Evaluation of statistical methods for meta-analysis

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Evidence to inform statistical methods

- Statistical theory
- Empirical data
  - impact of different methods on results
  - context of implementation
- Simulation studies
- Interpretation
  - by users of methods
  - by readers
Random-effects meta-analysis

\[
\sum \frac{\text{Effect}_i}{\left( \text{SE}_i^2 + \text{Het} \right)} \sum \frac{1}{\left( \text{SE}_i^2 + \text{Het} \right)}
\]

\[
\sum y_i w_i^* \sum w_i^*
\]

Some issues
- Choice of effect measure \( y_i \)
- Choice of estimator \( y_i \)
- Error in estimated \( \text{SE}_i \)
- Validity of normal distribution
- **Choice of heterogeneity estimator**
Methods to estimate the between-study variance and its uncertainty in meta-analysis

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Meta-analyses are typically used to estimate the overall/mean of an outcome of interest. However, inference about between-study variability, which is typically modelled using a between-study variance parameter, is usually an additional aim. The DerSimonian and Laird method, currently widely used by default to estimate the between-study variance, has been long challenged. Our aim is to identify known methods for estimation of the between-study variance and its corresponding uncertainty, and to summarise the simulation and empirical evidence that compares them. We identified 16 estimators for the between-study variance, seven methods to calculate confidence intervals, and several comparative studies. Simulation studies suggest that for both dichotomous and continuous data the estimator proposed by Paule and Mandel and for continuous data the restricted maximum likelihood estimator are better alternatives to estimate the between-study variance. Based on the scenarios and results presented in the published studies, we recommend the Q-profile method and the alternative approach based on a ‘generalised Cochran between-study variance statistic’ to compute corresponding confidence intervals around the resulting estimates. Our recommendations are based on a qualitative evaluation of the existing literature and expert consensus. Evidence-based recommendations require an extensive simulation study where all methods would be compared under the same scenarios. © 2015 The Authors. Research Synthesis Methods published by John Wiley & Sons Ltd Legal Statement.

Keywords: heterogeneity; mean squared error; bias; coverage probability; confidence interval
Empirical examination of differences in results

**An empirical examination of heterogeneity in 12894**

Dean Langan, Julian P. C. Emsley

Heterogeneity in meta-analysis is most commonly assessed by DerSimonian and Laird. However, this method, and similar methods to estimate heterogeneity include those proposed by Paule and Mandel, Sidik and Jonkman, and Hedges and Olkin. These methods provide statistical summaries of heterogeneity from the results of clinical trials. We compared the methods of meta-analysis, and found that (1) the overall effect size is the same; (2) the overall effect size is different; and (4) p-values testing the no-effect hypothesis are fixed by more than 50% when different heterogeneity models are used. Statistical significance at a 5% level was observed in some meta-analyses, and researchers should be cautious in interpreting results. Copyright © 2015 John Wiley & Sons Ltd.
On the basis of current evidence, we provisionally recommend the Paule-Mandel method for estimating the heterogeneity variance, and using this estimate to calculate the mean effect and its 95% confidence interval. However, further simulation studies are required to draw firm conclusions.
Meta-analysis of simulation study results

Meta-regression

Type I error = \( \alpha + \beta_1 \times \text{no. studies} \) 
+ \( \beta_2 \times \text{study size} \) 
+ \( \beta_3 \times \text{baseline risk} \) 
etc

Meta-análisis de simulaciones Monte Carlo

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META-ANÁLISIS DE SIMULACIONES MONTE CARLO

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RESUMEN

Los estudios de simulación Monte Carlo (MC) constituyen un procedimiento metodológico muy útil para investigar los efectos de la violación de los supuestos de las pruebas estadísticas sobre las tasas de error, en especial cuando la teoría estadística exacta no es capaz de determinar dichos efectos. Desafortunadamente, los estudios MC carecen de una estrategia general que guíe su interpretación, así como su integración. Se presenta una técnica meta-analítica desarrollada por Harwell (1992), basada en el modelo de regresión por mínimos cuadrados ponderados, para integrar cuantitativamente estudios MC sobre un mismo tema. La variable dependiente puede ser la tasa de error Tipo I, la tasa de error Tipo II o la potencia estadística; las variables predictoras son los parámetros y condiciones manipuladas en los estudios MC. La propuesta se ilustra con un ejemplo extraído del ámbito del meta-análisis. Finalmente, se discuten sus ventajas.

Palabras clave: Monte Carlo; meta-análisis; regresión ponderada
PROTOCOL

A Comprehensive Simulation Study to Compare Methods of Estimating Heterogeneity Variance in Meta-analysis

Version 3.0, 23/12/2014

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Reaching recommendations

• We need to understand the real world implications

• What properties do *meta-analyses* have?
Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data

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Background

Many meta-analyses contain only a small number of studies, making it difficult to estimate the extent of heterogeneity. Bayesian meta-analysis allows analysis of evidence on heterogeneity, and offers advantages over random-effects meta-analysis. To assist in the interpretation of statistical evidence on the likely extent of heterogeneity in small areas of health care.

Methods

Our analyses included 14,886 meta-analyses from the Cochrane Database of Systematic Reviews. We classed meta-analyses according to the type of outcome, type of intervention, and medical specialty. By modelling between-study heterogeneity from these meta-analyses simultaneously, using the same normal distribution, we investigated the impact of meta-analyses on the variance in estimates of the underlying heterogeneity. Predictive distributions were obtained for the heterogeneity in these meta-analyses.

Results

Between-study heterogeneity variances for the outcome of all-cause mortality were compared using a logistic regression model. The variance of 17% (95% CI 10–26) of variances for each meta-analysis comparing two active pharmaceutical interventions was on average 75% (95% CI 60–95) lower than that for variances of non-pharmacological interventions. Meta-analyses of data from randomised controlled trials of pharmaceutical interventions have generally smaller variance in heterogeneity than meta-analyses of non-pharmacological interventions.
Combine
• properties of the methods under different scenarios
with
• prevalence of those scenarios
Concluding remarks

• Recommendations for statistical methods should combine
  • theoretical considerations
  • technical properties as demonstrated through simulation studies
  • empirical data on whether it makes much difference in practice
  • information on which scenarios are most common (if properties of the methods vary by scenario)

• Simulation studies need to be informed by real world scenarios
• In most Cochrane meta-analyses, all methods for estimating between-study variance are poor and likely to be imprecise, with some positive or negative bias
• But confidence intervals for the meta-analysis are reasonably robust if done using Hartung-Knapp correction