Meta-Analysis

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- What is a meta-analysis; why perform a meta-analysis?
- How a meta-analysis work
  - some basic concepts and principles
- Steps of Meta-analysis
- Cautions on meta-analysis

What is Meta-analysis

- Meta-analysis is both a theory and a toolbox of statistical techniques for combining summary statistics from similar studies.
  - Individual studies often not large enough
  - Quantitative and more objective

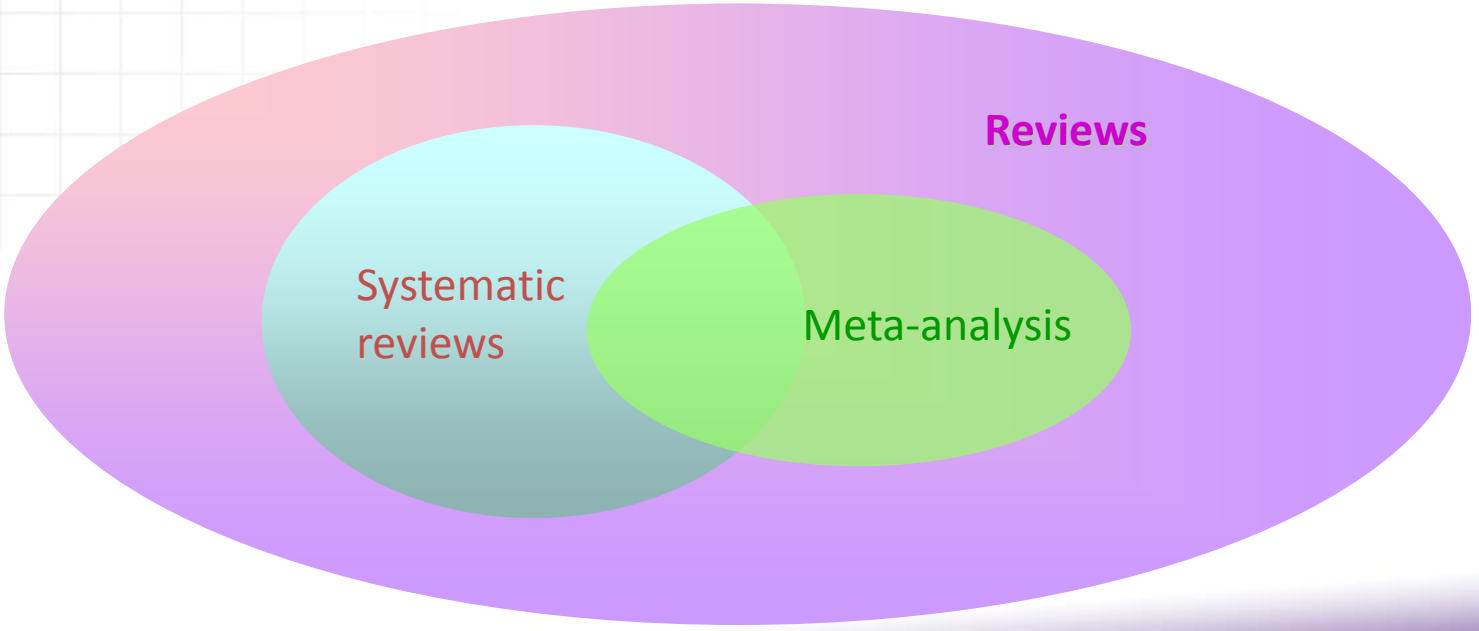
- Systematic review
  - uses a process to identify comprehensively all studies for a specific focused question
  - study characteristics are appraised
  - data are synthesized
  - results are interpreted

What Can A Systematic Review Offer?

- A summary of information
- Assessment of whether multiple studies are consistent, and can be generalised or vary by population subsets
- Limiting bias helps to improve reliability and accuracy of results
- Combing results can increase power and precision of estimates of effectiveness
- When few or no studies are found this can help to pinpoint crucial area and questions that need further research

How Is This Different From A Review?

- Literature reviews are usually one individual's opinions of the current stage of knowledge.
- This is inevitably limited and form a partial perspective.



What is Meta-analysis

- Comparing results from different studies to identify
  - Consistent patterns
  - Sources of disagreements among these results
- Primary objective:
  - Synthetic goal (estimation of summary)
  - Analytic goal (estimation of differences)

Meta-analysis is typically a two-stage process

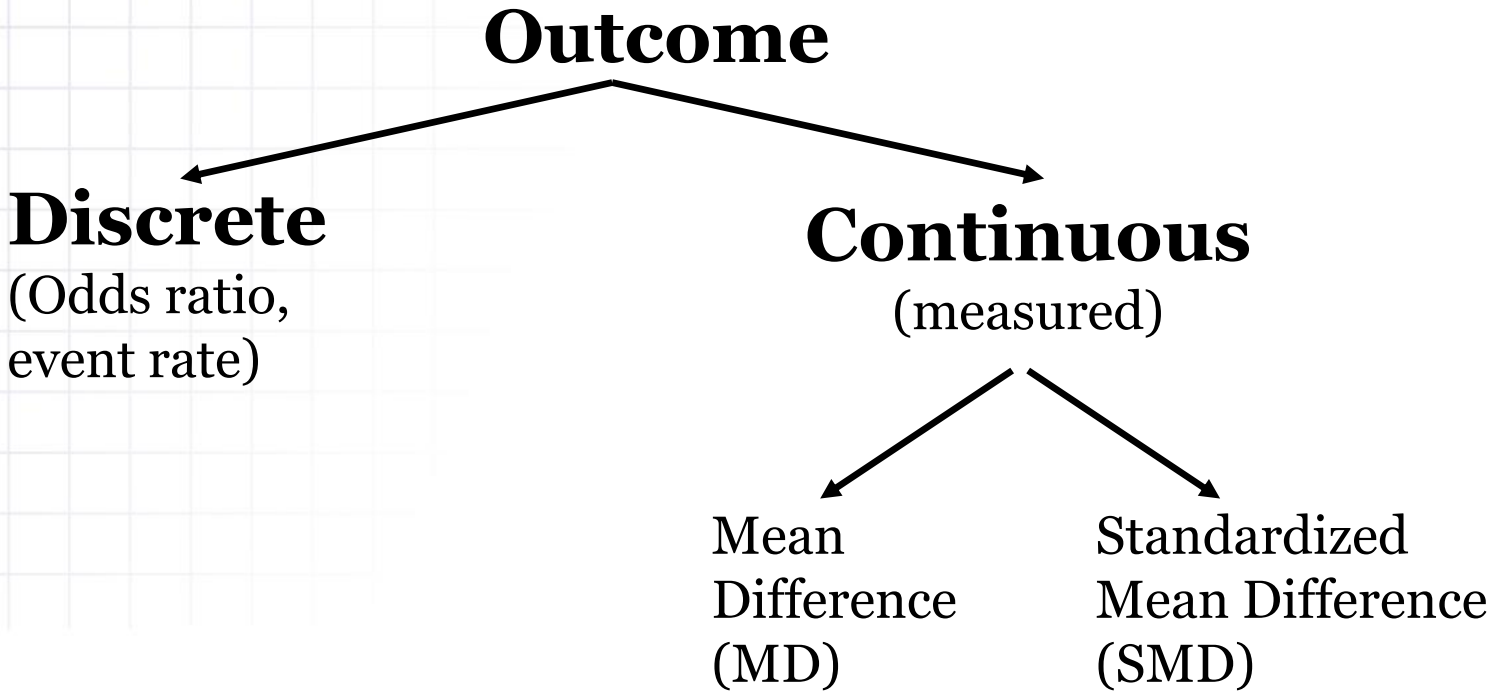
- A summary statistic for each study
- A summary (pooled) treatment effect estimate as a weighted average of the treatment effects estimated in the individual studies.

When can/should you do a traditional meta-analysis?

- When more than one study has estimated an effect
- When there are no differences in the study characteristics that are likely to substantially affect outcome
- When the outcome has been measured in similar ways

Calculating Effect Sizes

- The “dependent variable”: standardizes findings across studies such that they can be directly compared
- Any standardized index can be an “effect size” (e.g., standardized mean difference, correlation coefficient, odds ratio) as long as it meets the following
  - is comparable across studies (generally requires standardization)
  - represents the magnitude and direction of the relationship of interest
  - is independent of sample size


Outcome
Discrete
(Odds ratio, event rate)
Continuous
(measured)
Mean Difference (MD)
Standardized Mean Difference (SMD)

Continuous data

Weighted mean difference

- When the same outcome has been measured in the same way in each trial
- Result is in natural units

Standardised mean difference

- When the same outcome has been measured in the different ways in each trial
- Result needs to be converted into natural units

Mean Difference (MD)

- Each study used the same scale or variable
  - $mean_{summary} = \sum(weight_i \times mean_i) / \sum weight_i$
  - $mean_i = mean_{tx} - mean_{control}$
  - $weight_i = 1 / variance_i = 1 / SD_i^2$
    - (use pooled variance)
  - 95% CI = $mean_s$ +/- (1.96 x $(variance_s)^{\wedge 0.5}$)
    - $variance_s = 1 / \sum weight_i$

Averaging studies

- A simple average would give each study equal weight
- However, some studies are more likely to give an answer closer to the ‘true’ effect than others

Pooling the Results

- In a meta-analysis, the effects found across studies are combined or 'pooled' to produce a weighted average effect of all the studies.
- Each study is weighted according to some measure of its importance.

Weighting studies

- Give more weight to the more informative studies. Weight by:
  - Sample size (n)
  - Event rate
  - Homogeneity (inverse of the variance)
  - Quality
  - Other factors…

Inverse variance method

Larger studies which have smaller standard errors

more weight than

smaller studies which have larger standard errors.

Assessing between study heterogeneity

- Heterogeneity is variation between the studies' results
  - When effect sizes differ consistent with chance error, the effect size estimate is considered to be homogeneous.
  - When the variability in effect sizes is greater than expected by chance, the effects are considered to be heterogeneous

- The presence of heterogeneity affects the process of the meta-analysis

Statistical measures of heterogeneity

- The Chi² test measures the amount of variation in a set of trials, and tells us if it is more than would be expected by chance.
- Q statistic, τ^2, I^2, …
- Visual

Song et al. 2001. Methods for Exploring Heterogeneity in Meta-Analysis

How to deal with heterogeneity

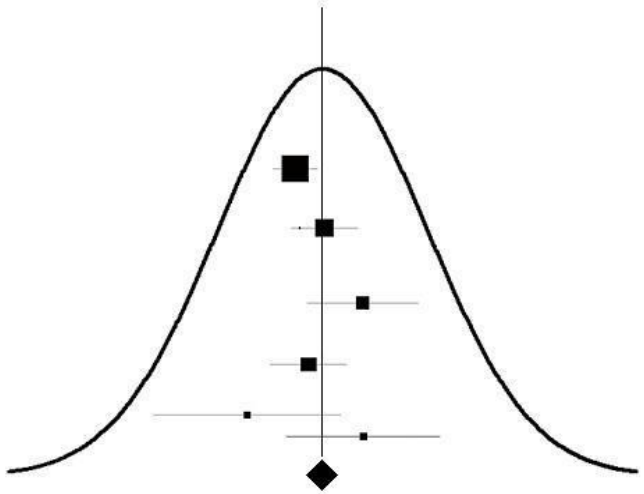
1. Do not pool at all
2. Ignore heterogeneity: use ***fixed effect model***
3. Allow for heterogeneity: use ***random effects model***
4. Explore heterogeneity: ***meta-regression***

Fixed effect model

- The difference between the studies is due to random error
  - Observed study effect = Fixed effect + error

Key assumption:

- There is one real value for the treatment effect
- All trials estimate this one value

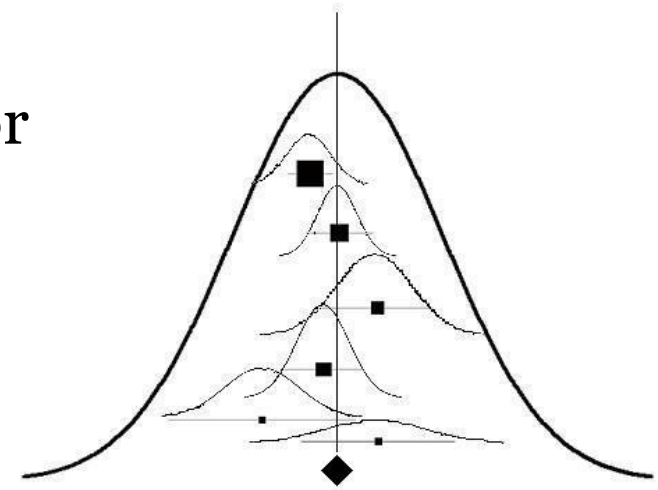


Random effects model

- Each study is seen as representing the mean of a distribution of studies
- There is still a resultant overall effect size

Key assumption:

- There are many possible real values for the treatment effect (depending on different conditions in different studies).
- Each trial estimates its own real value



Which model?

- The choice of model is determined by how much heterogeneity there is.
  - Fixed effect if the studies are relatively homogeneous.
  - Random effects there is significant heterogeneity between study results.

Fixed and random effects models

Fixed effects model - weights each study by the inverse of the sampling variance.

$$w_i = \frac{1}{se_i^2}$$

Random effects model - weights each study by the inverse of the sampling variance **plus** the variability across the population effects.

$$w_i = \frac{1}{se_i^2 + \hat{v}_\theta}$$

Where this is the random effects variance component

Subgroup Analysis

- Often of interest to examine a particular category of participants in a review
- This may be done when the heterogeneity between studies is significant (may 'explain' heterogeneity)

Sensitivity Analysis

- An analysis used to determine how sensitive the results of a study or systematic review are to the way it has be done
- Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumption about the data and the methods that were used.
- Can be used for taking the quality of the studies into account in the meta-analysis

Meta Regression

- Used to suggest reasons for observed heterogeneity.
- Attempts to identify significant relations between dependent variable and independent variable.
- Meta-regression should be weighted to take account of both within study variances and the residual between study heterogeneity (that is, heterogeneity not explained by the covariates in the regression).
- Various statistical methods for meta-regression have been published.
  - Thompson and Higgins. 2001. How should meta-regression analyses be undertaken and interpreted?

Publication Bias

- Empirical evidence shows studies with significant results are more likely to be published or cited than those with non-significant or un-favorable results.
- Publication bias occurs when there are systematic differences in conclusions between studies that are unpublished compared with those that are published
- Funnel plots

Drawing conclusions

An effect size is just a number

↓

Needs interpreting

↓

Needs to be done systematically & transparently

Steps of Meta-analysis

1. Identify research questions
2. Comprehensive data search
3. Unbiased selection and extraction process
4. Critical appraisal of data
5. Synthesis of data
6. Presentation and interpretation of Results

1. Identify research questions

- Lead on to your inclusion and exclusion criteria
- Helps you build your search strategy
- Get you thinking about what data to extract and what quality criteria are important
- Basic Considerations
  - Interesting
  - Novel
  - Relevant
  - Feasible

2. Comprehensive data search

- Basic Considerations
  - Experimental vs. non-experimental
  - Study design
  - Year of publication
  - Languages
  - Similarity of treatment and/or exposure (homogeneity)
  - Completeness of information
  - Qualification of researchers
  - Search strategy, including time period
  - Method of handling abstracts/unpublished studies
  - Description of an contact with authors
  - Methods of addressing non-English language articles

3. Unbiased selection and extraction process

- What might you improve the inclusion/exclusion sheet to better fit with the objectives of the review?

4. Critical appraisal of data

- What question will you ask about validity for the data?
  - Internal validity: The degree to which the results of a study are likely to approximate to the 'truth' for the circumstances being studied.
  - External validity: The degree to which the effects observed in the study are applicable to the outside world.

5. Synthesis of data

- Non-randomized controlled studies:
  - Statistical combination should not be a prominent part of the review
  - Exploration of possible source of heterogeneity may be more informative (sub-group, meta-regression, …)

- Identify possible solutions to cope with heterogeneity; perform sensitivity and subgroup analyses if appropriate and possible

6. Presentation and Interpretation of Results

RevMan Analyses 1.0 (Mefloquine for preventing malaria in non-immune adult travellers)

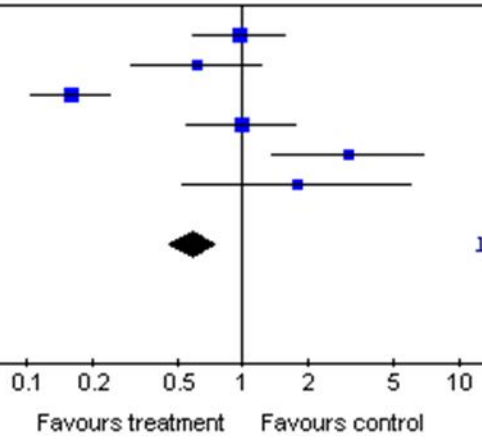
File Edit Display Sort Statistics Previous outcome Next outcome Window Help

Detail 01.01

Review: Mefloquine for preventing malaria in non-immune adult travellers
Comparison: 01 Mefloquine versus alternative chemoprophylaxis
Outcome: 01 Diarrhoea

Study or sub-category	Treatment n/N	Control n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
Arthur 1990	64/134	58/119		24.65	0.96 [0.59, 1.57]
Boudreau 1993	16/203	19/156		12.14	0.61 [0.30, 1.24]
Croft 1997a	29/183	103/176		32.64	0.16 [0.10, 0.25]
Croft 1997b	25/247	25/244		17.55	0.99 [0.55, 1.77]
Kollaritsch 1997	22/60	9/60		9.04	3.07 [1.36, 6.93]
Ohrt 1997	7/68	4/67		3.97	1.77 [0.52, 6.06]
Total (95% CI)	895	822		100.00	0.58 [0.45, 0.74]

Total events: 163 (Treatment), 218 (Control)
Test for heterogeneity: Chi² = 61.09, df = 5 (P < 0.00001), I² = 91.8%
Test for overall effect: Z = 4.36 (P < 0.0001)



Forest Plot: a simple visual representation of multiple studies

Questions to ask when assessing the quality of a Meta-analysis

- Was the review conducted according to a pre-specified protocol?
- Was the question focused and well formulated?
- Was the method of identifying all relevant information comprehensive?
- Was the data abstraction from each study appropriate?
- Was the information synthesized and summarized appropriately?
  - Whenever reviewers identifies significant differences between studies, they should try to explain possible reasons for these differences.

Criticisms of Meta-analysis

- Bias in Sampling the Findings.
  - bias by virtue of the inclusion/exclusion criteria
  - Not every computer assisted search will be complete
- Garbage In and Garbage Out
  - mixing together good and bad studies
- Singularity and Non-independence of Effects
  - If a study has more than one effect size, these can be used individually in analyses of subgroups or in examination of moderating variables, or they can be combined
- Combining Apples and Oranges

- Understanding of benefits and limitations of Meta-analysis (Heterogeneity among studies is one of the most common flaws in meta-analyses.)
  - studies are diverse
  - outcomes are diverse
  - the quality of included studies is poor
  - there are significant publication and/or reporting biases
  - ignoring the study effect while performing a regression analysis leads to biased estimates of the regression coefficients

- All of these involve reviewer judgment

- The key to designing a high quality meta-analysis is to identify an area where the effect of the treatment or exposure is uncertain and where a relatively homogenous body of literature exists.