Biases and other challenges in meta-analysis

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Session outline

- Meta-analysis, the pooling of information from separate studies that relate to the same outcome of interest, is now widely used in application. However practical and methodological challenges remain. This talk will focus on these issues and will comprise of two main sections. Firstly, I will discuss issues relating to bias, both within studies and across the entire evidence base. The first of these types of biases relates to ”known unknowns” because it refers to studies that have been included in the meta-analysis. However the second of these types of biases is perhaps even more challenging, as it refers to studies that have not been found, and so refers to ”unknown unknowns”.

Session outline

- In the second part of the talk I will discuss some of the main themes of current methodological interest, including multivariate, network and individual patient data meta-analysis. As we will see, issues relating to bias can become even more subtle as more sophisticated statistical methods are used. A theme running through the talk will be scientific reproducibility, which we will see also becomes more challenging when using more advanced statistical techniques.

What is a meta-analysis? Here are some ‘buzzwords’

- Systematic review.
- Cochrane (Collaboration).
- Evidence synthesis.

What is a meta-analysis? Here is a picture

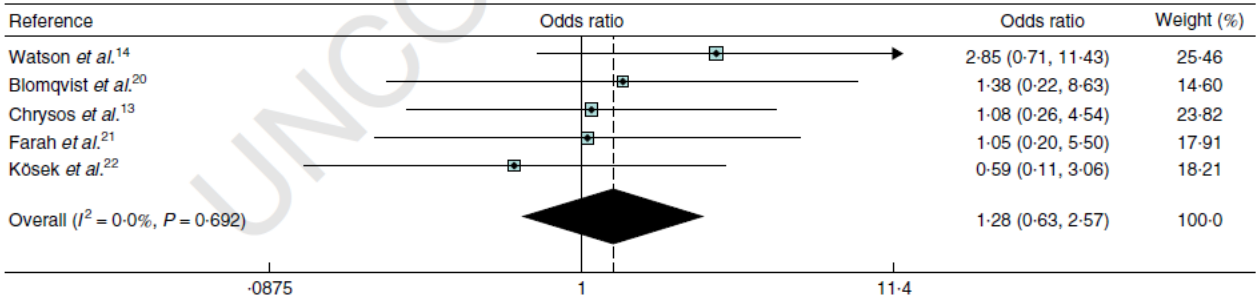


Fig. 3 Forest plot for postoperative dysphagia after laparoscopic Nissen fundoplication with or without short gastric vessel division. The pooled outcome was determined using a random-effects model. Odds ratios are shown with 95 per cent confidence intervals

Univariate random-effects meta-analysis

- In the previous example, the outcomes were log-odds ratios. We perform the analysis on the log-odds scale and convert the results to the odds scale at the end.
- $Y_i|\mu_i \sim N(\mu_i, s_i^2)$.
- $\mu_i \sim N(\mu, \tau^2)$.
- Therefore $Y_i \sim N(\mu, s_i^2 + \tau^2)$.

What does the random-effects model have to say about scientific reproducibility?

- If $\tau^2 > 0$ then the random-effects model says that there are differences between the true underlying effects (the μ_i) that we do not explain.
- Does this mean that the random-effects model concedes that scientific results are not reproducible?
- Taken literally, I think the answer is 'yes'. But being a bit more sensible, I think the answer is 'no'. The random-effects model makes no attempt to explain the differences in the true underlying study results, that is all. It is a pragmatic way to obtain a meaningful average whilst allowing for the fact that the results are heterogeneous.
- If we take $\tau^2 = 0$ then we have a fixed-effect, aka common-effect, aka fixed-effects model.

The first type of bias: the ‘known unknowns’

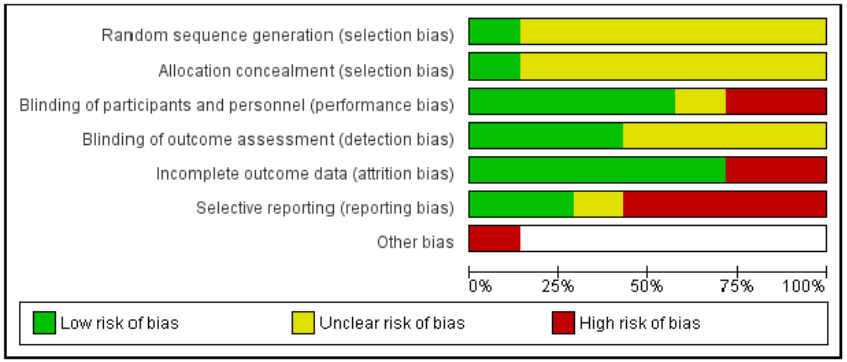
- Let us begin by talking about bias in the estimates we have in our sample.
- Under a common-effect model we assume that all studies provide an unbiased estimate of the ‘truth’ (whatever that means).
- But do we really believe in the strong common-effect assumption?
- I would argue that this assumption is always likely to be implausible (but then again I often make less-than-plausible assumptions, for one reason or another...).
- Another issue is that the random-effects model is often criticised on the grounds that it gives small studies too much weight.

The first type of bias: Meta-regression models

- $Y_i|\mu_i \sim N(\mu_i, s_i^2)$.
- $\mu_i \sim N(\mu, \tau^2)$.
- In a meta-regression model we instead assume that $\mu_i \sim N(\alpha + \beta x_i, \tau^2)$.
- This model can be used to explain the between-study heterogeneity (which I would argue arises due to bias in some, or more probably all, studies).
- But what are the difficulties with this approach?

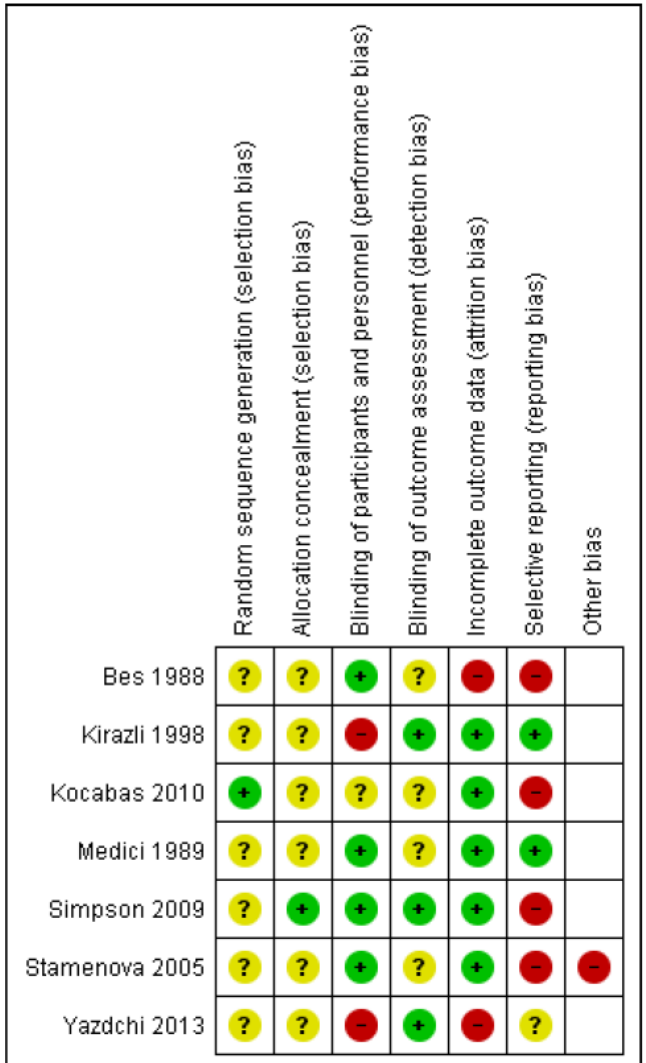
The first type of bias: The Cochrane risk of bias tool

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



The first type of bias: The Cochrane risk of bias tool

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



The first type of bias: And observational studies?

Special Issue Paper

Research Synthesis Methods

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(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1077

Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews

George A Wells,[a,b*†] Beverley Shea,[c] Julian PT Higgins,[d,e] Jonathan Sterne,[f] Peter Tugwell[b,g] and Barnaby C Reeves[h]

Background: There is increasing interest from review authors about including non-randomized studies (NRS) in their systematic reviews of health care interventions. This series from the Ottawa Non-Randomized Studies Workshop consists of six papers identifying methodological issues when doing this.

Aim: To format the guidance from the preceding papers on study design and bias, confounding and meta-analysis, selective reporting, and applicability/directness into checklists of issues for review authors to consider when including NRS in a systematic review.

Checklists: Checklists were devised providing frameworks to describe/assess: (1) study designs based on study design features; (2) risk of residual confounding and when to consider meta-analysing data from NRS; (3) risk of selective reporting based on the Cochrane framework for detecting selective outcome reporting in trials but extended to selective reporting of analyses; and (4) directness of evidence contributed by a study to aid integration of NRS findings into summary of findings tables.

Summary: The checklists described will allow review groups to operationalize the inclusion of NRS in systematic reviews in a more consistent way. The next major step is extending the existing Cochrane Risk of Bias tool so that it can assess the risk of bias to NRS included in a review.

The first type of bias: Bayesian modelling

J. R. Statist. Soc. A (2009)
172, *Part* 1, *pp.* 21–47

Bias modelling in evidence synthesis

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OnlineOpen: This article is available free online at www.blackwell-synergy.com

Summary. Policy decisions often require synthesis of evidence from multiple sources, and the source studies typically vary in rigour and in relevance to the target question. We present simple methods of allowing for differences in rigour (or lack of internal bias) and relevance (or lack of external bias) in evidence synthesis. The methods are developed in the context of reanalysing a UK National Institute for Clinical Excellence technology appraisal in antenatal care, which includes eight comparative studies. Many were historically controlled, only one was a randomized trial and doses, populations and outcomes varied between studies and differed from the target UK setting. Using elicited opinion, we construct prior distributions to represent the biases in each study and perform a bias-adjusted meta-analysis. Adjustment had the effect of shifting the combined estimate away from the null by approximately 10%, and the variance of the combined estimate was almost tripled. Our generic bias modelling approach allows decisions to be based on all available evidence, with less rigorous or less relevant studies downweighted by using computationally simple methods.

The first type of bias: A nice diagram

R. M. Turner, D. J. Spiegelhalter, G. C. S. Smith and S. G. Thompson

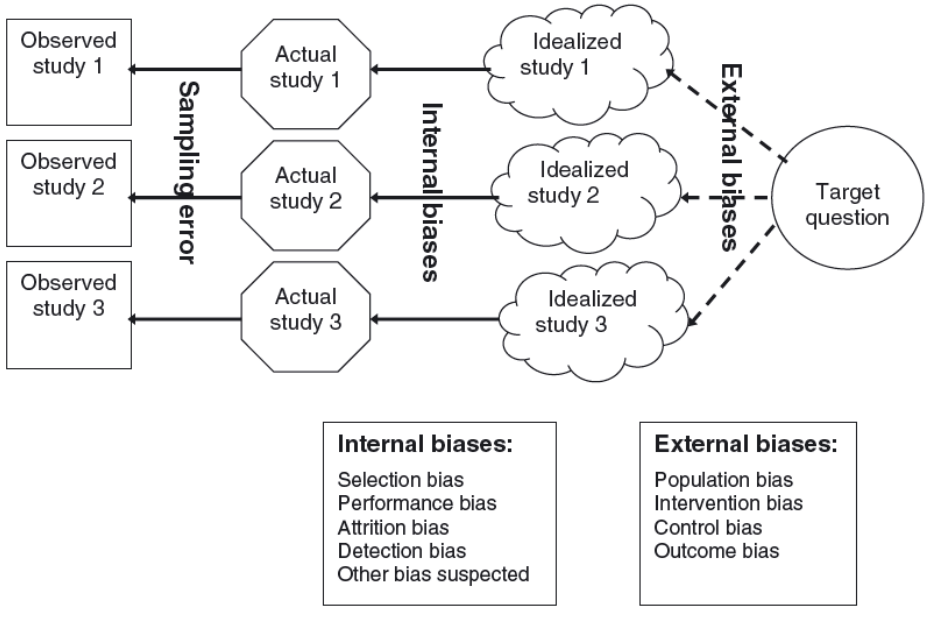

Fig. 1. Identifying internal and external biases

The first type of bias: scientific reproducibility

- We can see therefore that a variety of approaches to ‘dealing with’ the first type of bias have been proposed.
- How objective are these methods? Are they really quite subjective?
- What are the implications of using subjective methods for scientific reproducibility?

The second type of bias: the ‘unknown unknowns’

- Now let us discuss the estimates that we do not have in our sample.
- Thanks to trial registration, we may have some idea of how many estimates we do not have.
- But more probably, we do not even have much idea of how many estimates we have been unable to include in our analysis.
- Hence I will describe this type of bias as being due to ‘unknown unknowns’.

The second type of bias: so what is the problem?

- If the sample of estimates that we have is representative of the entire population then we have lost precision by failing to include all estimates but there is no bias.
- There is often the fear that the sample is not representative.
- This problem is often called ‘publication bias’. It was the topic of my PhD.
- For what reasons might publication bias occur in practice?

The second type of bias: A funnel plot

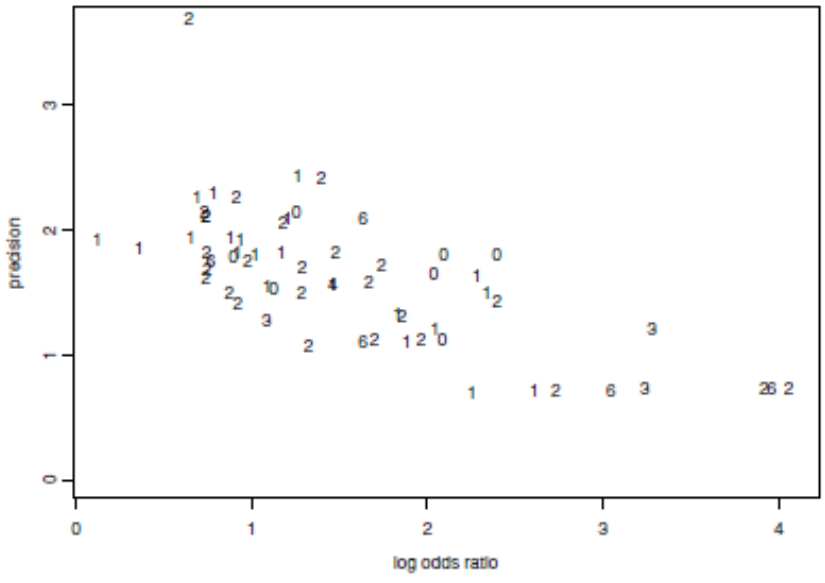

Figure 1. Funnel plot for aspirin data. Numerical values denote the impact factor of the journal in which studies are published, rounded to the nearest whole number.

The second type of bias: Statistical modelling

Biostatistics (2000), **1**, 3, *pp*. 247–262
Printed in Great Britain

Meta-analysis, funnel plots and sensitivity analysis

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SUMMARY

Publication bias is a major problem, perhaps *the* major problem, in meta-analysis (or systematic reviews). Small studies are more likely to be published if their results are 'significant' than if their results are negative or inconclusive, and so the studies available for review are biased in favour of those with positive outcomes. Correcting for this bias is not possible without making untestable assumptions. In this paper, a sensitivity analysis is suggested which is based on fitting a model to the funnel plot. Some examples are discussed.

Keywords: Funnel plots; Meta-analysis; Selectivity bias; Sensitivity analysis.

Multivariate meta-analysis

Research Article

Statistics in Medicine

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Multivariate meta-analysis: Potential and promise

Dan Jackson,[a*†] Richard Riley[b] and Ian R. White[a]

The multivariate random effects model is a generalization of the standard univariate model. Multivariate meta-analysis is becoming more commonly used and the techniques and related computer software, although continually under development, are now in place. In order to raise awareness of the multivariate methods, and discuss their advantages and disadvantages, we organized a one day 'Multivariate meta-analysis' event at the Royal Statistical Society. In addition to disseminating the most recent developments, we also received an abundance of comments, concerns, insights, critiques and encouragement. This article provides a balanced account of the day's discourse. By giving others the opportunity to respond to our assessment, we hope to ensure that the various view points and opinions are aired before multivariate meta-analysis simply becomes another widely used *de facto* method without any proper consideration of it by the medical statistics community. We describe the areas of application that multivariate meta-analysis has found, the methods available, the difficulties typically encountered and the arguments for and against the multivariate methods, using four representative but contrasting examples. We conclude that the multivariate methods can be useful, and in particular can provide estimates with better statistical properties, but also that these benefits come at the price of making more assumptions which do not result in better inference in every case. Although there is evidence that multivariate meta-analysis has considerable potential, it must be even more carefully applied than its univariate counterpart in practice.

Keywords: multivariate meta-analysis; random effects models; statistical software

Univariate random-effects meta-analysis (first outcome)

- Hopefully this is a reminder.
- $Y_{i1}|\mu_{i1} \sim N(\mu_{i1}, s_{i1}^2)$.
- $\mu_{i1} \sim N(\mu_1, \tau_1^2)$.
- Therefore $Y_{i1} \sim N(\mu_1, s_{i1}^2 + \tau_1^2)$.

Univariate random-effects meta-analysis (second outcome)

- Hopefully this is also a reminder.
- $Y_{i2}|\mu_{i2} \sim N(\mu_{i2}, s_{i2}^2)$.
- $\mu_{i2} \sim N(\mu_2, \tau_2^2)$.
- Therefore $Y_{i2} \sim N(\mu_2, s_{i2}^2 + \tau_2^2)$.

Multivariate random-effects meta-analysis (within studies)

- The within-studies distribution is now given by a multivariate normal distribution

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \Bigg| \begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix}, \begin{pmatrix} s_{i1}^2 & \rho_i s_{i1} s_{i2} \\ \rho_i s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix} \right)$$

Multivariate random-effects meta-analysis (between studies)

- The between-studies distribution is now given by a multivariate normal distribution

$$\begin{pmatrix} \mu_{i1} \\ \mu_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \kappa\tau_1\tau_2 \\ \kappa\tau_1\tau_2 & \tau_2^2 \end{pmatrix} \right)$$

Multivariate random-effects meta-analysis

- The marginal distribution of the outcome data is therefore

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \rho_i s_{i1} s_{i2} + \kappa\tau_1\tau_2 \\ \rho_i s_{i1} s_{i2} + \kappa\tau_1\tau_2 & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

Multivariate meta-analysis: bias and scientific reproducibility

- I do not think that multivariate meta-analysis directly results in any further difficulties related to scientific reproducibility. Having said that, does the use of more sophisticated statistical methods present challenges to scientific reproducibility in general?
- I think the issues relating to bias become complicated and subtle in the multivariate setting.

Network meta-analysis

Special Issue Paper

Research Synthesis Methods

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(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1037

Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool‡

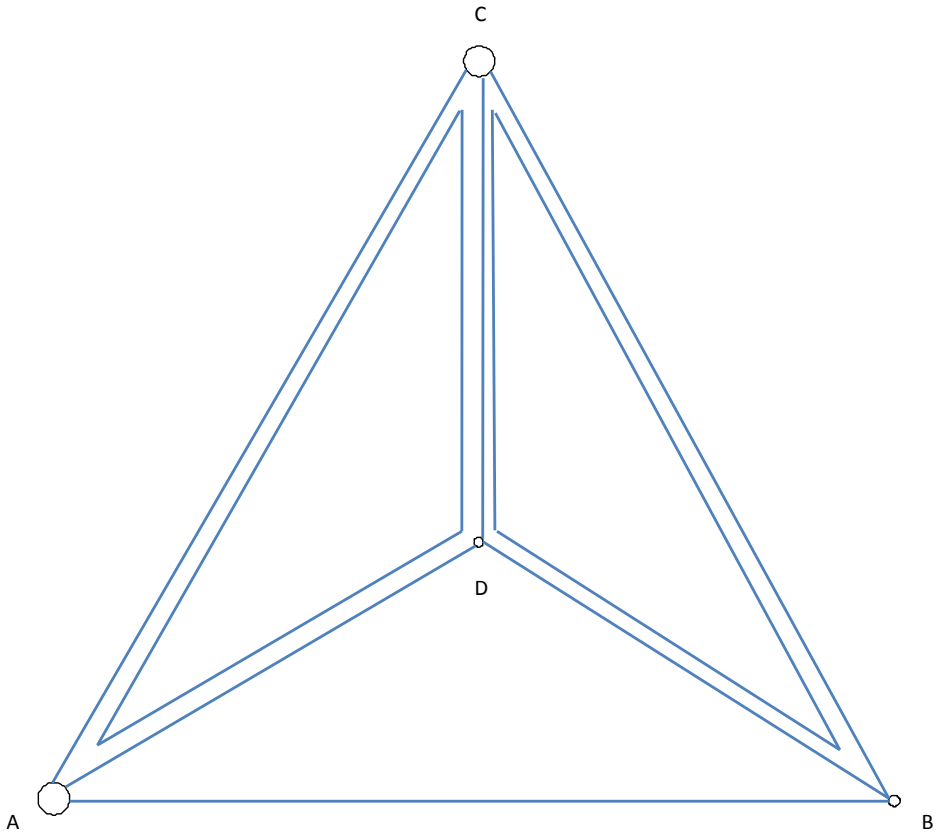
Georgia Salanti*†

The ever increasing number of alternative treatment options and the plethora of clinical trials have put systematic reviews and meta-analysis under a new perspective by emphasizing the need to make inferences about competing treatments for the same condition. The statistical component in reviews that compare multiple interventions, network meta-analysis, is the next generation evidence synthesis toolkit which, when properly applied, can serve decision-making better than the established pairwise meta-analysis. The criticism and enthusiasm for network meta-analysis echo those that greeted the advent of simple meta-analysis. The main criticism is associated with the difficulty in evaluating the assumption underlying the statistical synthesis of direct and indirect evidence. In the present article, the assumption of the network meta-analysis are presented using various formulations, the statistical and nonstatistical methodological considerations are elucidated, and the progress achieved in this field is summarized. Throughout, focus is put on highlighting the analogy between the concerns and difficulties that the scientific community had some time ago when advancing from individual trials to their quantitative synthesis via meta-analysis and those currently expressed about the transition from head-to-head meta-analyses to network meta-analysis.

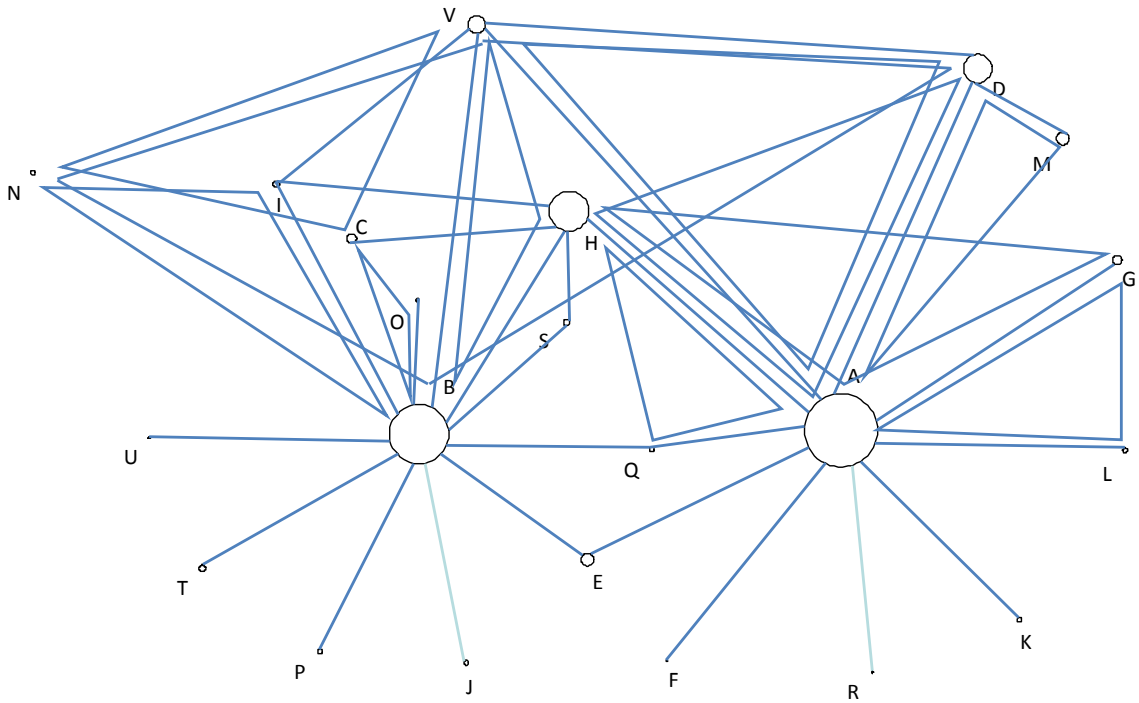
Keywords: assumptions; transitivity; consistency; systematic reviews; evidence-based practice

1. Introduction

A real example



Another real example



Statistical models for network meta-analysis

- The standard univariate random-effects model is $Y_i \sim N(\mu, s_i^2 + \tau^2)$.
- Another way to write this is $Y_i = \mu + \beta_i + \epsilon_i$, where $\beta_i \sim N(0, \tau^2)$ and $\epsilon_i \sim N(0, s_i^2)$.
- It is this way of writing meta-analysis models that has become popular in network meta-analysis.

Statistical models for network meta-analysis

Special Issue Paper

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Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression‡

Ian R. White,[a*†] Jessica K. Barrett,[a] Dan Jackson[a] and Julian P. T. Higgins[a,b]

Network meta-analysis (multiple treatments meta-analysis, mixed treatment comparisons) attempts to make the best use of a set of studies comparing more than two treatments. However, it is important to assess whether a body of evidence is consistent or inconsistent. Previous work on models for network meta-analysis that allow for heterogeneity between studies has either been restricted to two-arm trials or followed a Bayesian framework. We propose two new frequentist ways to estimate consistency and inconsistency models by expressing them as multivariate random-effects meta-regressions, which can be implemented in some standard software packages. We illustrate the approach using the `mvmeta` package in Stata.

Statistical models for network meta-analysis

- Let us assume that all studies compare two treatments (this is not true for either real example).
- If Y_i compares treatments I and J then we could assume the model $Y_i = \delta^{AJ} - \delta^{AI} + \beta_i + \epsilon_i$.
- This model makes the consistency assumption and we define $\delta^{AA} = 0$.
- The parameters δ^{AI} and δ^{AJ} are called 'basic parameters'.

Network meta-analysis: bias and scientific reproducibility

- I do not think that network meta-analysis directly results in any further difficulties related to scientific reproducibility. Having said that, does the use of more sophisticated statistical methods present challenges to scientific reproducibility in general?
- I think the issues relating to bias become complicated and subtle in the network meta-analysis setting.
- I am now working on multivariate network meta-analysis models. Issues relating to bias now become very complicated and subtle!

Individual patient data meta-analysis

- All the models above describe the study specific estimates and NOT the individual patient data (IPD).
- The individual patient data was used to estimate the study specific estimated effects.
- Usually we do not have the IPD and so we have to use the types of data and models that I have described.
- IPD meta-analyses, where possible, have many advantages.
- However issues around ‘data sharing’ raise further difficulties associated with scientific reproducibility.

Conclusions

- Methods for meta-analysis are becoming ever more sophisticated. For the most part, this is a good thing.
- I think that (both types of) bias is an even more serious and subtle issue in multivariate and network meta-analysis.
- IPD meta-analysis is a very good thing but raises further issues concerning scientific reproducibility and transparency.