Summarizing Evidence II: Meta-Analysis

EBCP Module #16
Outline of Module

- This module will address the following topics:
  - Meta-analysis
  - Forest plots
  - Heterogeneity
  - Funnel plots
  - Publication bias

- Excellent YouTube video that covers most of the material in this module (for those who prefer narration):
  - Intro to Systematic Reviews & Meta-analyses, by Rahul Patwari
Objectives of Module

Students who complete this module should be able to define the following terms:
- Forest plot
- Heterogeneity
- Funnel plot
- Publication bias

Students who complete this module should be able to:
- Distinguish between meta-analyses and systematic reviews.
- Recognize the importance of qualitative review in addition to quantitative review.
- Recognize methods to detect statistical heterogeneity in meta-analysis results.
- Recognize methods to detect publication bias
- Evaluate, interpret, and apply the results of a meta-analysis.
Quantitative Evidence Synthesis

- In the previous module, we studied systematic review as a method to synthesize evidence.
  - Systematic reviews provide a qualitative way to summarize a body of evidence relevant to a specific clinical question.
    - That is, systematic reviews provide a systematic way to look at different qualities and characteristics of a body of research, at a particular point in time.

- In certain circumstances, it may also be beneficial to summarize evidence using quantitative methods.
  - Meta-analysis provides a numerical approach to summarizing multiple studies on the same topic.
When to Use Meta-Analysis

- Meta-analysis for evidence summary should always be preceded by a good systematic review.
  - Evidence summaries may be published as systematic reviews alone or systematic reviews with meta-analysis.*

- Quantitative synthesis from meta-analysis is valid when:
  - Studies are methodologically similar (determined by systematic review)
  - Studies are not statistically heterogeneous (described later)
  - There is no evidence of significant publication bias (described later)

* Although rare, evidence summaries that use meta-analysis without ascertaining all relevant studies exist. They are of suspect quality because of the likelihood of bias, and should be read as such.
Recall the four parts of the systematic review process:

1. Defining a question (e.g., by PICO)
2. Conducting a literature search
3. Applying study inclusion criteria to choose studies (i.e., screening)
4. Appraising studies

The basic idea behind meta-analysis is to continue this objective process with a fifth step, in which study results are mathematically combined.

Remember that this step is only valid under certain conditions, as described on a previous slide.
Principles of Meta-Analysis

- Results from individual studies are frequently reported in simple statistics, such as prevalence or incidence, odds ratios, relative risk ratios, or hazard ratios.
  - Meta-analysis combines similar results to provide a summary measure.

- The primary output of a meta-analysis is often displayed as a *forest plot*.
  - A forest plot is a method to display both the results of each individual study and a summary statistic for those results.

- An example of a forest plot is shown on the following slide.
Forest Plot

Names of studies

- Smith et al. 1991
- Jones et al. 1993
- Smith et al. 1999
- Ng et al. 2004
- Chu et al. 2009

Summary measure

Point estimate and 95% confidence intervals for individual study

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. 1991</td>
<td>1.3 (0.5, 2.6)</td>
</tr>
<tr>
<td>Jones et al. 1993</td>
<td>2.1 (1.0, 3.4)</td>
</tr>
<tr>
<td>Smith et al. 1999</td>
<td>1.8 (0.9, 3.2)</td>
</tr>
<tr>
<td>Ng et al. 2004</td>
<td>2.3 (1.9, 2.7)</td>
</tr>
<tr>
<td>Chu et al. 2009</td>
<td>2.1 (1.8, 2.5)</td>
</tr>
</tbody>
</table>

Summary statistic and 95% CI

2.2 (1.9, 2.4)

Note on interpretation: Since the diamond that represents the summary statistic does not include the “no difference” point, which in this case would be 1.0, then we consider the overall summary result “statistically significant.”
Forest Plot Interpretation

- Some things that you should note when reading a forest plot:
  - **Point estimates and confidence intervals of individual studies**
    - Some studies have horizontal lines that cross the solid line at OR*=1 (no difference). The results of these individual studies were not statistically significant.
    - The confidence intervals of all studies in this example cross the blue dotted line originating at the apex of the summary statistic diamond (summary point estimate). This means that they are all generally statistically similar (that is, not very heterogeneous).
  - Point estimate box size – the black squares – reflects study weighting (based on precision of the individual study).

- **Point estimate and confidence intervals of the summary statistic**
  - The apex of the diamond represents the point estimate of overall effect size.
  - The sides of the diamond represent 95% confidence intervals.
  - In this example, the diamond does not cross OR=1. Therefore, the result is statistically significant.

* Note that other measure of effect size could be used, such as RR or HR.
Meta-Analysis Methods

- The statistical methods used in meta-analysis are complicated and beyond the scope of these modules.

- However, you should be familiar with a couple of concepts:
  1. Meta-analysis can be performed using study-level data or individual-level data.
     - Study-level data includes only the statistics (e.g., ORs) found in every included publication. Individual-level data must be obtained directly from researchers.
     - Using individual-level data in meta-analysis is generally superior to study-level data because it allows for additional control of data. However, this method is generally more difficult and is seen less often.
  2. Meta-analysis of study-level data can be done using fixed-effects or random-effects models.
     - The selection of these models reflects the authors’ assessment of the degree of statistical heterogeneity among studies.
Meta-Analysis: Evaluating Heterogeneity
As mentioned earlier, the quantitative synthesis that is possible with meta-analysis is only valid when:

- Studies are methodologically similar (determined by systematic review)
- Studies are not excessively heterogeneous
- There is no evidence of significant publication bias

What is statistical heterogeneity?
- And why does it matter?
Statistical Heterogeneity

- It is useful to distinguish between methodological differences and statistical heterogeneity.
  - Methodological differences between studies—such as using different follow-up times, participant selection criteria, dosing, or study endpoints—will result in differences in results.
    - These differences should be elaborated qualitatively in a systematic review.
    - Some authors call these differences “clinical heterogeneity.”
    - Clinical heterogeneity is a potential source for statistical heterogeneity
  - Statistical heterogeneity is apparent in the analysis of results.
    - The cause of such heterogeneity may be unknown, but its presence can be seen in forest plots and with heterogeneity statistics.
Statistical Heterogeneity

- The forest plot below shows a pattern consistent with significant statistical heterogeneity.
- Some studies have confidence intervals that do not cross the dashed blue vertical line that represents the point estimate of the summary statistic.

Note the $I^2$ statistic reported here – it is one way of quantifying heterogeneity.
Statistical Heterogeneity

- Heterogeneity can be detected using the $I^2$ and $Q$ statistics, among others.
  - You do not need to understand the details of how these statistics are derived or applied.
  - However, you should be familiar with their purpose, as they are commonly found in published meta-analyses.

For reference:
- An $I^2$ statistic of 0% indicates no heterogeneity. Greater values (up to 100%) indicate greater heterogeneity.
- A $Q$ statistic ranges from 0 to 1. It is a p-value for testing the null hypothesis that there is no heterogeneity. A smaller value (<0.1, usually) indicates heterogeneity.
Statistical heterogeneity in meta-analysis can be addressed in multiple ways:

- Sub-group analyses, in which studies are analyzed in groups (such as by large vs. small studies, or high-quality vs. low-quality studies, or shorter term vs. longer term studies, or pediatric vs. adult participants, etc.).
  - Sometimes this type of analysis provides a possible explanation for the source of the heterogeneity, which can be clinically important.
  - Ideally, authors of meta-analyses should develop hypotheses *a priori* to explain heterogeneity, and then test those hypotheses.

- Results may be combined using Random-effects models, which are more conservative than fixed-effects models and incorporate a greater degree of uncertainty into estimates.
Statistical Heterogeneity

- As previously stated, you will not need to know how to calculate $I^2$ or Q statistics or random vs. fixed-effects models.

- However, you should recognize that study heterogeneity presents a threat to the validity of a meta-analysis.
  - A meta-analysis that inappropriately combines widely varying study results can produce a summary statistic that may not be applicable to any particular group. (i.e. it may be meaningless in clinical practice)
  - The technique of sub-group analysis is helpful to improve the interpretation of results from heterogeneous studies.
    - Sometimes, a reason for statistical heterogeneity can be found and may help refine interpretation or provide hypotheses for future study.
Meta-Analysis: Evaluating Publication Bias
Publication Bias

- Another important issue to consider in reading a meta-analysis is the possibility of publication bias.
  - Publication bias results when studies are selectively published based on the nature or direction of the results.
    - For example, it has been shown that “positive” results (that is, statistically significant ones) are more likely to be published than “negative” ones.
    - The inclusion of grey literature in systematic reviews and meta-analyses may help to counteract publication bias.
  - Publication bias may invalidate meta-analysis findings and, like statistical heterogeneity, must be tested for.
Funnel Plot

- **A funnel plot** is a common tool to test for publication bias.
  - The funnel plots below show the effect size (e.g., OR, RR, etc.) on the x-axis and study sample size on the y-axis.*
  - Each dot represents a single study.
  - Smaller studies are expected to be less precise and so the “funnel” starts wide and becomes more narrow as studies (and precision) increase.

*Sometimes the y-axis may show more complicated statistics such as SE(log(OR)). These are often still a function of sample size, which is generally easier to think about.
Funnel Plot

- Basic interpretation of funnel plots:
  - In the plot on the left—where both sides of the “funnel” are approximately equally filled with blue dots—there is no apparent publication bias.
  - In the plot on the right—where the left side of the “funnel” has many more blue dots than the right side—there is likely publication bias.
Publication Bias

- The presence of publication bias, like other forms of bias, affects the validity of the meta-analysis.
  - It should be taken into consideration in the interpretation of results.
  - If extreme, it may completely invalidate the interpretation of summary statistics, because it suggests that the information on the topic that has been published really only represents “one side of the story.”
Key Points for Module 16

- Meta-analysis is used to provide quantitative synthesis of study results following a good systematic review.

- Quantitative synthesis using meta-analysis is valid when:
  - Studies are methodologically similar
  - Studies are not excessively heterogeneous
  - There is no evidence of significant publication bias

- Statistical heterogeneity can be identified with forest plots, $Q$ statistics and $I^2$ statistics.

- Publication bias can be assessed with funnel plots.
Please complete the online quiz, after completing any required reading.

Thank you!

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Key References


