
<td>Taylor 1990</td>
<td>47/84</td>
<td>20/82</td>
<td></td>
<td>4.4</td>
<td>3.89 [1.98, 8.03]</td>
</tr>
<tr>
<td>Tenzsawa 2001</td>
<td>8/117</td>
<td>1/111</td>
<td></td>
<td>1.0</td>
<td>4.75 [1.26, 17.99]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4574</td>
<td>3093</td>
<td></td>
<td>87.0</td>
<td>1.43 [1.24, 1.64]</td>
</tr>
<tr>
<td>Total events: 686 (Treatment), 473 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=52.42, df=13 p=0.0001 I² = 75.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=4.98 p&lt;0.000001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pooling continuous data: what you need

• Number of participants in each group, means and standard deviations

• Each trial will present, or allow you to calculate a *mean difference*.

• Mean difference is the difference between the means of the two groups
When to use MD / SMD

(Weighted) Mean Difference
• When studies have comparable outcome measures (i.e. Same scale, probably same length of follow-up etc)

Standardized Mean Difference
• When studies use different outcome measurements to address the same clinical outcome (e.g. different scales)
## Continuous data - Weighted Mean Difference

**Review:** Antibiotics for acute bronchitis (Version 02)

**Comparison:** 05 Days of cough

**Outcome:** 01 mean number of days of cough

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment N</th>
<th>Mean (SD)</th>
<th>Control N</th>
<th>Mean (SD)</th>
<th>WMD (fixed)</th>
<th>Weight %</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slott 1976</td>
<td>104</td>
<td>6.40 (2.60)</td>
<td>103</td>
<td>6.30 (3.00)</td>
<td>0.10 [-0.67, 0.87]</td>
<td>56.27</td>
<td></td>
</tr>
<tr>
<td>Villanueva 1984</td>
<td>59</td>
<td>7.67 (3.22)</td>
<td>54</td>
<td>9.41 (8.80)</td>
<td>-2.37 [-5.17, 1.29]</td>
<td>2.37</td>
<td></td>
</tr>
<tr>
<td>Schott 1987</td>
<td>15</td>
<td>9.40 (3.03)</td>
<td>15</td>
<td>10.80 (2.38)</td>
<td>-1.40 [-3.83, 0.53]</td>
<td>8.53</td>
<td></td>
</tr>
<tr>
<td>Yarnell 1984</td>
<td>26</td>
<td>4.70 (3.10)</td>
<td>26</td>
<td>6.20 (3.22)</td>
<td>-1.50 [-2.54, -0.46]</td>
<td>30.21</td>
<td></td>
</tr>
<tr>
<td>King 1986</td>
<td>88</td>
<td>8.76 (7.57)</td>
<td>42</td>
<td>8.94 (10.37)</td>
<td>-0.18 [-3.98, 3.59]</td>
<td>2.31</td>
<td></td>
</tr>
<tr>
<td><strong>Total (N=280)</strong></td>
<td>263</td>
<td>8.56 (7.07)</td>
<td>263</td>
<td>9.33 (8.27)</td>
<td>-0.78 [-1.16, -0.01]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 7.71, df = 4 (P = 0.10), I² = 48.1%

Test for overall effect: Z = 1.99 (P = 0.05)
Continuous data - Standardised Mean Difference

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment N</th>
<th>Treatment Mean (SD)</th>
<th>Control N</th>
<th>Control Mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stott 1976</td>
<td>104</td>
<td>5.40 (2.60)</td>
<td>103</td>
<td>6.30 (3.00)</td>
<td></td>
<td>38.61</td>
<td>0.04 [-0.24, 0.31]</td>
</tr>
<tr>
<td>Williamson 1984</td>
<td>35</td>
<td>7.57 (2.91)</td>
<td>34</td>
<td>10.41 (3.60)</td>
<td></td>
<td>13.39</td>
<td>-0.16 [-0.79, 0.53]</td>
</tr>
<tr>
<td>Schier 1987</td>
<td>16</td>
<td>9.40 (3.08)</td>
<td>15</td>
<td>10.80 (2.38)</td>
<td></td>
<td>5.58</td>
<td>-0.41 [-1.21, 0.12]</td>
</tr>
<tr>
<td>Verheij 1994</td>
<td>71</td>
<td>4.70 (3.10)</td>
<td>69</td>
<td>6.20 (3.20)</td>
<td></td>
<td>25.38</td>
<td>-0.47 [-0.81, -0.14]</td>
</tr>
<tr>
<td>King 1996</td>
<td>50</td>
<td>8.76 (7.57)</td>
<td>42</td>
<td>8.94 (10.37)</td>
<td></td>
<td>17.03</td>
<td>-0.02 [-0.43, 0.39]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>280</td>
<td>8.76 (7.57)</td>
<td>263</td>
<td></td>
<td></td>
<td>100.00</td>
<td>-0.18 [-0.35, -0.01]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 6.92$, df = 4 ($P = 0.14$), $I^2 = 42.2\%$
Test for overall effect: $Z = 2.06$ ($P = 0.04$)
Heterogeneity

- Indicates that effect varies a lot across studies
- If heterogeneity is present, a common, summary measure is hard to interpret
Types of heterogeneity

• Statistical
  - Excessive variation in the results of studies
  - Variation in treatment effects above that expected by chance
  – Some degree of statistical heterogeneity is inevitable?
Types of heterogeneity

- Clinical
  - Can be due to differences in:
    - Patient populations studied
    - Interventions used
    - Co-interventions
    - Outcomes measured
Types of heterogeneity

- **Methodological**
  - Variation in methods used in studies e.g. quality of allocation concealment
Identifying heterogeneity graphically

• If studies are estimating the same thing we would expect confidence intervals to overlap to a large extent

• Statistical heterogeneity may appear in a forest plot as poor overlap of confidence intervals

• Look for outliers
## Analysis 01.01. Comparison 01 All nursing intervention vs control trials, grouped by intensity of intervention, Outcome 01 Smoking cessation at longest follow-up

Review: Nursing interventions for smoking cessation  
Comparison: 01 All nursing intervention vs control trials, grouped by intensity of intervention  
Outcome: 01 Smoking cessation at longest follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High intensity intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen 1996</td>
<td>9/14</td>
<td>6/11</td>
<td></td>
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<td>1.18 [0.86, 1.62]</td>
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<tr>
<td>Carlsson 1997</td>
<td>16/32</td>
<td>9/35</td>
<td></td>
<td>1.8</td>
<td>2.70 [1.04, 7.44]</td>
</tr>
<tr>
<td>Curry 2003</td>
<td>4/116</td>
<td>3/147</td>
<td></td>
<td>0.8</td>
<td>1.26 [0.38, 5.63]</td>
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<td></td>
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<td>1.73 [1.09, 2.77]</td>
</tr>
<tr>
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<td>82/294</td>
<td>102/288</td>
<td></td>
<td>1.9</td>
<td>0.79 [0.31, 2.03]</td>
</tr>
<tr>
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<td>3/61</td>
<td></td>
<td>0.7</td>
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<td>22/43</td>
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<td>2.4</td>
<td>0.96 [0.41, 2.20]</td>
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<tr>
<td>Taylor 1990</td>
<td>47/84</td>
<td>20/82</td>
<td></td>
<td>4.4</td>
<td>3.68 [1.98, 6.83]</td>
</tr>
<tr>
<td>Tenzawaz 2001</td>
<td>8/117</td>
<td>1/111</td>
<td></td>
<td>1.0</td>
<td>4.75 [1.26, 17.99]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4574</td>
<td>3093</td>
<td></td>
<td>87.0</td>
<td>1.43 [1.24, 1.64]</td>
</tr>
</tbody>
</table>

Total events: 686 (Treatment), 473 (Control)  
Test for heterogeneity chi-square = 52.12, df = 13, p = 0.0001 M = 75.2%  
Test for overall effect z = 3.95, p = 0.0001

If heterogeneity is found

Statistical models for combining data:

• Fixed effects model
  - it is assumed that the true effect of treatment is the same value in each study (fixed); the differences between studies is solely due to random error
If heterogeneity is found

Statistical models for combining data:

• **Random effects model**
  
  – the treatment effects for the individual studies are assumed to vary around some overall average treatment effect
  
  – Studies tend to be weighted more equally
Identifying factors that can explain heterogeneity

- Sensitivity analysis
- Subgroup analysis
- Meta-regression
When can meta-analyses mislead?

- When a meta-analysis is done outside of a systematic review
- When quality issues are ignored
- When inadequate attention is given to heterogeneity
- When reporting biases are a problem
  - Publication bias
  - Time lag bias
  - Duplicate publication bias
  - Language bias
  - Outcome reporting bias
  - Citation bias

Meta-analysis software

- Free
  - RevMan [Review Manager]
  - Meta-Analyst
  - Epi Meta
  - Easy MA
  - Meta-Test
  - Meta-Stat
- Commercial
  - Comprehensive Meta-analysis
  - Meta-Win
  - WEasy MA
- General stats packages
  - Stata
  - SAS
  - S-Plus

REVMAN is a data entry, word processing and statistical package produced by the Cochrane Collaboration

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http://www.cochrane.org/

Thank you