Meta analysis: an overview

Pizza & Pilots presentation
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Outline:

What is a meta analysis

Meta analyses in action

Basic components
  Identifying studies
  Identifying an effect size
  Combining effects across studies

Issues
  Heterogeneity
  Publication bias

Conclusion
Meta-analysis is a formal method for analyzing the results of several or many randomized clinical trials (RCTs) for the following purposes:

- synthesize information across trials
- synthesize evidence on the true effect of an intervention
- support evidence based policy
- support a new study

A Meta-analyses is often helpful because there are a large number of similar trials being conducted on the same topic.

More highly regarded than a formal preview paper on the topic

Meta analysis is used in many fields of study

- Business
- Criminology
- Education
- Psychology
- Social Epidemiology
- Pharmacy
- Medicine
Reasons why this analysis is useful:

First, RCTs are large and expensive and we would like to gain as much information from them as possible.

Second, we intuitively expect well-performed RCTs to “agree with” one another.

Third, RCTs tend to be externally valid with respect to relative treatment effects, even if selection bias has made the comparison groups atypical for the diseased population.

By 1992 only 6 of the 33 RCTs used in the analysis were positive but the combined effect due to the meta analysis was overwhelmingly positive ($P = 0.0000008$)

Summary effect: 0.79 (95% C.I.: 0.72-0.87) implies the use of streptokinase reduces deaths due to MIs by 21%

32,000 patients randomized post 1977 in RCTs proved the meta-analysis to be correct

Were these RCTs ethical post 1977? Did millions of AMI patients do without a truly effective therapy?
Important contributions continued the Avandia story (2007)

Examined side effects of rosiglitazone on risk of CVD death and AMIs in Type 2 diabetes mellitus

None of the 42 studies included in the analysis were statistically powered to detect these side effects

Meta Analysis showed:

OR for AMI: 1.43 (95% C.I.: 1.03 - 1.98)
OR for CVD death: 1.64 (95% C.I.: 0.98 – 2.74)
Identifying Studies to be used in a Meta Analysis

Conduct an exhaustive literature search: published studies, known resources, abstracts, etc.

Abner et al.,
Current Aging Science, 2011
Example: **Meta-analysis of long-term antiplatelet therapy**

In the 11 randomized trials conducted, therapy consisted of aspirin (ASA), dipyramidole, sulphinpyrazone, or combinations and the endpoints were vascular events defined as myocardial infarction, stroke, or vascular death.

The aggregate effect is an odds ratio of 0.75 ($p < 0.00001$), demonstrating the efficacy of antiplatelet drugs in reducing vascular events (95% CI: 0.60 to 0.82).

Even though 8 of the 11 trials have confidence intervals that include an odds ratio of 1.0, the aggregate evidence from the meta-analysis in favor of treatment is compelling.
### Example 1: Meta analysis of 11 RCTs for Prolonged Antiplatelet Therapy - Case I fixed effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Data</th>
<th>P1</th>
<th>P2</th>
<th>Odds Ratio</th>
<th>Risk Ratio</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-I</td>
<td>58/615  76/624</td>
<td>0.0943</td>
<td>0.1218</td>
<td>0.7524</td>
<td>0.7759</td>
<td>-0.0274</td>
</tr>
<tr>
<td>C-II</td>
<td>128/847  185/878</td>
<td>0.1511</td>
<td>0.2107</td>
<td>0.6677</td>
<td>0.7180</td>
<td>-0.0595</td>
</tr>
<tr>
<td>P-I</td>
<td>244/1620  77/406</td>
<td>0.1506</td>
<td>0.1897</td>
<td>0.7552</td>
<td>0.7921</td>
<td>-0.0366</td>
</tr>
<tr>
<td>P-II</td>
<td>154/1563  218/1565</td>
<td>0.0985</td>
<td>0.1393</td>
<td>0.6760</td>
<td>0.7080</td>
<td>-0.0317</td>
</tr>
<tr>
<td>AMIS</td>
<td>395/2267  427/2257</td>
<td>0.1742</td>
<td>0.1892</td>
<td>0.9044</td>
<td>0.9211</td>
<td>-0.0167</td>
</tr>
<tr>
<td>CDP-A</td>
<td>88/758  110/771</td>
<td>0.1161</td>
<td>0.1427</td>
<td>0.7902</td>
<td>0.8146</td>
<td>-0.0244</td>
</tr>
<tr>
<td>GAMIS</td>
<td>39/317  49/309</td>
<td>0.1230</td>
<td>0.1586</td>
<td>0.7464</td>
<td>0.7779</td>
<td>-0.0315</td>
</tr>
<tr>
<td>ART</td>
<td>102/813  130/816</td>
<td>0.1255</td>
<td>0.1593</td>
<td>0.7578</td>
<td>0.7883</td>
<td>-0.0305</td>
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<tr>
<td>ARIS</td>
<td>38/365  57/362</td>
<td>0.1041</td>
<td>0.1575</td>
<td>0.6246</td>
<td>0.6641</td>
<td>-0.0495</td>
</tr>
<tr>
<td>MIC</td>
<td>65/672  106/668</td>
<td>0.0967</td>
<td>0.1587</td>
<td>0.5695</td>
<td>0.6114</td>
<td>-0.0419</td>
</tr>
<tr>
<td>ROME</td>
<td>9/40  19/40</td>
<td>0.2250</td>
<td>0.4750</td>
<td>0.3325</td>
<td>0.4872</td>
<td>-0.1547</td>
</tr>
</tbody>
</table>

[Combined]

Average: 0.7527  0.7883  -0.0363

Note: This report shows the input data and the three outcomes for each study in the analysis. The 'Average' values are actually weighted averages with weights based on the effects model that was selected.
How does relative weighting of studies occur?

Three possibilities:

1. Most popular: use the inverse of the variance associated with each effect being combined (smaller studies have larger variances and hence less weight)

2. Quality scores assigned to studies

3. Fit a random effects model
<table>
<thead>
<tr>
<th>C1</th>
<th>P1</th>
<th>P2</th>
<th>Odds Ratio</th>
<th>95.0% Lower Confidence Limit</th>
<th>95.0% Upper Confidence Limit</th>
<th>Percent Fixed Effects Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-I</td>
<td>0.0943</td>
<td>0.1218</td>
<td>0.7524</td>
<td>0.5248</td>
<td>1.0786</td>
<td>5.2916</td>
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<tr>
<td>C-II</td>
<td>0.1511</td>
<td>0.2107</td>
<td>0.6677</td>
<td>0.5211</td>
<td>0.8556</td>
<td>11.1695</td>
</tr>
<tr>
<td>P-I</td>
<td>0.1506</td>
<td>0.1897</td>
<td>0.7552</td>
<td>0.5694</td>
<td>1.0016</td>
<td>8.6133</td>
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<tr>
<td>P-II</td>
<td>0.0985</td>
<td>0.1393</td>
<td>0.6760</td>
<td>0.5430</td>
<td>0.8416</td>
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<td>AMIS</td>
<td>0.1742</td>
<td>0.1892</td>
<td>0.9044</td>
<td>0.7775</td>
<td>1.0520</td>
<td>30.0547</td>
</tr>
<tr>
<td>CDP-A</td>
<td>0.1161</td>
<td>0.1427</td>
<td>0.7902</td>
<td>0.5856</td>
<td>1.0661</td>
<td>7.6551</td>
</tr>
<tr>
<td>GAMIS</td>
<td>0.1230</td>
<td>0.1586</td>
<td>0.7464</td>
<td>0.4755</td>
<td>1.1718</td>
<td>3.3762</td>
</tr>
<tr>
<td>ART</td>
<td>0.1255</td>
<td>0.1593</td>
<td>0.7578</td>
<td>0.5733</td>
<td>1.0018</td>
<td>8.8144</td>
</tr>
<tr>
<td>ARIS</td>
<td>0.1041</td>
<td>0.1575</td>
<td>0.6246</td>
<td>0.4035</td>
<td>0.9668</td>
<td>3.5974</td>
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<tr>
<td>MIC</td>
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<td>0.1587</td>
<td>0.5695</td>
<td>0.4100</td>
<td>0.7909</td>
<td>6.3661</td>
</tr>
<tr>
<td>ROME</td>
<td>0.2250</td>
<td>0.4750</td>
<td>0.3325</td>
<td>0.1286</td>
<td>0.8596</td>
<td>0.7613</td>
</tr>
</tbody>
</table>

[Combined]
Average | 0.7527 | 0.6929 | 0.8178 |

Note: This report presents the outcome's value as well as a confidence interval. The 'Average' line presents the combined estimates for the group. The weights let you determine the influence of each study on the combined results.
Forest Plot

Antiplatelet Trial

Odds Ratio

Treatment Type
- Combined
- Individual
When should Merck have known about the risks of taking Vioxx?


Figure. Cumulative pooled analysis of investigator-reported cardiovascular thrombotic events and all-cause deaths among all randomized, placebo-controlled rofecoxib trials of 4 weeks’ duration or longer conducted by Merck & Co Inc (Whitehouse Station, New Jersey).
Output from NCSS: Meta-Analysis of Studies Comparing Two Proportions

Nondirectional Zero-Effect Test

<table>
<thead>
<tr>
<th>Rows</th>
<th>Outcome Measure</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>Odds Ratio</td>
<td>59.0466</td>
<td>11</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Note: This chi-square value tests the null hypothesis that all effects are zero versus the alternative that at least one study had a non-zero effect.

Directional Zero-Effect Test

<table>
<thead>
<tr>
<th>Rows</th>
<th>Outcome Measure</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>Odds Ratio</td>
<td>45.1381</td>
<td>1</td>
<td>0.0000</td>
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</tbody>
</table>

Note: This chi-square value tests the null hypothesis that all effects are zero versus the alternative that all studies had the same, non-zero effect.

Effect-Equality (Heterogeneity) Test

<table>
<thead>
<tr>
<th>Rows</th>
<th>Outcome Measure</th>
<th>Cochran's Q</th>
<th>DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>Odds Ratio</td>
<td>13.9085</td>
<td>10</td>
<td>0.1772</td>
</tr>
</tbody>
</table>

Note: This tests the null hypothesis that all effects are equal (homogeneous) versus the alternative that at least one effect had a different effect (heterogeneous). Sometimes this test is used to choose between the use of a Fixed Effect (homogeneous) model and a Random Effects (heterogeneous) model.
Addressing heterogeniety

1. Drop aberrant studies and re-compute the final effect size

2. Fit a random effects model (controversial but used heavily in practice)

3. Stratify studies into homogenous subsets and draw inference for each separately
Unavoidable limitation: **Publication Bias**

This almost always results when the medical literature is used as a source for studies. The published literature is neither a complete repository nor a random sample of trials actually performed.

“Negative” trials are less likely to appear in the literature than “positive” ones, creating publication bias.
Traditionally, the funnel plot was plotted with effect size on the X axis and the sample size or variance on the Y axis. Large studies appear toward the top of the graph and generally cluster around the mean effect size. Smaller studies appear toward the bottom of the graph, and (since smaller studies have more sampling error variation in effect sizes) tend to be spread across a broad range of values. This pattern resembles a funnel, hence the plot’s name (Light and Pillemer, 1984; Light et al., 1994).

The use of the standard error (rather than sample size or variance) on the Y axis has the advantage of spreading out the points on the bottom half of the scale, where the smaller studies are plotted. This could make it easier to identify asymmetry. This affects the display only, and has no impact on the statistics, and this is the route we follow here (Figure 30.2).
Figure 30.2 Passive smoking and lung cancer – funnel plot.
Figure 30.3 Passive smoking and lung cancer – funnel plot with imputed studies.
Analyses based on original data vs. published results

The earliest meta-analyses required only information in the published trial reports.

It is now clear that more than the published information is usually necessary to perform rigorous overviews.

The meta-analysts usually need to obtain and analyze the actual patient data from each trial to produce a credible result.

This can produce insights into the assessment of effects within subgroups, the interactions between two or more factors, or the more adequate control of confounding.
Conclusion: Meta-Analyses are useful but not without critics

1. Apples and oranges argument

2. Cited discrepancies with RCTs

3. Analyses are often poorly done

Bottom line: Meta analyses are here to stay simply because they yield provocative and potentially clinically meaningful results.