A Meta-analysis Primer

Theory & Practice (with R)

Part 1 of 2

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Outline

Background

Model selection

Quality assessment

Bias and how to check bias

Graphical display of the results and model diagnostics

Common mistakes

Good practice

Reporting

Meta-analysis software

Part 2:

Meta-analysis in R

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Example

A patient with severe angina will often be eligible for either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery. Results from eight published randomized trials were combined in a collaborative **meta-analysis** of 3371 patients (1661 CABG, 1710 PTCA) with a mean follow-up of 2.7 years. The main features of the trials are shown in Table 43.1. Results for the composite endpoint of cardiac death plus non-fatal myocardial infarction (MI) in the first year of follow-up are shown in Fig. 43.1. The estimated relative risks (RR) are for the PTCA group compared with the CABG group. The figure uses a logarithmic scale for the RR to achieve symmetrical confidence intervals (CI). Although the individual estimates of relative risk vary quite considerably, from reductions in risk to quite large increases in risk, all the confidence intervals overlap to some extent. A more formal assessment of heterogeneity is provided by **Cochran's Chi-squared test for homogeneity**, which gives a non-significant result (test statistic $Q = 10.8$, degrees of freedom $df = 8 - 1 = 7$, $P = 0.15$). However, $I^2 = 100 \times (Q - df)/Q = 100 \times (10.8 - 7)/10.8 = 35\%$, which suggests moderate inconsistency across the studies and advocates a cautious approach to interpreting the combined estimate of RR for all trials. Using a fixed effects meta analysis, we estimate this relative risk as 1.04 (95% CI 0.83 to 1.31), indicating that there was no evidence of a real overall difference between the two revascularization strategies. It may be of interest to note that, during early follow-up, the prevalence of angina was higher in PTCA patients than in CABG patients.

Table 43.1 Characteristics of eight randomized trials comparing percutaneous transluminal coronary angioplasty with coronary artery bypass graft.

	Country	Principal investigator	Single- or multi-vessel	Number of patients		Follow-up (years)
				CABG	PTCA	
Coronary Angioplasty Bypass Revascularisation Investigation (CABRI)	Europe	A.F. Rickards	Multi	513	541	1
Randomised Intervention on Treatment of Angina Trial (RITA)	UK	J.R. Hampton	Single ($n = 456$) Multi ($n = 555$)	501	510	4.7
Emory Angioplasty versus Surgery Trial (EAST)	USA	S.B. King	Multi	194	198	3+
German Angioplasty Bypass Surgery Investigation (GABI)	Germany	C.W. Hamm	Multi	177	182	1
The Toulouse Trial (Toulouse)	France	J. Puel	Multi	76	76	2.8
Medicine Angioplasty or Surgery study (MASS)	Brazil	W. Hueb	Single	70	72	3.2
The Lausanne trial (Lausanne)	Switzerland	J.-J. Goy	Single	66	68	3.2
Argentine Trial of PTCA versus CABG (ERACI)	Argentina	A. Rodriguez	Multi	64	63	3.8

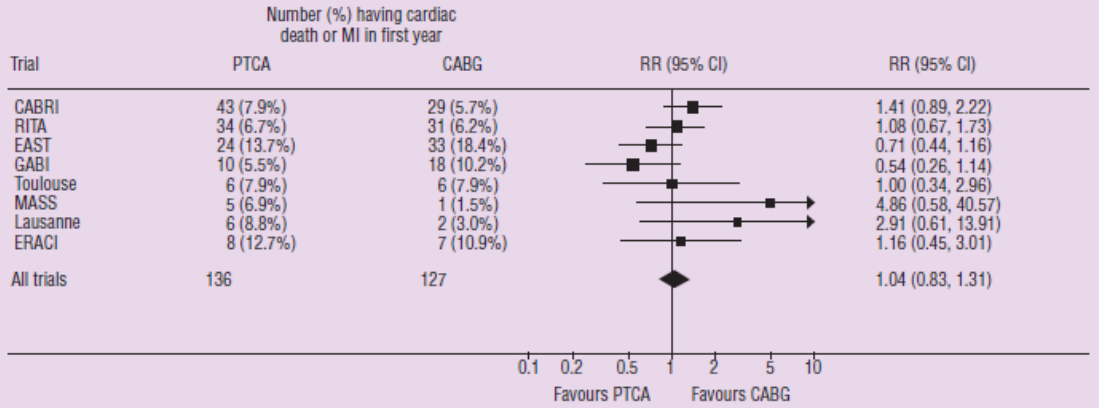
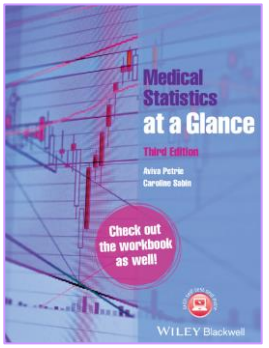


Figure 43.1 Forest plot of relative risk (RR) with 95% confidence interval of cardiac death or myocardial infarction (MI) for PTCA group compared with CABG group in first year since randomization.

Adapted from Pocock, S.J., Henderson, R.A., Rickards, A.F., *et al.* (1995) A meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet*, **346**, 1184–1189, with permission from Elsevier.



An Example

Original Investigation | Caring for the Critically Ill Patient

September 2, 2020

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Article Information

JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

https://jamanetwork.com/journals/jama/fullarticle/2770279

A meta-analysis of 10 randomised clinical trials with a clearly defined research question (*Is administration of systemic corticosteroids associated with reduced 28-day mortality in critically ill patients with COVID-19*?) and main outcome (*28-day mortality*) and several secondary outcomes which are assessed by the odds ratio (*effect size*) and its 95% confidence intervals. The summary result is presented in a forest plot. A table for the characteristics of included studies and a flowchart of study protocol are also included.

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A Hands-on Example

```
Study <- c("DEXA COVID-19", "CoDEX", "RECOVERY")
OR <- c(2.00, 0.80, 0.59)
lower.OR <- c(0.21, 0.49, 0.44)
upper.OR <- c(18.7, 1.31, 0.78)

library(meta)
result  <- metagen(log(OR), lower = log(lower.OR),
        upper = log(upper.OR),
        studlab = Study, sm = "OR")
result
```

```
                          OR           95%-CI     z   p-value
Fixed effect model    0.6461 [0.5052; 0.8262] -3.48  0.0005
Random effects model  0.6508 [0.5011; 0.8453] -3.22  0.0013
```

```
forest(result)
```

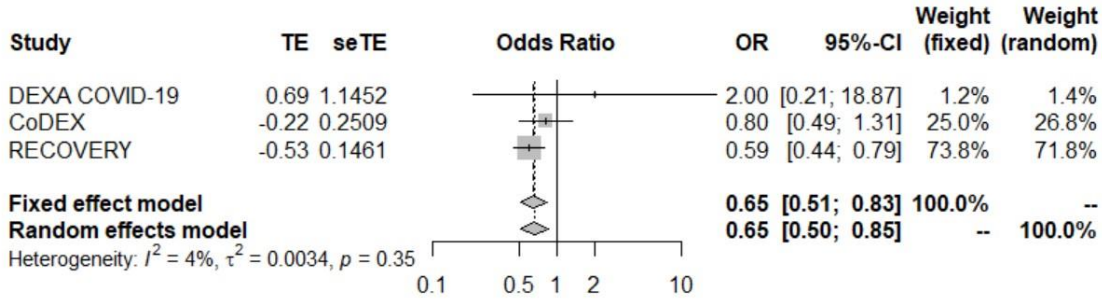
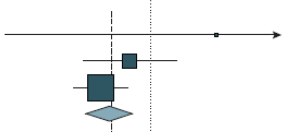


Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60



Original Investigation | Caring for the Critically Ill Patient

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Meta-analysis

Meta-analysis literally means "analysis of analyses"

It is a quantitative research synthesis method to summarise the results of lots of studies with a single summary statistics

It is a pooled analysis of similar studies but uses special statistical methods
(studies are weighted according to the inverse of their variance)

A meta-analysis provides a consolidated and quantitative review of a number of studies sometimes with conflicting results

When it is said to be the top method for providing strongest evidence for a treatment effect or causality, what is referred to is a meta-analysis of randomised clinical/controlled trials (RCTs)

Rigorously conducted and validated meta-analyses are useful tools in evidence-based medicine

Meta-analysis

Meta-analysis of observational or non-randomised studies

Observational studies are likely to be subject to unidentified sources of confounding and risk modification (unlike controlled trials) and pooling such findings may not lead to more certain outcomes

HIPPOKRATIA 2010, 14 (Suppl 1): 29-37

REVIEW ARTICLE

Meta-analysis in medical research

Haidich AB

Department of Hygiene and Epidemiology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece

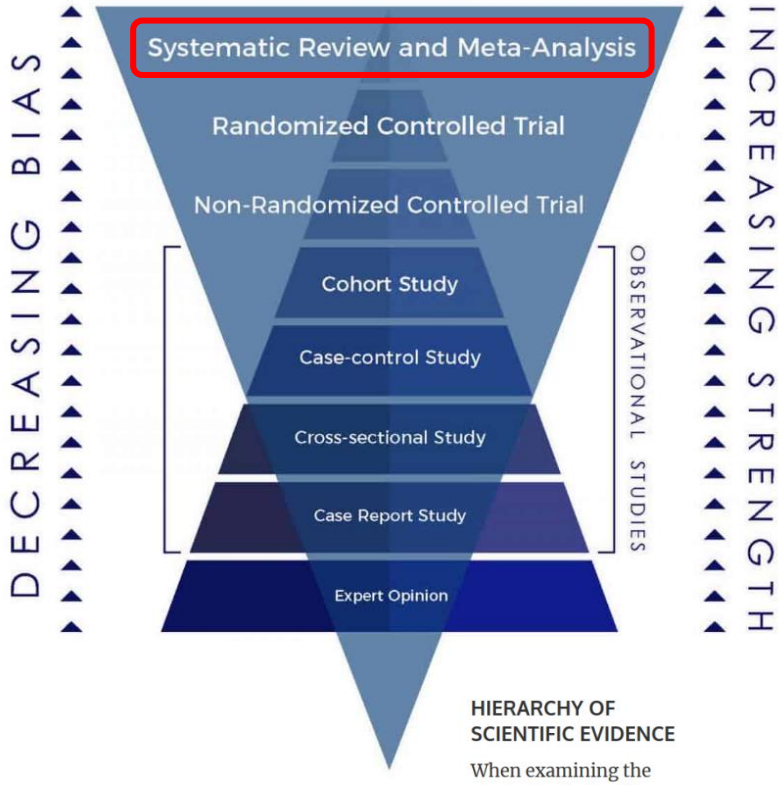
Meta-analysis

Spurious precision? Meta-analysis of observational studies

Matthias Egger, Martin Schneider, George Davey Smith

Meta-analysis of observational or non-randomised studies does not have the same value as "*meta-analysis of randomised controlled trials*"

Meta-analysis



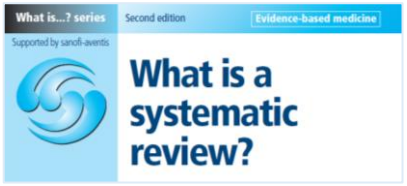
HIERARCHY OF SCIENTIFIC EVIDENCE

When examining the strength of scientific evidence, a number of factors comes into play. Of the most important factors, however, is study design. In the hierarchy of evidence, the strongest evidence results from randomized controlled trials (RCT) and intervention studies. By comparison, weaker evidence results from case reports and expert opinion.

"Meta-analysis of Randomised Controlled Trials"

Box 2. Hierarchies of evidence for questions of therapy, prevention, aetiology or harm[26]

Level 1a	Systematic review (with homogeneity) of randomised controlled trials (RCTs)
Level 1b	Individual RCT (with narrow confidence interval)
Level 1c	All-or-none studies
Level 2a	Systematic review (with homogeneity) of cohort studies
Level 2b	Individual cohort study (including low quality RCT; eg <80% follow-up)
Level 2c	'Outcomes' research; ecological studies
Level 3a	Systematic reviews (with homogeneity) of case-control studies
Level 3b	Individual case-control study
Level 4	Case series (and poor quality cohort and case-control studies)
Level 5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'



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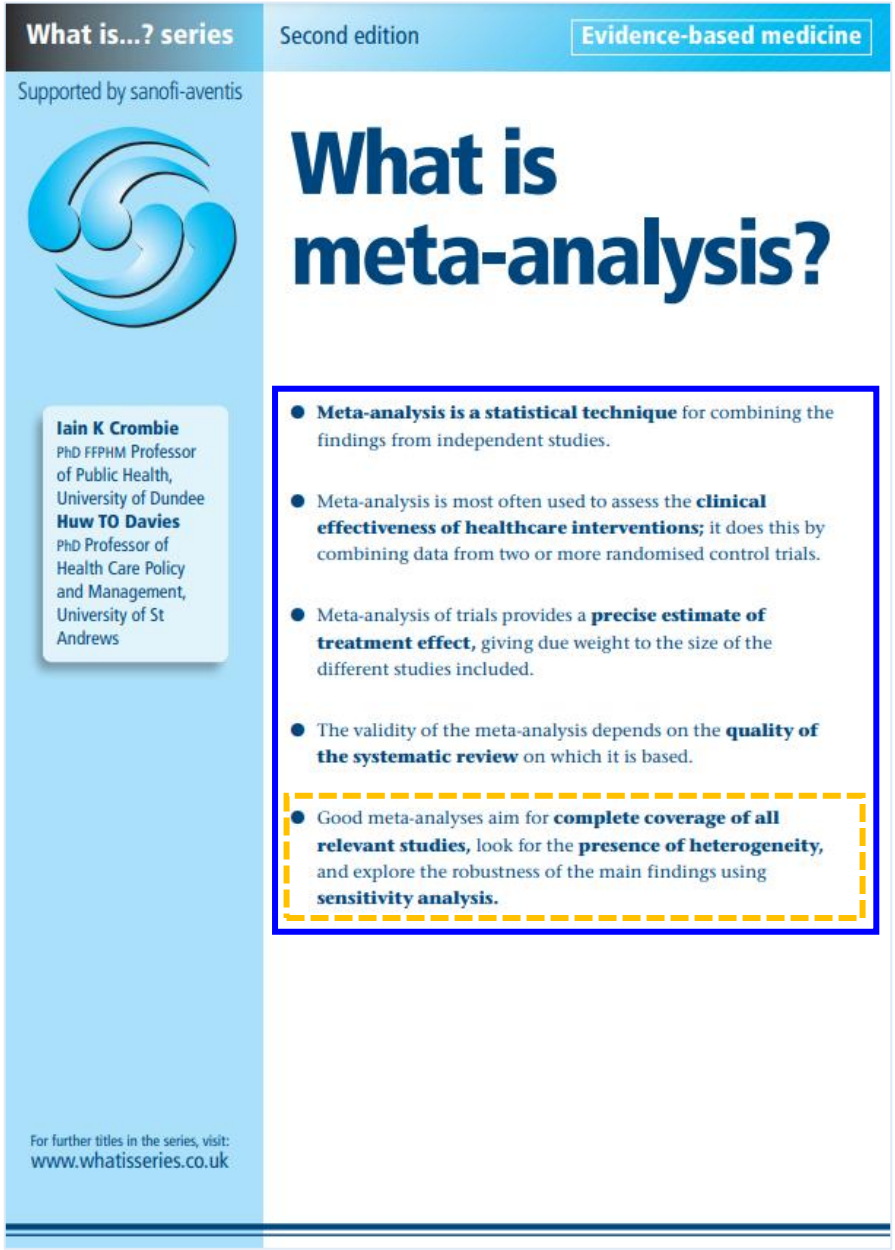
Meta-analysis



AIM FOR:

- **Full coverage of published and unpublished studies**
- **Heterogeneity assessment. If high, exploration of potential sources, followed by subgroup analysis or meta-regression**
- **Exploration of sources of bias (including publication bias)**
- **Sensitivity analysis for identification of influential studies**

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Meta-analysis

Rationale and Merits

When multiple small / low-powered studies are inconclusive or conflicting, a meta-analysis can be used for a conclusive result
Meta-analysis allows combination of several imprecise findings into a more precise one
(settles controversies arising from conflicting studies)

When multiple well-powered studies are available, obtaining a more precise summary effect size is the aim

When lots of studies with lots of heterogeneity are available, it is not a good idea to do a meta-analysis ("mixing oranges and apples")

When lots of studies with similar (non-conflicting) results are available, there is not much point in doing a meta-analysis other than obtaining a more precise summary result

Why perform a meta-analysis in a review?

Meta-analysis

Criticism and Perils

When there is a lot of heterogeneity, a meta-analysis is not a good method to use (likened to mixing oranges and apples)

When publication bias is evident, a meta-analysis will yield a misleading result

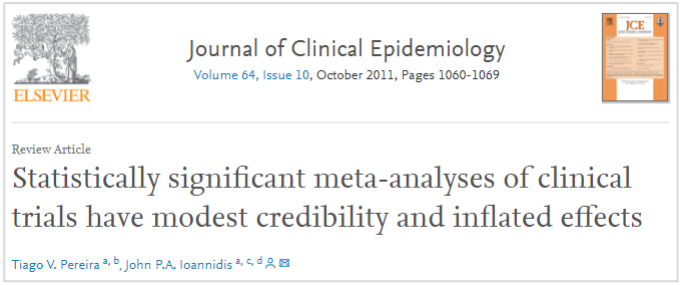
The results are meta-analysis are as good as the quality of individual studies included in the analysis

It is a utopic idea to be able to analyse all published and unpublished work on a specific subject

"There are some statistical methods to rule out some of the above criticism in the assessment of quality / validation of a meta-analysis"
(assessment of heterogeneity, publication bias and sensitivity analysis)

Meta-analysis

Criticism and Perils



Journal of Clinical Epidemiology
Volume 64, Issue 10, October 2011, Pages 1060-1069

Review Article

Statistically significant meta-analyses of clinical trials have modest credibility and inflated effects

Tiago V. Pereira [a, b], John P.A. Ioannidis [a, c, d]

The magnitude of observed effects, especially in meta-analyses with limited evidence, is often inflated.

As more studies are added to initial meta-analyses in time, the effect sizes (clinical significance) gets smaller suggesting that early studies tend to have inflated results (partly due to publication bias).

Temporal variation in effect sizes can be checked by subgroup analysis (by date) and by producing a Forest Plot which sorts the studies by their publication dates. Cumulative meta-analysis is another option.

Meta-analysis

Observational Studies vs Randomised Clinical Trials

Meta-analysis

Spurious precision? Meta-analysis of observational studies

Matthias Egger, Martin Schneider, George Davey Smith

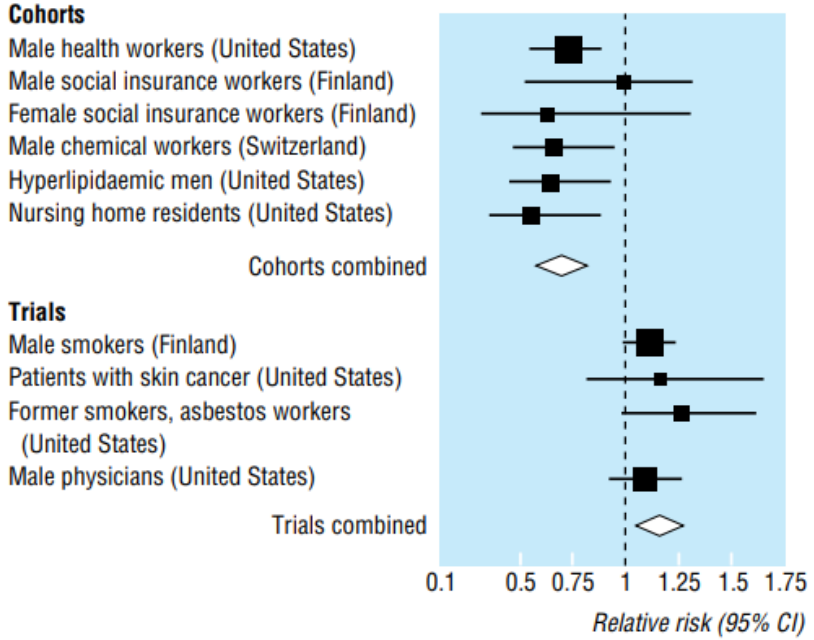


Fig 2 Meta-analysis of association between β carotene intake and cardiovascular mortality: results from observational studies show considerable benefit, whereas the findings from randomised controlled trials show an increase in the risk of death. Meta-analysis is by fixed effects model

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Meta-analysis

Observational Studies vs Randomised Clinical Trials

Pharmacological Research 163 (2021) 105229

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Misleading meta-analyses of observational studies may generate unjustified alarms: The case of medications for nausea and vomiting in pregnancy

Annalisa Biffi [a,b,*], Federico Rea [a,b], Anna Locatelli [c,d], Irene Cetin [e,f], Amelia Filippelli [a,g], Giovanni Corrao [a,b]

Conclusion

Observational investigations and meta-analyses of observational studies need cautious interpretations. Their susceptibility to several, often sneaky, sources of bias should be carefully evaluated.

Meta-analysis of Observational Studies in Epidemiology

A Proposal for Reporting

Donna F. Stroup, PhD, MSc; Jesse A. Berlin, ScD; Sally C. Morton, PhD; et al

» Author Affiliations

JAMA. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

Meta-analysis of observational or non-randomised studies does not have the same value as meta-analysis of randomised controlled trials

"*garbage in, garbage out*"

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Meta-analysis: Conduct

How to Conduct a Meta-analysis

(Systematic review followed by a meta-analysis)

Location of Studies for Inclusion

(Search criteria; databases to search; searching for unpublished studies)

Quality Assessment

(Inclusion-exclusion criteria; sensitivity analysis-after the meta-analysis)

Extracting/Calculating Effect Sizes

(Extract effect sizes, 95% CIs and sample sizes)

Checking Heterogeneity and Model Selection

Checking Publication Bias

Method Validation

Presenting Results

Meta-analysis: Conduct

PRISMA Guideline

thebmj

BMJ 2009;339:b2535 doi: 10.1136/bmj.b2535 (Published 21 July 2009)

RESEARCH METHODS & REPORTING

CrossMark

Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement

OPEN ACCESS

David Moher and colleagues introduce PRISMA, an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses

David Moher[1 2], Alessandro Liberati[3 4], Jennifer Tetzlaff[1], Douglas G Altman[5], for the PRISMA Group

Software and Tools

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Meta-analysis: Conduct

Meta-Analytic Methodology for Basic Research: A Practical Guide

Nicholas Mikolajewicz [1,2] and Svetlana V. Komarova [1,2]*

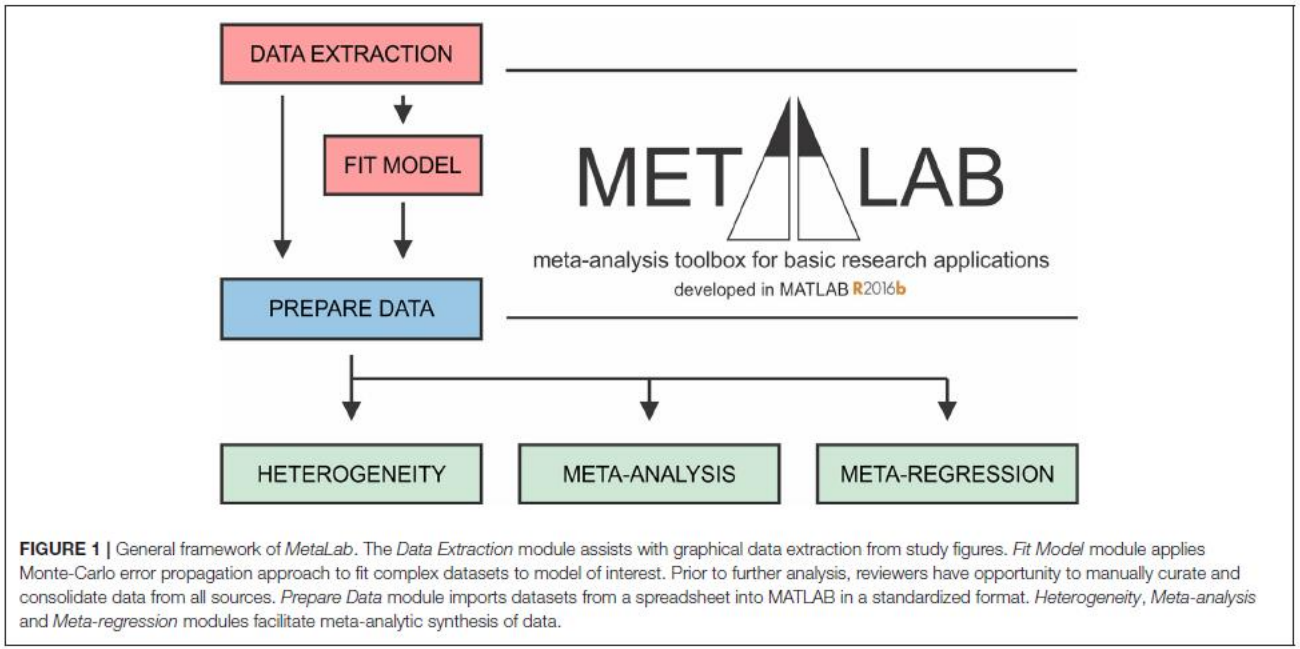

FIGURE 1 | General framework of *MetaLab*. The *Data Extraction* module assists with graphical data extraction from study figures. *Fit Model* module applies Monte-Carlo error propagation approach to fit complex datasets to model of interest. Prior to further analysis, reviewers have opportunity to manually curate and consolidate data from all sources. *Prepare Data* module imports datasets from a spreadsheet into MATLAB in a standardized format. *Heterogeneity*, *Meta-analysis* and *Meta-regression* modules facilitate meta-analytic synthesis of data.

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Meta-analysis: Conduct

Meta-Analytic Methodology for Basic Research: A Practical Guide

Nicholas Mikolajewicz [1,2] and Svetlana V. Komarova [1,2]*

STEPS IN QUANTITATIVE LITERATURE REVIEW

All meta-analytic efforts prescribe to a similar workflow, outlined as follows:

1) **Formulate research question**
   - Define primary and secondary objectives
   - Determine breadth of question
2) **Identify relevant literature**
   - Construct search strategy: rapid or systematic search
   - Screen studies and determine eligibility
3) **Extract and consolidate study-level data**
   - Extract data from relevant studies
   - Collect relevant study-level characteristics and experimental covariates
   - Evaluate quality of studies
   - Estimate model parameters for complex relationships (optional)
4) **Data appraisal and preparation**
   - Compute appropriate outcome measure
   - Evaluate extent of between-study inconsistency (heterogeneity)
   - Perform relevant data transformations
   - Select meta-analytic model
5) **Synthesize study-level data into summary measure**
   - Pool data and calculate summary measure and confidence interval
6) **Exploratory analyses**
   - Explore potential sources of heterogeneity (ex. biological or experimental)
   - Subgroup and meta-regression analyses
7) **Knowledge synthesis**
   - Interpret findings
   - Provide recommendations for future work

Meta-analysis: Conduct

British Journal of Mathematical and Statistical Psychology (2010), 63, 665–694

The British Psychological Society

www.bpsjournals.co.uk

Expert tutorial

How to do a meta-analysis

Andy P. Field[1]* and Raphael Gillett[2]*

Step 1: Do a literature search

Step 2: Decide on inclusion criteria

Step 3: Calculate the effect sizes

Step 4: Do the basic meta-analysis

Step 5: Do some more advanced analysis

Step 6: Write it up

To sum up, the analysis begins by collecting articles addressing the research question that you are interested in. This will include e-mailing people in the field for unpublished studies, electronic searches, searches of conference abstracts, and so on. Once the articles are selected, inclusion criteria need to be devised that reflect the concerns pertinent to the particular research question (which might include the type of control group used, clarity of diagnosis, the measures used, or other factors that ensure a minimum level of research quality). The included articles are then scrutinized for statistical details from which effect sizes can be calculated; the same effect size metric should be used for all studies (see the aforementioned electronic resources for computing these effect sizes). Next, decide on the type of analysis appropriate for your particular situation (fixed vs. random effects, Hedges' method or Hunter and Schmidt's, etc.) and then to apply this method (possibly using the SPSS resources produced to supplement this article). An important part of the analysis is to describe the effect of publication bias and to re-estimate the population effect under various publication bias models using the Vevea and Woods (2005) model. Finally, the results need to be written up such that the reader has clear information about the distribution of effect sizes (e.g., a stem-and-leaf plot), the effect size variability, the estimate of the population effect and its 95% confidence interval, the extent of publication bias (e.g., funnel plots, the rank correlation of the fail-safe *N*), and the influence of publication bias (Vevea and Woods's adjusted estimates).

Meta-Analysis Programs & Datasets

Field, A. P. & Gillett, R. (2010). How to do a meta-analysis. *British Journal of Mathematical and Statistical Psychology, 63,* 665-694.

Getting Started	Basic Meta-Analysis	Moderator Variable Analysis	Sensitivity to Publication Bias	Links

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Meta-analysis

Data Input

For a meta-analysis, the effect sizes (*yi*) and their variance (*vi*) from each study is needed. For most meta-analytical tools, these values (if ratios) have to be natural log (ln) transformed for data input.

Table 1 Common effect sizes and their sampling variances

Quantity of interest	Summary statistics	Effect size (y_i)	Approximate sampling variance (v_i)
Proportion	a: frequency of success b: frequency of failure $n = a + b$ $p = a/n$	$y_p = \log\left(\frac{a}{b}\right)$	$v_p = \frac{1}{a} + \frac{1}{b}$
Relative risk (RR) Odds ratio (OR)	a: frequency of success in Group 1 b: frequency of failure in Group 1 $n_1 = a + b$ c: frequency of success in Group 2 d: frequency of failure in Group 2 $n_2 = c + d$	$y_{RR} = \log\left(\frac{a \times n_2}{c \times n_1}\right)$ $y_{OR} = \log\left(\frac{a \times d}{b \times c}\right)$	$v_{RR} = \frac{1}{a} - \frac{1}{n_1} + \frac{1}{c} - \frac{1}{n_2}$ $v_{OR} = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$
Raw mean difference (RMD) Standardized mean difference (SMD)	$\bar{X}_1$: sample mean for Group 1 S_1^2: sample variance for Group 1 n_1: sample size for Group 1 $\bar{X}_2$: sample mean for Group 2 S_2^2: sample variance for Group 2 n_2: Sample size for Group 2 $S^2_{pooled} = \frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}$	$y_{RMD} = \bar{X}_1 - \bar{X}_2$ $y_{SMD} = \left(1 - \frac{3}{4(n_1+n_2)-9}\right)\frac{\bar{X}_1 - \bar{X}_2}{S_{pooled}}$	$v_{RMD} = S^2_{pooled}\left(\frac{1}{n_1} + \frac{1}{n_2}\right)$ $v_{SMD} = \frac{n_1+n_2}{n_1 n_2} + \frac{y^2_{SMD}}{2(n_1+n_2)}$
Correlation (r) Fisher's z transformed score (z)	r: sample correlation coefficient n: sample size	$y_r = r$ $y_z = 0.5 \times \log\left(\frac{1+r}{1-r}\right)$	$v_r = \frac{(1-r^2)^2}{n-1}$ $v_z = \frac{1}{n-3}$

Conducting a meta-analysis: basics and good practices

Mike W.-L. CHEUNG,[1] Roger C. M. HO,[2] Yonghao LIM[1] and Anselm MAK[3]

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Meta-analysis

Data Input

The variance may not be reported in individual papers, but can be estimated from confidence intervals

Calculation of Variance from CIs:

Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints (*Stat Med 1998*)

Section 4.1 gives the formula for calculating the variance of a hazard ratio from confidence interval limit values

Section 4.2 (example 2) shows a calculation. Note that the denominator inside the squared brackets is 2*1.96 = 3.92 if 95% CIs are used

Practical methods for incorporating summary time-to-event data into meta-analysis (*Trial 2007*)

Section "3. Report presents HR and confidence intervals" in page 4 of the paper gives the formula for the calculation of variance from CI limits

Use 2*1.96 as the denominator for 95% CI and 2*1.64 for a 90% CI

Meta-analysis

Model Selection

Random or Fixed Effect Model?

One of the decisions to be made when conducting a meta-analysis is whether to use a fixed-effects or a random-effects model. A fixed-effects model is based on the assumption that the sole source of variation in observed outcomes is that occurring within the study; that is, the effect expected from each study is the same. Consequently, it is assumed that the models are homogeneous; there are no differences in the underlying study population, no differences in subject selection criteria, and treatments are applied the same way.

Random-effects models have an underlying assumption that a distribution of effects exists, resulting in heterogeneity among study results, measured by the parameter τ^2 (tau-squared). Random-effects models is almost always the method of choice in medical research because the strong assumption that the effect of interest is the same in all studies is frequently untenable. The fixed effects model is definitely not appropriate when statistical heterogeneity (high τ^2) is present in the results of studies in the meta-analysis. In the random-effects model, studies are weighted with the inverse of their variance and the heterogeneity parameter. Therefore, it is usually a more conservative approach with wider confidence intervals than the fixed-effects model where the studies are weighted only with the inverse of their variance. The most commonly used random-effects method is the DerSimonian and Laird (DL) method.


HIPPOKRATIA 2010, 14 (Suppl 1): 29-37

REVIEW ARTICLE

Meta-analysis in medical research

Haidich AB

Department of Hygiene and Epidemiology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece

Kingston University London

Meta-analysis

Model Selection

Random or Fixed Effect Model?

If in doubt, use random effects (RE) model!

If the differences in effects sizes are due to exclusively within-study variability (random variation), the fixed effect model is the correct choice. The within-study variance is what happens when the same study is repeated many times (which yield slightly different results due to random variation). In real-life, this happens if the same protocol has been strictly adhered to in all studies to be included in a meta-analysis, which is almost never the case.

Meta-analysis

Statistical Power Analysis

14.2 Random-Effects Model

For power analyses assuming a random-effects model, we have to take the between-study heterogeneity variance τ^2 into account. Therefore, we need to calculate an adapted version of the standard error, σ^*_θ:

$$\sigma^*_\theta = \sqrt{\frac{\left(\frac{n_1+n_2}{n_1 n_2}\right) + \left(\frac{\theta^2}{2(n_1+n_2)}\right) + \tau^2}{K}} \tag{14.5}$$

The problem is that the value of τ^2 is usually not known before seeing the data. Hedges and Pigott (2001), however, provide guidelines that may be used to model either low, moderate or large between-study heterogeneity:

Low heterogeneity:

$$\sigma^*_\theta = \sqrt{1.33 \times \frac{\sigma^2_\theta}{K}} \tag{14.6}$$

Moderate heterogeneity:

$$\sigma^*_\theta = \sqrt{1.67 \times \frac{\sigma^2_\theta}{K}} \tag{14.7}$$

Large heterogeneity:

$$\sigma^*_\theta = \sqrt{2 \times \frac{\sigma^2_\theta}{K}} \tag{14.8}$$

The `power.analysis` function can also be used for random-effects meta-analyses. The amount of assumed between-study heterogeneity can be controlled using the `heterogeneity` argument. Possible values are `"low"`, `"moderate"` and `"high"`. Using the same values as in the previous example, let us now calculate the expected power when the between-study heterogeneity is moderate.

```
power.analysis(d = 0.2,
               k = 10,
               n1 = 25,
               n2 = 25,
               p = 0.05,
               heterogeneity = "moderate")
```


The R package `dmetar` has a `power.analysis()` function for statistical power analysis

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Meta-analysis

Statistical Power Analysis

How to calculate statistical power for your meta-analysis

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Category: Project

Description: An R script and excel file to calculate statistical power for your meta-analysis.

```
# The following script calculates statistical power for a meta-analysis to detect a
summary effect size of 0.2, with an average sample size per group of = 50, a total of 15
effect sizes, and moderate heterogeneity.

es <- 0.2 # Enter your summary effect size (Cohen's d equivalent)
as <- 50  # Average per number per group
mk <- 15  # Number of effect sizes
hg <- 1   # Heterogeneity (".33" for small, "1" for moderate, & "3" for large)

eq1 <- ((as+as)/((as)*(as))) + ((es^2)/(2*(as+as)))
eq2 <- hg*(eq1)
eq3 <- eq2+eq1
eq4 <- eq3/mk
eq5 <- (es/sqrt(eq4))
Power <- (1-pnorm(1.96-eq5)) # two-tailed
Power
```

Power Calculation For Meta Analysis.xlsx

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Meta-analysis

14.3.3 Meta-Analysis

Meta-analysis is the pooling varying results of various studies on the same parameter after a systematic review. The objective is to get a much more reliable estimate of the parameter of interest, which would be based on pooled *n*. For this, studies meeting prespecified quality criteria are selected after a comprehensive search of the literature. A particular relevant parameter, such as the OR, RR, or mean difference, is chosen and its value with CI is extracted from each selected study.

Sufficient care should be exercised in selecting the studies for meta-analysis. Generally, literature databases such as PubMed and Embase are searched for relevant terms, and the articles that do not happen to use these terms will not be included. Second, it is customary for studies to use the PECOS system, which stands for population, exposure (or intervention), control, outcome, and study design, and your chosen terms may have to specify at least one from each of these categories so that the chosen articles are on a uniform format without unduly restricting the search. Third, beware of the **file drawer effect** that operates when the studies with negative outcomes are not published. Perhaps more studies get "not significant" results, and they remain in the drawer (not sent for publication)—providing a skewed picture of the significant effect. This is in addition to the publication bias that gives priority to the studies with statistically significant findings out of those submitted for publication. Consider if it would be appropriate to give at least twice as much weight in meta-analysis to the studies with not significant results to possibly alleviate this bias.

Ideally, all the selected studies should have followed the same method of estimating the selected parameters. This would not happen in practice, and you may have to make adjustments so that they all have a common meaning for effect size. For something like mean difference, keep track of the scale of measurement. In some studies, the CI may not be available and you may have to calculate this based on the SE. Some studies give the mean and SD, and others the median and interquartile range (IQR). To convert the median or IQR to the mean or SD, see Wan et al. [12].

14.3.3.1 Forest Plot

A forest plot provides a graphical summary view of the varying results obtained in different studies. An example is in Figure 14.2, where ORs of probiotics in the prevention of antibiotic-associated diarrhea found in different studies are shown [13].

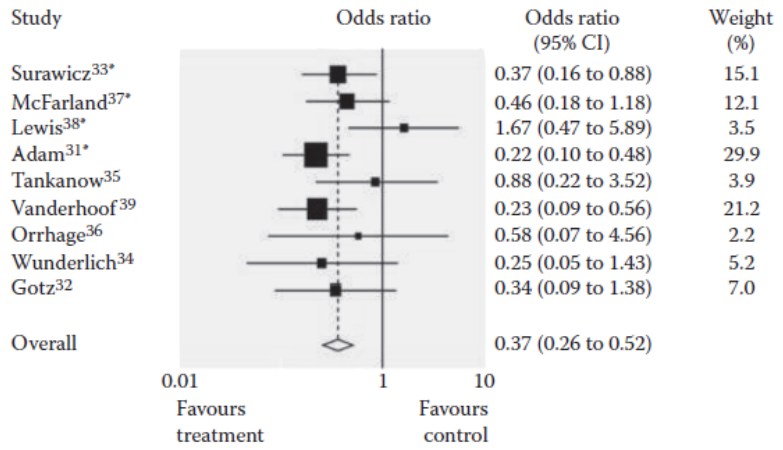

FIGURE 14.2
Plot of the log of ORs for the proportion of patients free of diarrhea in treatment groups compared with control groups. (Reproduced from D'Souza AL et al., *BMJ*, 324:1361, 2002. With permission.)

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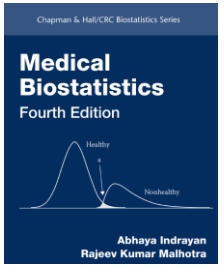

Threats to Validity of Meta-analyses

Quality of Included Studies

Heterogeneity

(τ^2 calculation; Q-statistics; I^2; H^2; G^2 - Forest plot; Baujat plot; Radial (Galbraith) plot; L'Abbe plot)

Publication Bias

(Funnel plot; contour-enhanced funnel plot; (Duval & Tweedie's) trim-and-fill plot; regression-based adjustment; Forest plot by publication date/cumulative meta-analysis)

Small Study Effects

Outliers and Influential Studies

(sensitivity /leave-one-out analysis; Baujat plot; Radial (Galbraith) plot)

Violation of Assumptions of Statistical Modelling

(Model diagnostics like Q-Q plot to check normal distribution of effect sizes)

Scoring the Quality of Clinical Trials for Meta-analysis

BMC Medical Research Methodology

Research article

Meta-analysis: Neither quick nor easy

Nancy G Berman*[1] and Robert A Parker[2]

Proposes a structured review of the quality of the study

Table 4 - Examples of meta-analyses to illustrate how other investigators have proceeded

Table 2. Questions for Study Evaluation -- Part 1	
A. UNBLINDED REVIEW	
Source of the Information	Was the paper published in a peer reviewed journal or, if not, was the study reviewed by some other group? Is the purpose of the trial indicated in the publication? If unpublished information from the investigator is required, are there problems of recall or missing information? Are the investigators well qualified to undertake the study? Are all institutional affiliations identified? When was the information collected?
Funding	How was the study funded? If outside funding was used, what was the role of the funding agency? Were the investigators independent of the sponsoring agency? Did the investigators have any financial interest in the outcome?
B. BLINDED REVIEW	
Study Design	Is the design described? Is the design appropriate to the study questions? Are there clear inclusion and exclusion criteria? Are the procedures for randomization (if appropriate) and blinding described? Are experimental methods, such as dosages and treatment schedules clearly defined?
Study Outcomes	Are the outcomes clearly defined, including methods of measurement? Do the outcome measures answer the study questions? If the study is unpublished, is the investigator willing to assure that this is final, clean data?
Study Subjects	Did the subjects meet the inclusion/exclusion criteria? Are methods of diagnosis defined and reliable? Are demographics for all subject groups included?
Controls	If there are parallel controls, are they comparable to the subjects? If it is a crossover study, is there sufficient wash-out time? If historical controls are used is the data of good quality from known sources? Can it be determined that they are comparable to the subjects? If population parameters, e.g. norms, are used, how were they derived and were they from subjects comparable to the study population?

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Scoring the Quality of Clinical Trials for Meta-analysis

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robvis

Create publication quality risk-of-bias assessment figures

About

robvis makes it easy to produce high quality figures that summarise the risk-of-bias assessments performed as part of a systematic review or research synthesis project.

Citation

If you use *robvis* to create risk-of-bias plots for your study, please remember to cite the tool.

More details and downloadable citation files can be found in the "About" tab.

Found a bug?

Please email me

OR

Log an issue on GitHub

Quick start

Upload your data

Setting up your own data

To ensure that this app works as expected, the uploaded risk-of-bias assessment summary table must follow a certain format. For clarity, your data should be laid out as follows:

- The first column contains details about the study such as author and year of publication.
- The second and subsequent columns contain the judgements in each domain of the assessment tool. The number of columns containing domain-level assessments will vary by tool used.

Two further optional columns can also be included in the uploaded data:

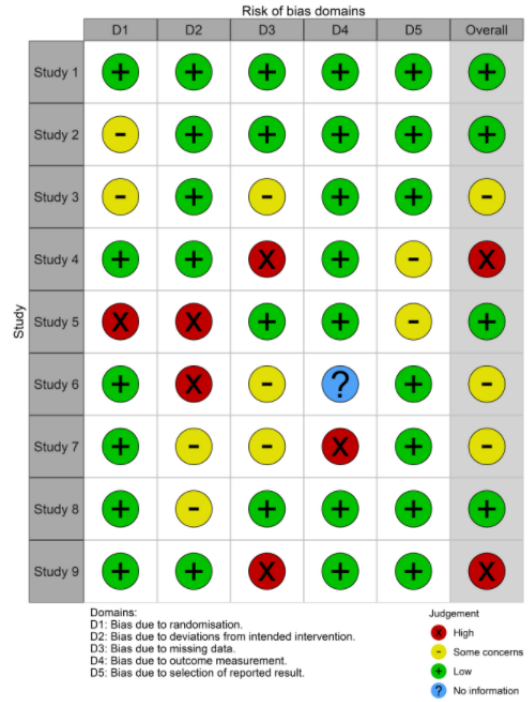
- A column (named "Overall") containing the overall risk-of-bias judgements for each study.
- A column (named "Weight") which contains some measure of the result's precision (e.g. the weight assigned to that result in a meta-analysis, or the sample size of the analysis that produced the result). To reproduce 'equally' weighted bar charts as have traditionally been presented in Cochrane Reviews to date, the cells in this column may all be set to 1.

Excel example datasets/templates

The quickest and easiest way to correctly set up your risk-of-bias assessment summary table is to replace the example data contained in the Excel templates below with your own data, and then upload the file to the app. Alternatively, you can enter the data directly into the app by hand. Templates for the major risk-of-bias tools supported by the app are available, in addition to a "Generic" template for use with any domain-bases assessment tool (including ROB1).

RoB2.0 dataset | RoB2.0 (Cluster) dataset | ROBINS dataset

QUADAS dataset | QUIPS dataset | Generic dataset



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Research Synthesis Methods

SPECIAL ISSUE PAPER | Open Access

Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments

Luke A. McGuinness | Julian P. T. Higgins

First published: 26 April 2020 | https://doi.org/10.1002/jrsm.1411 | Citations: 156

Scoring the Quality of Clinical Trials for Meta-analysis

Words of Caution

The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis

Peter Jüni, MD
Anne Witschi, MD
Ralph Bloch, MD, PhD
Matthias Egger, MD, MSc

Conclusions Our data indicate that the use of summary scores to identify trials of high quality is problematic. Relevant methodological aspects should be assessed individually and their influence on effect sizes explored.

JAMA. 1999;282:1054-1060 www.jama.com

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Scoring the Quality of Clinical Trials for Meta-analysis

Words of Caution

ELSEVIER

Journal of Clinical Epidemiology 59 (2006) 1249–1256

Journal of Clinical Epidemiology

Adjustment of meta-analyses on the basis of quality scores should be abandoned

Peter Herbison[a,*], Jean Hay-Smith[b], William J. Gillespie[c]

Objective: To find if a particular quality score was better than others at validly scoring the quality of randomized controlled trials, both by examining the consistency of dividing studies into high and low quality and using a large study as a reference standard.

Study Design and Setting: Observational study of meta-analyses from the Cochrane Library. These had to have binary outcomes that included more than 10 studies, one or more of which randomized more than 500 people into each group.

Results: Eighteen systematic reviews, with 65 meta-analyses using binary outcomes, were included and the included trials were scored for 43 different quality scores. None of these scores was better at dividing the studies in to low and high quality, and none of the scores was better over the 65 meta-analyses in making the result closer to the reference standard.

Conclusion: None of the quality scores found appeared to measure quality validly. It is a mistake to assign meaning to the result of a quality score.

Using various available scores for quality assessment is not encouraged

Assessing the Quality of Clinical Trials for Meta-analysis

European Heart Journal (2014) 35, 3336–3345
doi:10.1093/eurheartj/ehu424

REVIEW

Statistical tutorials

Systematic reviews and meta-analyses of randomized trials: principles and pitfalls

Bruno R. da Costa[1,2,3] and Peter Jüni[1,3]*

Box 4 Items for methodological assessment

Generation of allocation sequences
Adequate in preventing selection bias if sequences are unpredictable: random numbers generated by computer, table of random numbers, drawing of lots or envelopes, tossing a coin, shuffling cards, throwing dice, etc.

Concealment of allocation sequences
Adequate in preventing selection bias if patients and investigators enrolling patients cannot foresee assignment: a priori numbered or coded drug containers of identical appearance prepared by an independent pharmacy; central randomization (performed at a remote site); sequentially numbered, sealed, opaque envelopes; etc.

Blind adjudication of events
Adequate in preventing detection bias if the adjudication of events used in the analysis is performed by an independent external clinical events committee that is not aware of which treatment patients were allocated to. Blind adjudication of events is not necessary for overall mortality as an outcome.

Intention to treat analysis
Adequate in preventing attrition bias if all patients randomized are analysed in the group they were originally allocated to. In time-to-event analyses, up to 10% loss to follow-up may be acceptable, provided that the percentage of patients lost to follow-up is similar between groups, and all randomized patients are initially included in the analysis and only censored at the time they were lost to follow-up.

Heterogeneity

"The included studies are homogeneous if they share a common underlying true effect size; otherwise, they are heterogeneous. A fixed-effect model is customarily used when the studies are deemed homogeneous, while a random-effects model is used for heterogeneous studies" (Lin, 2016)

If the sole source of variation in observed outcomes is the within study variability, then there is no heterogeneity and the effect expected from each study is more or less the same (subject to random variation) > homogeneity

Clinical heterogeneity: Variability in the participants, interventions and outcomes
Methodological heterogeneity: Variability in study design and risk of bias

Sources of heterogeneity include:
Differences in the underlying study populations
Differences in subject selection criteria
Differences in the treatments and their applications

"Statistical examination of variability or heterogeneity in study results is a major step of the meta-analysis process"

If heterogeneity is present, the source should be explored and the summary measure must be interpreted with caution (generalisation becomes difficult)

Heterogeneity: what is it and why does it matter?

Posted on 29th November 2018 by Maximilian Siebert

It is important to note that there are different types of heterogeneity:

- **Clinical**: Differences in participants, interventions or outcomes
- **Methodological**: Differences in study design, risk of bias
- **Statistical**: Variation in intervention effects or results

How to deal with heterogeneity?

Once you have detected variability in your results you need to deal with it. Here are some steps on how you can treat this issue:

- Check your data for mistakes – Go back and see if you maybe typed in something wrong
- Don't do a meta-analysis if heterogeneity is too high – Not every systematic review needs a meta-analysis
- Explore heterogeneity – This can be done by subgroup analysis or meta-regression
- Perform a random effects meta-analysis – Bear in mind that this approach is for heterogeneity that cannot be explained because it's due to chance
- Changing the effect measures – Let's say you use the Risk Difference and have high heterogeneity, then try out Risk Ratio or Odds Ratio

Box 1: Statistical assessments of heterogeneity

Meta-analysts typically use 2 statistical approaches to evaluate the extent of variability in results between studies: Cochran's Q test and the I^2 statistic.

Cochran's Q test

- Cochran's Q test is the traditional test for heterogeneity. It begins with the null hypothesis that all of the apparent variability is due to chance. That is, the true underlying magnitude of effect (whether measured with a relative risk, an odds ratio or a risk difference) is the same across studies.
- The test then generates a probability, based on a χ^2 distribution, that differences in results between studies as extreme as or more extreme than those observed could occur simply by chance.
- If the *p* value is low (say, less than 0.1) investigators should look hard for possible explanations of variability in results between studies (including differences in patients, interventions, measurement of outcomes and study design).
- As the *p* value gets very low (less than 0.01) we may be increasingly uncomfortable about using single best estimates of treatment effects.
- The traditional test for heterogeneity is limited, in that it may be underpowered (when studies have included few patients it may be difficult to reject the null hypothesis even if it is false) or overpowered (when sample sizes are very large, small and unimportant differences in magnitude of effect may nevertheless generate low *p* values).

I^2 statistic

- The I^2 statistic, the second approach to measuring heterogeneity, attempts to deal with potential underpowering or overpowering. I^2 provides an estimate of the percentage of variability in results across studies that is likely due to true differences in treatment effect, as opposed to chance.
- When I^2 is 0%, chance provides a satisfactory explanation for the variability we have observed, and we are more likely to be comfortable with a single pooled estimate of treatment effect.
- As I^2 increases, we get increasingly uncomfortable with a single pooled estimate, and the need to look for explanations of variability other than chance becomes more compelling.
- For example, one rule of thumb characterizes I^2 of less than 0.25 as low heterogeneity, 0.25 to 0.5 as moderate heterogeneity and over 0.5 as high heterogeneity.

If the differences in effects sizes are due to exclusively within-study variability (random variation), the fixed effect model is the correct choice. The within-study variance is what happens when the same study is repeated many times (which yield slightly different results due to random variation).

Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results

Rose Hatala, Sheri Keitz, Peter Wyer, Gordon Guyatt, for the Evidence-Based Medicine Teaching Tips Working Group

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Heterogeneity

The I^2 > 50% "Guideline"

There are no iron-clad rules determining when exactly further analyses of the between-study heterogeneity are warranted. An approach that is sometimes used in practice is to check for outliers and influential cases when I^2 is greater than 50%. When this threshold is reached, we can assume at least moderate heterogeneity, and that (more than) half of the variation is due to true effect size differences.

This "rule of thumb" is somewhat arbitrary, and, knowing the problems of I^2 we discussed, in no way perfect. However, it can still be helpful from a practical perspective, because we can specify **a priori**, and in a consistent way, when we will try to get a more robust version of the pooled effect in our meta-analysis.

What should be avoided at any cost is to remove outlying and/or influential cases without any stringent rationale, just because we like the results. Such outcomes will be heavily biased by our "researcher agenda" (see Chapter 1.3), even if we did not consciously try to bend the results into a "favorable" direction.

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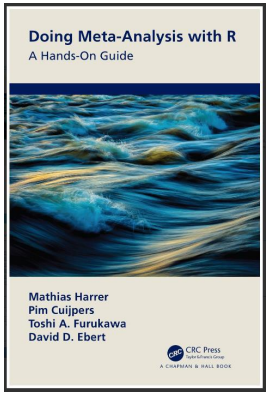


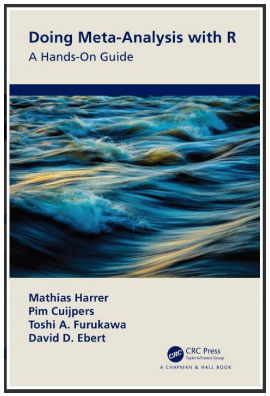
5.1.4 Heterogeneity Variance τ^2 & Standard Deviation τ

Tau-squared (τ^2) quantifies the **variance** of the true effect sizes underlying the data used in meta-analysis. When the square root of τ^2 is taken, the result is tau (τ), which is the **standard deviation** of the true effect sizes.

A great asset of τ is that it is expressed on the same scale as the effect size metric. This means that we can interpret it in the same as one would interpret, for example, the mean and standard deviation of the sample's age in a primary study. The value of τ tells us something about the **range** of the true effect sizes.

The **95% confidence interval** of the true effect sizes can be calculated by multiplying τ with 1.96, and then adding and subtracting this value from the pooled effect size.

*** **Calculation of heterogeneity measures is based on the tau value** ***



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Heterogeneity

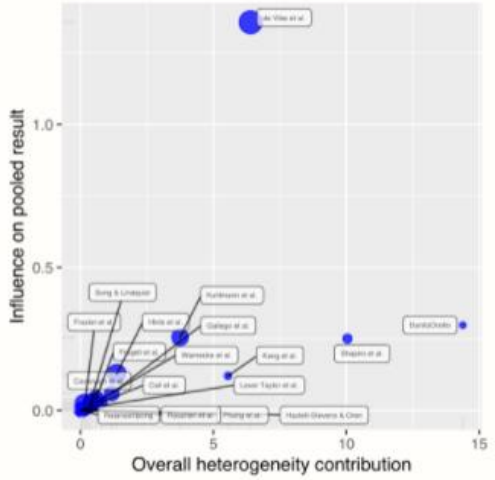
Baujat plots are diagnostic plots to detect studies which overly contribute to the heterogeneity in a meta-analysis

5.4.2.1 **Baujat Plot**

A Baujat plot can be printed using the `plot` function and by specifying `"baujat"` in the second argument:

```
plot(m.gen.inf, "baujat")
```

Copy



Baujat plots (Baujat et al. 2002) are diagnostic plots to detect studies which overly contribute to the heterogeneity in a meta-analysis. The plot shows the contribution of each study to the overall **heterogeneity** (as measured by Cochran's Q) on the **horizontal** axis, and its **influence** on the **pooled effect size** on the **vertical** axis.

This "influence" value is determined through the leave-one-out method, and expresses the standardized difference of the overall effect when the study is included in the meta-analysis, versus when it is not included.

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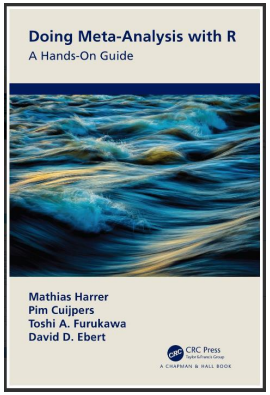

Heterogeneity

Methods for calculation of the tau value

A *random-effects model* can be fitted with the same code but setting the `method` argument to one of the various estimators for the amount of heterogeneity:

- `method="DL"` = DerSimonian-Laird estimator,
- `method="HE"` = Hedges estimator,
- `method="HS"` = Hunter-Schmidt estimator,
- `method="HSk"` = Hunter-Schmidt estimator with a small sample-size correction,
- `method="SJ"` = Sidik-Jonkman estimator,
- `method="ML"` = maximum-likelihood estimator,
- `method="REML"` = restricted maximum-likelihood estimator,
- `method="EB"` = empirical Bayes estimator,
- `method="PM"` = Paule-Mandel estimator,
- `method="GENQ"` = generalized Q-statistic estimator.

For a description of the various estimators, see Brannick et al. (2019), DerSimonian and Kacker (2007), Raudenbush (2009), Viechtbauer (2005), and Viechtbauer et al. (2015). Note that the Hedges estimator is also called the 'variance component estimator' or 'Cochran estimator', the Sidik-Jonkman estimator is also called the 'model error variance estimator', and the empirical Bayes estimator is actually identical to the Paule-Mandel estimator (Paule & Mandel, 1982). Finally, the generalized Q-statistic estimator is a general method-of-moments estimator (DerSimonian & Kacker, 2007) requiring the specification of weights (the HE and DL estimators are just special cases with equal and inverse variance weights, respectively).

Package 'metafor'

Heterogeneity

Methods for calculation of the tau value and heterogeneity metrics

Comparison of commonly used methods in random effects meta-analysis: application to preclinical data in drug discovery research

Ezgi Tanriver-Ayder [1, 2], Christel Faes [3], Tom van de Casteele [2], Sarah K McCann [4], Malcolm R Macleod [1]

Restricted maximum likelihood (REML) and Bayesian methods should be preferred over DerSimonian and Laird (DL) for estimating heterogeneity in meta-analysis especially when there is high heterogeneity in the observed treatment effects across studies.

BIOMETRICS 73, 156–166
March 2017
DOI: 10.1111/biom.12543

Alternative Measures of Between-Study Heterogeneity in Meta-Analysis: Reducing the Impact of Outlying Studies

Lifeng Lin,* Haitao Chu, and James S. Hodges

Outliers can have great impact on conventional measures of heterogeneity and the conclusions of a meta-analysis… This article proposes several new heterogeneity measures. In the presence of outliers, the proposed measures are less affected than the conventional ones.

Original Article
Research Synthesis Methods
Received 26 June 2014; Revised 20 May 2015; Accepted 24 June 2015 Published online 2 September 2015 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1164

Methods to estimate the between-study variance and its uncertainty in meta-analysis†

Areti Angeliki Veroniki,[a]* Dan Jackson,[b] Wolfgang Viechtbauer,[c] Ralf Bender,[d] Jack Bowden,[e] Guido Knapp,[f] Oliver Kuss,[g] Julian PT Higgins,[h,i] Dean Langan[i] and Georgia Salanti[j]

….. 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 (PM) and for continuous data the restricted maximum likelihood (REML) estimator are better alternatives to estimate the between-study variance…..

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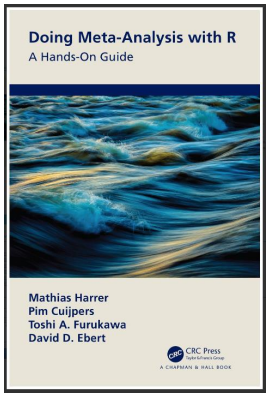
Heterogeneity

Prediction Interval

I^2 is not sensitive to changes in the number of studies in the analysis. It is relatively easy to interpret, and many researchers understand what it means. Generally, it is not a bad idea to include I^2 as a heterogeneity measure in our meta-analysis report, especially if we also provide a confidence interval for this statistic so that others can assess how precise the estimate is. However, despite its common use in the literature, I^2 is not a perfect measure for heterogeneity either. It still heavily depends on the precision of the included studies (Borenstein *et al*. 2017; Rücker *et al*. 2008). I^2 is simply the percentage of variability not caused by sampling error ϵ. If our studies become increasingly large, the sampling error tends to zero, while at the same time, I^2 tends to 100% (simply because the studies have a greater sample size). Only relying on I^2 is therefore not a good option.

The value of τ^2 and τ, on the other hand, is insensitive to the number of studies, **and** their precision. Yet, it is often hard to interpret how relevant τ^2 is from a practical standpoint. Imagine, for example, that we found that the variance of true effect sizes in our study was $\tau^2 = 0.08$. It is often difficult for ourselves, and others, to determine if this amount of variance is meaningful or not.

Prediction intervals (PIs) are a good way to overcome this limitation (IntHout *et al*. 2016). Prediction intervals give us a range into which we can expect the effects of future studies to fall based on present evidence. Say that our prediction interval lies completely on the "positive" side favouring the intervention. This means that, despite varying effects, the intervention is expected to be beneficial in the future across the contexts we studied. If the prediction interval includes zero, we can be less sure about this, although it should be noted that broad prediction intervals are quite common.



Prediction intervals from random-effects meta-analyses are a useful device for presenting the extent of between-study variation

Heterogeneity

Prediction Interval

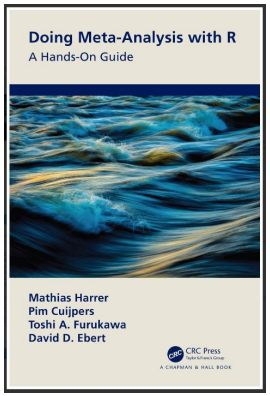
"The *Prediction Interval* represents the expected range of the true effects in future studies, making it easier to apply meta- analysis results to clinical practice. The PI is wider than the CI due to the heterogeneity between existing studies in a meta-analysis and future studies. A meta-analysis may have a CI not encompassing the null value (thus implying a statistically significant effect), but its PI could encompass the null, indicating that a future study could have opposite results" (*Al Amer & Lin, 2021*)

Heterogeneity

Reporting the Amount of Heterogeneity In Your Meta-Analysis

Here is how we could report the amount of heterogeneity we found in our example:

> *"The between-study heterogeneity variance was estimated at $\hat{\tau}^2$ = 0.08 (95%CI: 0.03-0.35), with an I^2 value of 63% (95%CI: 38-78%). The prediction interval ranged from g = -0.06 to 1.21, indicating that negative intervention effects cannot be ruled out for future studies."*



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Heterogeneity

5.4 Outliers & Influential Cases

As mentioned before, between-study heterogeneity can be caused by one or more studies with extreme effect sizes that do not quite "fit in". This may distort our pooled effect estimate, and it is a good idea to reinspect the pooled effect after such **outliers** have been removed from the analysis.

On the other hand, we also want to know if the pooled effect estimate we found is robust, meaning that it does not depend heavily on one single study. Therefore, we also want to know whether there are studies which heavily push the effect of our analysis into one direction. Such studies are called **influential cases**, and we will devote some time to this topic later in this chapter.

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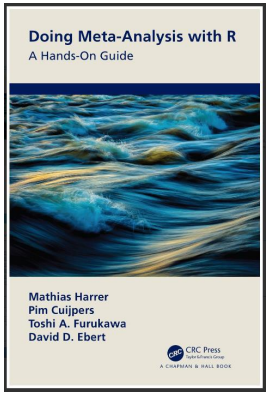

Heterogeneity

Reporting the Results of Influence Analyses

Let us assume we determined that "DanitzOrsillo", "de Vibe et al." and "Shapiro et al." are influential studies in our meta-analysis. In this case, it makes sense to also report the results of a sensitivity analysis in which these studies are excluded.

To make it easy for readers to see the changes associated with removing the influential studies, we can create a table in which both the original results, as well as the results of the sensitivity analysis are displayed. This table should at least include the pooled effect, its confidence interval and p-value, as well as a few measures of heterogeneity, such as prediction intervals and the I^2 statistic (as well as the confidence interval thereof).

It is also important to specify which studies were removed as influential cases, so that others understand on which data the new results are based. Below is an example of how such a table looks like for our `m.gen` meta-analysis from before:

Analysis	g	95%CI	p	95%PI	I^2	95%CI
Main Analysis	0.58	0.38-0.78	<0.001	-0.06-1.22	63%	39-78
Infl. Cases Removed[1]	0.48	0.36-0.60	<0.001	0.36-0.61	5%	0-56

[1]Removed as outliers: DanitzOrsillo, de Vibe, Shapiro.

This type of table is very convenient because we can also add further rows with results of other sensitivity analyses. For example, if we conduct an analysis in which only studies with a low risk of bias (Chapter 1.4.5) were considered, we could report the results in a third row.

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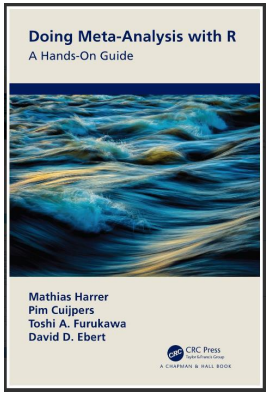

Heterogeneity

5.6 Summary

- In meta-analyses, we do not only have to pay attention to the pooled effect size, but also to the **heterogeneity** of the data on which this average effect is based. The overall effect does not capture that the true effects in some studies may differ substantially from our point estimate.
- Cochran's Q is commonly used to quantify the variability in our data. Because we know that Q follows a χ^2 distribution, this measure allows us to detect if more variation is present than what can be expected based on sampling error alone. This **excess variability** represents true differences in the effect sizes of studies.
- A statistical test of Q, however, heavily depends on the type of data at hand. We should not only rely on Q to assess the amount of heterogeneity. There are other measures, such as I^2, τ or prediction intervals, which may be used additionally.
- The average effect in a meta-analysis can be biased when there are **outliers** in our data. Outliers do not always have a large impact on the results of a meta-analysis. But when they do, we speak of **influential cases**.
- There are various methods to identify outlying and influential cases. If such studies are detected, it is advisable to recalculate our meta-analysis without them to see if this changes the interpretation of our results.

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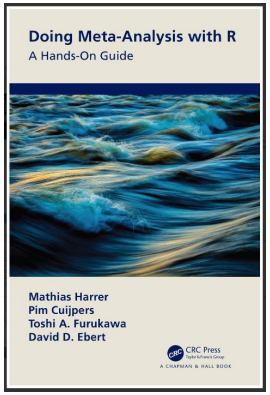
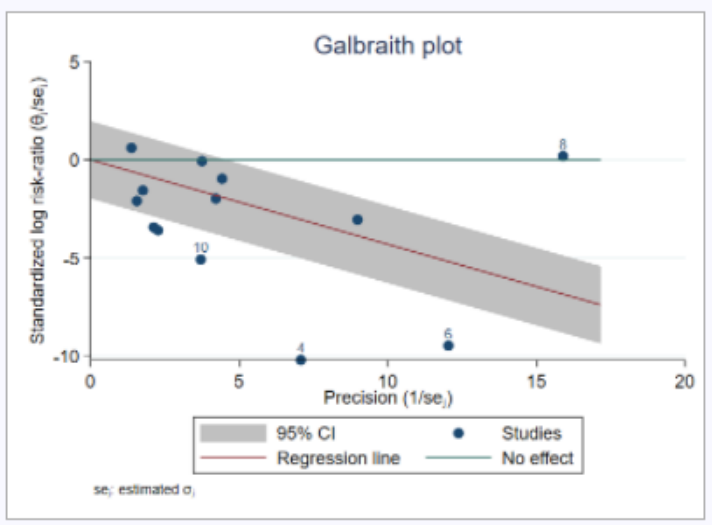
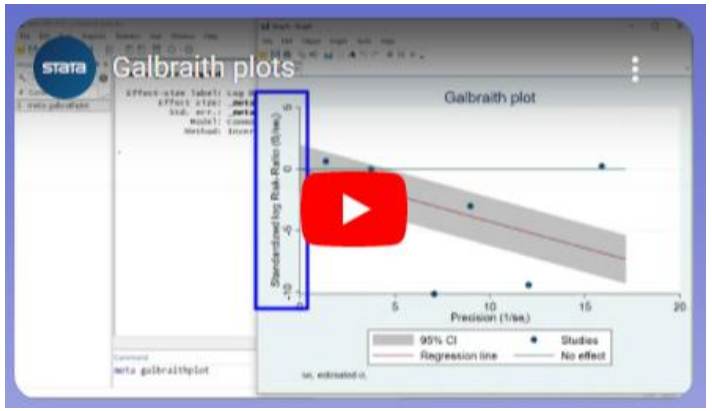


Heterogeneity

Radial (Galbraith) Plot





Another plot type that summarises the meta-analysis results (an alternative or supplement to forest plot)

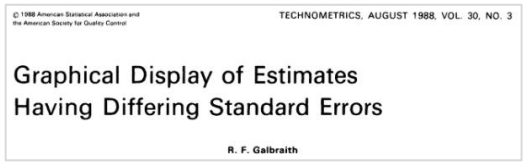
The y-axis is the (ln) effect size and the x-axis is the precision (reciprocal of standard error); each study is shown according to its effect size and precision

It shows the no effect line (across from y=0) and the regression line through the origin whose slope of this line corresponds to the estimate of the overall effect size

The slope of an imaginary line from the origin (x=0; y=0) to any point representing a single study is equal to the (ln) effect size estimate corresponding to that point

It visualises the degree of heterogeneity of effect sizes: in the absence of substantial heterogeneity, around 95% of the studies to lie within the shaded area (95% CI)

It shows the outliers (any study falling outside the shaded area)



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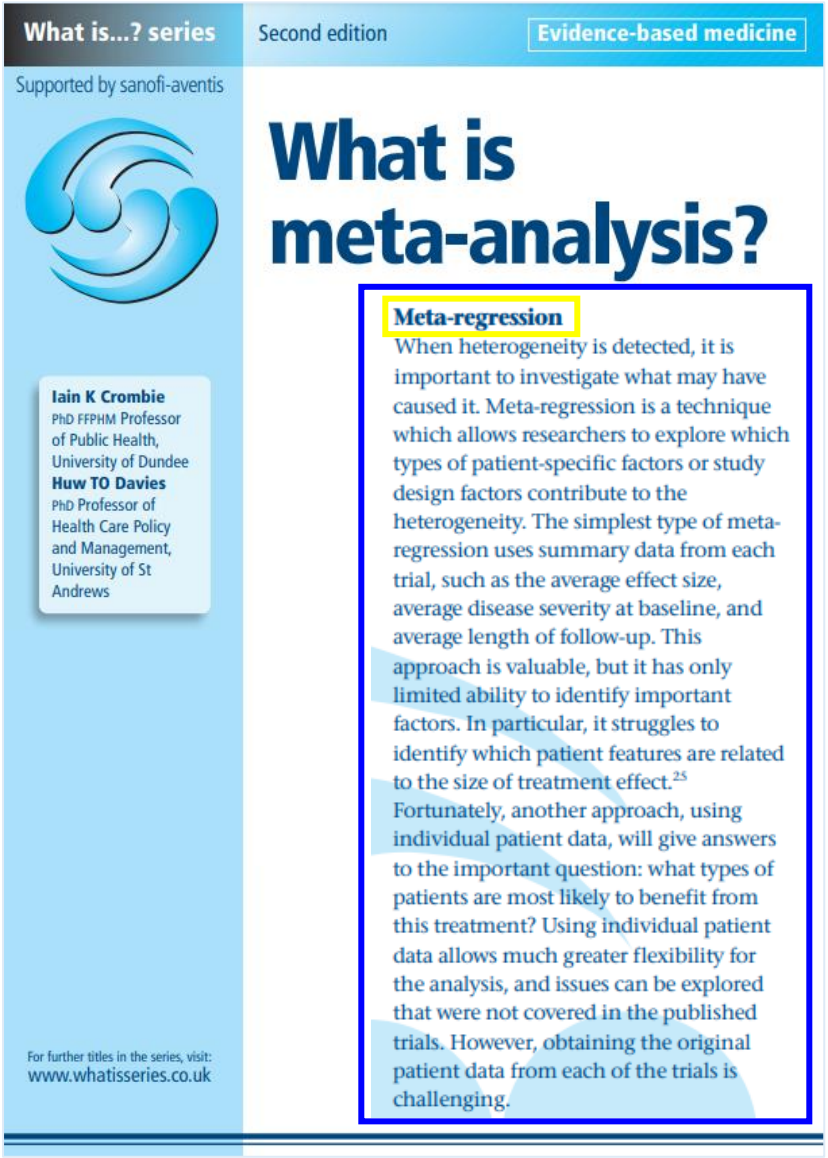
Heterogeneity

Meta-regression



Meta-regression is weighted regression of effect size on one or more covariates

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Graphical Display of Results and Model Diagnostics

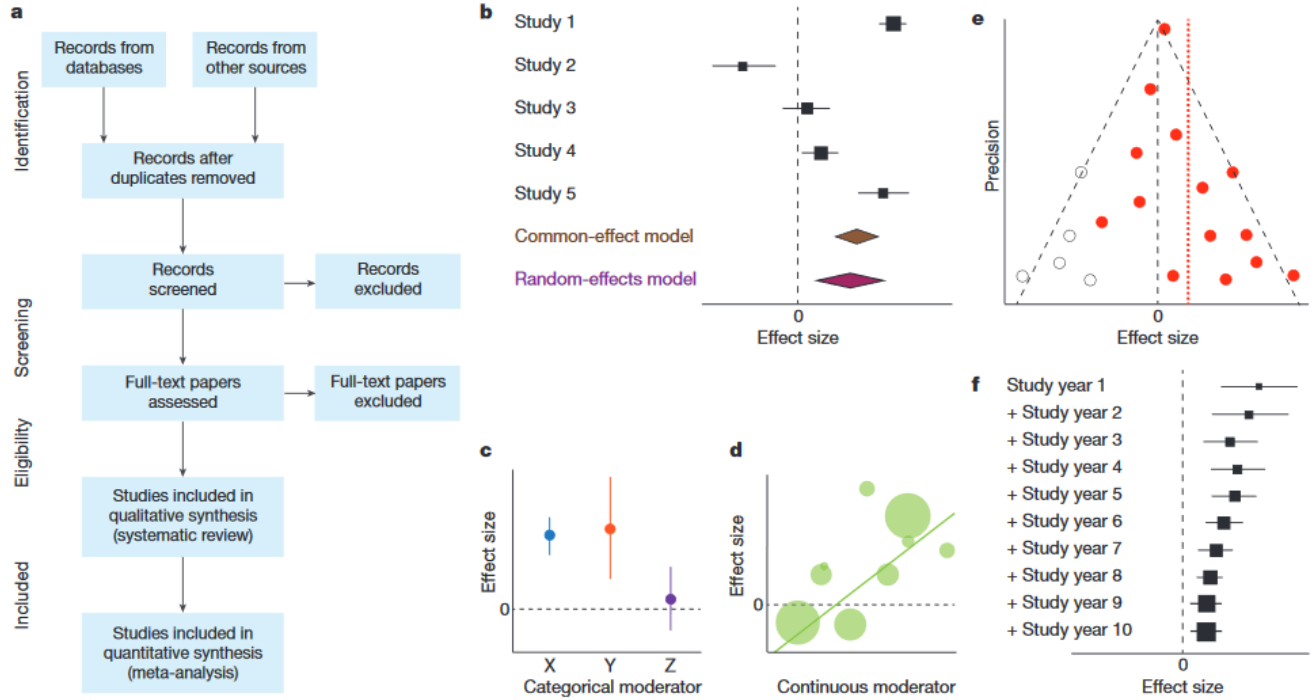

Figure 1 | Various charts and plots common to meta-analysis. **a**, A PRISMA flow diagram[12], which describes information flow (the number of relevant publications) at the four stages of the systematic review process ('identification', 'screening', 'eligibility' and 'included'). **b**, A 'forest' plot of the various means (symbol centres), confidence limits (95% confidence intervals; whiskers) and precision (indicated by the size or 'weight' of the symbols, with larger symbols indicating greater precision) of the effect-size determined from individual studies (black), and the overall means (symbol centres) and 95% confidence intervals (symbol widths) determined using meta-analysis with a common-effect (or fixed-effect) model (brown) and a random-effects model (purple). This type of plot is used to represent effect sizes and their confidence intervals graphically. **c**, A summary 'forest' plot of the mean effect sizes and 95% confidence intervals for different groups of studies. This type of plot may be used to assess categorical moderators (denoted X, Y and Z here) and are common in EEC and some social sciences. **d**, A 'bubble' plot showing a line predicted from a meta-regression analysis; the sizes of the bubbles reflect the sample sizes of the individual studies. This type of plot may be used to assess continuous predictors (such as publication year or length of a treatment). **e**, A 'funnel' plot displays the effect size against the precision with which it is estimated, which relates to its weight. Here we illustrate data (red points, with the dotted red line indicating an overall effect) that display 'funnel asymmetry', which could indicate publication bias, along with data (open circles) obtained after applying the trim-and-fill method, a sensitivity analysis that corrects for a potential publication bias. **f**, A 'forest' plot of a cumulative meta-analysis in which outcomes are added into the analysis in chronological order, demonstrating an increase in precision and a convergence of effect sizes as studies are added, and a temporal trend across studies. The dashed black lines in **b**–**f** indicate 'no effect' of an intervention on the outcome.

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Meta-analysis and the science of research synthesis

Jessica Gurevitch[1], Julia Koricheva[2], Shinichi Nakagawa[3,4] & Gavin Stewart[5]

Graphical Display of Results and Model Diagnostics

Table 1 A taxonomy of graphical displays for meta-analysis

Category	Key properties of displays in this category
01 - Forest plot-like	Display of study effects, their confidence intervals, and a summary effect or study-group summary effects.
02 - Funnel plot-like	Bivariate display of study effect size (or functions thereof) and study precision (or functions thereof).
03 - Continuous effect moderators	Display of the association of effect sizes and continuous covariates for the explanation of between-study heterogeneity.
04 - Robustness, outlier, and influence diagnostics	Illustrates the sensitivity of meta-analytic estimates, or the influence of single studies/outliers.
05 - Cumulative meta-analysis and time trends	Depicts the cumulative development of a meta-analytic estimate over time.
06 - Effect-size distribution	Depicts study effect-size distributions, but no meta-analytic summary statistics.
07 - Study or subgroup characteristics	Plot of study (or study-group) features other than effect size, standard error, or meta-analytic estimates.
08 - More than one effect size per study (multivariate)	Depicts more than one effect size per study.
09 - Combined effect(s) only	Displays meta-analytic summary effect(s), but not study-level effects.
10 - Study selection and *p*-value based	Displays primarily based on the *p* values of study results; usually for publication bias assessment.
11 - Network meta-analysis	Displays specifically proposed to visualize results of a network meta-analysis.

Kossmeier *et al. BMC Medical Research Methodology* (2020) 20:26
https://doi.org/10.1186/s12874-020-0911-9

BMC Medical Research Methodology

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Charting the landscape of graphical displays for meta-analysis and systematic reviews: a comprehensive review, taxonomy, and feature analysis

Michael Kossmeier*, Ulrich S. Tran and Martin Voracek*

Graphical Display of Results and Model Diagnostics

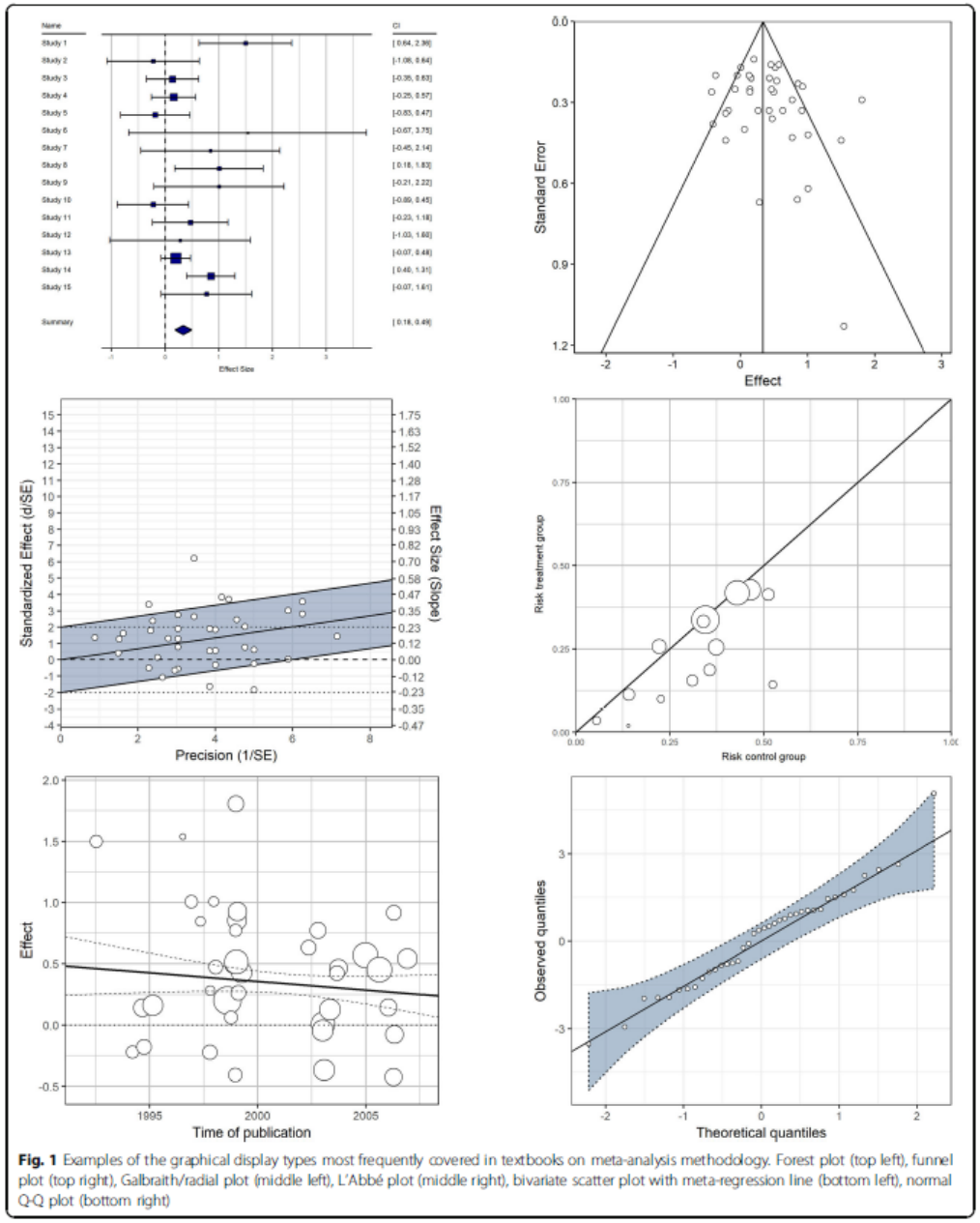

Fig. 1 Examples of the graphical display types most frequently covered in textbooks on meta-analysis methodology. Forest plot (top left), funnel plot (top right), Galbraith/radial plot (middle left), L'Abbé plot (middle right), bivariate scatter plot with meta-regression line (bottom left), normal Q-Q plot (bottom right)

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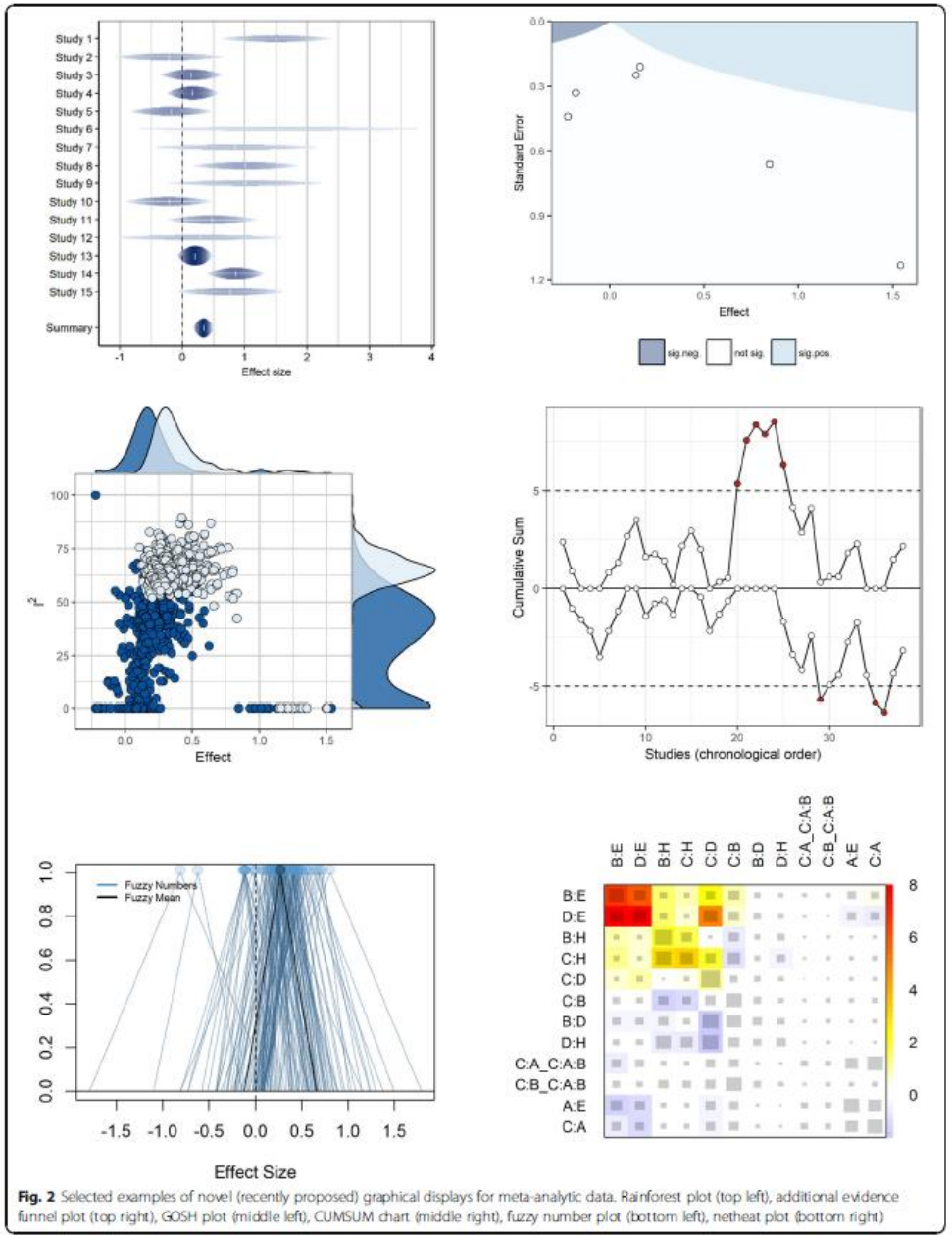

Fig. 2 Selected examples of novel (recently proposed) graphical displays for meta-analytic data. Rainforest plot (top left), additional evidence funnel plot (top right), GOSH plot (middle left), CUMSUM chart (middle right), fuzzy number plot (bottom left), netheat plot (bottom right)

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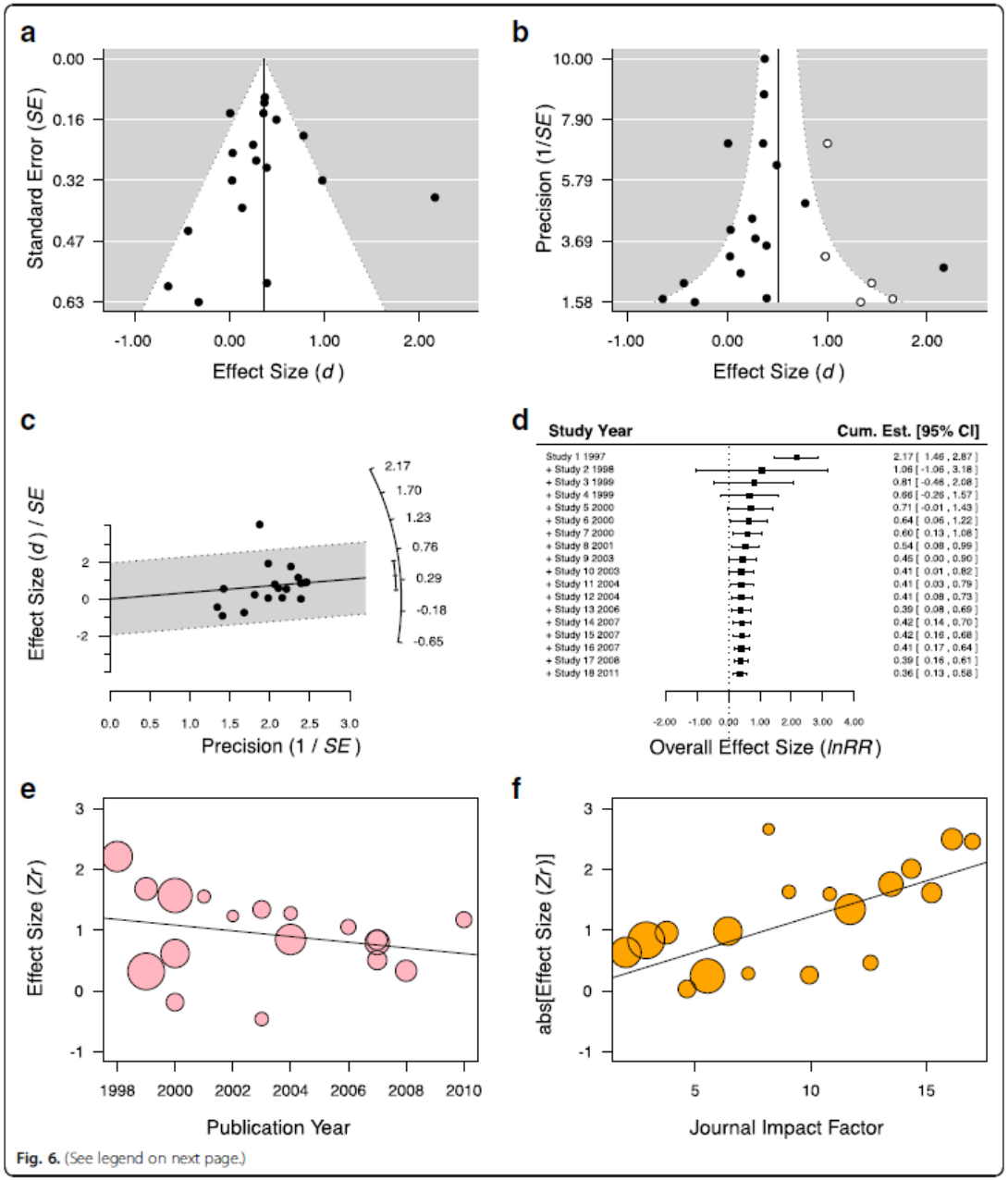

Fig. 6. (See legend on next page.)

Nakagawa *et al. BMC Biology* (2017) 15:18
DOI 10.1186/s12915-017-0357-7

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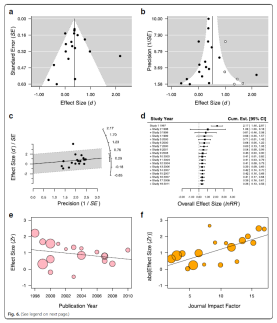
Meta-evaluation of meta-analysis: ten appraisal questions for biologists

Shinichi Nakagawa[1,2*], Daniel W. A. Noble[1], Alistair M. Senior[3,4] and Malgorzata Lagisz[1]

Graphical Display of Results and Model Diagnostics



(See figure on previous page.)
Fig. 6. Graphical assessment tools for testing for publication bias. **a** A funnel plot showing greater variance among effects that have larger standard errors (*SE*) and that are thus more susceptible to sampling variability. Some studies in the lower right corner of the plot, opposite to most major findings, with large SE (less likely to detect significant results) are potentially missing (not shown), suggesting publication bias. **b** Often funnel plots are depicted using precision (1/SE), giving a different perspective of publication bias, where studies with low precision (or large SE) are expected to show greater sampling variability compared to studies with high precision (or low SE). Note that the data in panel **b** are the same as in panel **a**, except that a trim-and-fill analysis has been performed in **b**. A trim-and-fill analysis estimates the number of studies missing from the meta-analysis and creates 'mirrored' studies on the opposite side of the funnel (*unfilled dots*) to estimate how the overall effect size estimate is impacted by these missing studies. **c** Radial (Galbraith) plot in which the slope should be close to zero, if little publication bias exists, indicating little asymmetry in a corresponding funnel plot (compare it with **b**); radial plots are closely associated with Egger's tests. **d** Cumulative meta-analysis showing how the effect size changes as the number of studies on a particular topic increases. In this situation, the addition of effect size estimates led to convergence on an overall estimate of 0.36, and the confidence intervals decrease as the precision of the estimate increases. **e** Bubble plot showing a temporal trend in effect size (*Zr*) across years. Here effect sizes are weighted by their precision; larger bubbles indicate more precise estimates and smaller bubbles less precise. **f** Bubble plot of the relationship between effect size and impact factors of journals, indicating that larger magnitudes of effect sizes (the absolute values of *Zr*) tend to be published in higher impact journals

Nakagawa *et al. BMC Biology* (2017) 15:18
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Graphical Display of Results and Model Diagnostics

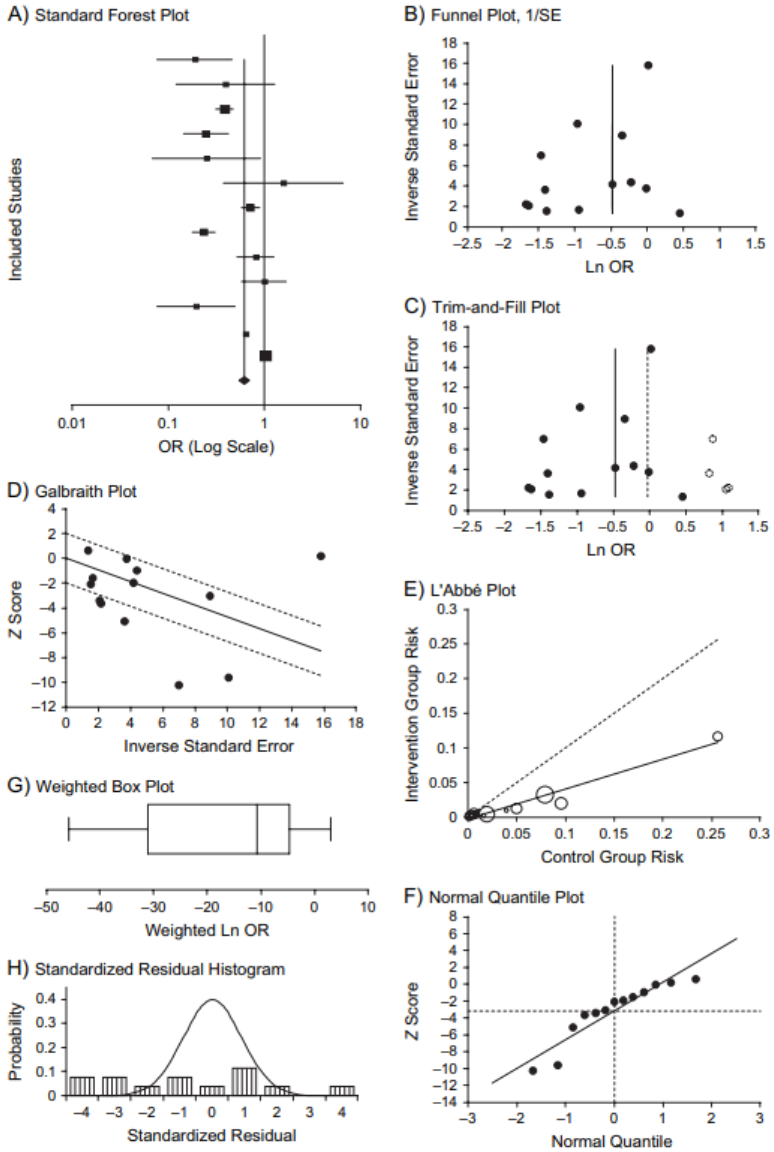


Figure 1. Graphs corresponding to 8 types of plots available in meta-analysis software for the assessment of heterogeneity and publication bias in meta-analyses. Two variations of the funnel plot and 1 variation of the box plot were included in the assessments but are not shown here. SE, standard error.

American Journal of Epidemiology
Vol. 169, No. 2
DOI: 10.1093/aje/kwn340
Advance Access publication December 8, 2008

Practice of Epidemiology

More Than Numbers: The Power of Graphs in Meta-Analysis

Leon Bax, Noriaki Ikeda, Naohito Fukui, Yukari Yaju, Harukazu Tsuruta, and Karel G. M. Moons

Kingston University London

Graphical Display of Results and Model Diagnostics

THE CAMPBELL COLLABORATION
What helps? What harms? Based on what evidence?

Graphical Representation of Meta-analysis Findings

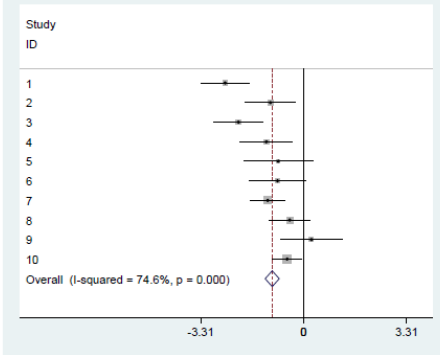
Emily E. Tanner-Smith
Associate Editor, Campbell Methods Coordinating Group
Research Assistant Professor, Vanderbilt University

Campbell Collaboration Colloquium
Chicago, IL
May 22nd, 2013

General suggestions – forest plots

- Always include forest plots (or summary forest plots) if possible/appropriate
- Not recommended with fewer than 2 studies
- Plot ratio effect size measures on the log scale, but include axis labels on the original anti-logged scale
- Include reference lines at the null value
- State the confidence level for confidence intervals
- Blocks for each study should be proportionate to study weight
- Sort studies in a meaningful order (e.g., effect size magnitude)
- State the direction of results
- Include prediction intervals for random effects analyses
- Include numerical data on plots (if possible)

What's wrong with this forest plot?

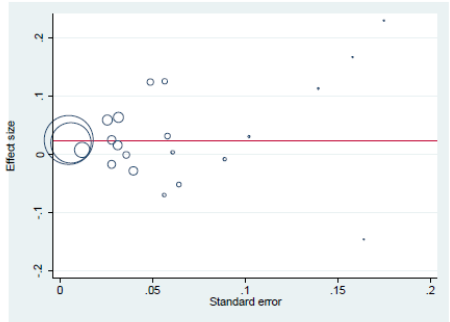


- Uninformative study labels
- Seemingly random order of effect sizes
- Unclear direction of effect sizes
- Does not include data
- Unspecified confidence level
- General aesthetics (white space)

General suggestions – funnel plots

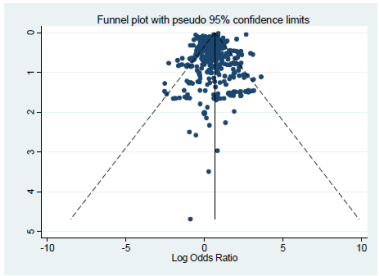
- Not recommended with fewer than 10 studies
- Plot effect sizes on the horizontal axis
- Plot the standard error of the effect size on the vertical axis (generally)
- Plot ratio effect size measures on the log scale, but include axis labels on the original anti-logged scale
- All points should be the same size (weights/precision represented in the vertical axis)
- Include 95% pseudo-confidence limits from a fixed effect analysis
- Include contours if possible
- Data in graphs should generally be available elsewhere in the review (except in very large reviews)
- Use different plotting symbols to distinguish subgroups, when appropriate

What's wrong with this funnel plot?



- Effect size on vertical axis
- Points are not all the same size
- Vague labeling of axes and reference line
- No confidence bands

Funnel plots



Source: Wilson, S. J., Tanner-Smith, E. E., Lipsey, M. W., Steinka-Fry, K., & Morrison, J. (2011). Dropout prevention and intervention programs: Effects on school completion and dropout among school aged children and youth. Campbell Systematic Reviews, 8. doi: 10.4073/csr.2011.8

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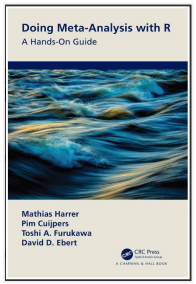
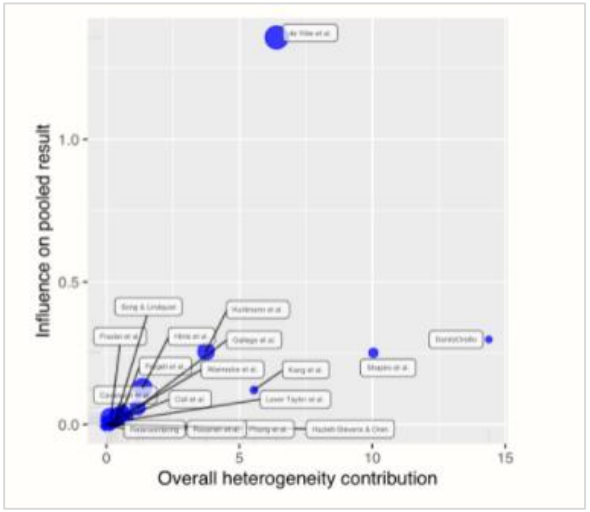
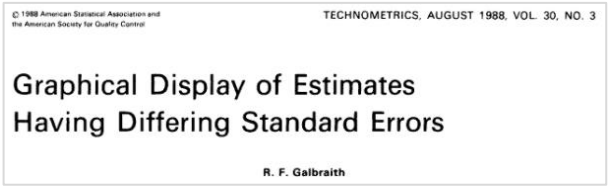
Heterogeneity

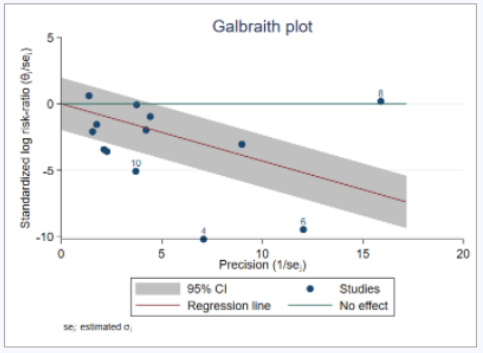
Baujat plots are diagnostic plots to detect studies which overly contribute to the heterogeneity in a meta-analysis

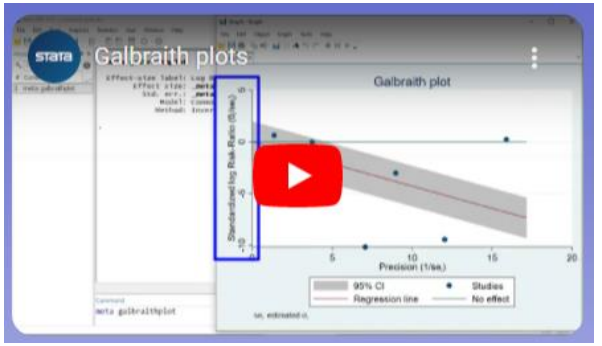




Radial (Galbraith) plots visualises the degree of heterogeneity of effect sizes and highlight the outliers







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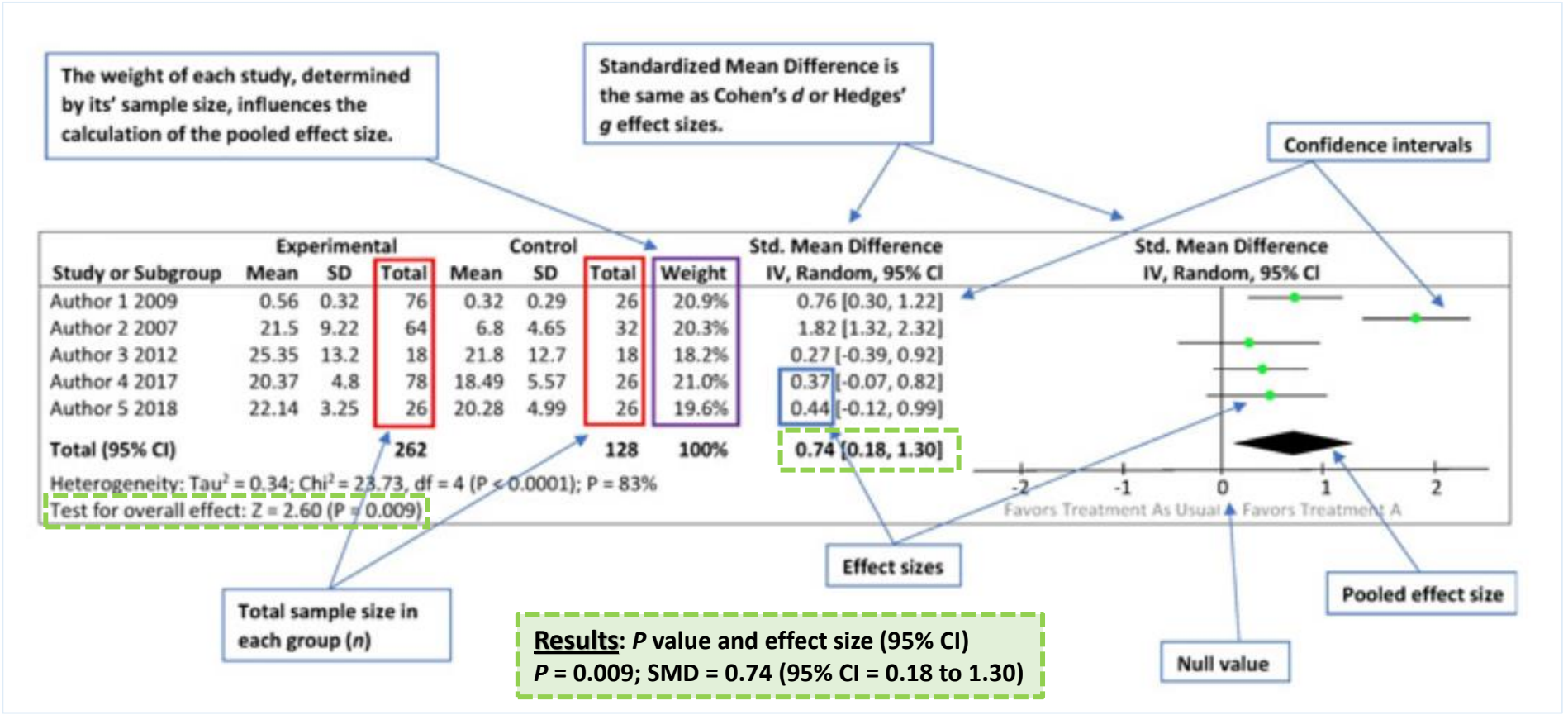
Presentation of Results



Statistics Refresher

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Presentation of Results

Forest Plot

A required plot for presentation of a meta-analysis

Tutorial: How to read a forest plot

Posted on 11th July 2016 by Nathan Cantley

1. **Each horizontal line on a forest plot represents an individual study with the result plotted as a box and the 95% confidence interval of the result displayed as the line.**
2. **The implication of each study falling on one side of the vertical line or the other depends on the statistic being used.**
3. **If the individual study crosses the vertical line, it means the null value lies within the 95% confidence interval. This implies the study result is in fact the null value and therefore the study did not observe a statistically significant difference between the treatment and control groups.**
4. **The diamond at the bottom of the forest plot shows the result when all the individual studies are combined together and averaged. The horizontal points of the diamond are the limits of the 95% confidence intervals and are subject to the same interpretation as any of the other individual studies on the plot.**
5. **The I2 statistic gives you an idea of the heterogeneity of the studies, i.e. how consistent they are. If the I2 value is >50% it might mean the studies are inconsistent due to a reason other than chance. This might make the conclusions you draw from the forest plot questionable.**

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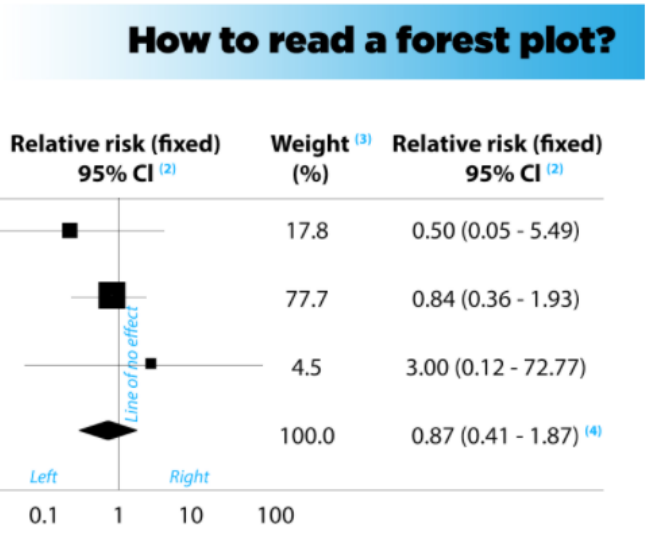
Presentation of Results

Forest Plot

How to read a forest plot

Often, we have 6 columns in a forest plot.



Test for herterogeneity Chi-square = 0.79, df = 2, $p = 0.67$, $I^2 = 0.0\%$ (5)
Test for overall effect $z = 0.35$, $p = 0.7$ (6)

(1) N = total number in group, n = number in group with the outcome.
(2) Outcome of interest in picture and in number. Fixed effect model used for meta-analysis.
(3) Influence of studies on overall meta-analysis.
(4) Overall effect.
(5) Heterogeneity (I^2) = 0%. So, we use fixed effect model.
(6) *p* value indicating level of statistical significance

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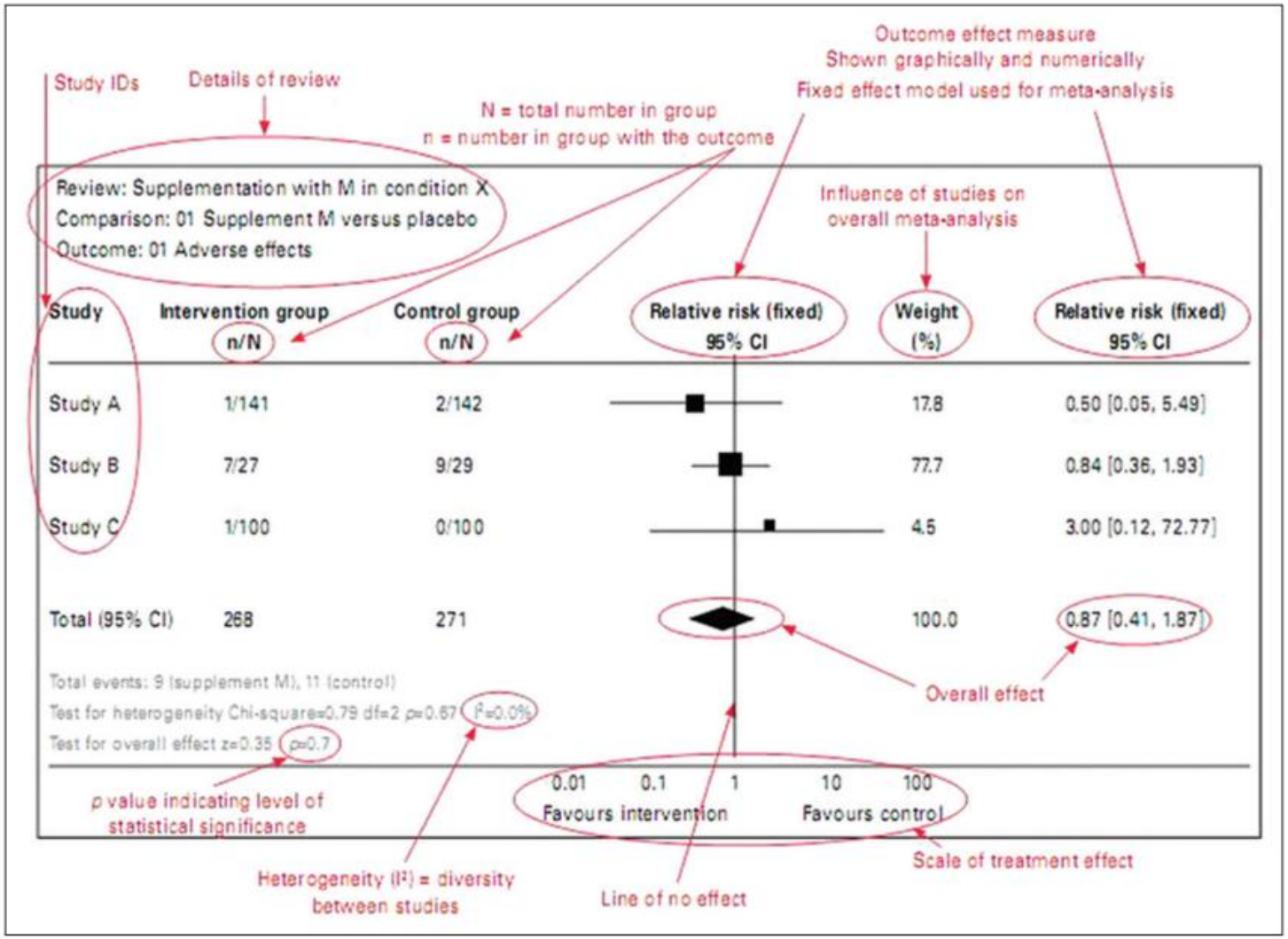
Presentation of Results

Forest Plot



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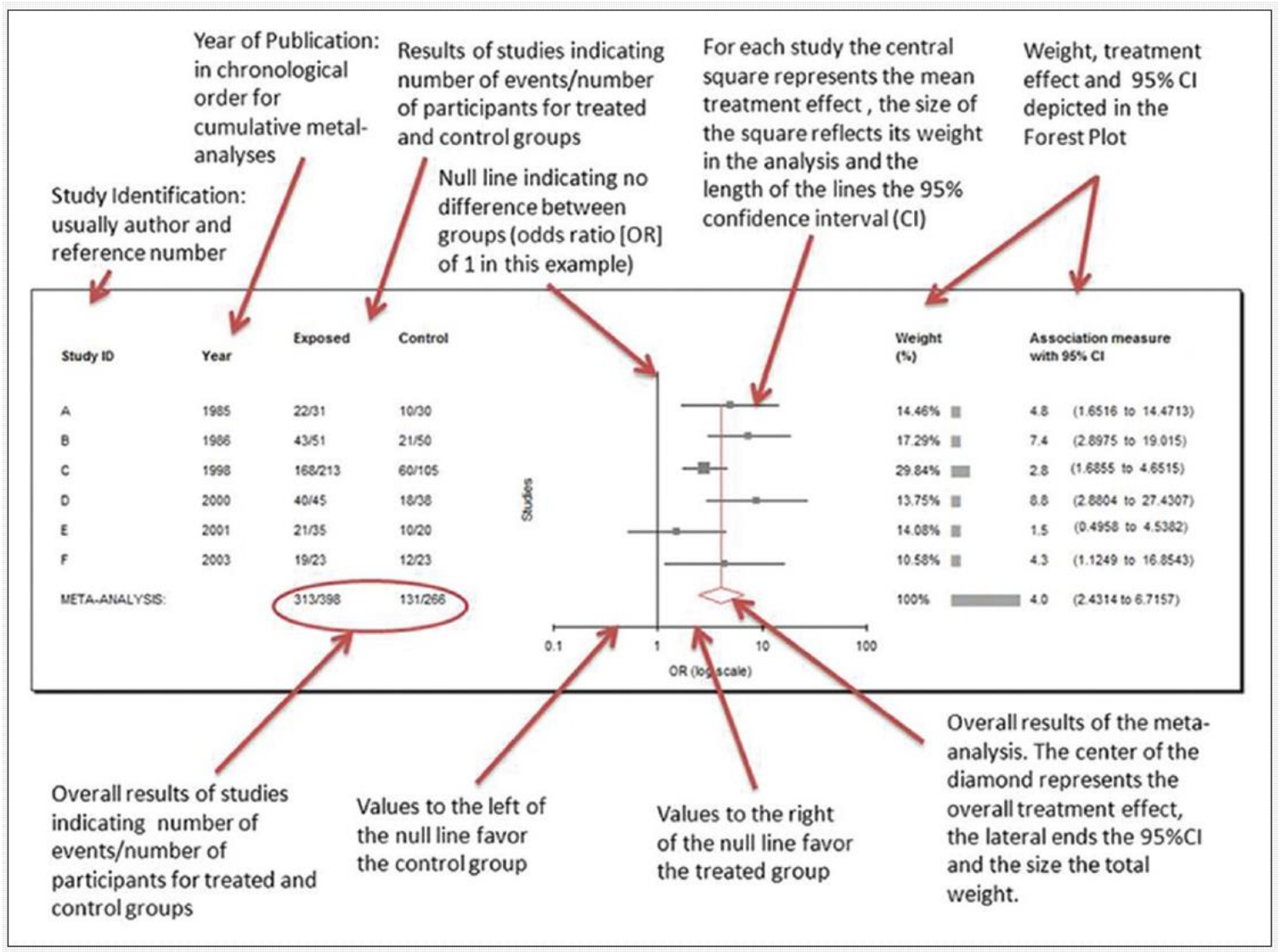
Presentation of Results

Forest Plot



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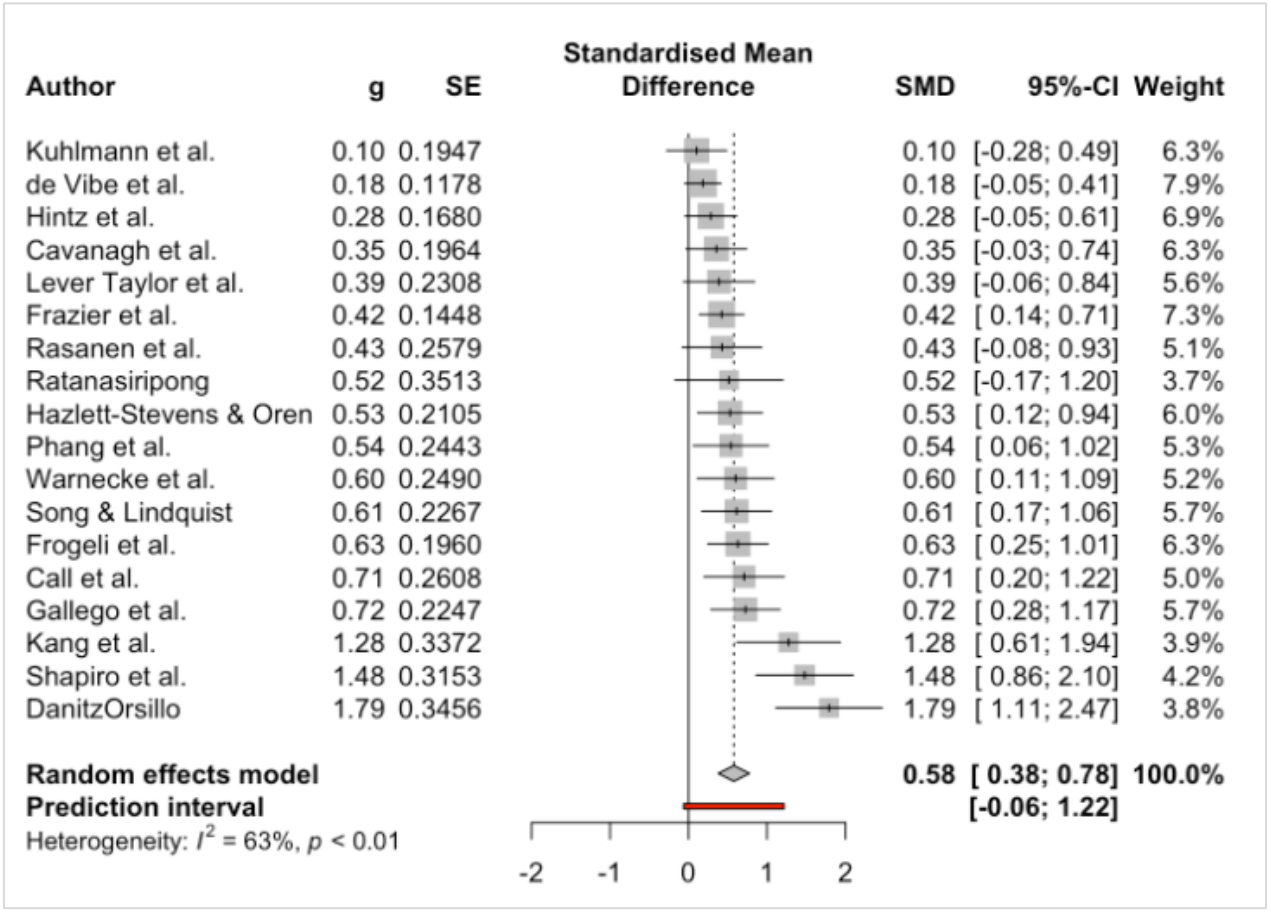
Presentation of Results

Forest Plot



Doing Meta-Analysis in R: A Hands-on Guide

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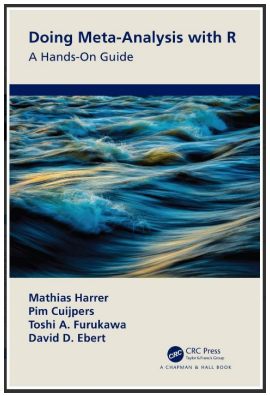
Presentation of Results

Forest Plot

6.5 Summary

- It is conventional to visualize the results of meta-analyses through forest plots.
- Forest plots contain a graphical representation of each study's effect size and confidence interval, and also show the calculated overall effect. Furthermore, they contain the effect size data that was used for pooling.
- It is also possible to add other kinds of information to a forest plot, for example the quality rating that each study received.
- Forest plots can only display results assuming a fixed significance threshold, usually $p < 0.05$. To visualize how results change for varying significance thresholds, drapery plots can be generated in addition.



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Presentation of Results

Forest Plot: Additional Resources

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Trusted evidence.
Informed decisions.
Better health.

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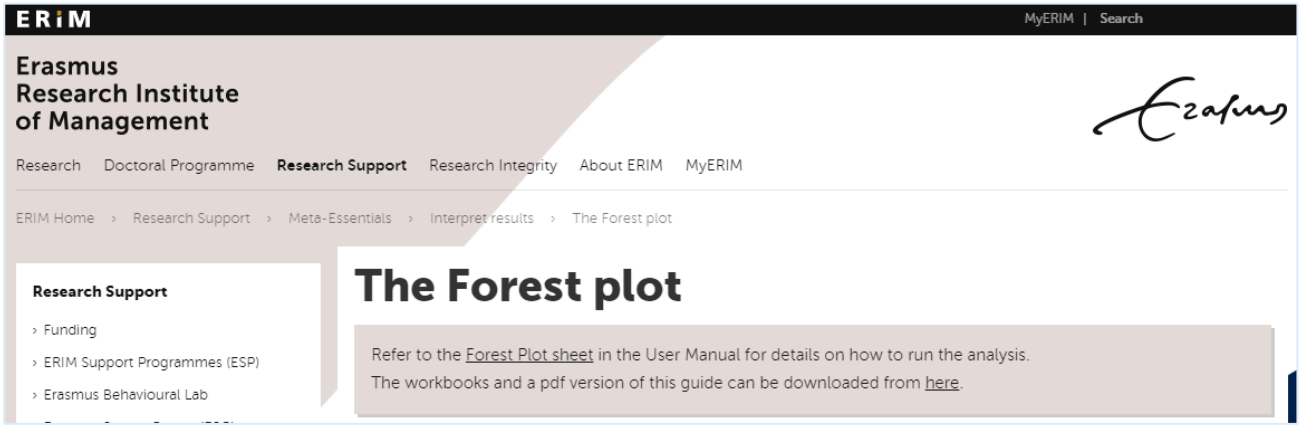
How to read a forest plot?



Understanding the Basics of Meta-Analysis and How to Read a Forest Plot: As Simple as It Gets

Chittaranjan Andrade, MD

Kingston University London

Presentation of Results

Forest Plot: Additional Resources

How to read a forest plot in a meta-analysis

Sedgwick, Philip. **BMJ : British Medical Journal (Online); London** Vol. 351, (Jul 24, 2015). DOI:10.1136/bmj.h4028

Tutorial: How to read a forest plot

Posted on 11th July 2016 by Nathan Cantley

Forest plot at a glance

Posted on 1st July 2016 by Tran Quang Hung

6 Forest Plots

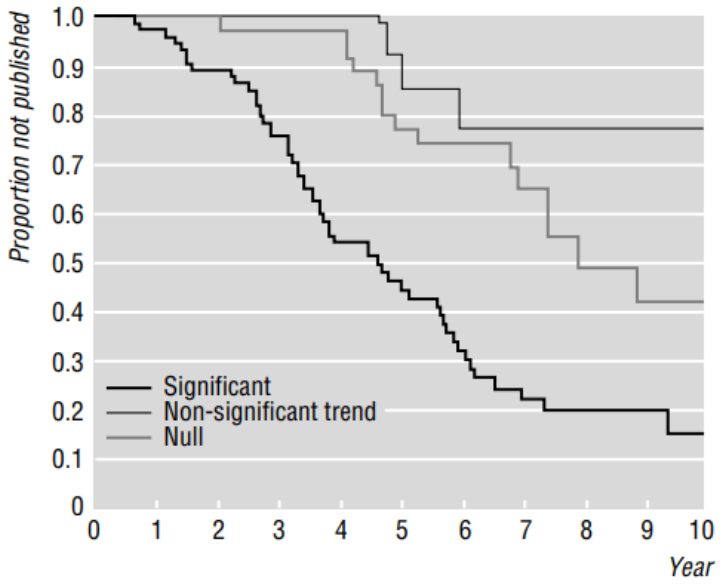
Doing Meta-Analysis in R: A Hands-on Guide

Kingston University London

Publication Bias

Publication bias is real and a significant problem

Objectives: To determine the extent to which publication is influenced by study outcome.
Design: A cohort of studies submitted to a hospital ethics committee over 10 years were examined retrospectively by reviewing the protocols and by questionnaire. The primary method of analysis was Cox's proportional hazards model.
Setting: University hospital, Sydney, Australia.
Studies: 748 eligible studies submitted to Royal Prince Alfred Hospital Ethics Committee between 1979 and 1988.
Main outcome measures: Time to publication.
Results: Response to the questionnaire was received for 520 (70%) of the eligible studies. Of the 218 studies analysed with tests of significance, those with positive results ($P < 0.05$) were much more likely to be published than those with negative results ($P \geq 0.10$) (hazard ratio 2.32 (95% confidence interval 1.47 to 3.66), $P = 0.0003$), with a significantly shorter time to publication (median 4.8 *v* 8.0 years). This finding was even stronger for the group of 130 clinical trials (hazard ratio 3.13 (1.76 to 5.58), $P = 0.0001$), with median times to publication of 4.7 and 8.0 years respectively.



No at risk						
Significant	75	67	38	19	8	2
Non-significant trend	15	15	15	11	3	2
Null	39	39	37	20	8	6

Fig 2 Proportion of quantitative clinical trials not published, according to type of results

Publication bias: evidence of delayed publication in a cohort study of clinical research projects

Jerome M Stern, R John Simes

Kingston University London

Publication Bias

Funnel Plot

14.3.3.2 Validity of Meta-Analysis

Results based on a small sample size or with a high SE in different studies will obviously spread across a broad range of values. If you plot ORs in three studies each with a small sample size, they are likely to be far apart from one another compared with ORs in another three studies with a large sample size each. If you are reviewing a large number of studies—some of small size and some of large size—and plot the OR on the horizontal axis and the sample size on the vertical axis, the plot will generally be as shown in Figure 14.3. This is called a **funnel plot** because of its resemblance to an inverted funnel. This exercise is done before meta-analysis to convince yourself that the values are consistent across studies. Herein lies the basic difference between simple pooling and meta-analysis. In simple pooling, the first step is combining and then comparison. In meta-analysis, the first step is comparison and then pooling. Also, note that inclusion of underpowered inconclusive studies is unlikely to lead to any firm conclusion.

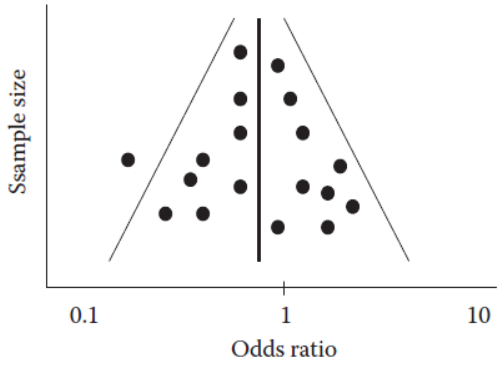
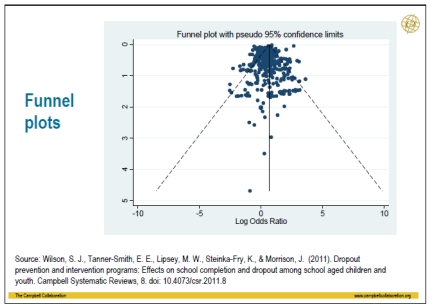


FIGURE 14.3
Typical funnel plot.

Funnel plot is based on the general statistical principle that "sampling error decreases as sample size increases"



In a funnel plot, you can have any other effect size, such as RR and difference in means or proportions, in place of OR. On the vertical axis, you can have the inverse of the SE instead of sample size. An asymmetric shape of the funnel plot raises suspicion over the results of meta-analysis since the selected studies may suffer from publication bias, favoring either a higher or lower effect size. It also suggests the possibility of a systematic bias in smaller studies. Check if most of smaller studies tend to give a larger (or smaller) effect size than larger studies. If so, the bias is evident and the results of the meta-analysis would be invalid. When biased studies are not included in meta-analysis, heterogeneity among results of various studies does not cause much of a problem. Your final CI would depict this.

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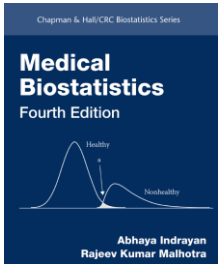
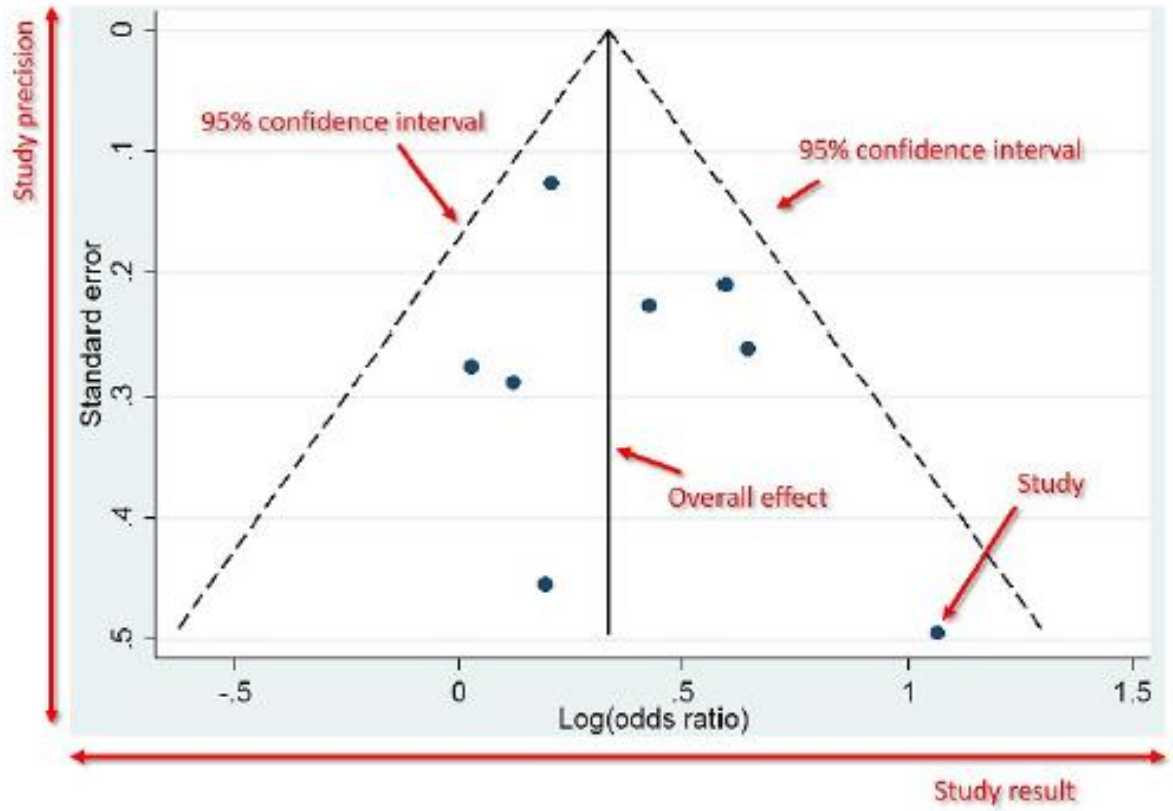


Publication Bias

Funnel Plot



This is an annotated funnel plot used to assess asymmetry of which the main reason is publication bias (but there are others). Note that the results falling to the left of the vertical line for overall effect are not negative studies but their effect sizes are smaller than the overall (summary) effect size. This vertical line is not to be confused with the null effect line in a forest plot.

Also note that the dotted lines indicate the confidence interval limits which gets wider towards the bottom because the study precision decreases towards the bottom (hence the funnel shape).

Publication Bias

Funnel Plot

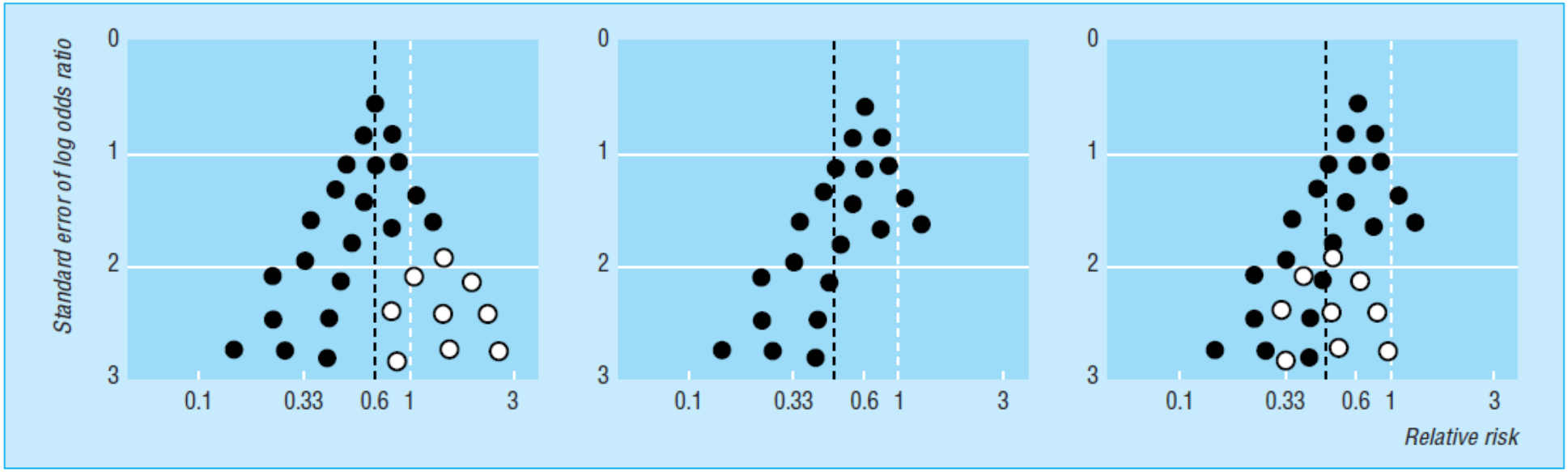


Fig 1 Hypothetical funnel plots: left, symmetrical plot in absence of bias (open circles are smaller studies showing no beneficial effects); centre, asymmetrical plot in presence of publication bias (smaller studies showing no beneficial effects are missing); right, asymmetrical plot in presence of bias due to low methodological quality of smaller studies (open circles are small studies of inadequate quality whose results are biased towards larger effects). Solid line is pooled odds ratio and dotted line is null effect (1). Pooled odds ratios exaggerate treatment effects in presence of bias

Note that publication bias is not the only reason for asymmetry in a funnel plot!

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Investigating and dealing with publication and other biases in meta-analysis

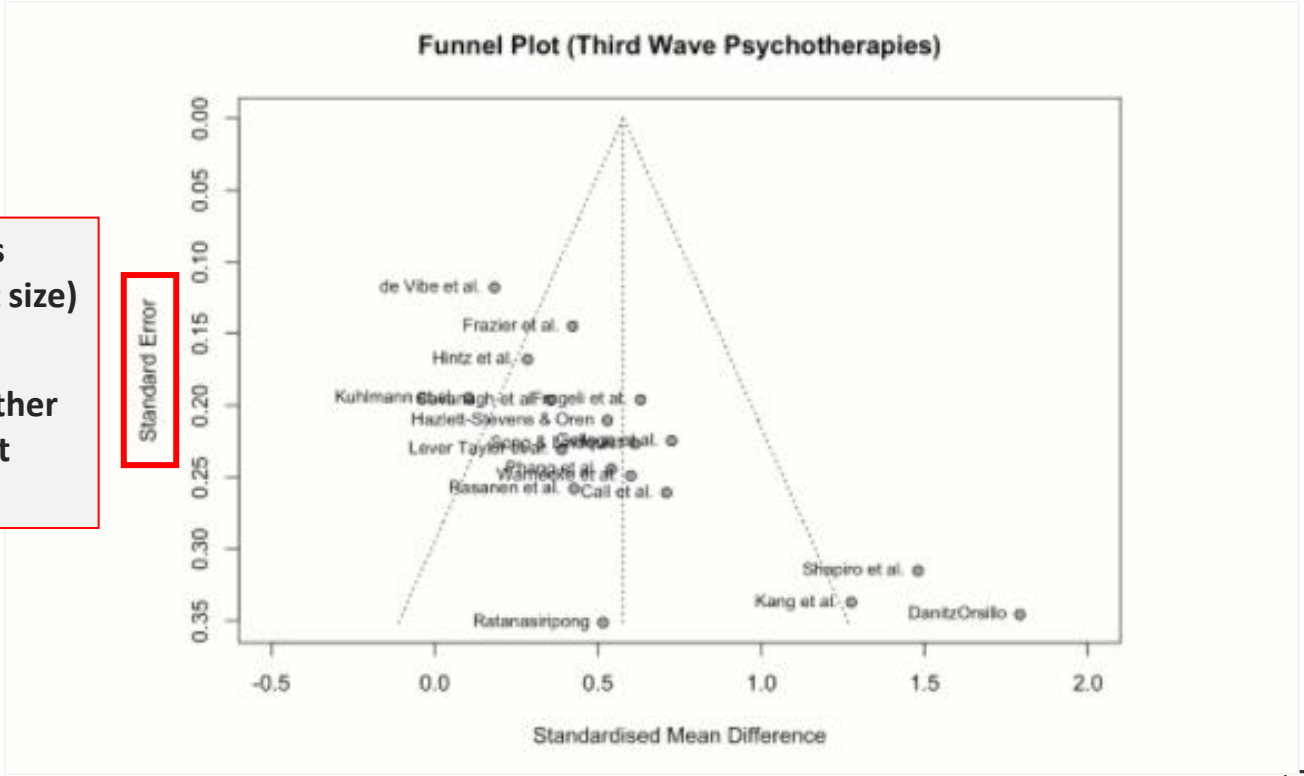
BMJ 2001 ; 323 doi: https://doi.org/10.1136/bmj.323.7304.101 (Published 14 July 2001)
Cite this as: *BMJ* 2001;323:101

Publication Bias

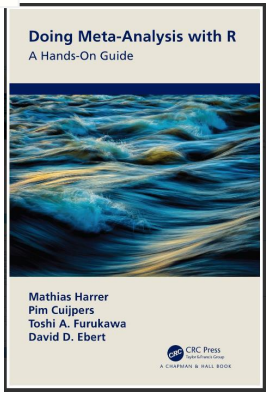
Funnel Plot

Preferred metric for y-axis is standard error (of the effect size) as a measure of precision.

Sample size, variance and other metrics are possible, but not recommended.



As discussed, the resulting funnel plot shows the effect size of each study (expressed as the standardized mean difference) on the x-axis, and the standard error (from large to small) on the y-axis. To facilitate the interpretation, the plot also includes the idealized funnel-shape that we expect our studies to follow. The vertical line in the middle of the funnel shows the average effect size. Because we used a random-effects model when generating `m.gen`, the funnel plot also uses the random-effects estimate.



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Publication Bias

Funnel Plot

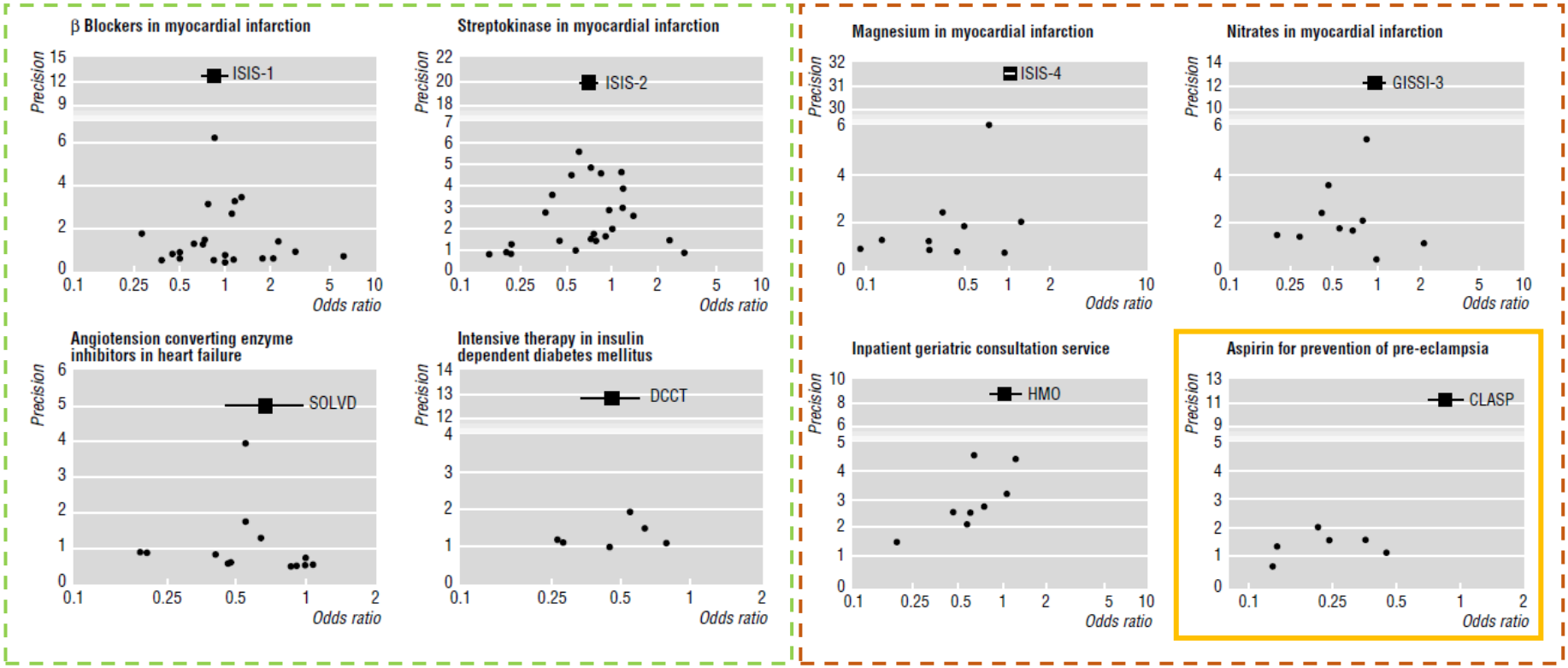

Fig 2 Funnel plots and single large trials. Points indicate odds ratios from trials included in meta-analysis; squares with horizontal lines show odds ratio from large trial with 95% confidence interval. See table 1 for abbreviations of trial names

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Bias in meta-analysis detected by a simple, graphical test

Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder

Publication Bias

Funnel Plot

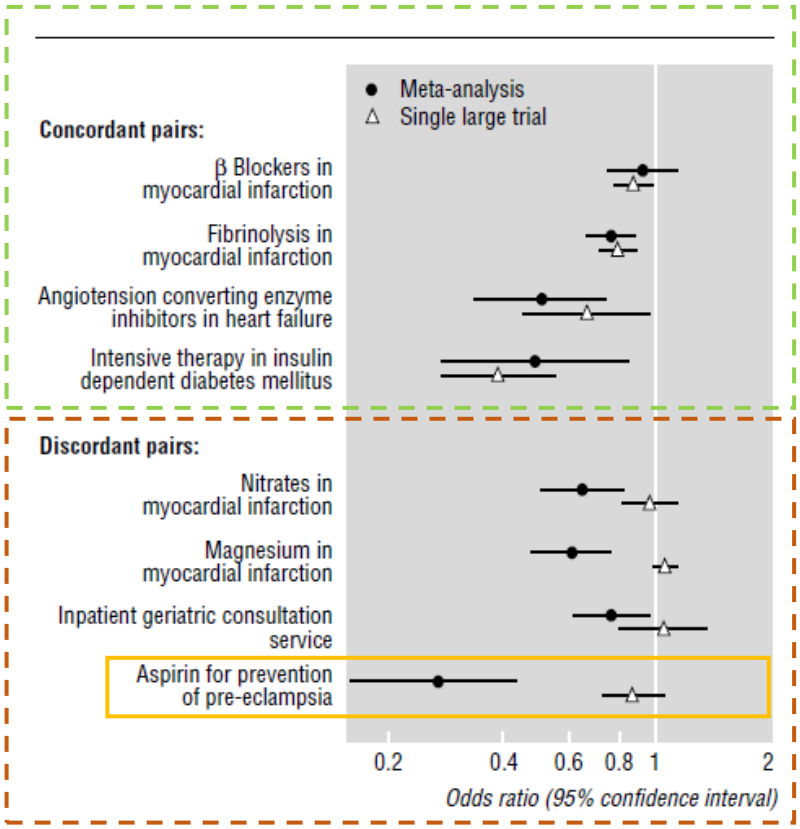

Fig 1 Results from four concordant and four discordant pairs of meta-analysis and large scale randomised controlled trial

Table 2 Analysis of funnel plot asymmetry

Meta-analysis	No of trials	Linear regression analysis: Intercept (90% CI)	Linear regression analysis: P value
Results concordant with single large trial			
β Blockers in myocardial infarction[19]	26	0.44 (–0.11 to 1.00)	0.19
Streptokinase in myocardial infarction[17]	20	0.59 (–1.30 to 2.48)	0.59
Angiotensin converting enzyme inhibitors in heart failure[26]	13	–0.14 (–0.44 to 0.16)	0.43
Intensive treatment in insulin-dependent diabetes mellitus[21]	6	–0.75 (–2.53 to 1.03)	0.44
Results discordant with single large trial			
Magnesium in myocardial infarction[27]	10	–1.19 (–2.26 to –0.12)	0.068
Nitrates in myocardial infarction[24]	10	–1.84 (–3.25 to –0.43)	0.043
Inpatient geriatric consultation service[14]	8	–2.60 (–4.84 to –0.37)	0.069
Aspirin for preventing pre-eclampsia[29]	6	0.37 (–1.84 to 2.59)	0.75

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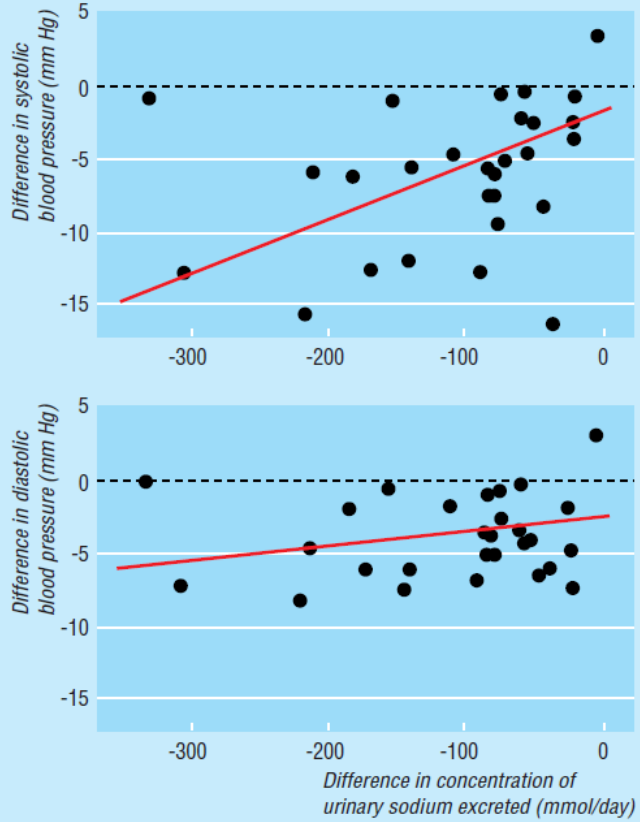

Fig 2 Regression lines, adjusted for number of measurements of urinary sodium concentration, of predicted change in blood pressure for change in concentration of urinary sodium from randomised controlled trials of reduction in dietary sodium. Intercepts indicate decline in blood pressure even if diets in intervention and control groups were identical, which may indicate presence of bias. Modified from Midgley et al[20]

Egger's regression line

Summary recommendations on investigating and dealing with publication and other biases in a meta-analysis

Examining for bias

- Check for funnel plot asymmetry with graphical and statistical methods
- Use meta-regression to look for associations between key measures of trial quality and size of treatment effect
- Use meta-regression to examine other possible explanations for heterogeneity
- If available, examine associations between size of treatment effect and changes in biological markers or patients' adherence to treatment

Dealing with bias

- If there is evidence of bias, report this with the same prominence as any combined estimate of treatment effect
- Consider sensitivity analyses to establish whether the estimated treatment effect is robust to reasonable assumptions about the effect of bias
- Consider excluding studies of lower quality
- If sensitivity analyses show that a review's conclusions could be seriously affected by bias, then consider recommending that the evidence to date be disregarded

Investigating and dealing with publication and other biases in meta-analysis

BMJ 2001 ; 323 doi: https://doi.org/10.1136/bmj.323.7304.101 (Published 14 July 2001)
Cite this as: *BMJ* 2001;323:101

Publication Bias

Funnel Plot

Statistical tests of asymmetry

metafor (version 1.9-2)

regtest: Carry Out a Regression Tests for Funnel Plot Asymmetry

Description

The function `regtest` is generic. It can be used to carry out various tests for funnel plot asymmetry, including Egger's regression test and variations thereof.

Egger M, Davey Smith G, Schneider M, & Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34

metafor (version 0.5-0)

ranktest: Rank Correlation Test for Funnel Plot Asymmetry

Description

Rank correlation test for funnel plot asymmetry by Begg and Mazumdar (1994).

Begg CB, & Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101

metapb: Detecting and Quantifying Publication Bias/Small-Study...

In altmeta: Alternative Meta-Analysis Methods

Description | Usage | Arguments | Details | Value | References | Examples

View source: R/metapb.R

Description

Performs the regression test and calculates skewness for detecting and quantifying publication bias/small-study effects.

Lin L & Chu H. Quantifying publication bias in meta-analysis. Biometrics 2018;74:785-94

Publication Bias

Funnel Plot

Meta-analysis results are not the final words

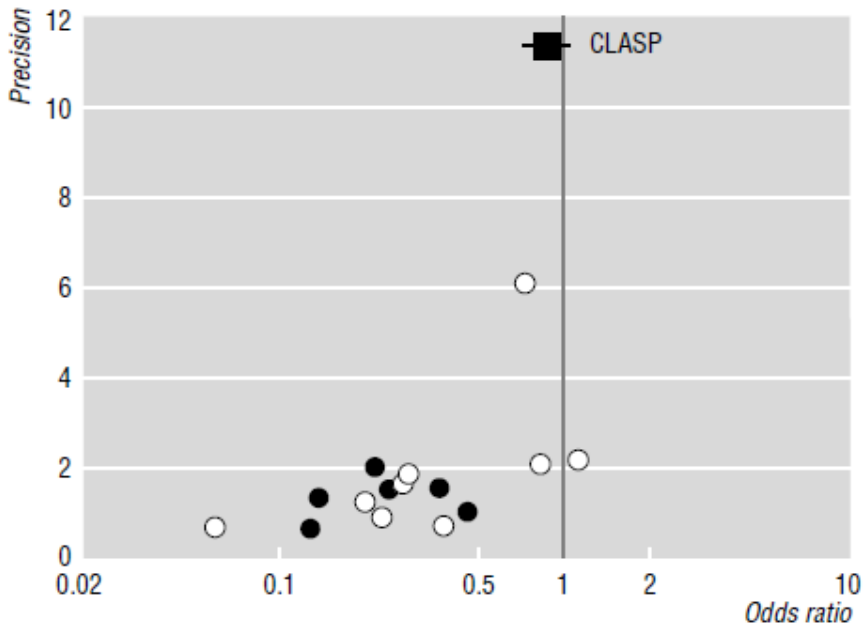

Fig 3 Funnel plot of trials of low dose aspirin in the prevention of pre-eclampsia. Trials included in Imperiale and Stollenwerk's 1991 meta-analysis (closed circles),[29] trials published in subsequent years (1990 to 1993, open circles) and the large 1994 CLASP (collaborative low-dose aspirin study in pregnancy) trial (square with horizontal line indicating 95% confidence interval)[30]

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Bias in meta-analysis detected by a simple, graphical test

Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder

Publication Bias

Funnel Plot

There are reasons for funnel plot asymmetry other than publication bias

Sources of asymmetry in funnel plots

Selection bias
- Publication bias
- Location biases:
  - English language bias
  - Citation bias
  - Multiple publication bias

True heterogeneity
- Size of effect differs according to study size:
  - Intensity of intervention
  - Differences in underlying risk

Data irregularities
- Poor methodological design of small studies
- Inadequate analysis
- Fraud

Artefactual
- Choice of effect measure

Chance

- Critical examination of systematic reviews for publication and related biases should be considered a routine procedure

Note that publication bias is not the only reason for asymmetry in a funnel plot!

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Bias in meta-analysis detected by a simple, graphical test

Matthias Egger, George Davey Smith, Martin Schneider, Christoph Minder

Publication Bias

Funnel Plot

Contour-enhanced Funnel Plot

The Stata Journal (2008)
8, Number 2, pp. 242–254

Contour-enhanced funnel plots for meta-analysis

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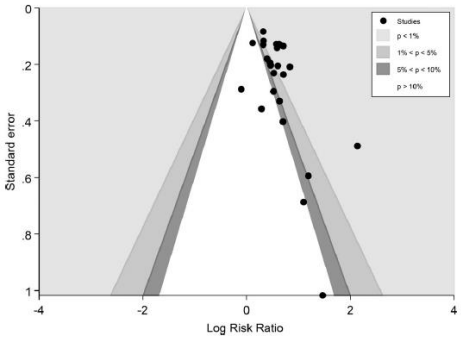
Abstract. Funnel plots are commonly used to investigate publication and related biases in meta-analysis. Although asymmetry in the appearance of a funnel plot is often interpreted as being caused by publication bias, in reality the asymmetry could be due to other factors that cause systematic differences in the results of large and small studies, for example, confounding factors such as differential study quality. Funnel plots can be enhanced by adding contours of statistical significance to aid in interpreting the funnel plot. If studies appear to be missing in areas of low statistical significance, then it is possible that the asymmetry is due to publication bias. If studies appear to be missing in areas of high statistical significance, then publication bias is a less likely cause of the funnel asymmetry. It is proposed that this enhancement to funnel plots should be used routinely for meta-analyses where it is possible that results could be suppressed on the basis of their statistical significance.



ELSEVIER
Journal of Clinical Epidemiology 61 (2008) 991–996
Journal of Clinical Epidemiology

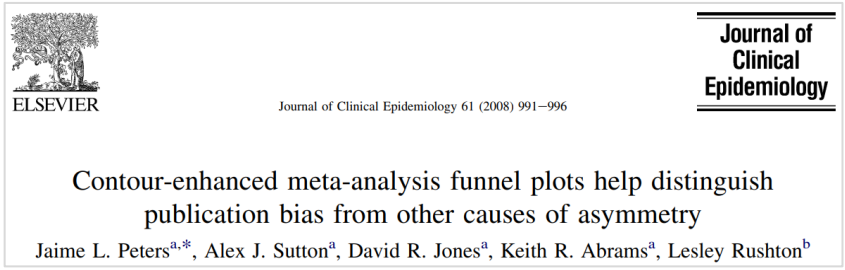
Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry

Jaime L. Peters[a,*], Alex J. Sutton[a], David R. Jones[a], Keith R. Abrams[a], Lesley Rushton[b]
[a]*Department of Health Sciences, University of Leicester, UK*
[b]*Department of Epidemiology and Public Health, Imperial College London*

Publication Bias

Funnel Plot

Contour-enhanced Funnel Plot



ELSEVIER

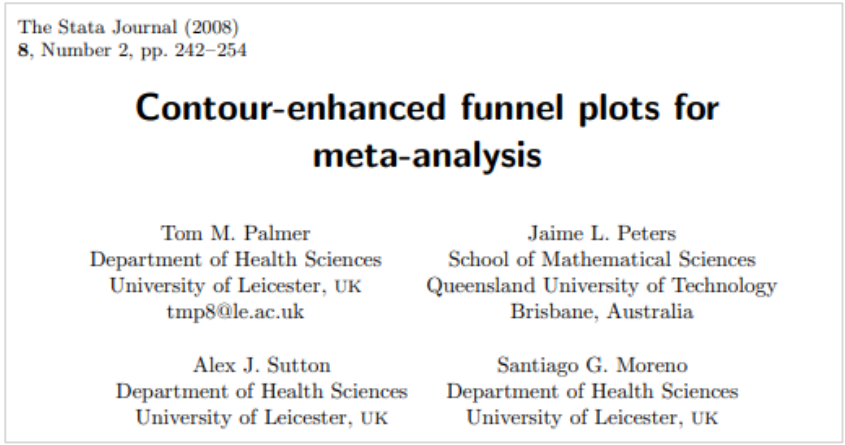
Journal of Clinical Epidemiology 61 (2008) 991–996

Journal of Clinical Epidemiology

Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry

Jaime L. Peters[a,*], Alex J. Sutton[a], David R. Jones[a], Keith R. Abrams[a], Lesley Rushton[b]

The contour overlay aids the interpretation of the funnel plot. For example, if studies appear to be missing in areas of statistical non-significance, then this adds credence to the possibility that the asymmetry is due to **publication bias**. Conversely, if the supposed missing studies are in areas of higher statistical significance, this would suggest the cause of the asymmetry may be more likely to be due to **factors other than publication bias**, such as variable study quality.



The Stata Journal (2008)
8, Number 2, pp. 242–254

Contour-enhanced funnel plots for meta-analysis

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Although asymmetry in the appearance of a funnel plot is often interpreted as being caused by publication bias, in reality **the asymmetry could be due to other factors** that cause **systematic differences in the results of large and small studies, for example, confounding factors such as differential study quality**.

If studies appear to be missing **in areas of low statistical significance**, then it is possible that the asymmetry is due to publication bias. If studies appear to be missing in **areas of high statistical significance**, then publication bias is a less likely cause of the funnel asymmetry.

Publication Bias

Funnel Plot

Contour-enhanced Funnel Plot

TABLE 1 Possible sources of asymmetry in funnel plots (adapted from Egger et al[52])

1. Publication bias and other reporting biases
   - Entire study reports, or particular results, of smaller studies are unavailable because of the *P* value, magnitude or direction of effect.
2. Poor methodological quality leading to spuriously inflated effects in smaller studies
   - Asymmetry can arise when some smaller studies are of lower methodological quality and produce larger intervention effect estimates.
3. True heterogeneity
   - Substantial benefit may be seen only in patients at high risk for the outcome that is affected by the intervention, and usually these high-risk patients are more likely to be included in small, early studies.[55]
   - Some interventions may have been implemented more thoroughly in smaller trials and may, therefore, have resulted in larger intervention effect estimates.[56]
4. Artefactual
   - Some effect estimates are naturally correlated with their standard errors, and this can produce spurious asymmetry in a funnel plot.[57,58]
5. Chance

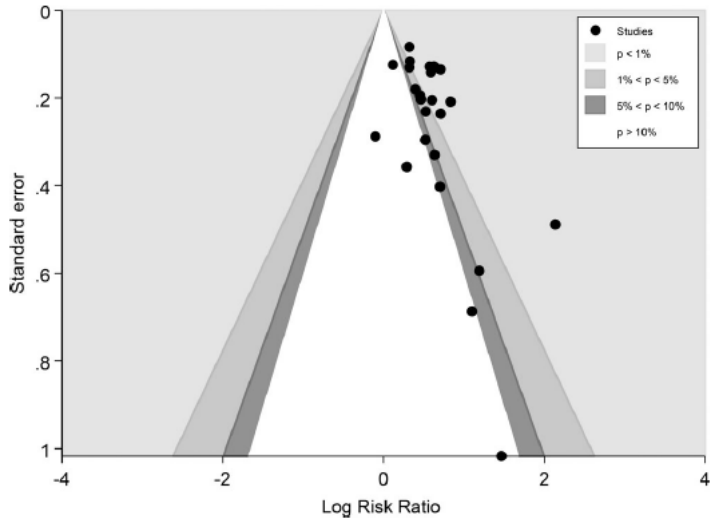

FIGURE 4 Contour-enhanced funnel plot for meta-analysis of the effect of selective serotonin reuptake inhibitors (SSRIs) versus placebo on treatment response (Clinical Global Impressions Improvement scale [CGI-I]).[61] There is a suggestion of missing results in the left-hand side of the plot, where results would be unfavorable to SSRIs and in the area of statistical nonsignificance (ie, the white area where $P > .10$), which adds credence to the possibility that the asymmetry is due to reporting biases

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DOI: 10.1002/jrsm.1468
REVIEW
Research Synthesis Methods WILEY

Investigating and dealing with publication bias and other reporting biases in meta-analyses of health research: A review

Matthew J. Page[1] | Jonathan A. C. Sterne[2,3] | Julian P. T. Higgins[2] | Matthias Egger[4]

Kingston University London

Publication Bias

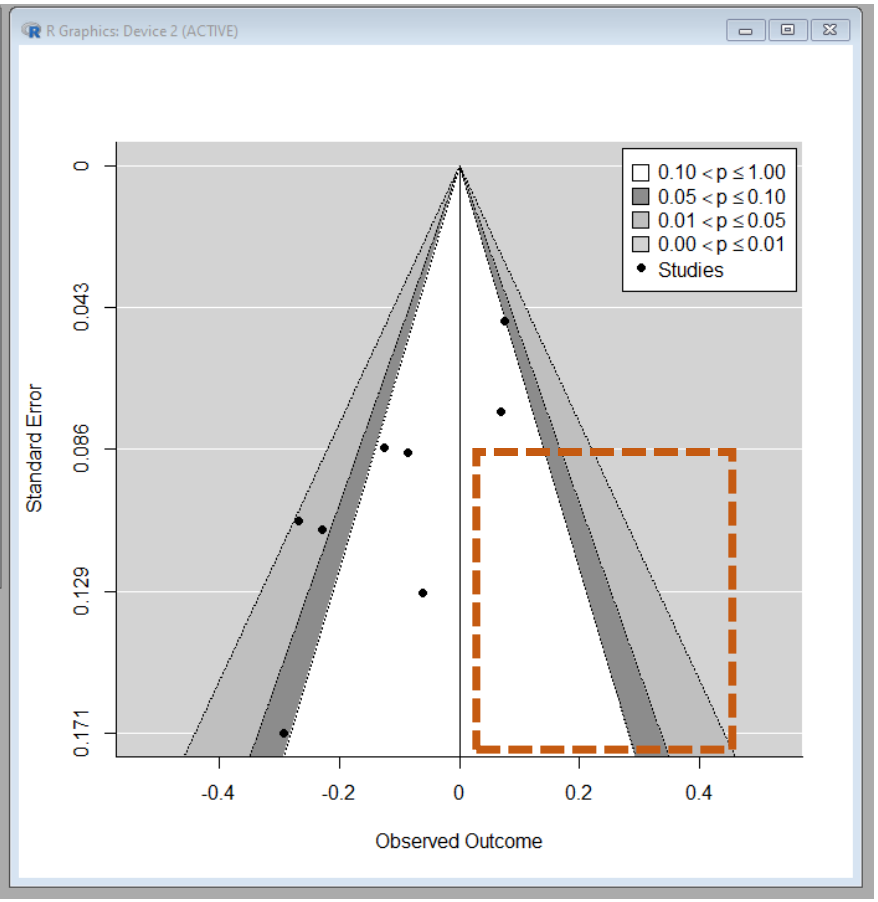
Funnel Plot

Contour-enhanced Funnel Plot

R Console

```
> results

Random-Effects Model (k = 8; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.01 (SE = 0.01)
tau (square root of estimated tau^2 value):      0.11
I^2 (total heterogeneity / total variability):   61.97%
H^2 (total variability / sampling variability):  2.63

Test for Heterogeneity:
Q(df = 7) = 19.08, p-val < .01

Model Results:

estimate     se    zval  pval  ci.lb  ci.ub
   -0.09   0.05  -1.64  0.10  -0.19   0.02

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> plot(results, transf = exp, qqplot = TRUE) # generates four plots (incl. fore$
There were 27 warnings (use warnings() to see them)
> forest.rma(results, transf = exp)
> funnel(results, level = c(90, 95, 99), shade = c("white", "gray55", "gray75")$
>
```

R package: **metafor**



Absence of results in the marked area suggests publication bias (missing studies with unfavourable outcomes and higher SEs). Also, the top four studies with the least variation (lowest SE) are in the non-significant area. SE: standard error (reversed y-axis)

Publication Bias

Funnel Plot

Trim and Fill Plot

One of the most common methods to adjust for funnel plot asymmetry is the **Duval & Tweedie trim and fill method** (Duval and Tweedie 2000). The idea behind this method is simple: it imputes "missing" effects until the funnel plot is symmetric. The pooled effect size of the resulting "extended" data set then represents the estimate when correcting for small-study effects. This is achieved through a simple algorithm, which involves the "trimming" and "filling" of effects (Schwarzer, Carpenter, and Rücker 2015, chap. 5.3.1):

- **Trimming**. First, the method identifies all the outlying studies in the funnel plot. In our example from before, these would be all small studies scattered around the right side of the plot. Once identified, these studies are **trimmed**: they are removed from the analysis, and the pooled effect is recalculated without them. This step is usually performed using a fixed-effect model.

- **Filling**. For the next step, the recalculated pooled effect is now assumed to be the center of all effect sizes. For each trimmed study, one additional effect size is added, mirroring its results on the other side of the funnel. For example, if the recalculated mean effect is 0.5 and a trimmed study has an effect of 0.8, the mirrored study will be given an effect of 0.2. After this is done for all trimmed studies, the funnel plot will look roughly symmetric. Based on all data, including the trimmed and imputed effect sizes, the average effect is then recalculated again (typically using a random-effects model). The result is then used as the estimate of the corrected pooled effect size.

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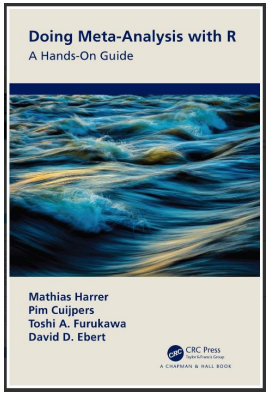

Publication Bias

Funnel Plot

Trim and Fill Plot

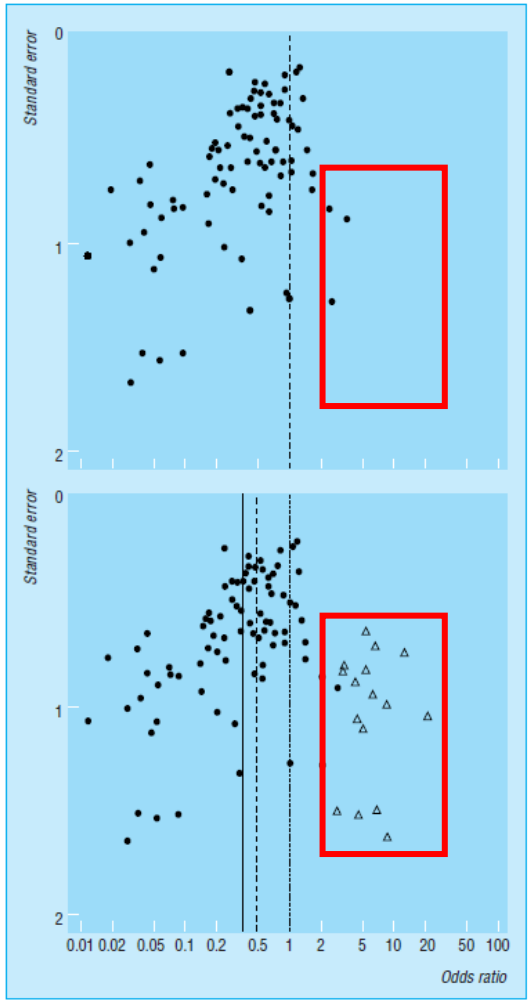

Fig 3 Asymmetrical funnel plot of 89 randomised controlled trials comparing homoeopathic medicine with placebo identified by Linde et al[25] (top) and application of the "trim and fill" method (bottom). Solid circles represent the 89 trials and open diamonds "filled" studies. Solid line is original (random effects) estimate of pooled odds ratio (0.41), dashed line is adjusted estimate (0.52, including filled studies), and dotted line is null value (1)

Clear evidence of missing publications with undesirable results

Investigating and dealing with publication and other biases in meta-analysis

BMJ 2001 ; 323 doi: https://doi.org/10.1136/bmj.323.7304.101 (Published 14 July 2001)
Cite this as: *BMJ* 2001;323:101

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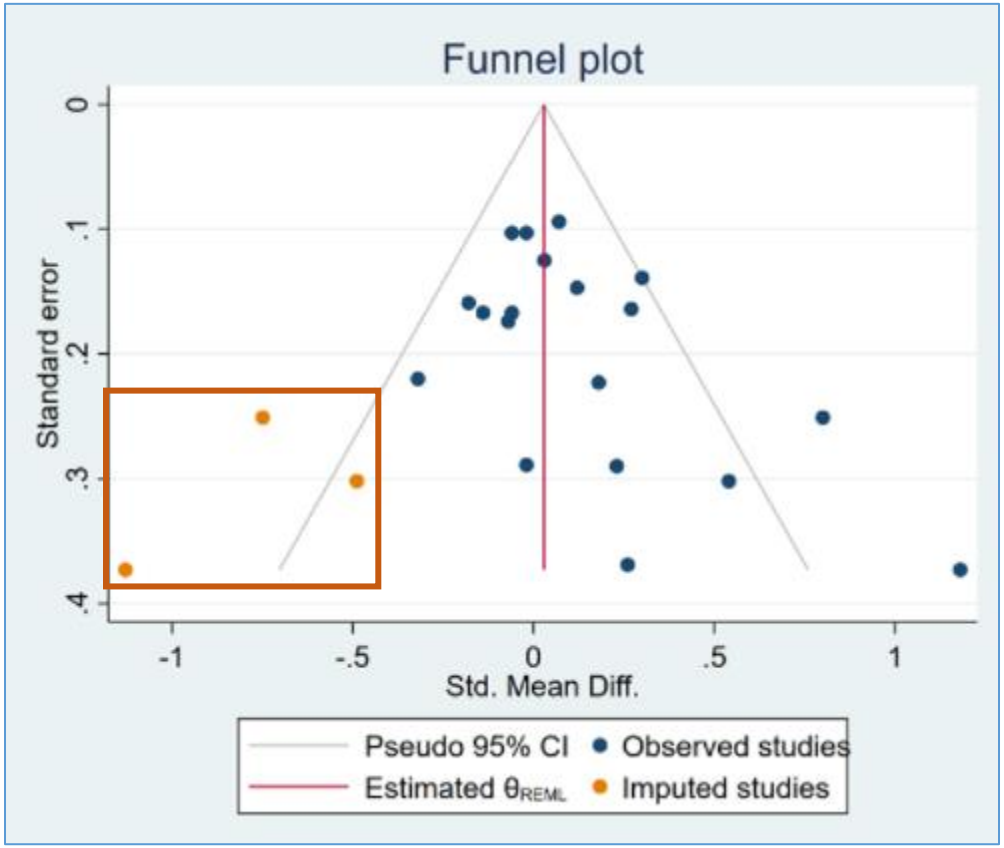
Publication Bias

Funnel Plot

Trim and Fill Plot

Presumed missing studies



STATA

» Home » Products » Features » Meta-analysis

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Publication Bias

Funnel Plot

Trim and Fill Plot & Egger test (linear regression or linreg)

Reporting the Results of Egger's Test

For Egger's tests, it is usually sufficient to report the value of the intercept, its 95% confidence interval, as well as the t and p-value. In the **{dmetar}** package, we included a convenience function called `eggers.test`. This function is a wrapper for `metabias`, and provides the results of Egger's test in a format suitable for reporting. In case you do not have **{dmetar}** installed, you can find the function's source code online. Here is an example:

```
eggers.test(m.gen)
```

	Intercept	ConfidenceInterval	t	p
Egger's test	4.111	2.347-5.875	4.677	0.00025

Egger test requires a minimum of 10 included studies to be valid (and many more if there is substantial heterogeneity)

Statistical Power of Funnel Plot Asymmetry Tests

It is advisable to only test for funnel plot asymmetry when our meta-analysis includes a sufficient number of studies. When the number of studies is low, the statistical power of Eggers' or Peters' test may not be high enough to detect real asymmetry. It is generally recommended to only perform a test when $K \geq 10$ (Sterne et al. 2011).

By default, `metabias` will throw an error when the number of studies in our meta-analysis is smaller than that. However, it is possible (although not advised) to prevent this by setting the `k.min` argument in the function to a lower number.

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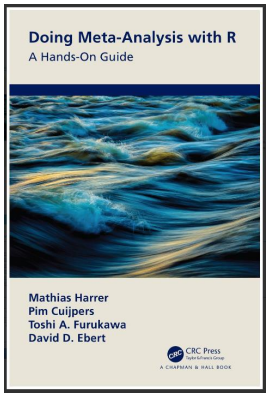

Publication Bias

Funnel Plot

Evidence based medicine

The case of the misleading funnel plot

Joseph Lau, John P A Ioannidis, Norma Terrin, Christopher H Schmid, Ingram Olkin

Evidence based medicine insists on rigorous standards to appraise clinical interventions. Failure to apply the same rules to its own tools could be equally damaging

Summary points

Methods used by evidence based medicine should be evaluated with rigorous standards

The funnel plot is widely used in systematic reviews and meta-analyses as a test for publication bias

Asymmetry of the funnel plot, either visually interpreted or statistically tested, does not accurately predict publication bias

Inappropriate or misleading use of funnel plot tests may do more harm than good

ELSEVIER

Journal of Clinical Epidemiology 53 (2000) 477–484

Journal of Clinical Epidemiology

Misleading funnel plot for detection of bias in meta-analysis

Jin-Ling Tang[a,*], Joseph LY Liu[b]

[a]*Department of Community and Family Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong*
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Abstract

Publication and other forms of selection biases pose a threat to the validity of meta-analysis. Funnel plots are usually used to detect such biases; asymmetrical plots are interpreted to suggest that biases are present. Using 198 published meta-analyses, we demonstrate that the shape of a funnel plot is largely determined by the arbitrary choice of the method to construct the plot. When a different definition of precision and/or effect measure were used, the conclusion about the shape of the plot was altered in 37 (86%) of the 43 meta-analyses with an asymmetrical plot suggesting selection bias. In the absence of a consensus on how the plot should be constructed, asymmetrical funnel plots should be interpreted cautiously. These findings also suggest that the discrepancies between large trials and corresponding meta-analyses and heterogeneity in meta-analyses may also be determined by how they are evaluated.

Keywords: Funnel plot; Meta-analysis; Randomized controlled trials; Selection bias; Publication bias; Statistical method; Systematic reviews

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Publication Bias

Funnel Plot

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Research Methods & Reporting

Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials

BMJ 2011 ; 343 doi: https://doi.org/10.1136/bmj.d4002 (Published 22 July 2011)
Cite this as: *BMJ* 2011;343:d4002

Publication Bias

Selection Models

9.2.3 Selection Models

The last type of publication bias method we cover are so-called **selection models**. Although selection models have been proposed to examine the impact of selective publication for some time (Hedges 1992, 1984; Iyengar and Greenhouse 1988; Hedges and Vevea 1996), interest in their application has particularly increased in the last few years (McShane, Böckenholt, and Hansen 2016; Carter et al. 2019).

All publication bias methods we covered previously are based on some kind of "theory", which is used to explain why and how selective publication affects the results of a meta-analysis. Small-study effect methods, for example, assume that a study's risk of non-publication is proportional to its sample and effect size. P-curve is based on the idea that a p-value of 0.05 serves as a "magic threshold", where results with $p \geq 0.05$ are generally much more likely to be missing in our data than statistically significant findings.

Selection models can be seen as a generalized version of these methods. They allow to model **any** kind of process through which we think that publication bias has affected our results. This makes them very versatile: selection models can be used to model our data based on very simple, or highly sophisticated hypotheses concerning the genesis of publication bias.

The idea behind all selection models is to specify a distribution which predicts, often in a highly idealized way, how likely it is that some study is published (i.e. "selected"), depending on its results. Usually, this result is the study's p-value, and a selection model can be seen like a function that returns the probability of publication for varying values of p. Once such a selection function has been defined, it can be used to "remove" the assumed bias due to selective publication, and derive a corrected estimate of the true effect size.

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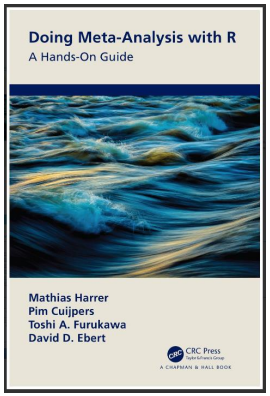

Publication Bias

9.5 Summary

- Publication bias occurs when some studies are systematically missing in the published literature, and thus in our meta-analysis. Strictly defined, publication bias exists when the probability of a study to get published depends on its results. However, there is also a range of other **reporting biases**. These reporting biases also influence how likely it is that a finding will end up in our meta-analysis. Examples are citation bias, language bias, or outcome reporting bias.
- It is also possible that **published** evidence is biased, for example due to questionable research practices (QRPs). Two common QRPs are p-hacking and HARKing, and both can increase the risk of overestimating effects in a meta-analysis.
- Many publication bias methods are based on the idea of **small-study effects**. These approaches assume that only small studies with a surprisingly high effect size obtain significant results and are therefore selected for publication. This leads to an asymmetric funnel plot, which can be a sign of publication bias. But it does not have to be. Various "benign" causes of small-study effects are also possible.
- A relatively novel method, **p-curve**, is based on the idea that we can control for evidential value just by looking at the pattern of significant ($p < 0.05$) effects in our data. It can be used to test for both the presence and absence of a true effect, and can estimate its magnitude.
- **Selection models** are a very versatile method and can be used to model different publication bias processes. However, they only provide valid results when the assumed model is adequate, and often require a very large number of studies. A very simple selection model, the three-parameter model, can also be used for smaller data sets.
- No publication bias method consistently outperforms all the others. It is therefore advisable to always apply **several** techniques, and interpret the corrected effect size cautiously. Thorough searches for unpublished evidence mitigate the risk of publication bias in a much better way than current statistical approaches.

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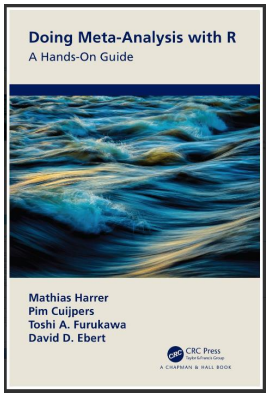

Publication Bias

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DOI: 10.1002/jrsm.1482

BRIEF METHOD NOTE

Research Synthesis Methods WILEY

A confidence interval robust to publication bias for random-effects meta-analysis of few studies

Masayuki Henmi[1] | Satoshi Hattori[2] | Tim Friede[3]

Highlights

1 What is already known?

- Estimated overall effects from meta-analyses might be impacted by publication bias
- A confidence interval for the overall effect has been proposed that is to some extent robust to the selection of studies

2 What is new?

- The performance of the robust confidence interval previously proposed is assessed in meta-analyses with few studies and found not to work well in this setting
- The approach is refined resulting in improved coverage probabilities of the confidence intervals in particular in meta-analyses with few studies

3 Potential impact for RSM readers outside the authors' field

- The refined approach is recommend for application in meta-analyses with few studies yielding more reliable results

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Beware of Small Study Effects

Annals of Internal Medicine®

Academia and Clinic | December 4, 2001

Reported Methodologic Quality and Discrepancies between Large and Small Randomized Trials in Meta-Analyses

Lise L. Kjaergard, MD, John Villumsen, MSc, Christian Gluud, MD, DrMSc

Data Synthesis:

Fourteen meta-analyses involving 190 randomized trials from eight therapeutic areas were included. Compared with large trials, intervention effects were exaggerated in small trials with inadequate allocation sequence generation (ratio of odds ratios, 0.46 [95% CI, 0.25 to 0.83]; $P = 0.011$), inadequate allocation concealment (ratio of odds ratios, 0.49 [CI, 0.27 to 0.86]; $P = 0.014$), and no double blinding (ratio of odds ratios, 0.52 [CI, 0.28 to 0.96]; $P = 0.01$). Large trials did not differ significantly from small trials with adequate generation of the allocation sequence, adequate allocation concealment, or adequate double blinding. No association was seen between reported follow-up and intervention effects. The Jadad scale provided no additional information because the scale and the quality components overlapped substantially.

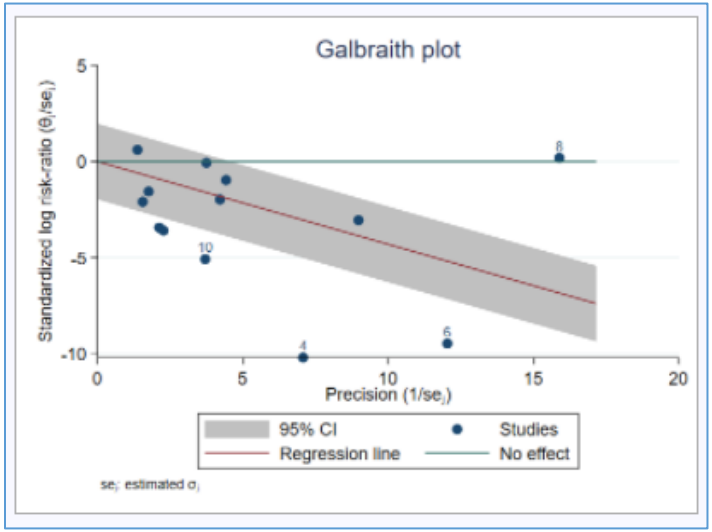
Conclusions:

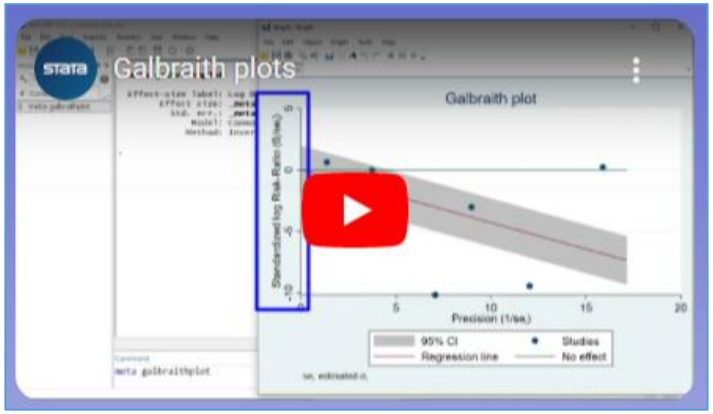
Inadequate generation of the allocation sequence, allocation concealment, and double blinding lead to exaggerated estimates of intervention benefit and may contribute to discrepancies between the results of large randomized trials and small randomized trials in meta-analyses.

" In 2001, a study examined the influence of study size on study outcome (Kjaergard et al, 2001). Specifically a meta-analysis reviewed 190 randomized trials involving 8 different therapeutic interventions divided the various studies into those with more than 1000 participants and those with less than thousand participants. The results of this analysis were that the smaller sized studies had more positive therapeutic effects than those studies with the larger size. These researchers also reported that the larger studies were systematically less likely to report a positive effect, suggesting bias was easier to occur and have an impact in smaller studies. These researchers also looked at other bias control measures such as randomization and blinding and concluded that inadequate randomization and blinding leads to exaggerated estimates of the intervention's benefit. " (Clark & Mulligan, 2011)

Outlier Detection

Radial (Galbraith) Plot





Another plot type that summarises the meta-analysis results (an alternative or supplement to forest plot)

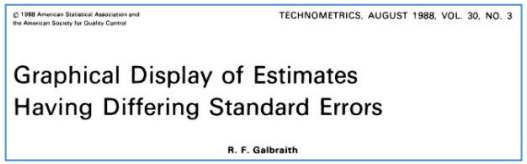
The y-axis is the (ln) effect size and the x-axis is the precision (reciprocal of standard error); each study is shown according to its effect size and precision

It shows the no effect line (across from y=0) and the regression line through the origin whose slope of this line corresponds to the estimate of the overall effect size

The slope of an imaginary line from the origin (x=0; y=0) to any point representing a single study is equal to the (ln) effect size estimate corresponding to that point

It visualises the degree of heterogeneity of effect sizes: in the absence of substantial heterogeneity, around 95% of the studies to lie within the shaded area (95% CI)

It shows the outliers (any study falling outside the shaded area)


TECHNOMETRICS, AUGUST 1988, VOL. 30, NO. 3

Graphical Display of Estimates Having Differing Standard Errors

R. F. Galbraith

Kingston University London

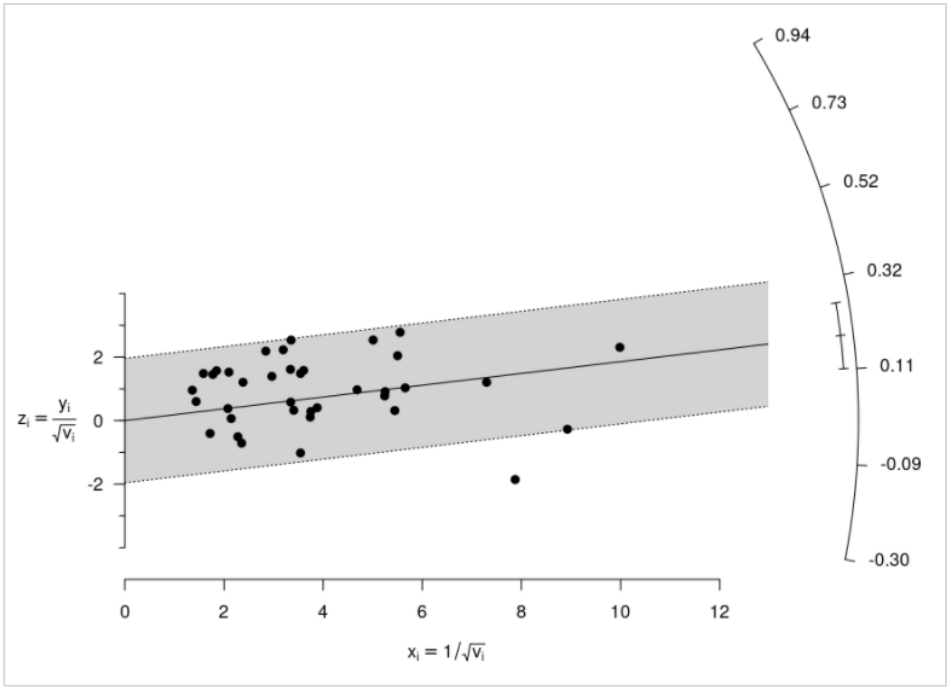
Outlier Detection

Radial (Galbraith) Plot

Radial (Galbraith) Plot

Description

The radial plot (also called Galbraith plot) was introduced by Rex Galbraith (1988a, 1988b, 1994) and can be useful in the meta-analytic context to examine the data for heterogeneity. For a fixed-effects model, the plot shows the inverse of the standard errors on the horizontal axis against the observed effect sizes or outcomes standardized by their corresponding standard errors on the vertical axis. On the right hand side of the plot, an arc is drawn corresponding to the observed effect sizes or outcomes. A line projected from (0,0) through a particular point within the plot onto this arc indicates the value of the observed effect size or outcome for that point. An example of such a plot is shown below



x-axis: precision (1/SE)
y-axis: standardised effect size (ln)
Summary effect size estimate: slope of the straight line (where it crosses the arc shows the value in natural log)

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A Meta-Analysis Package for R

Outlier Detection

Graphical Display of Study Heterogeneity (GOSH) Plot

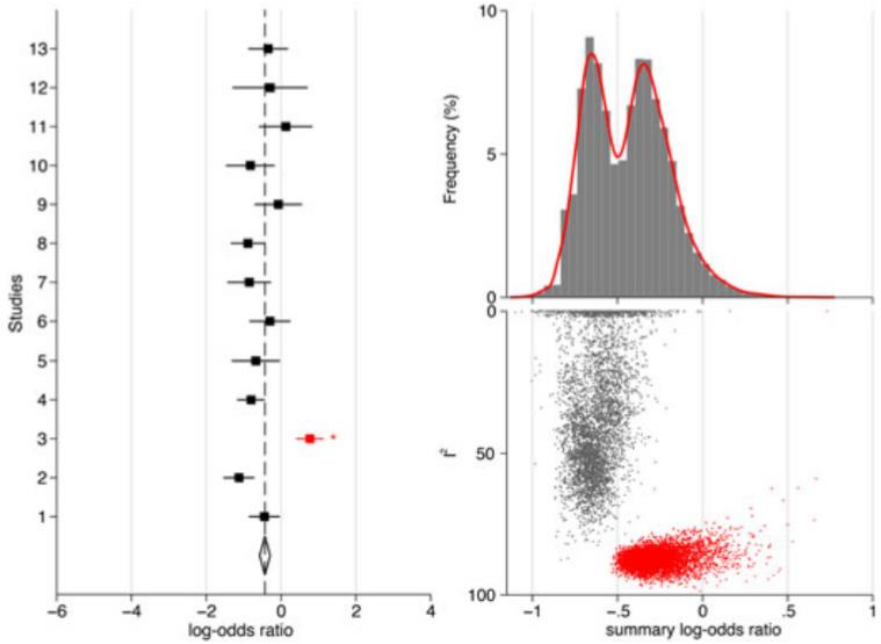

Figure 5. Juxtaposed forest plot, histogram of all-subsets summary effect sizes, and scatterplot of I^2 against summary effect sizes for a heterogeneous meta-analysis from Figure 2 (the first example from Figure 2(a)). Layout is similar to Figure 3. Note that contrary to the unimodal histograms in the homogeneous examples, the histograms from heterogeneous meta-analyses are multimodal. Modes correspond to subsets that include influential studies (here, a single outlying study marked with an asterisk and shown in red). In the scatter plot of I^2 values over summary estimates, we colored red points corresponding to subsets including this influential study.

Original Article

Research Synthesis Methods

Received 26 February 2012, Revised 3 June 2012, Accepted 25 June 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1053

GOSH – a graphical display of study heterogeneity

Ingram Olkin,[a*†] Issa J. Dahabreh[b,c] and Thomas A. Trikalinos[c]

Estimates from individual studies included in a meta-analysis often are not in agreement, giving rise to statistical heterogeneity. In such cases, exploration of the causes of heterogeneity can advance knowledge by formulating novel hypotheses. We present a new method for visualizing between-study heterogeneity using combinatorial meta-analysis. The method is based on performing separate meta-analyses on all possible subsets of studies in a meta-analysis. We use the summary effect sizes and other statistics produced by the all-subsets meta-analyses to generate graphs that can be used to investigate heterogeneity, identify influential studies, and explore subgroup effects. This graphical approach complements alternative graphical explorations of data. We apply the method to numerous biomedical examples, to allow readers to develop intuition on the interpretation of the all-subsets graphical display. The proposed graphical approach may be useful for exploratory data analysis in systematic reviews. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: all-subsets; meta-analysis; combinatorial meta-analysis; heterogeneity; exploratory data analysis; outliers

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Model Assessment

Quantile-Quantile Plot

Evaluation of the Normality Assumption

Psychological Methods
1998, Vol. 3, No. 1, 46–54

1082-989X/98/$3.00

Using the Normal Quantile Plot to Explore Meta-Analytic Data Sets

Morgan C. Wang
University of Central Florida

Brad J. Bushman
Iowa State University

In a meta-analysis, graphical displays can be used to check statistical assumptions for numerical procedures and they can be used to discover important patterns in the data. The authors propose the normal quantile plot as a preferred alternative to the funnel plot for such purposes. The normal quantile plot, like the funnel plot, can be used to investigate whether all studies come from a single population and to search for publication bias. However, the normal quantile plot is easier to interpret than the funnel plot, especially when it includes 95% confidence bands. In addition, the normal quantile plot can be used to check the normality assumption for numerical procedures. The funnel plot cannot be used for this latter purpose.

In a Q-Q plot, two distributions are plotted against each other. If one of those is the standard normal distribution, it checks the fit of the observed distribution to normal distribution.

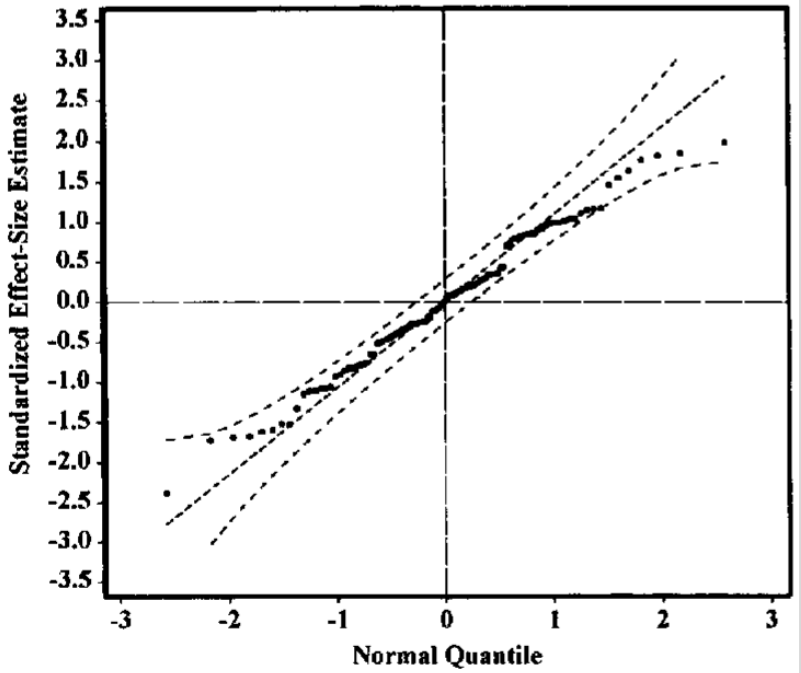

Figure 9. Normal quantile plot for simulated set with a mean of 0 and standard deviation of 1 ($N = 100$).

" If the observed data have a standard normal distribution, the points on the plot will fall close to the line X = Y and the plot should look like *Figure 9* (on the right). " Note that all points fall within the 95% confidence bands.

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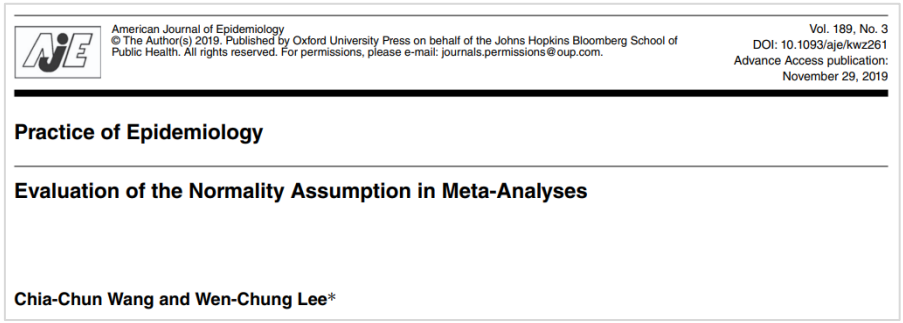
Model Assessment

Quantile-Quantile Plot

Evaluation of the Normality Assumption



American Journal of Epidemiology
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DOI: 10.1093/aje/kwz261
Advance Access publication:
November 29, 2019

Practice of Epidemiology

Evaluation of the Normality Assumption in Meta-Analyses

Chia-Chun Wang and Wen-Chung Lee*

"In meta-analysis, a distributional assumption for calculation of the confidence interval of the mean effect and prediction of the underlying effects of future studies"

"… methods estimating the mean effect and its confidence interval are relatively robust against nonnormality, estimation of prediction intervals is substantially influenced by nonnormal heterogeneity."

"Due to having different within-study standard errors in meta-analysis with heterogeneity, conventional methods for evaluating normality cannot be used directly, and standardization is needed."

"A normal Q-Q plot plots standardised effect sizes against the standard normal distribution to check goodness-of-fit"

"We recommend routine examination of the
normality assumption with the proposed framework in future meta-analyses."

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Model Assessment

Quantile-Quantile Plot

Evaluation of the Normality Assumption

Received: 26 March 2018 | Revised: 5 June 2018 | Accepted: 14 June 2018

DOI: 10.1002/bimj.201800071

REVIEW ARTICLE

Biometrical Journal

When should meta-analysis avoid making hidden normality assumptions?

Dan Jackson[1] | Ian R. White[2]

Abstract

Meta-analysis is a widely used statistical technique. The simplicity of the calculations required when performing conventional meta-analyses belies the parametric nature of the assumptions that justify them. In particular, the normal distribution is extensively, and often implicitly, assumed. Here, we review how the normal distribution is used in meta-analysis. We discuss when the normal distribution is likely to be adequate and also when it should be avoided. We discuss alternative and more advanced methods that make less use of the normal distribution. We conclude that statistical methods that make fewer normality assumptions should be considered more often in practice. In general, statisticians and applied analysts should understand the assumptions made by their statistical analyses. They should also be able to defend these assumptions. Our hope is that this article will foster a greater appreciation of the extent to which assumptions involving the normal distribution are made in statistical methods for meta-analysis. We also hope that this article will stimulate further discussion and methodological work.

" If the normality of effect sizes cannot be confirmed by Q-Q plot, the estimated summary effect size and its 95% CI as well is the prediction interval are not valid. In that case, advanced methods not assuming normal distribution should be used. "

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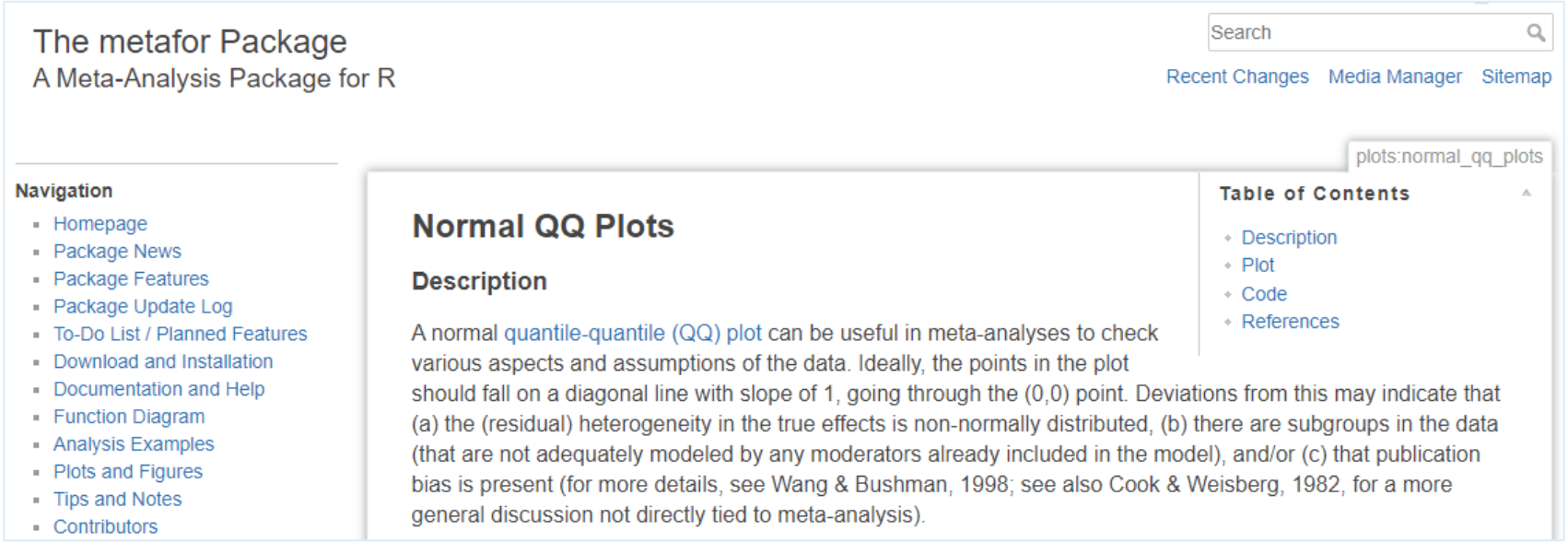
Model Assessment

Quantile-Quantile Plot

Evaluation of the Normality Assumption



The metafor Package
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plots:normal_qq_plots

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Normal QQ Plots

Description

A normal quantile-quantile (QQ) plot can be useful in meta-analyses to check various aspects and assumptions of the data. Ideally, the points in the plot should fall on a diagonal line with slope of 1, going through the (0,0) point. Deviations from this may indicate that (a) the (residual) heterogeneity in the true effects is non-normally distributed, (b) there are subgroups in the data (that are not adequately modeled by any moderators already included in the model), and/or (c) that publication bias is present (for more details, see Wang & Bushman, 1998; see also Cook & Weisberg, 1982, for a more general discussion not directly tied to meta-analysis).

Model Assessment

L'Abbe Plot

A L'Abbe plot plots the binary outcomes (like event rates) in the experimental/intervention group against the event rate in the control group, as an aid to exploring the heterogeneity of effect estimates within a meta-analysis (L'Abbé *et al*. 1987; Song, 1999). It allows comparison of study-specific event rates in the two groups (similar to comparison of effect sizes in forest plot).

A practical approach to reading and interpreting meta-analyses

Gesine Weckmann, Jean-François Chenot, Katrin C. Reber

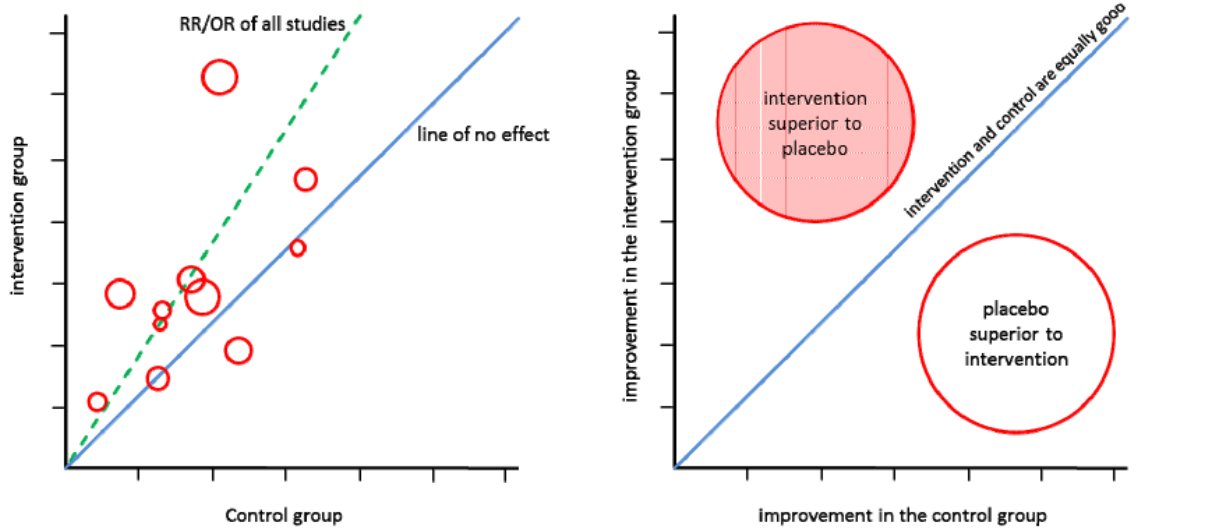

fig.2: L' Abbé plot a. The blue line represents the line of no effect. The dotted green line represents the combined effect of all studies as RR or OR. The red circles represent the results of individual studies, with size representing study weight.
b. Schematic representation of a L' Abbé plot [11, 12]

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Model Assessment

L'Abbe Plot

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L'Abbé Plot

Description

In a L'Abbé plot (based on L'Abbé, Detsky, & O'Rourke, 1987), the arm-level outcomes for two experimental groups (e.g., treatment and control group) are plotted against each other. In the example below, the points show the log risk (of a tuberculosis infection) in the treatment (x axis) and control (y axis) group. Points falling on the solid diagonal line represent studies where the risk of infection did not differ between the two groups. Points falling below this line represent studies where the risk was lower in the treated (vaccinated) group. The dashed line indicates the estimated effect based on the fitted model (which is linear on the log scale for the log risk ratio). The size of the points is an inverse function of the precision of the estimates (so larger points correspond to more precise estimates).

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- Description
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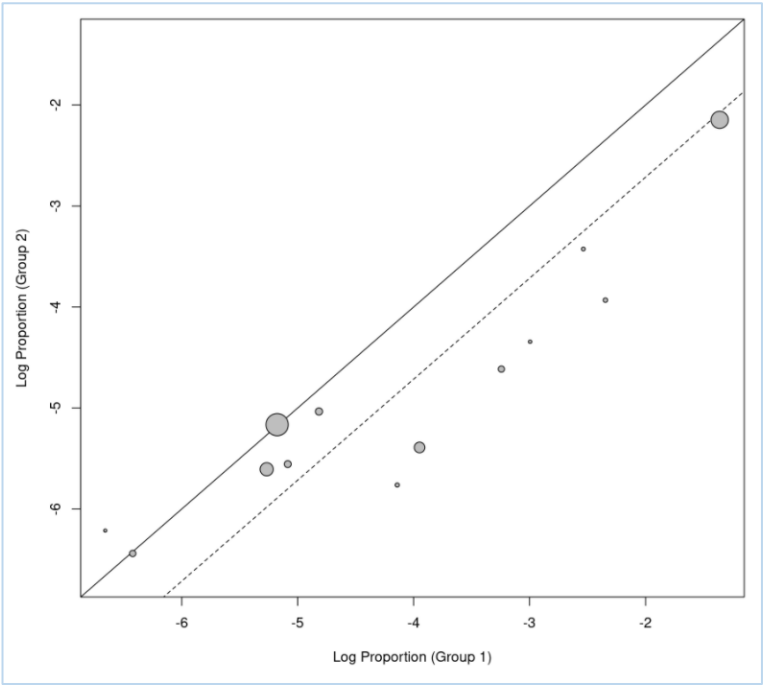

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Meta-analysis: Common Mistakes

Table 2: Frequent issues and pitfalls encountered in meta-analyses

Common statistical pitfalls
Inclusion of studies with overlapping data (i.e. some patients contributing to the results of multiple studies)
Literature search limited to a single database[a]
Assessment of heterogeneity and inconsistency
Selection of random- versus fixed-effect model
Identification of proper outcome measure
Addressing different lengths of follow-up across studies
Accounting for differences in the design of included studies (RCTs versus observational)
Ignoring difference in the methodological quality across included studies
Exploring sources of heterogeneity (subgroup analysis and meta-regression)

[a]The following databases should be investigated for a comprehensive literature search: PubMed, Cochrane Library, Google Scholar, Embase, Scopus, ScienceDirect, Web of Science, major scientific or congress websites.

Cite this article as: Buccheri S, Sodeck GH, Capodanno D. Statistical primer: methodology and reporting of meta-analyses. Eur J Cardiothorac Surg 2018;53:708–13.

Statistical primer: methodology and reporting of meta-analyses†

Sergio Buccheri[a], Gottfried H. Sodeck[b] and Davide Capodanno[a,*]

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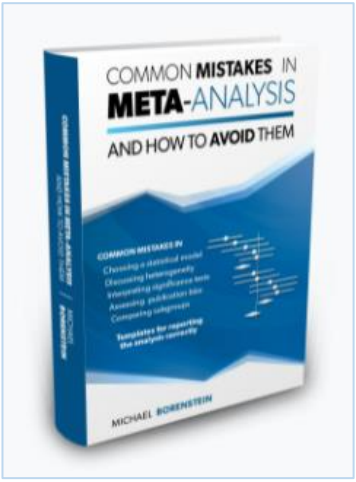
Meta-analysis: Common Mistakes



I^2 is not an absolute measure of heterogeneity in a meta-analysis — YouTube

Common mistakes in Meta-Analysis and How to Avoid Them
Fixed-effect vs. Random-effects — YouTube

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Many researchers believe *that the I^2 statistic tells us how much the effect size varies.*

In fact, an I^2 value of 10% could correspond to substantial heterogeneity while an I^2 value of 90% could correspond to trivial heterogeneity.

Many readers assume *that if the effect is statistically significant, the treatment works in all populations.*

In fact, the treatment could be helpful in some populations and harmful in others.

Many meta-analysts *use a significance test to choose between the fixed-effect and random-effects models.*

In fact, the selection of a model must be based on the goals of the analysis.

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Meta-analysis: Common Mistakes

Cochrane

Common errors in meta-analysis

Lessons from the Cochrane Review Screening Programme

November 2017

Kerry Dwan

Kingston University London

Meta-analysis: Common Mistakes

The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey

John P.A. Ioannidis, Thomas A. Trikalinos

"Meta-analysts should refrain from inappropriate or unmeaningful application of funnel-plot asymmetry tests. Readers should not be misled that publication bias has been documented or excluded according to inappropriate use or interpretation of funnel plots."

BMJ 2011;342:d4002 doi: 10.1136/bmj.d4002

RESEARCH METHODS & REPORTING

Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials

Funnel plots, and tests for funnel plot asymmetry, have been widely used to examine bias in the results of meta-analyses. Funnel plot asymmetry should not be equated with publication bias, because it has a number of other possible causes. This article describes how to interpret funnel plot asymmetry, recommends appropriate tests, and explains the implications for choice of meta-analysis model

Jonathan A C Sterne *professor*[1], Alex J Sutton *professor*[2], John P A Ioannidis *professor and director*[3], Norma Terrin *associate professor*[4], David R Jones *professor*[2], Joseph Lau *professor*[4], James Carpenter *reader*[5], Gerta Rücker *research assistant*[6], Roger M Harbord *research associate*[1], Christopher H Schmid *professor*[4], Jennifer Tetzlaff *research coordinator*[7], Jonathan J Deeks *professor*[8], Jaime Peters *research fellow*[9], Petra Macaskill *associate professor*[10], Guido Schwarzer *research assistant*[6], Sue Duval *assistant professor*[11], Douglas G Altman *professor*[12], David Moher *senior scientist*[7], Julian P T Higgins *senior statistician*[13]

Summary points

- Inferences on the presence of bias or heterogeneity should consider different causes of funnel plot asymmetry and should not be based on visual inspection of funnel plots alone
- They should be informed by contextual factors, including the plausibility of publication bias as an explanation for the asymmetry
- Testing for funnel plot asymmetry should follow the recommendations detailed in this article
- The fixed and random effects estimates of the intervention effect should be compared when funnel plot asymmetry exists in a meta-analysis with between study heterogeneity

"... simple double counting of the same studies, double counting of some aspects of the studies, inappropriate imputation of results, and assigning spurious precision to individual studies. "

BMC Medical Research Methodology

BioMed Central

Commentary

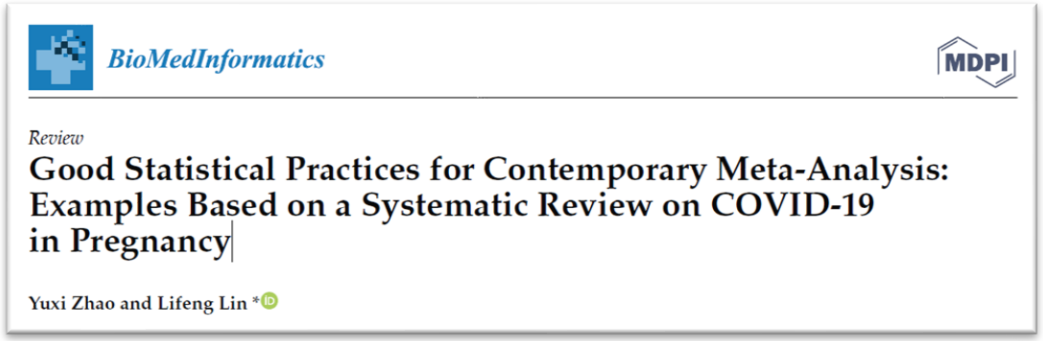
Open Access

Overstating the evidence – double counting in meta-analysis and related problems

Stephen J Senn

Kingston University London

Meta-analysis: Good Practice



BioMedInformatics MDPI

Review

Good Statistical Practices for Contemporary Meta-Analysis: Examples Based on a Systematic Review on COVID-19 in Pregnancy

Yuxi Zhao and Lifeng Lin *

- **Providing Sufficient Information of Included Studies**
- **Providing Information for Reproducibility of Meta-Analyses**
- **Using Appropriate Terminologies**
- **Double-Checking Presented Results**
- **Considering Alternative Estimators of Between-Study Variance**
- **Considering Alternative Confidence Intervals**
- **Reporting Prediction Intervals**
- **Assessing Small-Study Effects Whenever Possible**
- **Considering One-Stage Methods**

> Systematic reviews and meta-analyses are a type of transdisciplinary research. Therefore, in addition to many statistical considerations reviewed in this article, non-statistical guidance is also crucial for conducting high-quality meta-research. For example, heterogeneity between studies may be assessed beyond the statistical perspectives [101]. To aid the statistical assessment of small-study effects, researchers are suggested to search for relevant unpublished studies (e.g., on preprint servers and trial registries), include them in meta-analyses, and explore their potential differences from the published studies [100]. Of course, because the unpublished studies are not peer-reviewed, they could be subject to a high risk of bias. The risk of bias must be carefully appraised if incorporating such studies in the systematic review [102].

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Meta-analysis: Good Practice


PLOS COMPUTATIONAL BIOLOGY

EDITORIAL

Ten simple rules for carrying out and writing meta-analyses

Diego A. Forero[1,2]*, Sandra Lopez-Leon[3], Yeimy González-Giraldo[4], Pantelis G. Bagos[5]

Rule 1: Specify the topic and type of the meta-analysis

Rule 2: Follow available guidelines for different types of meta-analyses

Rule 3: Establish inclusion criteria and define key variables

Rule 4: Carry out a systematic search in different databases and extract key data

Rule 5: Contact authors of primary articles to ask for missing data

Rule 6: Select the best statistical models for your question

Rule 7: Use available software to carry metastatistics

Rule 8: The records and study report must be complete and transparent

Rule 9: Provide enough data in your manuscript

Rule 10: Provide context for your findings and suggest future directions

Kingston University London

Meta-analysis: Good Practice

Nakagawa *et al. BMC Biology* (2017) 15:18
DOI 10.1186/s12915-017-0357-7

BMC Biology

REVIEW Open Access

Meta-evaluation of meta-analysis: ten appraisal questions for biologists

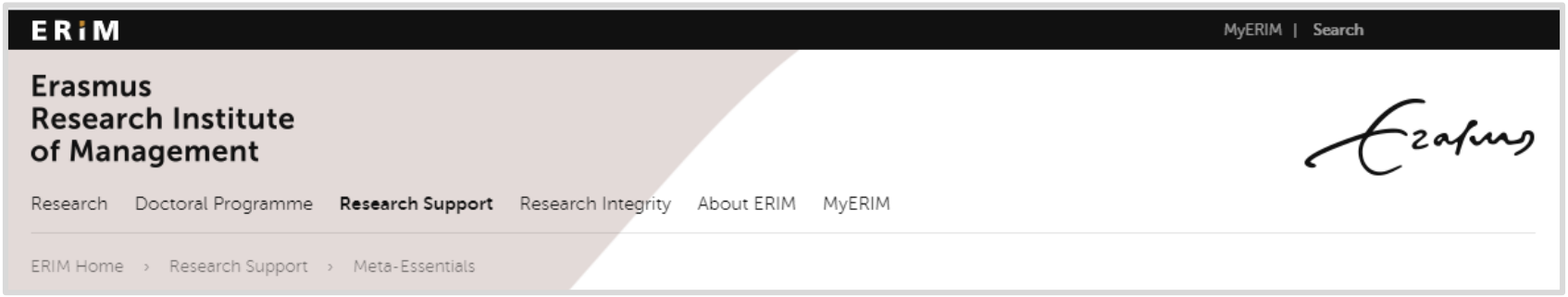
Shinichi Nakagawa[1,2*], Daniel W. A. Noble[1], Alistair M. Senior[3,4] and Malgorzata Lagisz[1]

Conducting a meta-analysis: basics and good practices

Mike W.-L. CHEUNG,[1] Roger C. M. HO,[2] Yonghao LIM[1] and Anselm MAK[3]

Kingston University London

Meta-analysis: Good Practice



- **Meta-Essentials**
  - User manual
  - **Interpret results**
    - Assumptions
    - **The Forest plot**
      - Confidence interval: hypothesis testing
      - Estimating the extent of heterogeneity
      - Prediction interval
      - Model
    - Subgroup analysis
    - Moderator analysis
    - Publication bias analysis
    - Conclusion
  - Frequently Asked Questions
  - References to Meta-Essentials
  - Download

Meta-Essentials_1.5_01.zip

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Meta-analysis: Good Practice

Box 1 Things to do in systematic reviews and meta-analysis

- Write-up a review protocol
- Do trial selection and data extraction in duplicate and independently by two or more reviewers
- Assess the methodological quality of trials included in the systematic review
- Use appropriate methods to pool effect estimates from different trials to preserve within-trial comparisons
- Estimate statistical heterogeneity
- Use a forest plot to display results
- Conduct stratified analyses to investigate whether treatment effect estimates depend on specific trial characteristics
- Build funnel plots and conduct asymmetry tests to investigate small-study effects
- Write-up the manuscript following recommendations of the PRISMA statement

Box 2 Things not to do in systematic reviews and meta-analysis

- Do not use quality assessment tools to derive summary quality scores
- Do not use tests of heterogeneity to decide whether fixed- or random-effects models should be used in analysis
- Do not simply sum up across trials the number of events and the number of patients within experimental and control groups as if they belonged to a single large trial
- Do not pool risk differences without a strong rationale
- Do not use meta-regression to investigate the association between baseline risk and treatment effect
- Do not investigate the association between treatment effect and patient characteristics aggregated at trial level, such as mean age or the percentage of females, in meta-regression

European Heart Journal (2014) **35**, 3336–3345
doi:10.1093/eurheartj/ehu424

REVIEW

Statistical tutorials

Systematic reviews and meta-analyses of randomized trials: principles and pitfalls

Bruno R. da Costa[1,2,3] and Peter Jüni[1,3]*

Kingston University London

Meta-analysis: Good Practice

1 Decisions based simply on visual inspection of forest plots and funnel plots, vote counting, placement of point estimates and confidence intervals, and similar visual reading methods are tenuous. Forest plots are useful to visualize and they may be routinely complemented also by cumulative meta-analysis plots [52] and recursive evaluation of how the summary effects change over time [53,54]. The advantage of these plots is that they are easy to standardize for all meta-analyses regardless of topic. However, inferences should not be made based on plain visualization alone. Funnel plots in particular are mostly misleading and subject to so much variability and subjectivity of interpretation [14,15,55,56] that their isolated use without formal testing may even have to be abandoned entirely.

2 Evaluation of statistical heterogeneity should continue to be performed and both measures of the statistical significance and amount of heterogeneity are useful to consider [19]. However, the uncertainty of these metrics is essential to report and acknowledge in making inferences [21]. The Q statistic should be interpreted cautiously and with consideration of the power it has in the given setting (number of studies, amount of data). The I^2 statistic should also be provided with 95% confidence intervals. In some cases, extreme homogeneity may also be of interest to evaluate.

3 With limited evidence (as in most meta-analyses), it should be acknowledged that inferences about statistical heterogeneity may often be uncertain and strong statements should be avoided or tempered appropriately, regardless of the results.

4 Statistical heterogeneity inferences cannot be directly translated to clinical/pragmatic heterogeneity inferences. The process of determining clinical/pragmatic heterogeneity should be thoroughly and rationally described in a meta-analysis. One should be able to see what potential reasons of clinical/pragmatic heterogeneity are considered, whether any of them has any additional external support, and, if so, what that support is (other clinical data, biological considerations, speculations, other) and how strong it is considered to be. The limitations of the process, including the typically post hoc nature, should be fully acknowledged.

5 Pinpointing to a very specific reason(s) of clinical/pragmatic heterogeneity in a typical retrospective meta-analysis is a brave leap of faith, and it can also be a grave mistake. Explanations of heterogeneity are often seemingly the most exciting part in a meta-analysis and the best opportunity for new knowledge to be derived from the meta-analysis, but the exploratory nature of such statements should be fully acknowledged.

6 There are no single statistical tests that can document or exclude bias in meta-analysis with certainty. In most meta-analyses in current practice, the applied statistical tests are either inappropriate or meaningless or both and they should either not be used at all or applied with full appreciation and acknowledgement of their limitations.

7 One should give a lot of thought to the prior odds of bias being present in a body of evidence before applying any fancy statistical tests to detect bias. For example, a prospective meta-analysis with standardized definition, collection of data, analysis and reporting among the participating teams is likely to have little or no reporting bias. Trials from a prospective registry should not have publication bias, no matter what the 'statistical tests of publication bias' show; differences between small and larger studies in these cases would have to be due to other reasons or chance. On the other hand, research in a field with small studies, strong conflicts of interest, intense competition for generating 'positive' results and prior documentation of publication bias should have high prior odds of bias before doing the meta-analysis [25]. Even if no signal is shown in statistical tests for bias, the odds of bias remain high.

8 When any statistical tests are applied, they should be applied using models that have, at a minimum, sound statistical properties (e.g. proper type I error) and they should be interpreted strictly for what they stand. For example, if ever used, asymmetry regression tests should be stated to evaluate small-study effects (whether small studies differ from larger ones in their results), not all types of bias or publication bias in particular.

9 No retrospective meta-analysis without full prospective registration of the relevant research can be stated to be protected from publication bias. Small summary effects in retrospective meta-analyses may be easily the result of publication and reporting biases. This does not mean that one should disregard these effects. Often this will be the best evidence available, and decisions may be made to try to reap the benefits suggested by these effects, even if their credibility is low [57]. However, extra caution is due. Similarly, publication bias cannot be proven until the unpublished 'negative' studies have been found – typically this is impossible.

Journal of Evaluation in Clinical Practice ISSN 1356-1294

Interpretation of tests of heterogeneity and bias in meta-analysis

John P. A. Ioannidis MD

Kingston University London

Reporting a Meta-analysis

thebmj

BMJ 2009;339:b2535 doi: 10.1136/bmj.b2535 (Published 21 July 2009)

RESEARCH METHODS & REPORTING

Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement

OPEN ACCESS

David Moher and colleagues introduce PRISMA, an update of the QUOROM guidelines for reporting systematic reviews and meta-analyses

David Moher[1 2], Alessandro Liberati[3 4], Jennifer Tetzlaff[1], Douglas G Altman[5], for the PRISMA Group

Reporting a Meta-analysis

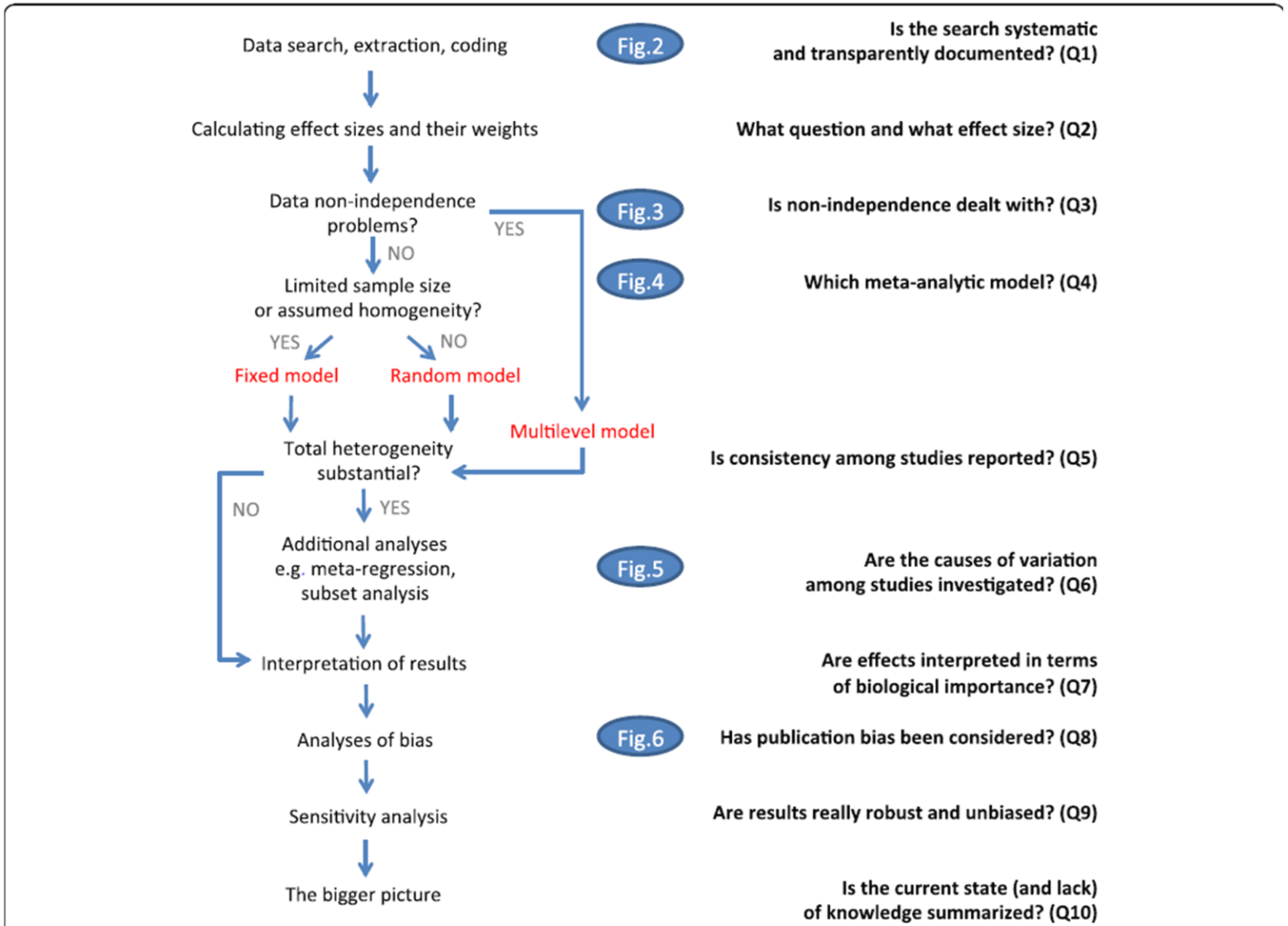


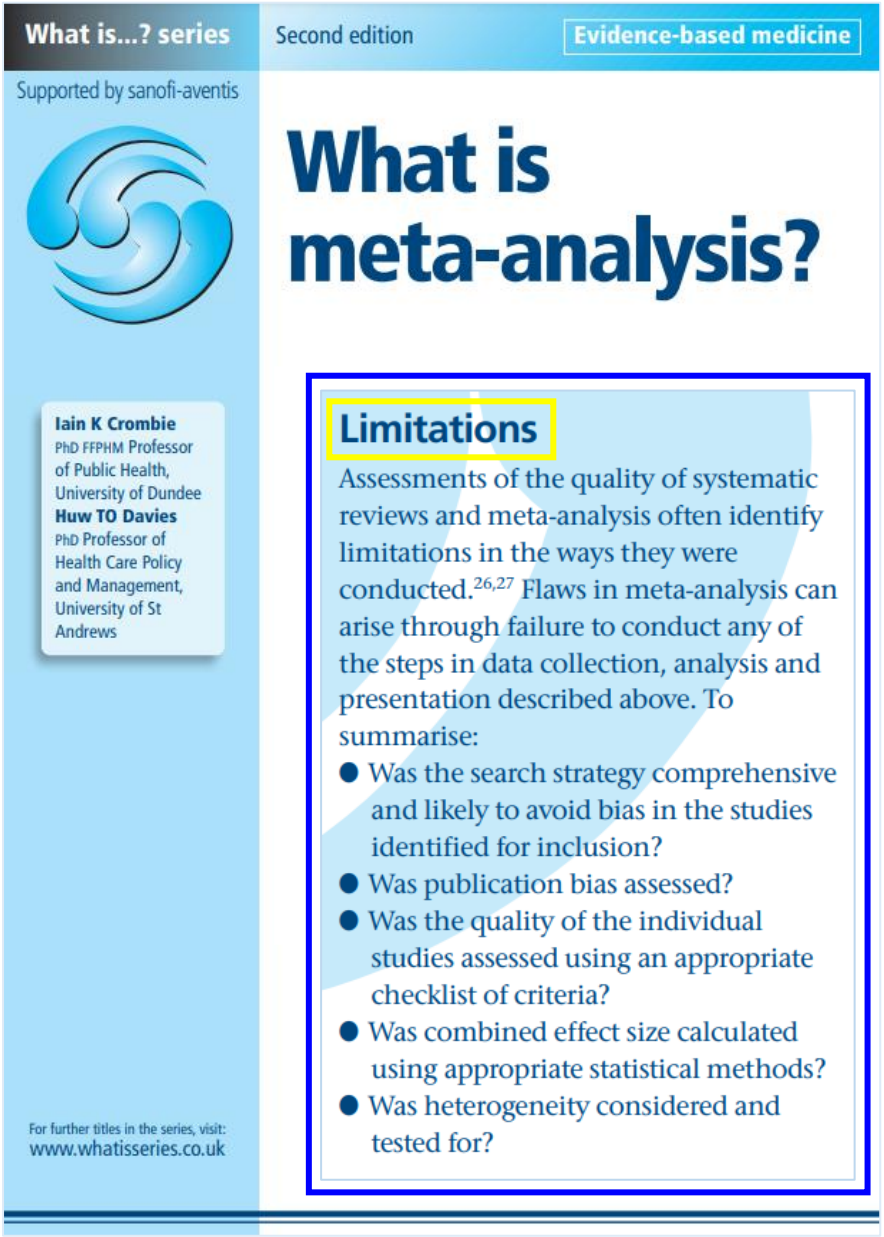
Fig. 1. Mapping the process (on the *left*) and main evaluation questions (on the *right*) for meta-analysis. References to the relevant figures (Figs. 2, 3, 4, 5 and 6) are included in the *blue ovals*

BMC Biology
Open Access
REVIEW
Nakagawa *et al. BMC Biology* (2017) 15:18
DOI 10.1186/s12915-017-0357-7

Meta-evaluation of meta-analysis: ten appraisal questions for biologists

Shinichi Nakagawa[1,2*], Daniel W. A. Noble[1], Alistair M. Senior[3,4] and Malgorzata Lagisz[1]

Limitations of Meta-analysis



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What is meta-analysis?

Iain K Crombie
PhD FFPHM Professor of Public Health, University of Dundee
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PhD Professor of Health Care Policy and Management, University of St Andrews

Limitations

Assessments of the quality of systematic reviews and meta-analysis often identify limitations in the ways they were conducted.[26,27] Flaws in meta-analysis can arise through failure to conduct any of the steps in data collection, analysis and presentation described above. To summarise:

- Was the search strategy comprehensive and likely to avoid bias in the studies identified for inclusion?
- Was publication bias assessed?
- Was the quality of the individual studies assessed using an appropriate checklist of criteria?
- Was combined effect size calculated using appropriate statistical methods?
- Was heterogeneity considered and tested for?

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And, Finally

What the Reviewers Will Be Checking

How to Review a Meta-analysis

Mark W. Russo, MD, MPH

Table 1. Checklist for Meta-analysis

Study question	• Objectives clearly stated • Clinically relevant and focused study question included • Effectiveness of intervention not convincingly demonstrated in clinical trials
Literature search	• Comprehensive literature search conducted • Searched information sources listed (ie, PubMed, Cochrane database) • Terms used for electronic literature search provided • Reasonable limitations placed on search (ie, English language) • Manual search conducted through references of articles, abstracts • Attempts made at collecting unpublished data
Data abstraction	• Structured data abstraction form used • Number of authors (>2) who abstracted data given • Disagreements listed between authors and how they were resolved • Characteristics of studies listed (ie, sample size, patient demographics) • Inclusion and exclusion criteria provided for studies • Number of excluded studies and reasons for exclusion included
Evaluation of results	• Studies were combinable • Appropriate statistical methods used to combine results • Results displayed • Sensitivity analysis conducted
Evaluation for publication bias	• Publication bias addressed through evaluation methods such as funnel plot or sensitivity analysis
Applicability of results	• Results were generalizable
Funding source	• Funding source(s) stated • No conflict of interest seen

And, Finally

What the Reviewers Will Be Checking

Short List of Questions to Guide the Reviewer

When reviewing a meta-analysis, consider commenting on the following:

1. **Clinical variables and outcomes.** Were the clinical variables and outcomes well described and appropriate for the research question? Was the potential for heterogeneity in the definitions and measurements of the clinical variables and outcomes assessed?
2. **The selection of studies included in the analysis.** Was a comprehensive search strategy clearly outlined? Were multiple specific search engines used? Were appropriate inclusion and exclusion criteria applied? Was a flowchart of study selection presented? Was the risk of publication bias assessed?
3. **The analysis and interpretation of the findings.** Was heterogeneity of the included studies evaluated and reported? Was the quality of the evidence assessed and reported (eg, with GRADE methodology)? Was a sensitivity analysis performed? Were forest plots provided? Were limitations described? Was the interpretation of the findings reasonable?

[**Supplement** An Overview of Study Design and Statistical Considerations]

CHEST

Meta-Analysis

Check for updates

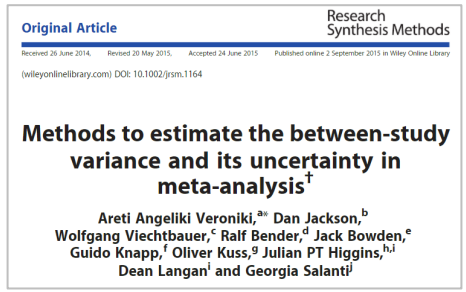
Adrian V. Hernandez, MD, PhD; Katherine M. Marti, PharmD; and Yuani M. Roman, MD, MPH

Kingston University London

Meta-analysis: Software

Table 1. Software option (with packages or macros) for each τ^2 estimation method. To our knowledge, routines for Hartung and Makambi, two-step DerSimonian and Laird, positive DerSimonian and Laird, two-step Hedges and Olkin, Rukhin Bayes, positive Rukhin Bayes, and non-parametric bootstrap methods are not available in any of the software options listed below. The relevant references for the underlying packages and macros are presented at the end of the table.

		Estimation methods (packages/macros)									
Software	License type	DerSimonian and Laird (DL)	Paule and Mandel (PM)	Hedges and Olkin (HO)	Hunter and Schmidt (HS)	Maximum likelihood (ML)	Restricted maximum likelihood (REML)	Approximate restricted maximum likelihood (AREML)	Sidik and Jonkman (SJ)	Full Bayes (FB)	Bayes modal (BM)
Comprehensive Meta-Analysis (Borenstein *et al.*, 2005) www.meta-analysis.com/	Commercial	Yes	—	—	—	Yes	—	—	—	—	—
Excel using the MetaEasy AddIn (Kontopantelis and Reeves, 2009) http://www.jstatsoft.org/v30/i07	Freeware	Yes	—	—	—	Yes	—	—	—	—	—
HLM (Raudenbush *et al.*, 2004) http://www.ssicentral.com/hlm/	Commercial	—	—	—	—	Yes	Yes	—	—	—	—
Meta-DiSc (Zamora *et al.*, 2006) ftp://ftp.hrc.es/pub/programas/metadisc/	Freeware	Yes	—	—	—	Yes	Yes	—	—	—	—
Metawin (Rosenberg *et al.*, 2000) http://www.metawinsoft.com/	Commercial	Yes	—	—	—	Yes	—	—	—	—	—
MIX (Bax, 2011) www.mix-for-meta-analysis.info/	Commercial	Yes	—	—	—	—	—	—	—	—	—
MLwin (Rasbash *et al.*, 2014) http://www.bristol.ac.uk/cmm/software/mlwin/	Freeware	—	—	—	—	Yes	Yes	—	—	Yes	—
Open Meta Analyst (Wallace *et al.*, 2012) http://www.cebm.brown.edu/open_meta	Freeware	Yes	Yes	Yes	—	Yes	Yes	—	Yes	—	—
RevMan (The Nordic Cochrane Centre, 2014) www.cochrane.org/	Freeware	Yes	—	—	—	—	—	—	—	—	—
R (R Development Core Team, 2008) http://www.r-project.org/	Freeware	Yes (meta, metafor, netmeta, mvmeta)	Yes (meta, metafor)	Yes (meta, metafor, mvmeta)	Yes (meta, metafor)	Yes (meta, metaSEM, metafor, mvmeta)	Yes (meta, metaSEM, metafor, mvmeta)	—	Yes (meta, metafor)	Yes (R2WinBUGS, BRugs, rjugs)	Yes (blme)



Original Article — Research Synthesis Methods

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Methods to estimate the between-study variance and its uncertainty in meta-analysis†

Areti Angeliki Veroniki,[a*] Dan Jackson,[b] Wolfgang Viechtbauer,[c] Ralf Bender,[d] Jack Bowden,[e] Guido Knapp,[f] Oliver Kuss,[g] Julian PT Higgins,[h,i] Dean Langan[i] and Georgia Salanti[j]

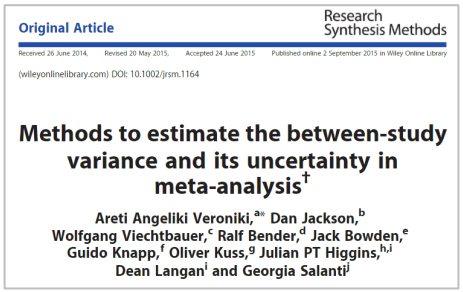
Kingston University London

Meta-analysis: Software

Table 1. (Continued)

Software	License type	Estimation methods (packages/macros): DerSimonian and Laird (DL)	Paule and Mandel (PM)	Hedges and Olkin (HO)	Hunter and Schmidt (HS)	Maximum likelihood (ML)	Restricted maximum likelihood (REML)	Approximate restricted maximum likelihood (AREML)	Sidik and Jonkman (SJ)	Full Bayes (FB)	Bayes modal (BM)
SAS (SAS Institute Inc., 2003) http://www.sas.com/technologies/analytics/statistics/stat/	Commercial	Yes (marandom.sas)	—	—	—	Yes (marandom.sas, PROC IML, PROC MIXED, PROC GLIMMIX)	Yes (PROC IML, PROC MIXED, PROC GLIMMIX)	—	—	Yes (SASBUGS, RASmacro, PROC MCMC)	—
Stata (StataCorp, 2013) www.stata.com/	Commercial	Yes (metareg, metan, metaan, mvmeta)	Yes (metareg)	—	—	Yes (metareg, metaan, mvmeta)	Yes (metareg, metaan, mvmeta)	—	—	—	Yes (gllamm)
SPSS (IBM Corp., 2013) http://www.spss.co.in/	Commercial	Yes (meanes.sps, metaf.sps, metareg.sps)	—	—	—	Yes (metaf.sps, metareg.sps)	—	Yes (metaf.sps, metareg.sps)	—	—	—
BUGS (Thomas, 1994), OpenBUGS (Thomas, 2010), or WinBUGS (Lunn *et al.*, 2000) www.mrc-bsu.cam.ac.uk/bugs/	Freeware	—	—	—	—	—	—	—	—	Yes	—

R: meta (http://cran.r-project.org/web/packages/meta/meta.pdf), metafor (Viechtbauer, 2013) (http://www.metafor-project.org/doku.php), netmeta (http://cran.r-project.org/web/packages/netmeta/netmeta.pdf), mvmeta (http://cran.r-project.org/web/packages/mvmeta/mvmeta.pdf), metaSEM (http://courses.nus.edu.sg/course/psycwlm/Internet/metaSEM/), R2WinBUGS (http://cran.r-project.org/web/packages/R2WinBUGS/R2WinBUGS.pdf), BRugs (http://cran.r-project.org/web/packages/BRugs/BRugs.pdf), rjugs (http://cran.r-project.org/web/packages/rjags/rjags.pdf), blme (http://cran.r-project.org/web/packages/blme/blme.pdf)
SAS: marandom.sas (http://www.senns.demon.co.uk/SAS%20Macros/SASMacros.html), PROC IML (http://support.sas.com/documentation/cdl/en/imlug/63541/PDF/default/imlug.pdf), PROC MIXED (https://support.sas.com/documentation/cdl/en/statugmixed/61807/PDF/default/statugmixed.pdf), PROC GLIMMIX (https://support.sas.com/documentation/cdl/en/statugglmmix/61788/PDF/default/statugglmmix.pdf), SASBUGS (Zhang *et al.*, 2008), RASmacro (https://github.com/rsparapa/rasmacro), PROC MCMC (http://support.sas.com/documentation/cdl/en/statugmcmc/63125/PDF/default/statugmcmc.pdf)
Stata: metareg (Harbord and Higgins, 2008), metan (Harris *et al.*, 2008), metaan (Kontopantelis and Reeves, 2010), mvmeta (White, 2009), gllamm (Rabe-Hesketh *et al.*, 2003) (http://www.gllamm.org/programs.html)
SPSS: meanes.sps (http://mason.gmu.edu/~dwilsonb/ma.html), metaf.sps (http://mason.gmu.edu/~dwilsonb/ma.html), metareg.sps (http://mason.gmu.edu/~dwilsonb/ma.html)



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Meta-analysis: Software

Rule 7: Use available software to carry metastatistics

There are several very user-friendly and freely available programs for carrying out meta-analyses [43,44], either within the framework of a statistical package such as Stata or R or as stand-alone applications. Stata and R [50–52] have dozens of routines, mostly user written, that can handle most meta-analysis tasks, even complex analyses such as network meta-analysis and meta-analyses of GWASs and gene expression studies (https://cran.r-project.org/web/views/MetaAnalysis.html; https://www.stata.com/support/faqs/statistics/meta-analysis). There are also stand-alone packages that can be useful for general applications or for specific areas, such as OpenMetaAnalyst [53], NetworkAnalyst [54], JASP [55], MetaGenyo [56], Cochrane RevMan (https://community.cochrane.org/help/tools-and-software/revman-5), EpiSheet (krothman.org/episheet.xls), GWAR [57], GWAMA [58], and METAL [59]. Some of these programs are web services or stand-alone software. In some cases, certain programs can present issues when they are run because of their dependency on other packages.


PLOS COMPUTATIONAL BIOLOGY

EDITORIAL

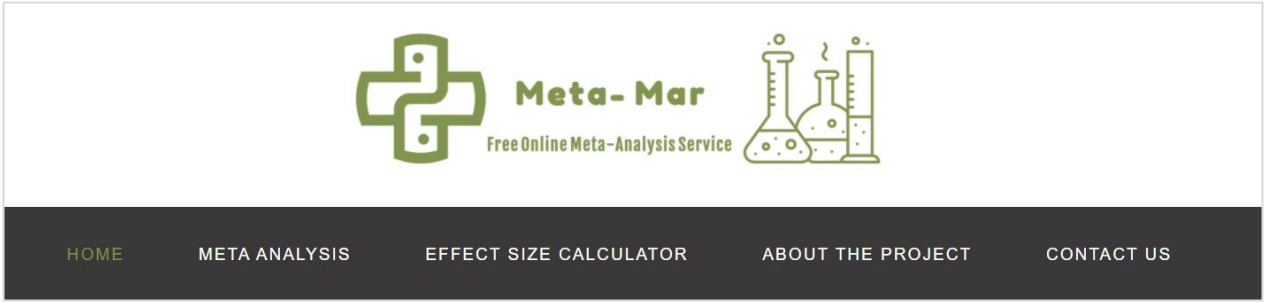
Ten simple rules for carrying out and writing meta-analyses

Diego A. Forero[1,2]*, Sandra Lopez-Leon[3], Yeimy González-Giraldo[4], Pantelis G. Bagos[5]

13 Best Free Meta-Analysis Software To Use

Kingston University London

Meta-analysis with Meta-Mar (online)



http://www.meta-mar.com

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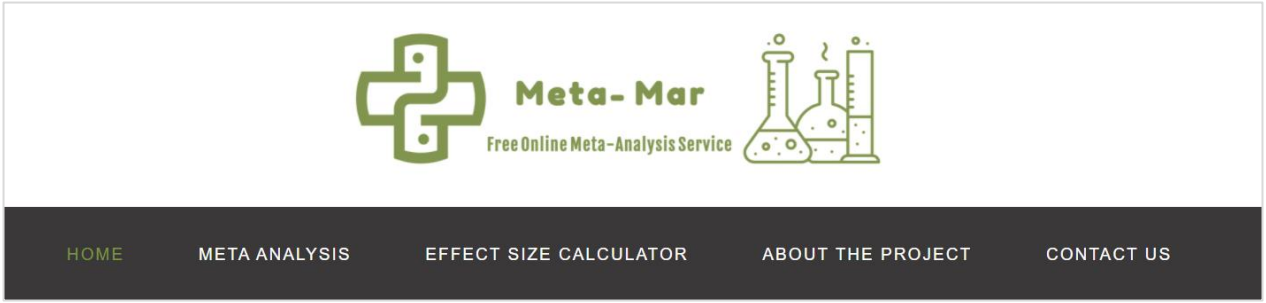
Meta-analysis with Meta-Mar (online)



Why Meta-Mar?

Meta-Mar is a free online meta-analysis service developed as an adjunctive tool for running a full meta-analysis (including meta-regression and subgroup analysis) or can be used as a calculator/convertor of effect sizes!

- Possibility of choosing the Data entry methods between **manual Data entry** or **.xlsx upload**.
- Calculation of effect sizes based on **SMD** , **Correlation** and **Ratios** models for every single study.
- Calculation of the overall effect size of the analysis based on fixed and random effect models.
- Calculation of **Fail-N Safe** based on fixed and random effect models.
- Calculation of **heterogeneity** of the analysis (**Q Cochrane**, I^2 and **Tau**^{2}).
- Possibility of **meta regression** and **subgroup analysis**.
- Visualization of **Forest Plot** and **Funnel Plot**.
- Possibility of exporting the results of the analysis via a .xlsx file.
- Finally and regardless of your analysis, you may just want to use an **Effect Size Calculator**

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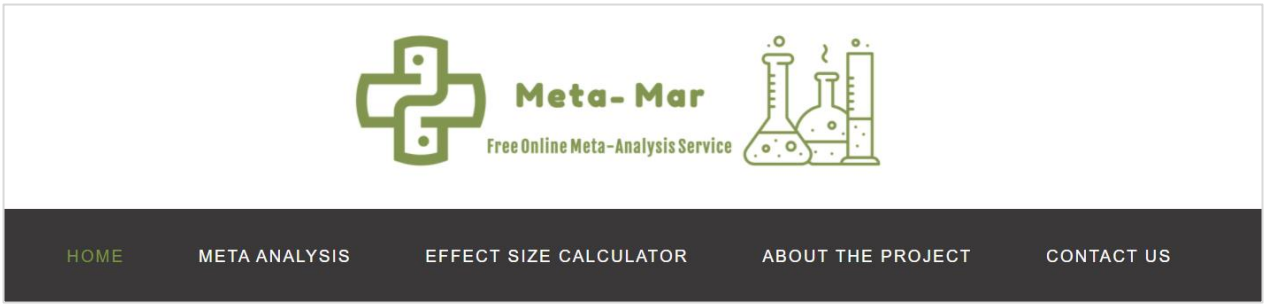
Meta-analysis with Meta-Mar (online)



Excel Spreadsheet Upload

Study name	Group 1			Group 2			Moderator *(optional)*
	Sample size	Mean	Standard Deviation	Sample size	Mean	Standard Deviation	

Study name	Correlation Coefficient	sample size	Moderator *(optional)*

Study name	Group 1		Group 2		Moderator *(optional)*
	Events	Non-Events	Events	Non-Events	

Add a Study

Calculate

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Meta-analysis with Meta-Mar (online)

Meta- Mar
Free Online Meta-Analysis Service

HOME | META ANALYSIS | EFFECT SIZE CALCULATOR | ABOUT THE PROJECT | CONTACT US

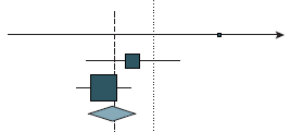
Study name	Group 1		Group 2		Moderator (optional)	
	Events	Non-Events	Events	Non-Events		
DEXA COVID-19	2	7	2	12		Remove
CoDEX	69	128	76	128		Remove
RECOVERY	95	324	283	683		Remove

Results based on Odds Ratio

	Ln(Odds Ratio average)	Odds Ratio average	SE	95%CI	z score	p value	Heterogeneity
Fixed Effect Model	-0.26	0.77	0.113	[0.616,0.961]	2.312	0.02077	I^2=0.0%, Chi^2=1.533, df=2
Random Effect Model	-0.26	0.77	0.113	[0.616,0.961]	2.312	0.02077	0.0%, Tau^2=0.0

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60



Original Investigation | Caring for the Critically Ill Patient

September 2, 2020

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Article Information

JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

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Meta-analysis: Software

ERIM Home Research Support Meta-Essentials

Meta-Essentials: workbooks for meta-analysis

Meta-Essentials is a free tool for meta-analysis. It facilitates the integration and synthesis of effect sizes from different studies. The tool consists of a set of workbooks designed for Microsoft Excel that, based on your input, automatically produces all the required statistics, tables, figures, and more. The workbooks can be downloaded from here. We also provide a user manual to guide you in using the tool (PDF / online) and a text on how to interpret the results of meta-analyses (PDF / online).

Meta-Essentials has evolved into a tool that can be used for both research and teaching purposes. Especially for relatively straightforward meta-analyses (excluding for instance meta-regressions and meta-sem), *Meta-Essentials* is a very easy and intuitive tool to use.

Please also see our Frequently Asked Questions. If you have any other questions, please do not hesitate to contact us.

We designed *Meta-Essentials* for Microsoft Excel. However, *Meta-Essentials* also works with the freely available WPS Office 2016 Free and Microsoft Excel Online (free registration required).

Introduction, comparison and validation of Meta-Essentials: A free and simple tool for meta-analysis

Received: 25 August 2016 | Revised: 14 July 2017 | Accepted: 24 July 2017

DOI: 10.1002/jrsm.1260

SOFTWARE REVIEW

WILEY Research Synthesis Methods

Introduction, comparison, and validation of *Meta-Essentials*: A free and simple tool for meta-analysis

Robert Suurmond | Henk van Rhee | Tony Hak

Kingston University London

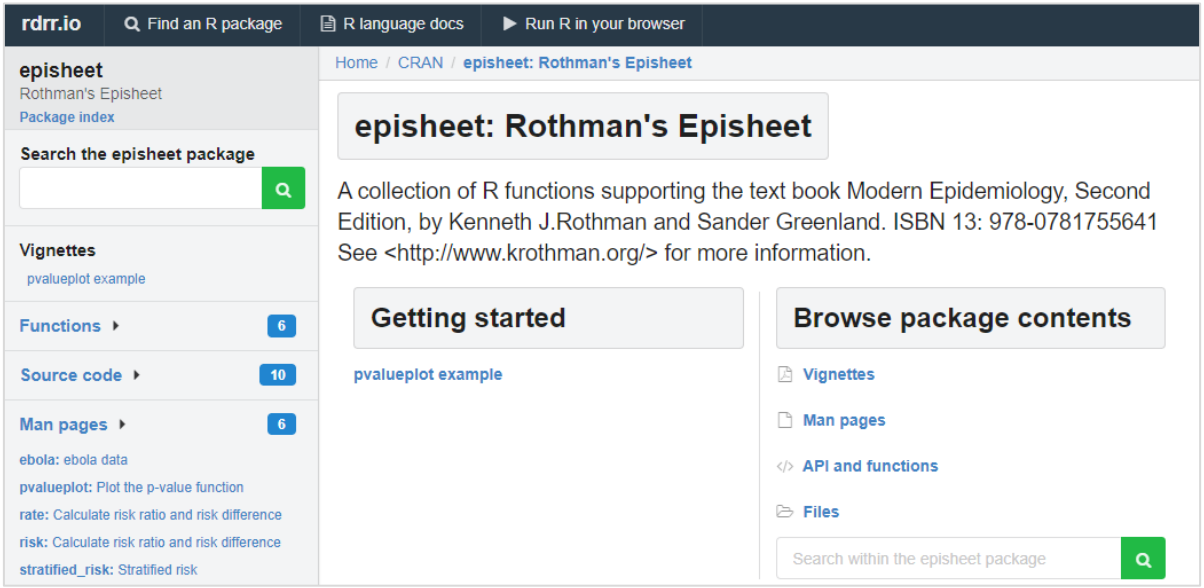
Meta-analysis with Excel

Episheet

Purpose

Episheet is a downloadable Excel spreadsheet used for analyzing epidemiologic data.

R Package: episheet



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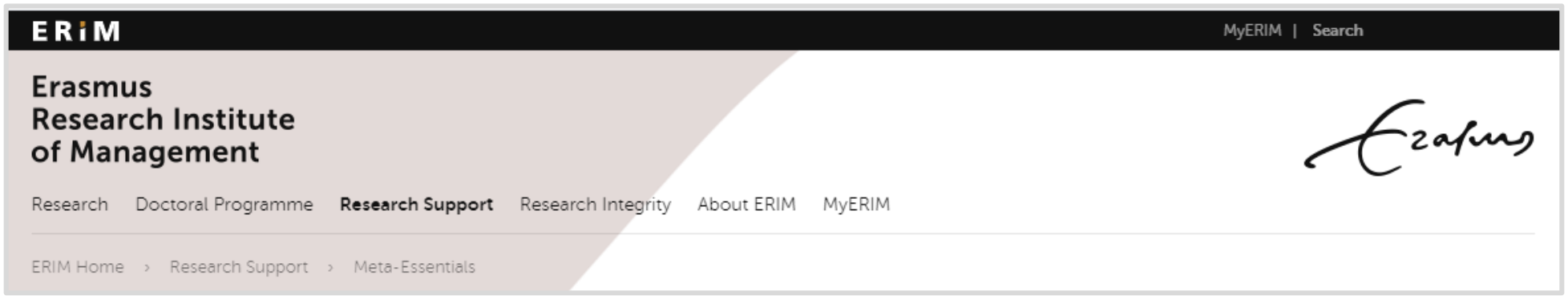
Meta-analysis with Excel



Meta-Essentials: workbooks for meta-analysis

Meta-Essentials is a free tool for meta-analysis. It facilitates the integration and synthesis of effect sizes from different studies. The tool consists of a set of workbooks designed for Microsoft Excel that, based on your input, automatically produces all the required statistics, tables, figures, and more. The workbooks can be downloaded from here. We also provide a user manual to guide you in using the tool (PDF / online) and a text on how to interpret the results of meta-analyses (PDF / online).

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Please also see our Frequently Asked Questions. If you have any other questions, please do not hesitate to contact us.

We designed *Meta-Essentials* for Microsoft Excel. However, *Meta-Essentials* also works with the freely available WPS Office 2016 Free and Microsoft Excel Online (free registration required).

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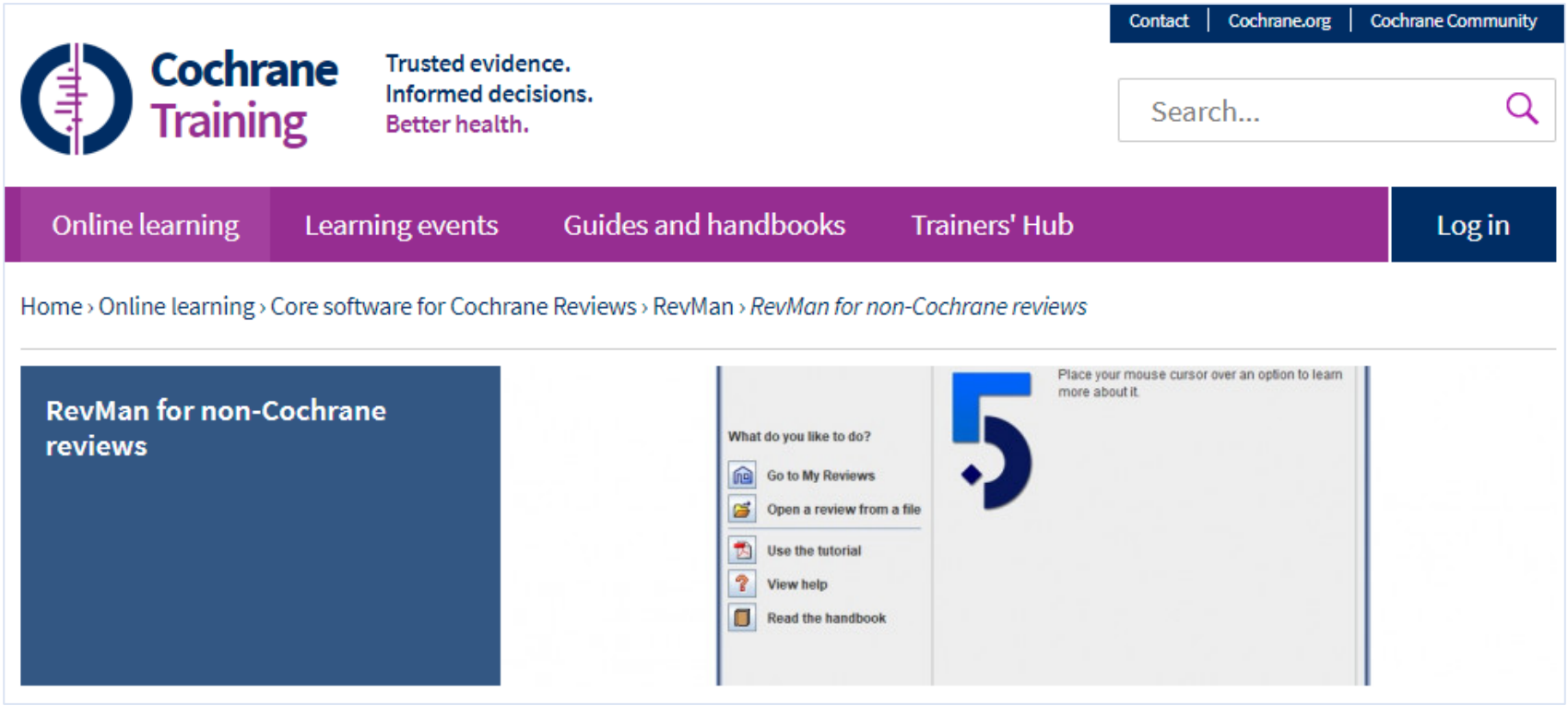
Meta-Essentials_1.5_01.zip

Meta-analysis with RevMan



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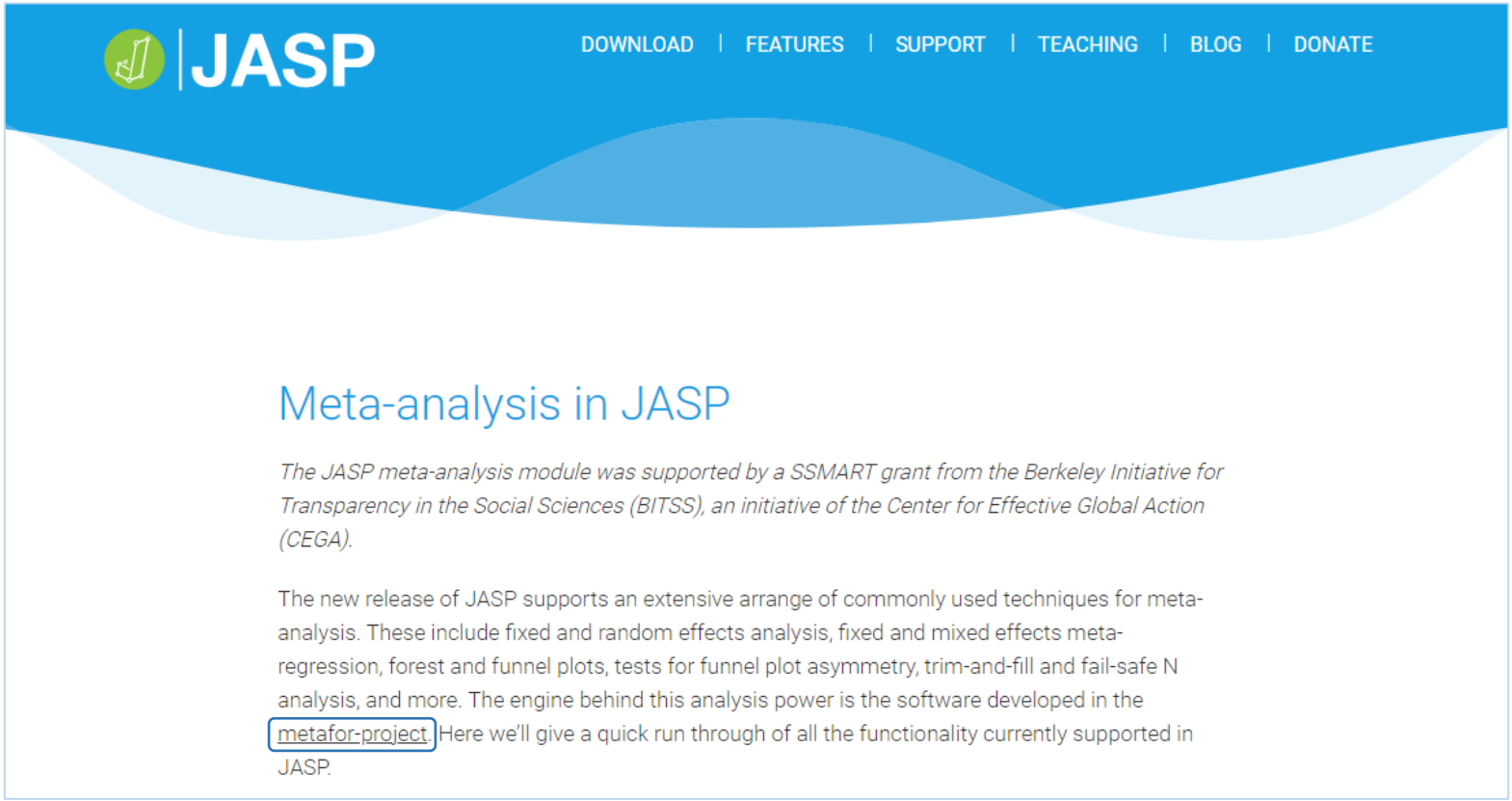
Meta-analysis with JASP



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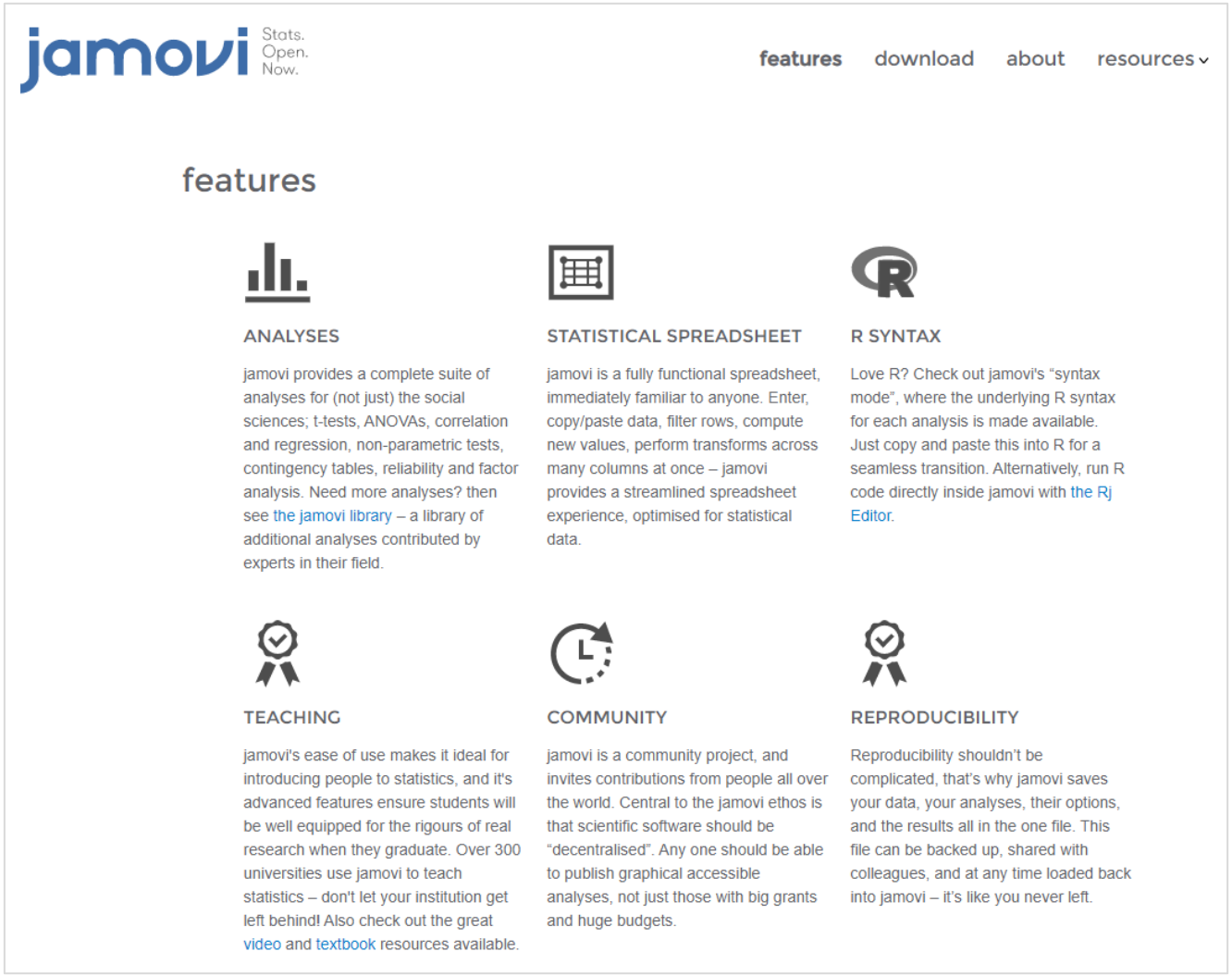
Meta-analysis with *jamovi* (online)



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features download about resources

features

ANALYSES

jamovi provides a complete suite of analyses for (not just) the social sciences; t-tests, ANOVAs, correlation and regression, non-parametric tests, contingency tables, reliability and factor analysis. Need more analyses? then see the jamovi library – a library of additional analyses contributed by experts in their field.

STATISTICAL SPREADSHEET

jamovi is a fully functional spreadsheet, immediately familiar to anyone. Enter, copy/paste data, filter rows, compute new values, perform transforms across many columns at once – jamovi provides a streamlined spreadsheet experience, optimised for statistical data.

R SYNTAX

Love R? Check out jamovi's "syntax mode", where the underlying R syntax for each analysis is made available. Just copy and paste this into R for a seamless transition. Alternatively, run R code directly inside jamovi with the Rj Editor.

TEACHING

jamovi's ease of use makes it ideal for introducing people to statistics, and it's advanced features ensure students will be well equipped for the rigours of real research when they graduate. Over 300 universities use jamovi to teach statistics – don't let your institution get left behind! Also check out the great video and textbook resources available.

COMMUNITY

jamovi is a community project, and invites contributions from people all over the world. Central to the jamovi ethos is that scientific software should be "decentralised". Any one should be able to publish graphical accessible analyses, not just those with big grants and huge budgets.

REPRODUCIBILITY

Reproducibility shouldn't be complicated, that's why jamovi saves your data, your analyses, their options, and the results all in the one file. This file can be backed up, shared with colleagues, and at any time loaded back into jamovi – it's like you never left.

https://www.jamovi.org/features.html

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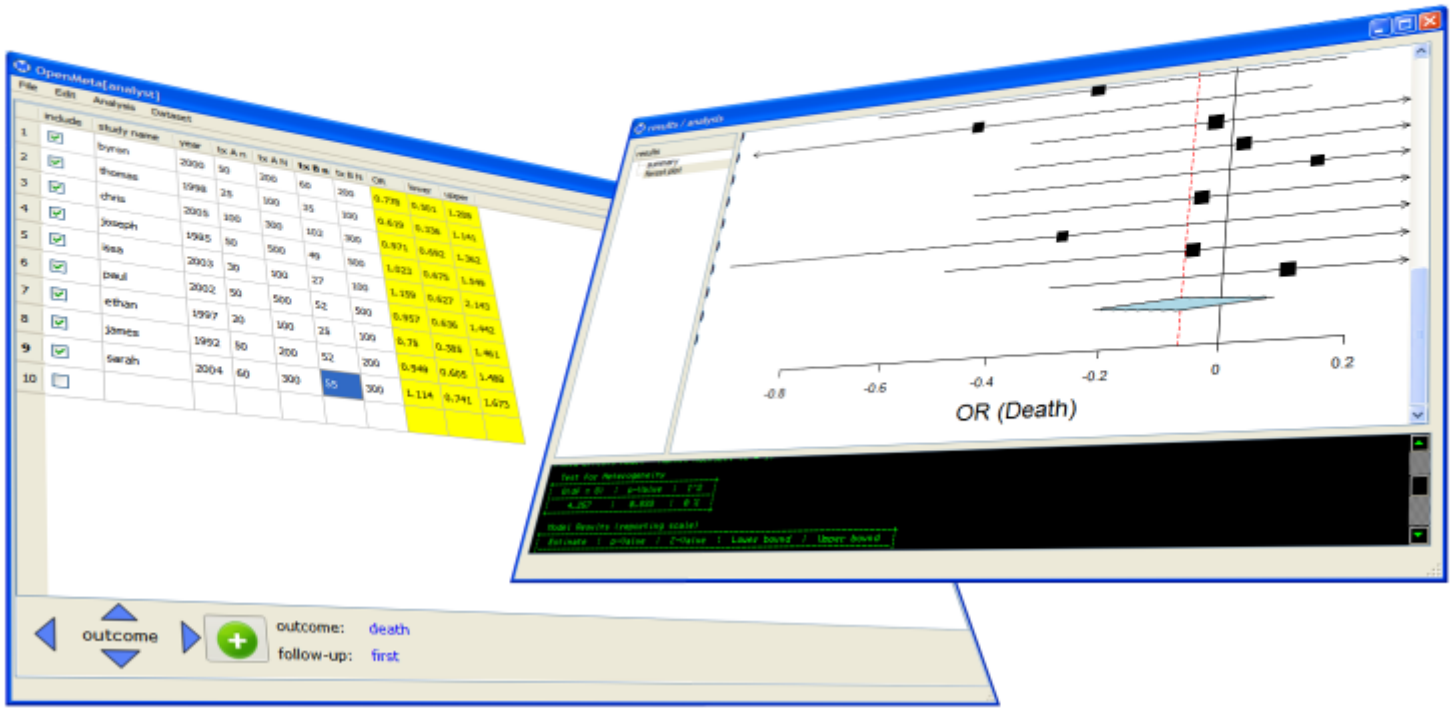
Meta-analysis with OpenMeta(Analyst)

OpenMeta[Analyst]

completely open-source, cross-platform software for advanced meta-analysis.

Home | Download | Help | Discussion Forum



Open Meta-Analyst Help

OpenMetaAnalyst for Windows 10 (64-bit) (current version)

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Meta-analysis with MEDCALC (Free Trial)

MEDCALC®
easy-to-use statistical software

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Manual » Meta-analysis

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- Window menu
- Help menu
- Spreadsheet overview
- Appendices

Meta-analysis: introduction

A meta-analysis integrates the quantitative findings from separate but similar studies and provides a numerical estimate of the overall effect of interest (Petrie et al., 2003).

Different weights are assigned to the different studies for calculating the summary or pooled effect. The weighing is related with the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in the calculation of the pooled effect size.

The effect of interest can be:

- an average of a continuous variable
- a correlation between two variables
- an odds ratio, suitable for analyzing retrospective studies
- a relative risk (risk ratio) or risk difference, suitable for analyzing prospective studies
- a proportion
- the area under the ROC curve

The agreement or disagreement between the studies is examined using different measures of heterogeneity.

Meta-analysis: generic inverse variance method

Command: Statistics
└ Meta-analysis
└ Generic inverse variance method

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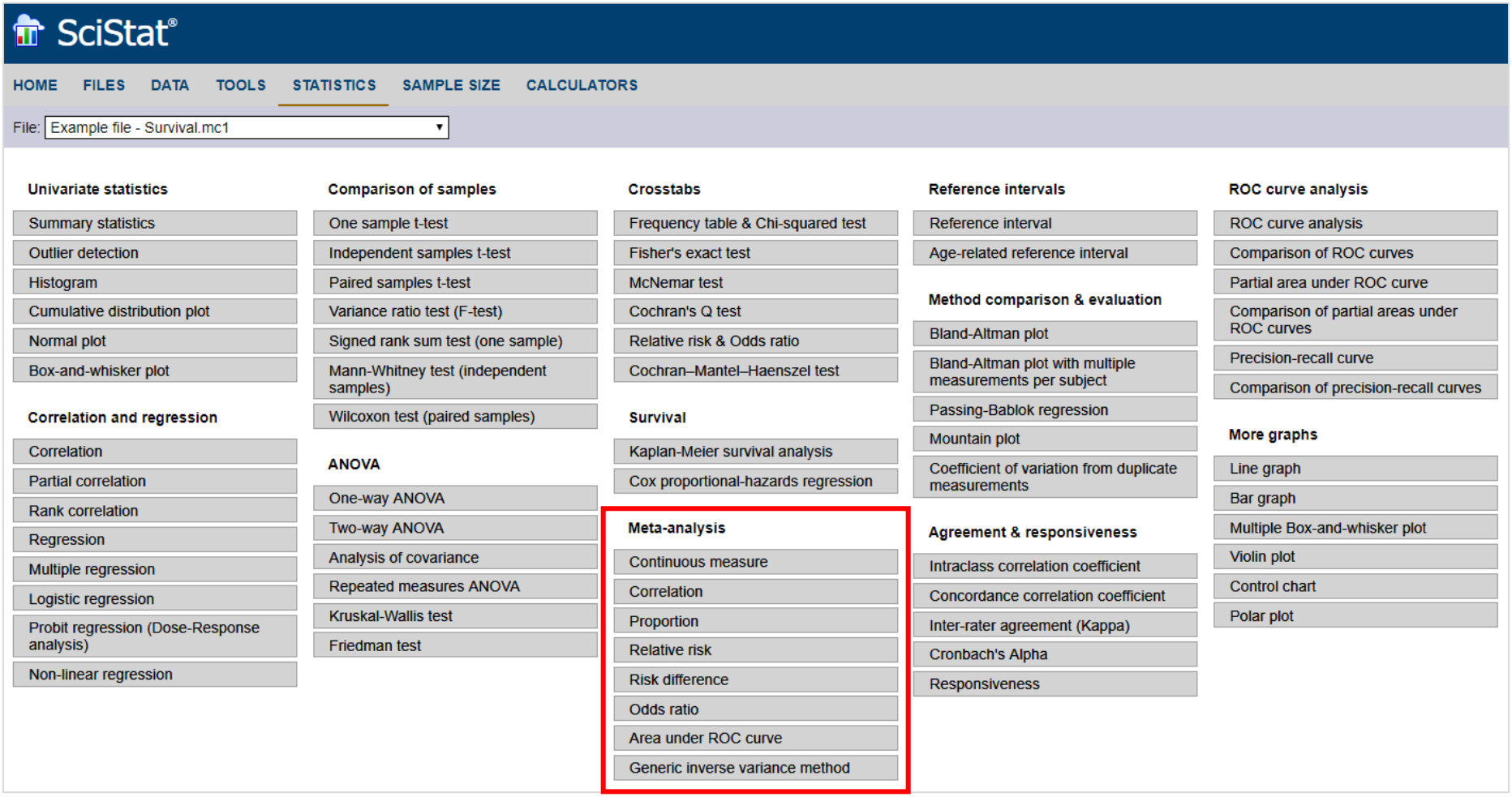
Meta-analysis with SciStat (online)



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https://www.scistat.com

Meta-analysis with MetaLab

A Matlab Toolbox for all Stages of Meta-analysis

frontiers in Physiology

METHODS
published: 27 March 2019
doi: 10.3389/fphys.2019.00203

Meta-Analytic Methodology for Basic Research: A Practical Guide

Nicholas Mikolajewicz [1,2] *and Svetlana V. Komarova* [1,2*]

[1] *Faculty of Dentistry, McGill University, Montreal, QC, Canada,* [2] *Shriners Hospital for Children-Canada, Montreal, QC, Canada*

Basic life science literature is rich with information, however methodically quantitative attempts to organize this information are rare. Unlike clinical research, where consolidation efforts are facilitated by systematic review and meta-analysis, the basic sciences seldom use such rigorous quantitative methods. The goal of this study is to present a brief theoretical foundation, computational resources and workflow outline along with a working example for performing systematic or rapid reviews of basic research followed by meta-analysis. Conventional meta-analytic techniques are extended to accommodate methods and practices found in basic research. Emphasis is placed on handling heterogeneity that is inherently prevalent in studies that use diverse experimental designs and models. We introduce *MetaLab*, a meta-analytic toolbox developed in MATLAB R2016b which implements the methods described in this methodology and is provided for researchers and statisticians at Git repository (https://github.com/NMikolajewicz/MetaLab). Through the course of the manuscript, a rapid review of intracellular ATP concentrations in osteoblasts is used as an example to demonstrate workflow, intermediate and final outcomes of basic research meta-analyses. In addition, the features pertaining to larger datasets are illustrated with a systematic review of mechanically-stimulated ATP release kinetics in mammalian cells. We discuss the criteria required to ensure outcome validity, as well as exploratory methods to identify influential experimental and biological factors. Thus, meta-analyses provide informed estimates for biological outcomes and the range of their variability, which are critical for the hypothesis generation and evidence-driven design of translational studies, as well as development of computational models.

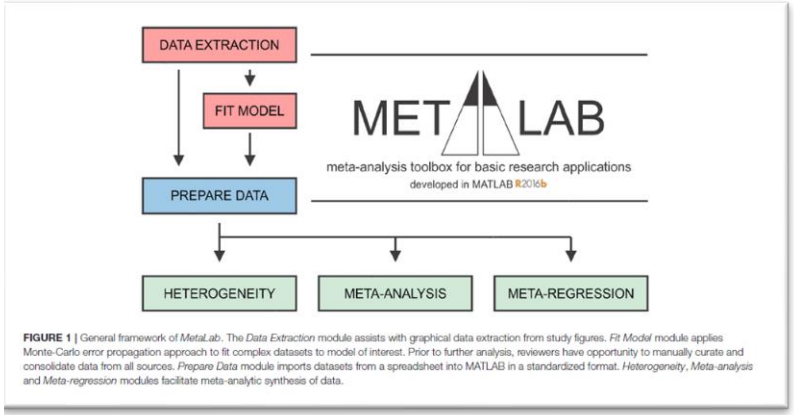
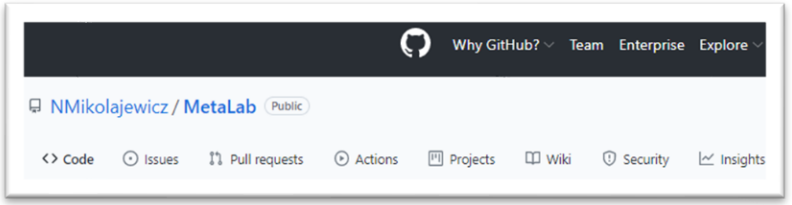


FIGURE 1 | General framework of *MetaLab*. The *Data Extraction* module assists with graphical data extraction from study figures. *Fit Model* module applies Monte-Carlo error propagation approach to fit complex datasets to model of interest. Prior to further analysis, reviewers have opportunity to manually curate and consolidate data from all sources. *Prepare Data* module imports datasets from a spreadsheet into MATLAB in a standardized format. *Heterogeneity*, *Meta-analysis* and *Meta-regression* modules facilitate meta-analytic synthesis of data.



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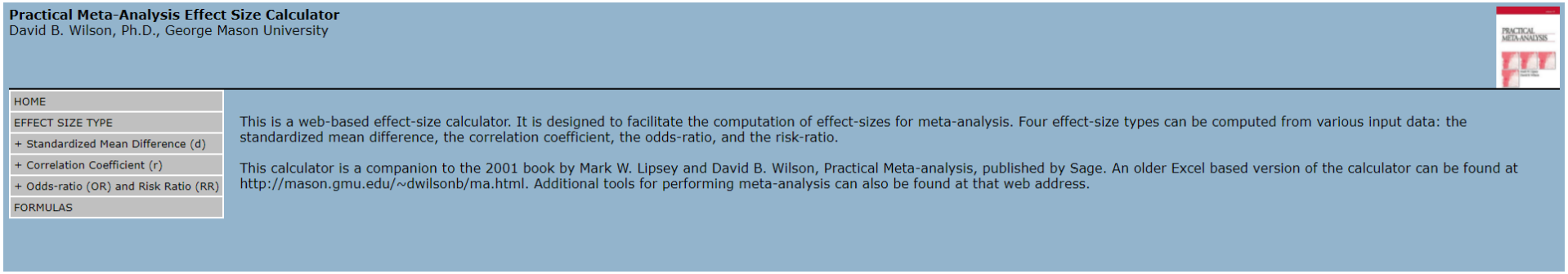
Meta-analysis: Effect Size Calculator



Alternatively:

use R package `metafor`'s effect size calculation function `escalc()`

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Further Reading

Cochrane Handbook for Systematic Reviews of Interventions

Version 6.2, 2021

Senior Editors: Julian Higgins[1], James Thomas[2]
Associate Editors: Jacqueline Chandler[3], Miranda Cumpston[4,5], Tianjing Li[6], Matthew Page[4], Vivian Welch[7]

Further Reading

BMJ 1997/98: A Set of Six Articles (Egger *et al*)

Meta-analysis
Potentials and promise
Matthias Egger, George Davey Smith

Meta-analysis
Principles and procedures
Matthias Egger, George Davey Smith, Andrew N Phillips

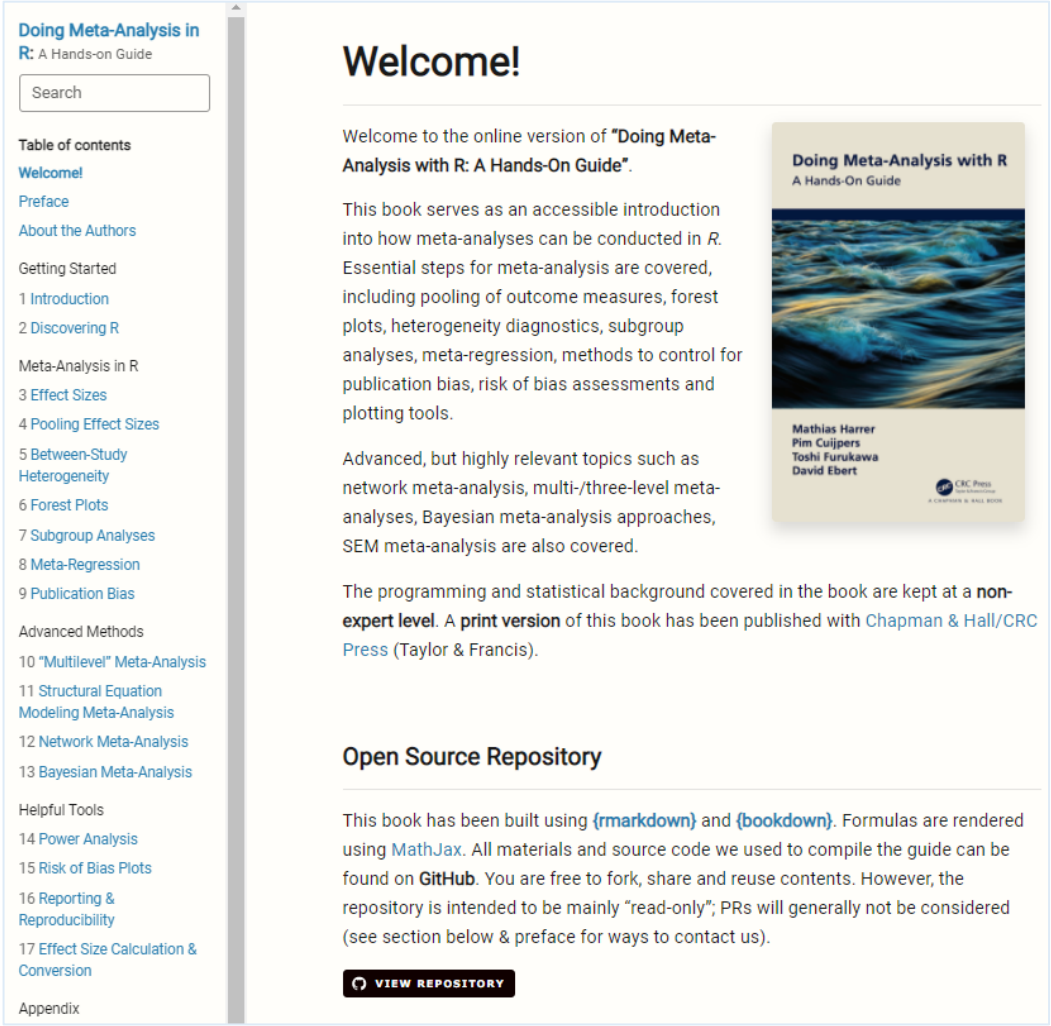
Meta-analysis
Beyond the grand mean?
George Davey Smith, Matthias Egger, Andrew N Phillips

Meta-analysis
Bias in location and selection of studies
Matthias Egger, George Davey Smith

Meta-analysis
Spurious precision? Meta-analysis of observational studies
Matthias Egger, Martin Schneider, George Davey Smith

Meta-analysis
Unresolved issues and future developments
George Davey Smith, Matthias Egger

Further Reading



Doing Meta-Analysis in R: A Hands-on Guide

Search

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11 Structural Equation Modeling Meta-Analysis
12 Network Meta-Analysis
13 Bayesian Meta-Analysis

Helpful Tools

14 Power Analysis
15 Risk of Bias Plots
16 Reporting & Reproducibility
17 Effect Size Calculation & Conversion

Appendix

Welcome!

Welcome to the online version of **"Doing Meta-Analysis with R: A Hands-On Guide"**.

This book serves as an accessible introduction into how meta-analyses can be conducted in *R*. Essential steps for meta-analysis are covered, including pooling of outcome measures, forest plots, heterogeneity diagnostics, subgroup analyses, meta-regression, methods to control for publication bias, risk of bias assessments and plotting tools.

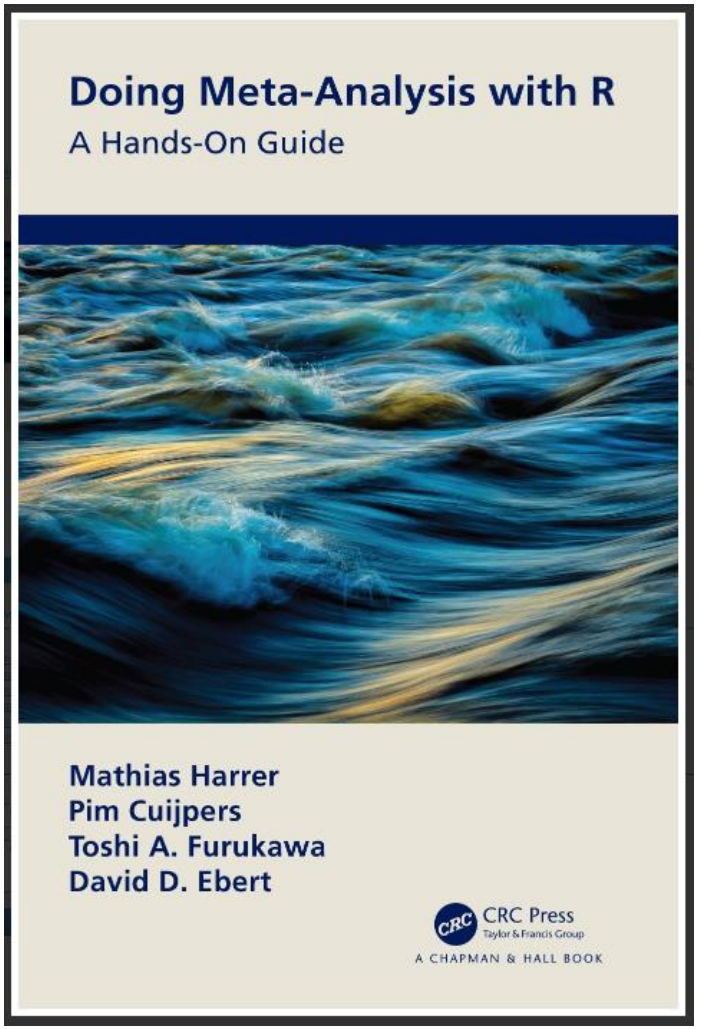
Advanced, but highly relevant topics such as network meta-analysis, multi-/three-level meta-analyses, Bayesian meta-analysis approaches, SEM meta-analysis are also covered.

The programming and statistical background covered in the book are kept at a **non-expert level**. A **print version** of this book has been published with Chapman & Hall/CRC Press (Taylor & Francis).

Open Source Repository

This book has been built using **{rmarkdown}** and **{bookdown}**. Formulas are rendered using MathJax. All materials and source code we used to compile the guide can be found on **GitHub**. You are free to fork, share and reuse contents. However, the repository is intended to be mainly "read-only"; PRs will generally not be considered (see section below & preface for ways to contact us).

VIEW REPOSITORY



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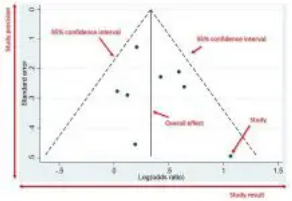
dmetar

Further Reading



What Is A Funnel Plot And How To Read Them?

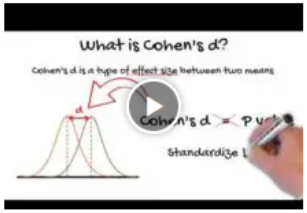
Meta-analysis

In this article, I will explain what a funnel plot is, based on their use in meta-analyses, and discuss what they show. What is a...

What Is A Forest Plot And How To Read Them?

Meta-analysis

In this article, I will explain what a forest plot is and describe the different components of a forest plot by using an example...



What Is And How To Calculate Cohen's d?

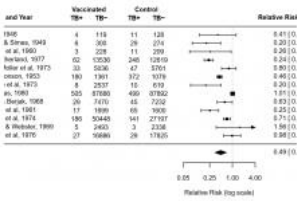
Maths

What is Cohen's d? Cohen's d is a type of effect size between two means. An effect size is a quantitative measure of the magnitude for...

Cohen's d Calculator: A Quick And Easy Method

Maths

Below is the Cohen's d calculator. Simply enter the groups mean and standard deviation values into the calculator, click the calculate button and Cohen's...



13 Best Free Meta-Analysis Software To Use

Meta-analysis

There is a range of software and programs available to use when performing meta-analyses. Frustratingly, not all of them are free to use and...

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TTB TOP TIP BIO

Further Reading

HIPPOKRATIA 2010, 14 (Suppl 1): 29-37

REVIEW ARTICLE

Meta-analysis in medical research

Haidich AB

Department of Hygiene and Epidemiology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece

[Papers by Egger M *et al* in Pubmed]

Front. Physiol., 27 March 2019 | https://doi.org/10.3389/fphys.2019.00203

Meta-Analytic Methodology for Basic Research: A Practical Guide

Nicholas Mikolajewicz[1,2] and Svetlana V. Komarova[1,2*]

NICE Guidelines Technical Support Unit

Meta-Analysis of Event Outcomes

Guideline Methodology Document 3

Version 1 (January 2021)

Caitlin Daly[1], Sumayya Anwer[2], Nicky J Welton[1], Sofia Dias[2], AE Ades[1]

Cite this article as: Buccheri S, Sodeck GH, Capodanno D. Statistical primer: methodology and reporting of meta-analyses. Eur J Cardiothorac Surg 2018;53:708–13.

Statistical primer: methodology and reporting of meta-analyses†

Sergio Buccheri[a], Gottfried H. Sodeck[b] and Davide Capodanno[a,*]

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Further Reading

Meta-analysis

ORDER STATA

Combine results of multiple studies to estimate an overall effect. Use forest plots to visualize results. Evaluate study heterogeneity with subgroup analysis or meta-regression. Use funnel plots and formal tests to explore publication bias and small-study effects. Assess the impact of publication bias on results with trim-and-fill analysis. Perform cumulative meta-analysis. Use the meta suite of commands, or let the Control Panel interface guide you through your entire meta-analysis.

Learn about **meta-analysis**.

See **what's new in meta-analysis**.

Watch **Meta-analysis in Stata**.

Data setup and effect sizes
- Effect sizes for binary data
  - Odds ratio
  - Peto's odds ratio
  - Risk ratio
  - Risk difference
- Effect sizes for continuous data
  - Hedges's g
  - Cohen's d
  - Glass's delta (two versions)
  - Unstandardized mean difference
- Generic (precomputed) effect sizes
- Transformed effect sizes such as correlations and efficacies
- Different methods for zero-cells adjustment with binary data
- Update declared meta-analysis settings at any time
- Describe declared meta-analysis settings

Meta-analysis models
- Common-effect model
  - Inverse-variance method
  - Mantel–Haenszel method
- Fixed-effects model
  - Inverse-variance method
  - Mantel–Haenszel method
- Random-effects model
  - Iterative methods: REML, MLE, and empirical Bayes
  - Noniterative methods: DerSimonian–Laird, Hedges, Sidik–Jonkman, and Hunter–Schmidt
  - Knapp–Hartung standard-error adjustment
  - Prediction intervals
  - Sensitivity analysis: User-specified values for heterogeneity parameters tau2 and I2

Meta-analysis summary
- Standard meta-analysis
- Forest plots
- Subgroup meta-analysis
  - One grouping variable
  - Multiple grouping variables
  - Subgroup forest plots
- Cumulative meta-analysis
  - Standard analysis
  - Stratified analysis
  - Cumulative forest plots
- **Leave-one-out meta-analysis** New

Watch **Leave-one-out meta-analysis**.

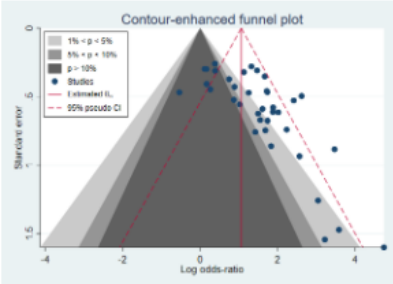
Forest plots
- Standard forest plot

Small-study effects
- Funnel plots
- Tests for small-study effects

Funnel plots
- Standard funnel plots
- Contour-enhanced funnel plots
- Two-sided or one-sided significance contours
- Multiple precision metrics for the y-axis
- Stratified funnel plots
- Fully customizable

Tests for funnel-plot asymmetry or small-study effects
- Egger regression-based test
- Harbord regression-based test
- Peters regression-based test
- Begg rank correlation test
- Adjust for moderators to account for heterogeneity
- Traditional and random-effects versions

Publication bias
- Funnel plots
- Tests for funnel-plot assymetry
- Nonparametric trim-and-fill method
  - Three estimators for number of missing studies
  - Impute studies on the left or right side of the funnel plot
  - Nine estimation methods for the iteration stage
  - Nine estimation methods for the pooling stage
  - Choose the side of the funnel plot with missing studies
  - Standard and contour-enhanced funnel plot for the observed and imputed studies



Multivariate meta-regression New
- Multivariate meta-analysis
- Fixed-effects and random-effects multivariate meta-regression
- Estimation methods: REML, MLE, Jackson–White–Riley
- Multivariate heterogeneity statistics

stata
» Home » Products » Features » Meta-analysis

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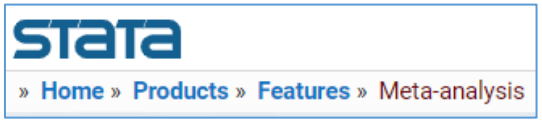
Further Reading

Let's see it work

- Example dataset: Effects of teacher expectancy on pupil IQ
- Prepare your data for meta-analysis
- Meta-analysis summary
- Forest plot
- Heterogeneity
  - Summary measures and homogeneity test
  - Subgroup analysis
  - Meta-regression
  - Postestimation: bubble plots
- Small-study effects and publication bias
  - Standard and contour-enhanced funnel plots
  - Tests for funnel-plot asymmetry
  - Trim-and-fill analysis
- Cumulative meta-analysis



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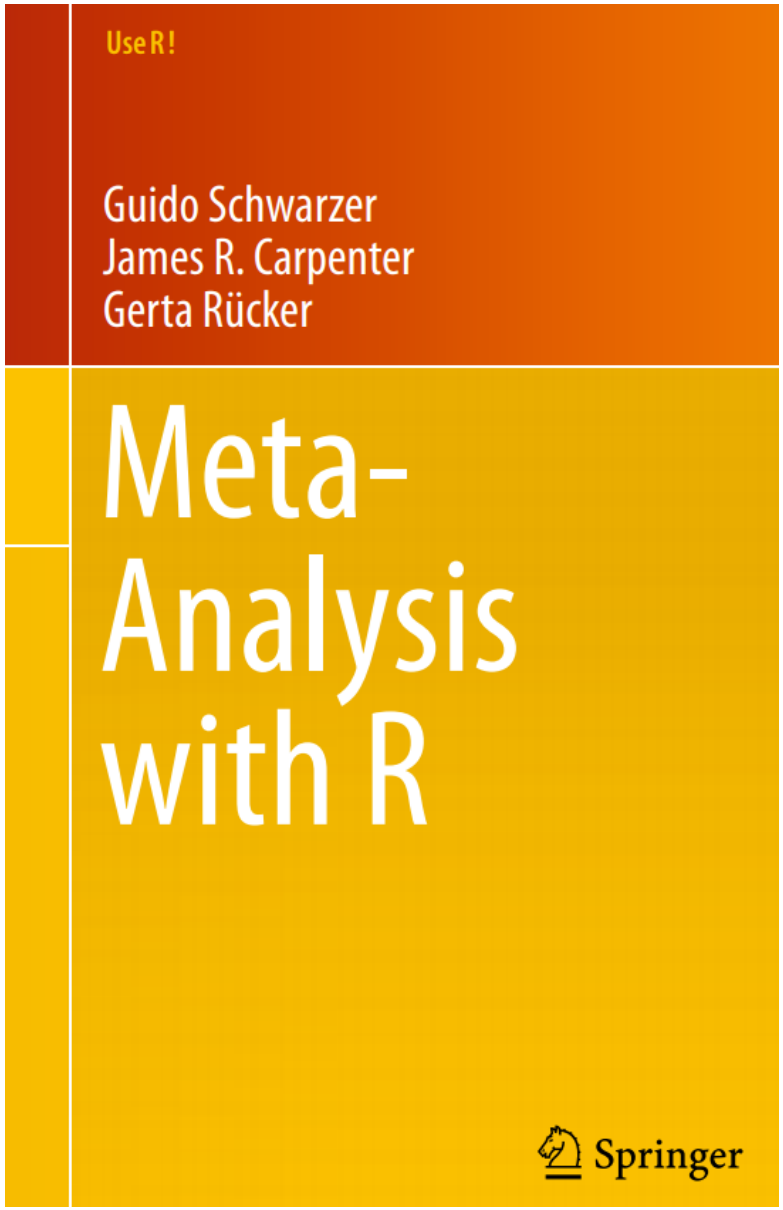
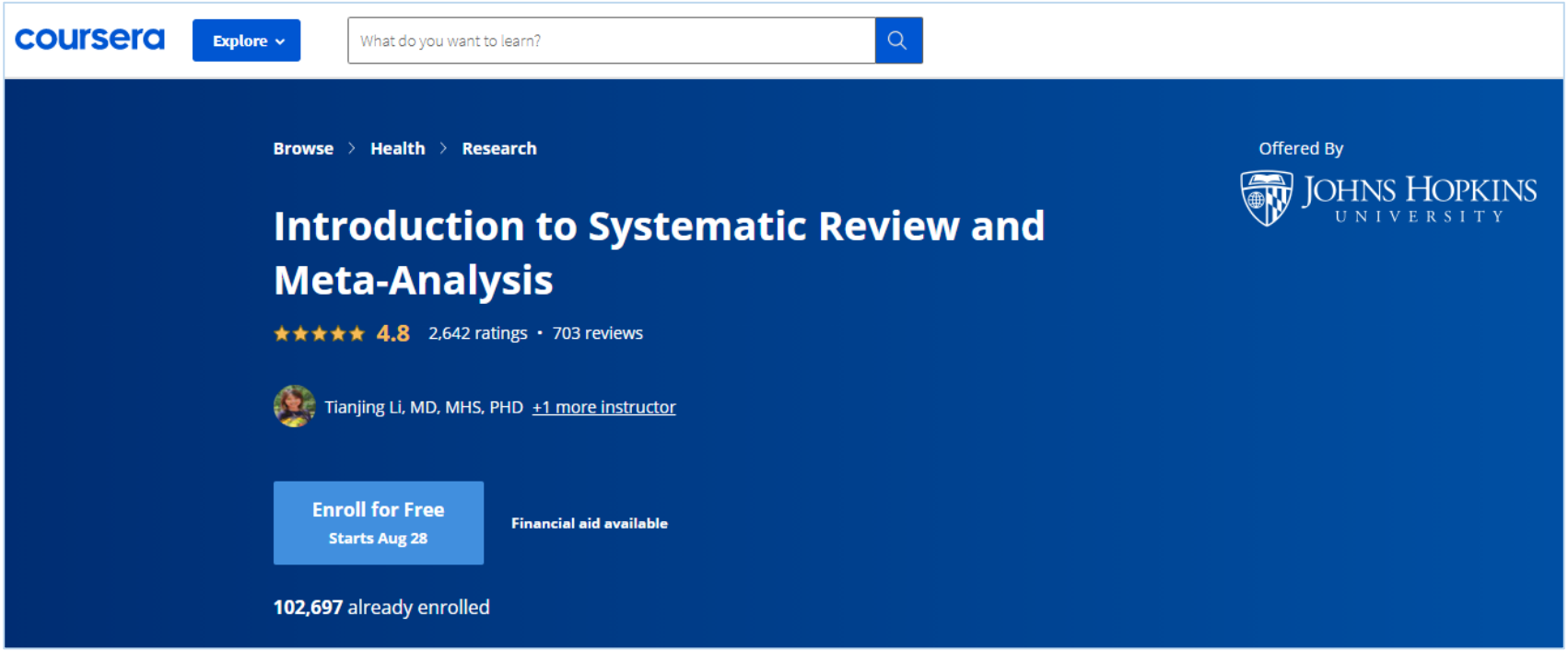
Further Reading



Based on R package "`meta`"

Further Study



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End of Part 1 of 2

A Meta-analysis Primer

Theory & Practice (with R)

Part 2 of 2

Mehmet Tevfik DORAK, MD PhD

School of Life Sciences, Pharmacy & Chemistry

Kingston University London

http://www.dorak.info

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Outline

Background

Model selection

Quality assessment

Bias and how to check bias

Graphical display of the results and model diagnostics

Common mistakes

Good practice

Reporting

Meta-analysis software

Meta-analysis in R

Meta-analysis

What is R?

Using R for Statistics and Graphics

Mehmet Tevfik DORAK, MD, PhD

Basic information about R and links for R users
R Notes (PDF) R Links (PDF)

Session 1
(R basics and syntax)
PPT PPTX PDF Script
Video recordings (KU only): Part 1 & Part 2

Session 2
(Descriptive statistics and related graphics)
PPT PPTX PDF Script
Video recordings (KU only): Part 1 & Part 2

Session 3
(Inferential statistics I: Categorical data analysis)
PPT PPTX PDF Script
Video recordings (KU only): Part 1 & Part 2 (Appendix)

Session 4
(Inferential statistics II: Correlation, t-test, ANOVA and regression)
PPT PPTX PDF Script
Video recordings (KU only): Part 1 & Part 2 & Part3a / 3b

Session 5
(Beyond basic statistics: Statistical power; meta-analysis; survival analysis; ROC curve analysis)
PPT PPTX PDF
Video recordings (KU only): Part 1 & Part 2
Scripts for session 5:
pwr.R survival.R survival_time-to-event sample size calculation.R epiR_meta.R rmeta_cochrane.R roc_cutoff.R
jv.csv

All sessions (1-5) as a single file (updated)
PPTX (25Mb) PDF (16Mb)

Scripts
installation1.R
demo1.R
quantmod.R contingency.R tiff.R
s1.R s2.R s3.R s4.R
merge_files.R
pwr.R
survival.R survival_time-to-event sample size calculation.R
epiR_meta.R rmeta_cochrane.R
roc_cutoff.R

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Meta-analysis in R

An Introduction to Meta-analysis in R

by Gilbert Lazarus

Created on 21 January 2021

Outline

In this guide, you will learn:

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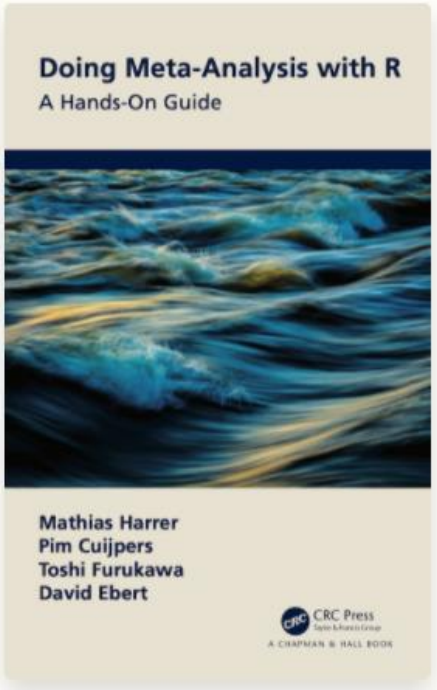
Meta-analysis in R

Welcome!

Welcome to the online version of **"Doing Meta-Analysis with R: A Hands-On Guide"**.

This book serves as an accessible introduction into how meta-analyses can be conducted in *R*. Essential steps for meta-analysis are covered, including pooling of outcome measures, forest plots, heterogeneity diagnostics, subgroup analyses, meta-regression, methods to control for publication bias, risk of bias assessments and plotting tools.

Advanced, but highly relevant topics such as network meta-analysis, multi-/three-level meta-analyses, Bayesian meta-analysis approaches, SEM meta-analysis are also covered.



The programming and statistical background covered in the book are kept at a **non-expert level**. A **print version** of this book has been published with Chapman & Hall/CRC Press (Taylor & Francis).

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Meta-analysis in R

metafor

The metafor Package
A Meta-Analysis Package for R

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metafor

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External Links

- Wolfgang Viechtbauer
- The R Project
- CRAN

The metafor Package: A Meta-Analysis Package for R

The metafor package is a free and open-source add-on for conducting meta-analyses with the statistical software environment R. The package consists of a collection of functions that allow the user to calculate various effect size or outcome measures, fit fixed-, random-, and mixed-effects models to such data, carry out moderator and meta-regression analyses, and create various types of meta-analytical plots.

On this website, you can find:

- some news concerning the package and/or its development,
- a more detailed description of the package features,
- a log of the package updates that have been made over the years,
- a to-do list and a description of planned features to be implemented in the future,
- information on how to download and install the package,
- information on how to obtain documentation and help with using the package,
- some analysis examples that illustrate various models, methods, and techniques,
- a little showcase of plots and figures that can be created with the package,
- some tips and notes that may be useful when working with the package,
- a list of people that have in some shape or form contributed to the development of the package,
- a frequently asked questions section, and
- some links to other websites related to software for meta-analysis.

The metafor package was written by Wolfgang Viechtbauer. It is licensed under the GNU General Public License Version 2. For citation info, type `citation(package='metafor')` in R. To report any issues or bugs, please go here.

metafor.txt · Last modified: 2021/02/08 21:48 by Wolfgang Viechtbauer

Journal of Statistical Software
August 2010, Volume 36, Issue 3. http://www.jstatsoft.org/

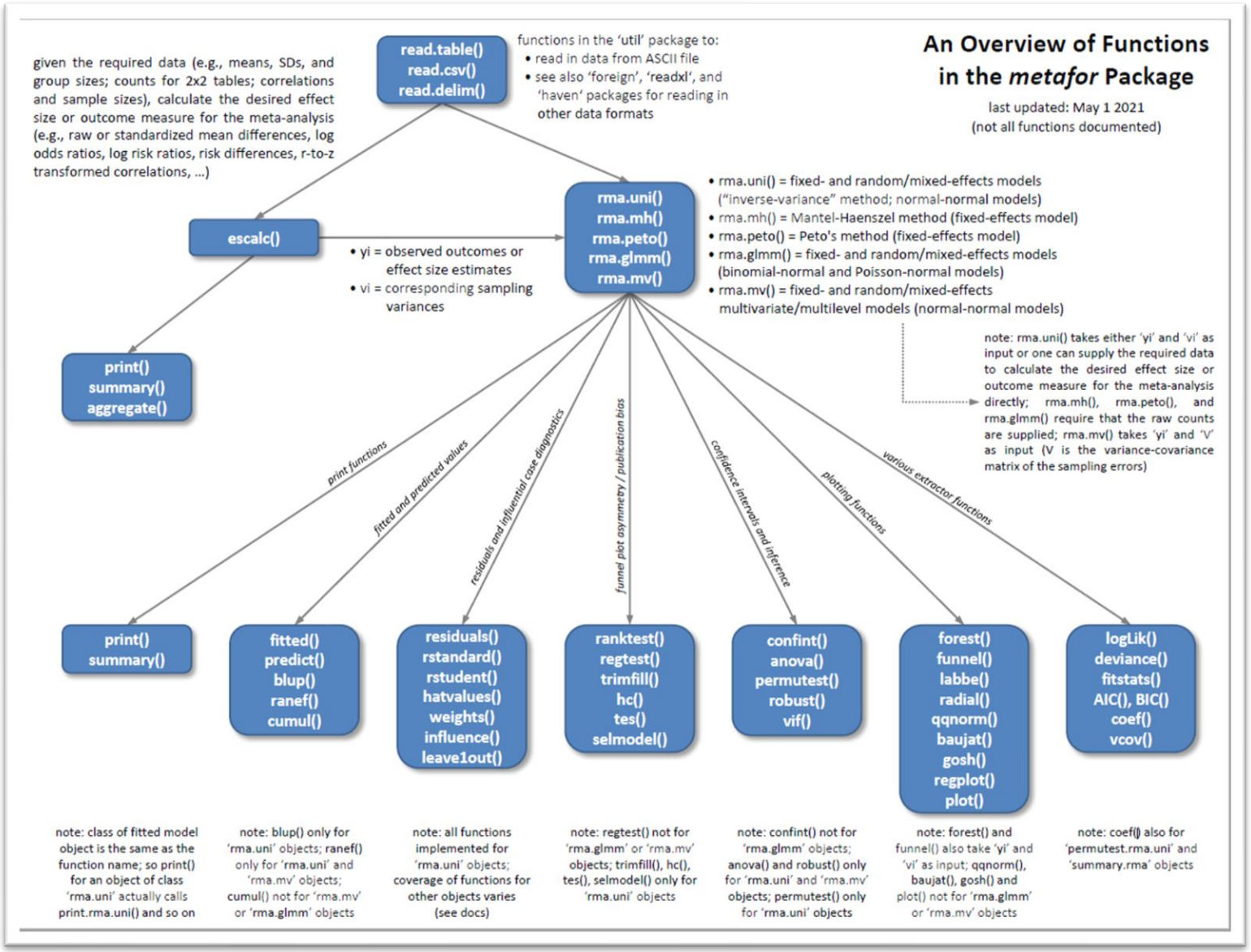
Conducting Meta-Analyses in R with the metafor Package

Wolfgang Viechtbauer
Maastricht University

Kingston University London

Meta-analysis in R

metafor



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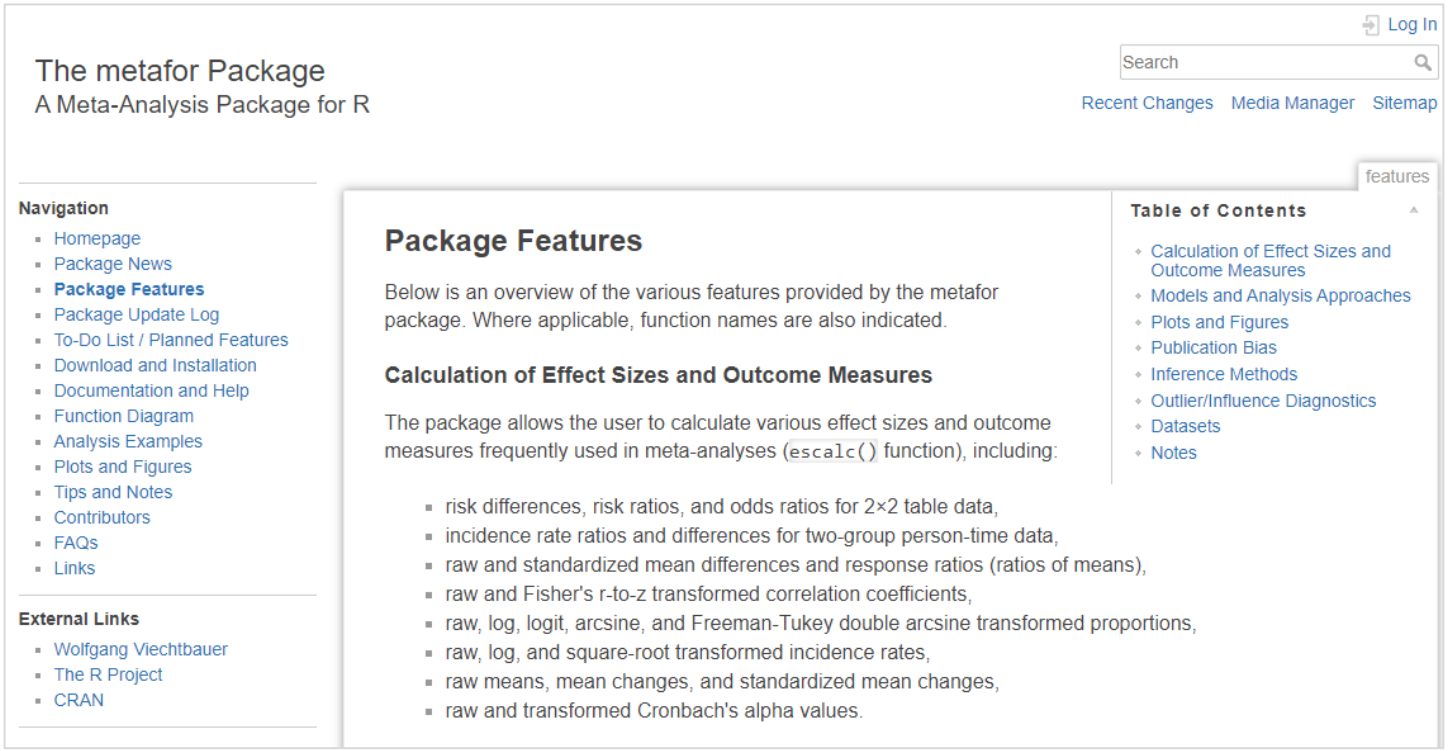
Meta-analysis in R

metafor



The metafor Package
A Meta-Analysis Package for R

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features

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- The R Project
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Package Features

Below is an overview of the various features provided by the metafor package. Where applicable, function names are also indicated.

Table of Contents

- Calculation of Effect Sizes and Outcome Measures
- Models and Analysis Approaches
- Plots and Figures
- Publication Bias
- Inference Methods
- Outlier/Influence Diagnostics
- Datasets
- Notes

Calculation of Effect Sizes and Outcome Measures

The package allows the user to calculate various effect sizes and outcome measures frequently used in meta-analyses (`escalc()` function), including:

- risk differences, risk ratios, and odds ratios for 2×2 table data,
- incidence rate ratios and differences for two-group person-time data,
- raw and standardized mean differences and response ratios (ratios of means),
- raw and Fisher's r-to-z transformed correlation coefficients,
- raw, log, logit, arcsine, and Freeman-Tukey double arcsine transformed proportions,
- raw, log, and square-root transformed incidence rates,
- raw means, mean changes, and standardized mean changes,
- raw and transformed Cronbach's alpha values.

Outlier/Influence Diagnostics

Various methods are available to identify outliers and/or influential studies, and for conducting sensitivity analyses, including:

- raw/standardized/studentized residuals (`residuals()`, `rstandard()`, and `rstudent()` functions),
- DFFITS values, Cook's distances, covariance ratios, and DFBETAS values (`influence()` function),
- model weights and hat values (`weights()` and `hatvalues()` functions),
- leave-one-out analyses (`leave1out()` and `influence()` functions).

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Meta-analysis in R

metafor

- The metafor package provides a comprehensive collection of functions for conducting meta-analyses in R
- It can be used to calculate various effect size or outcome measures and then allows the user to fit fixed- and random-effects models to these data
- For meta-analyses of 2×2 tables, proportions, incidence rates, and incidence rate ratios, the package provides functions that implement specialized methods
- Various methods are available to assess model fit, to identify outliers and/or influential studies, and for conducting sensitivity analyses (e.g., standardized residuals, Cook's distances, leave-one-out analyses)
- Due to its efficiency, weighted estimation with inverse-variance weights is the preferred method for random-effects models
- The package provides functions for creating forest, funnel, radial (Galbraith), normal quantile-quantile, L'Abbé, Baujat, bubble, and GOSH plots
- The presence of funnel plot asymmetry and its impact on the results can be examined via the (Begg's) rank and Egger's regression test, the trim and fill method, and by applying a variety of selection models

- The `rma.uni` function can be used in conjunction with any of the usual effect size or outcome measures used in meta-analyses (which can be computed using the `escalc` function)
- The Mantel-Haenszel method is implemented in the `rma.mh` function for studies providing data in the form of 2×2 tables or in the form of event counts for two groups

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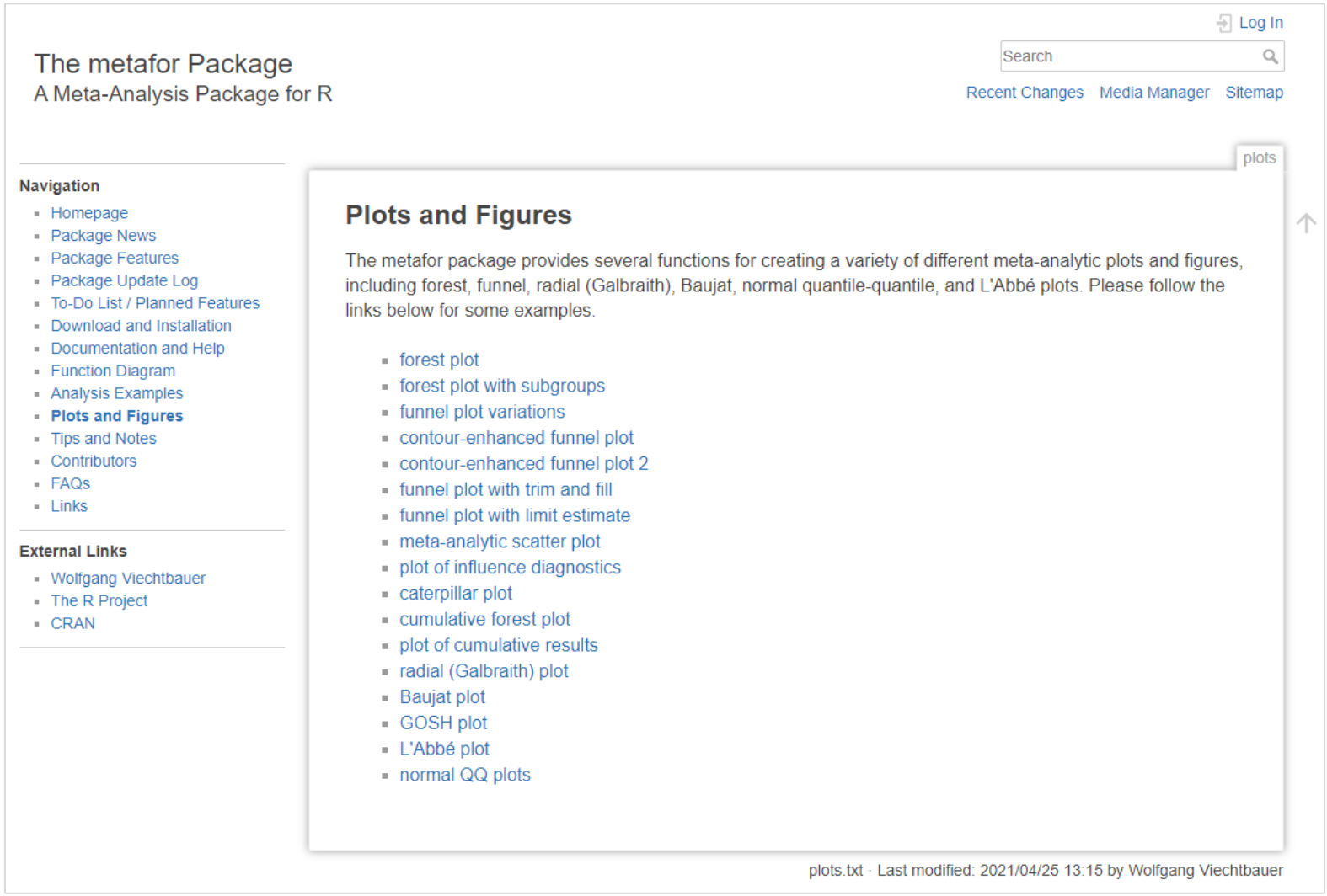
Meta-analysis in R

metafor



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The metafor Package

A Meta-Analysis Package for R

plots

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External Links

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- The R Project
- CRAN

Plots and Figures

The metafor package provides several functions for creating a variety of different meta-analytic plots and figures, including forest, funnel, radial (Galbraith), Baujat, normal quantile-quantile, and L'Abbé plots. Please follow the links below for some examples.

- forest plot
- forest plot with subgroups
- funnel plot variations
- contour-enhanced funnel plot
- contour-enhanced funnel plot 2
- funnel plot with trim and fill
- funnel plot with limit estimate
- meta-analytic scatter plot
- plot of influence diagnostics
- caterpillar plot
- cumulative forest plot
- plot of cumulative results
- radial (Galbraith) plot
- Baujat plot
- GOSH plot
- L'Abbé plot
- normal QQ plots

plots.txt · Last modified: 2021/04/25 13:15 by Wolfgang Viechtbauer

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Meta-analysis in R

metafor

An introduction to meta-analysis

Vernon Visser

30 May 2019

Introduction to meta-analysis

As the number of scientific studies continues to grow exponentially, so does the opportunity to gain insights on a specific hypothesis using data from a large number different studies. Literature reviews are useful for providing a synthesis on the current understanding of a particular research topic, but are largely qualitative in nature and are unable to quantitatively assess conflicting results from different studies. Meta-analysis provides a statistical framework for combining and comparing different studies to test a specific research hypothesis.

Getting started in R

Load packages and get data

```
library(metafor) #Install this package first if you do not have it
dat = read.csv('Gouda-Vossos_S2.csv')
head(dat)
```

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Meta-analysis in R

metafor: input data

`escalc()`

metafor 3.1-25 | Introduction | Functions | Diagram | JSS Article (pdf) | Changelog

Calculate Effect Sizes and Outcome Measures

The function can be used to calculate various effect sizes or outcome measures (and the corresponding sampling variances) that are commonly used in meta-analyses.

```
escalc(measure, ai, bi, ci, di, n1i, n2i, x1i, x2i, t1i, t2i,
       m1i, m2i, sd1i, sd2i, xi, mi, ri, ti, sdi, r2i, ni, yi, vi, sei,
       data, slab, subset, include,
       add=1/2, to="only0", drop00=FALSE, vtype="LS",
       var.names=c("yi","vi"), add.measure=FALSE,
       append=TRUE, replace=TRUE, digits, ...)
```

Arguments

measure
a character string to specify which effect size or outcome measure should be calculated. See 'Details' for possible options and how the data needed to compute the selected effect size or outcome measure should then be specified.

ai
vector to specify the 2×2 table frequencies (upper left cell).

bi
vector to specify the 2×2 table frequencies (upper right cell).

ci
vector to specify the 2×2 table frequencies (lower left cell).

di
vector to specify the 2×2 table frequencies (lower right cell).

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Script file: meta_analysis.R (link for download)

Meta-analysis in R

metafor: input data

`escalc()`

Outcome: Quantitative (days)

Effect size: Differences between means

Assembling Data for a Meta-Analysis of Standardized Mean Differences

Suppose the goal of a meta-analysis is to aggregate the results from studies contrasting two groups (e.g., treatment versus control) and each study measured an outcome of interest using some quantitative scale. A commonly used effect size measure used to quantify the size of the group difference is then the standardized mean difference (also commonly known as Cohen's d).

Studies on the Length of Hospital Stay of Stroke Patients

Results from 9 studies on the length of the hospital stay of stroke patients under specialized care and under conventional/routine (non-specialist) care.

```
dat.normand1999
```

Format

The data frame contains the following columns:

study	`numeric`	study number
source	`character`	source of data
n1i	`numeric`	number of patients under specialized care
m1i	`numeric`	mean length of stay (in days) under specialized care
sd1i	`numeric`	standard deviation of the length of stay under specialized care
n2i	`numeric`	number of patients under routine care
m2i	`numeric`	mean length of stay (in days) under routine care
sd2i	`numeric`	standard deviation of the length of stay under routine care

Details

The 9 studies provide data in terms of the mean length of the hospital stay (in days) of stroke patients under specialized care and under conventional/routine (non-specialist) care. The goal of the meta-analysis was to examine the hypothesis whether specialist stroke unit care will result in a shorter length of hospitalization compared to routine management.

study	source	n1i	m1i	sd1i	n2i	m2i	sd2i
1	Edinburgh	155	55	47	156	75	64
2	Orpington-Mild	31	27	7	32	29	4
3	Orpington-Moderate	75	64	17	71	119	29
4	Orpington-Severe	18	66	20	18	137	48
5	Montreal-Home	8	14	8	13	18	11
6	Montreal-Transfer	57	19	7	52	18	4
7	Newcastle	34	52	45	33	41	34
8	Umea	110	21	16	183	31	27
9	Uppsala	60	30	27	52	23	20

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Meta-analysis in R

metafor: input data

escalc()

```
# Meta-analysis with SMDs

library(metafor)
# copy data into 'data' and examine data
data <- dat.normand1999
data

# using the escalc() function, calculate mean differences and corresponding sampling variances
data <- escalc(measure="MD", m1i=m1i, sd1i=sd1i, n1i=n1i, m2i=m2i, sd2i=sd2i, n2i=n2i, data=data,
slab=source)
data # last two columns are the calculated yi and vi values

# meta-analysis of mean differences using a random-effects model
result <- rma(yi, vi, data=data)
result

# using the escalc() function, calculate standardised mean differences (SMD) and corresponding sampling
variances
data <- escalc(measure="SMD", m1i=m1i, sd1i=sd1i, n1i=n1i, m2i=m2i, sd2i=sd2i, n2i=n2i, data=data,
slab=source)
data  # last two columns are the calculated yi and vi values

# meta-analysis of mean differences using a random-effects model
result <- rma(yi, vi, data=data)
result

# plots
forest(result)
funnel(result)

# TRY THIS:
forest(result, addpred = TRUE, order = "obs", showweights = TRUE, header = TRUE, transf = exp)
                                        # ordered by observed effect sizes of included studies
```

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Meta-analysis in R

metafor: input data

`escalc()`

Outcome: Count data (events)
Effect size: Odds/Risk ratio

Assembling Data for a Meta-Analysis of (Log) Odds Ratios

Suppose the goal of a meta-analysis is to aggregate the results from studies contrasting two groups (e.g., treatment versus control) and each study measured a dichotomous outcome of interest (e.g., treatment success versus failure). A commonly used effect size measure used to quantify the size of the group difference (i.e., the size of the treatment effect) is then the odds ratio.

Studies on the Effectiveness of the BCG Vaccine Against Tuberculosis

Results from 13 studies examining the effectiveness of the Bacillus Calmette-Guerin (BCG) vaccine against tuberculosis.

```
dat.bcg
```

Format

The data frame contains the following columns:

trial	`numeric`	trial number
author	`character`	author(s)
year	`numeric`	publication year
tpos	`numeric`	number of TB positive cases in the treated (vaccinated) group
tneg	`numeric`	number of TB negative cases in the treated (vaccinated) group
cpos	`numeric`	number of TB positive cases in the control (non-vaccinated) group
cneg	`numeric`	number of TB negative cases in the control (non-vaccinated) group
ablat	`numeric`	absolute latitude of the study location (in degrees)
alloc	`character`	method of treatment allocation (random, alternate, or systematic assignment)

trial	author	year	tpos	tneg	cpos	cneg	ablat	alloc
1	Aronson	1948	4	119	11	128	44	random
2	Ferguson & Simes	1949	6	300	29	274	55	random
3	Rosenthal et al	1960	3	228	11	209	42	random
4	Hart & Sutherland	1977	62	13536	248	12619	52	random
5	Frimodt-Moller et al	1973	33	5036	47	5761	13	alternate
6	Stein & Aronson	1953	180	1361	372	1079	44	alternate
7	Vandiviere et al	1973	8	2537	10	619	19	random
8	TPT Madras	1980	505	87886	499	87892	13	random
9	Coetzee & Berjak	1968	29	7470	45	7232	27	random
10	Rosenthal et al	1961	17	1699	65	1600	42	systematic
11	Comstock et al	1974	186	50448	141	27197	18	systematic
12	Comstock & Webster	1969	5	2493	3	2338	33	systematic
13	Comstock et al	1976	27	16886	29	17825	33	systematic

Details

The 13 studies provide data in terms of 2×2 tables in the form:

	TB positive	TB negative
vaccinated group	`tpos`	`tneg`
control group	`cpos`	`cneg`

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Meta-analysis in R

metafor: input data

`escalc()`

```
# Meta-analysis with risk ratios

library(metafor)

# copy data into 'data' and examine data
data <- dat.bcg
data

# using the escalc() function, calculate log risk ratios and corresponding sampling variances
  # same with odds ratios (OR) by changing measure= to "OR")
data <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=data, slab=author)
data  # last two columns are the calculated yi and vi values

# meta-analysis of risk reatios using a random-effects model
result <- rma(yi, vi, data=data)
result

# average risk ratio with 95% CI
predict(result, transf=exp)

# plots
forest(result)
funnel(result)

# TRY THIS:
forest(result, addpred = TRUE, order = "obs", showweights = TRUE, header = TRUE, transf = exp)
                                          # ordered by observed effect sizes of included studies
```

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Meta-analysis in R

metafor: input data

`escalc()`

Outcome: Correlation

Effect size: Correlation coefficient

Measures for Two Quantitative Variables

The (Pearson or product-moment) correlation coefficient quantifies the direction and strength of the (linear) relationship between two quantitative variables and is therefore frequently used as the outcome measure for meta-analyses. Two alternative measures are a bias-corrected version of the correlation coefficient and Fisher's r-to-z transformed correlation coefficient.

For these measures, one needs to specify `ri`, the vector with the raw correlation coefficients, and `ni`, the corresponding sample sizes. The options for the `measure` argument are then:

- `"COR"` for the *raw correlation coefficient*,
- `"UCOR"` for the *raw correlation coefficient* corrected for its slight negative bias (based on equation 2.3 in Olkin & Pratt, 1958),
- `"ZCOR"` for *Fisher's r-to-z transformed correlation coefficient* (Fisher, 1921).

Studies on the Validity of Employment Interviews

Results from 160 studies on the correlation between employment interview assessments and job performance.

```
dat.mcdaniel1994
```

Format

The data frame contains the following columns:

study	`numeric`	study number
ni	`numeric`	sample size of the study
ri	`numeric`	observed correlation
type	`character`	interview type (j = job-related, s = situational, p = psychological)
struct	`character`	interview structure (u = unstructured, s = structured)

	study	ni	ri	type	struct
1	1	123	0.00	j	s
2	2	95	0.06	p	u
3	3	69	0.36	j	s
4	4	1832	0.15	j	s
5	5	78	0.14	j	s
6	6	329	0.06	j	s

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Meta-analysis in R

metafor: input data

`escalc()`

```
# Meta-analysis with correlation coefficients


library(metafor)

# copy data into 'data' and examine data
data <- dat.mcdaniel1994
data

# calculate r-to-z transformed correlations and corresponding sampling variances
data <- escalc(measure="ZCOR", ri=ri, ni=ni, data=data, slab=study)

# meta-analysis of the transformed correlations using a random-effects model
result <- rma(yi, vi, data=data)
result

# plots
forest(result)
funnel(result)


# TRY THIS:
forest(result, addpred = TRUE, order = "obs", showweights = TRUE, header = TRUE, transf = exp)
                                          # ordered by observed effect sizes of included studies
```

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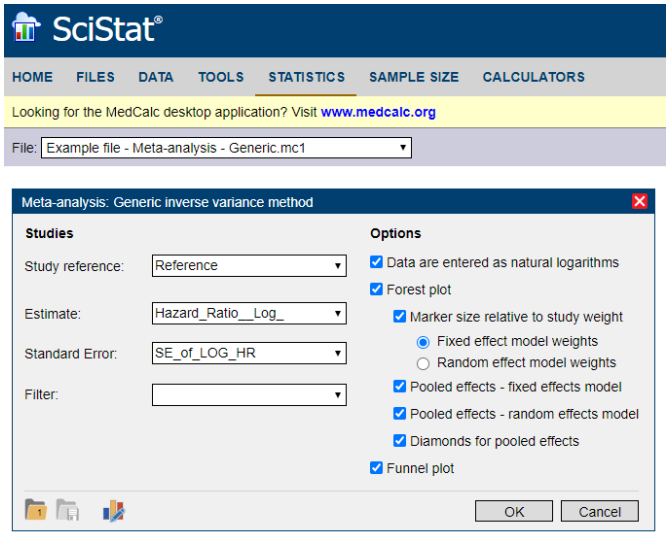
Meta-analysis in R

Generic inverse variance method

In studies using time-to-event outcomes (survival studies), the hazard ratio is the effect size, and the generic inverse variance method is the preferred approach for meta-analysis.

The input data for such studies if the natural log (ln) of HR and natural log (ln) of its standard error (square root of its variance). These are called *yi* and *vi*, respectively by some R packages (*metafor* and *meta*).

For an online example, see: https://www.scistat.com/stats/statistics.php?id=1628
Choose Example file - Meta-analysis - Generic mc1



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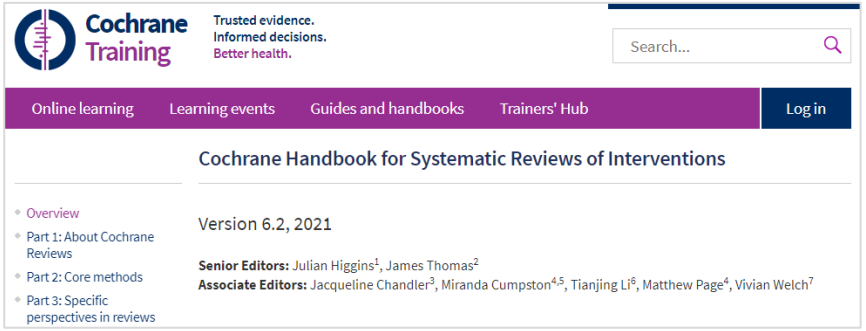
Meta-analysis in R

Generic inverse variance method

10.3 A generic inverse-variance approach to meta-analysis #section-10-3

A very common and simple version of the meta-analysis procedure is commonly referred to as the **inverse-variance method**. This approach is implemented in its most basic form in RevMan, and is used behind the scenes in many meta-analyses of both dichotomous and continuous data.

The inverse-variance method is so named because the weight given to each study is chosen to be the inverse of the variance of the effect estimate (i.e. 1 over the square of its standard error). Thus, larger studies, which have smaller standard errors, are given more weight than smaller studies, which have larger standard errors. This choice of weights minimizes the imprecision (uncertainty) of the pooled effect estimate.



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Meta-analysis in R

metafor: meta-analysis with hazard ratios

A meta-analysis using hazard ratios and 95% confidence intervals

```
  # Data from Steurer et al. (2006)
  # https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004270.pub2/full

# Create vectors for the hazard ratios and 95% CI lower and upper limits from each study
study <- c("FCG on CLL 1996", "Leporrier 2001", "Rai 2000", "Robak 2000")
HR <- c(0.55, 0.92, 0.79, 1.18)
lower.HR <- c(0.28, 0.79, 0.59, 0.64)
upper.HR <- c(1.09, 1.08, 1.05, 2.17)
data <- cbind(study, HR, lower.HR, upper.HR)
data <- as.data.frame(data)
data$HR=as.numeric(data$HR); data$lower.HR=as.numeric(data$lower.HR); data$upper.HR=as.numeric(data$upper.HR)

# Calculate yi and vi from the HR and 95% CI values entered into the data frame created above
data$yi = log(data$HR)
data$vi = ((log(upper.HR) - log(lower.HR))/3.92)^2
data

library(metafor)
# Run meta-analysis:
result <- rma.uni(yi = data$yi, vi = data$vi, slab = study)
result

# Generate plots based on the R object 'results'
plot(result, addpred = TRUE, showweights = TRUE, header = TRUE, transf = exp, qqplot = TRUE)
  # or: forest and funnel plots can be generated separately:
forest(results, addpred = TRUE, order = "obs", showweights = TRUE, header = TRUE, transf = exp)
                                    # ordered by observed effect sizes of included studies
funnel(result)
funnel(result, level = c(90, 95, 99), shade = c("white", "gray55", "gray75"), refline = 0,
       legend = TRUE)          # contour-enhanced funnel plot

# trimfill method for assessing publication bias
trimfill(result)
```

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Meta-analysis in R

metafor: meta-analysis with hazard ratios

A meta-analysis using hazard ratios and 95% confidence intervals
Cont…

```
# Statistical assessment of publication bias (funnel plot asymmetry):
ranktest(result)
regtest(result)

tes(result)                                  # test of excess significance "tes"

install.packages("numDeriv")
library(numDeriv)
sel <- selmodel(result, type="power")            # fitting selection models (selmodel) to identify the model of
                                                 # potential publication bias in a meta-analysis
sel                                              # displays the selection model test result
```

Meta-analysis in R

Welcome!

Welcome to the online version of **"Doing Meta-Analysis with R: A Hands-On Guide"**.

This book serves as an accessible introduction into how meta-analyses can be conducted in *R*. Essential steps for meta-analysis are covered, including pooling of outcome measures, forest plots, heterogeneity diagnostics, subgroup analyses, meta-regression, methods to control for publication bias, risk of bias assessments and plotting tools.

Advanced, but highly relevant topics such as network meta-analysis, multi-/three-level meta-analyses, Bayesian meta-analysis approaches, SEM meta-analysis are also covered.

The programming and statistical background covered in the book are kept at a **non-expert level**. A **print version** of this book has been published with Chapman & Hall/CRC Press (Taylor & Francis).

Open Source Repository

This book has been built using **{rmarkdown}** and **{bookdown}**. Formulas are rendered using MathJax. All materials and source code we used to compile the guide can be found on **GitHub**. You are free to fork, share and reuse contents. However, the repository is intended to be mainly "read-only"; PRs will generally not be considered (see section below & preface for ways to contact us).

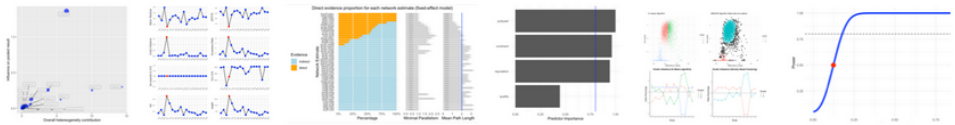
VIEW REPOSITORY

Contents

R Package

dmetar

Doing Meta-Analysis in R



The **dmetar** package serves as the companion R package for the guide **Doing Meta-Analysis in R** by Mathias Harrer, Pim Cuijpers, Toshi Furukawa and David Daniel Ebert. The package contains utility functions to facilitate the conduction of meta-analyses using the **meta**, **metafor**, **netmeta** and **gemtc** packages.

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Meta-analysis in R

A nontechical primer for conducting a meta-analysis to synthesize correlational data

A companion R script implementing the analysis described in Quintana (2015).

Quintana DS (2015). From pre-registration to publication: a nontechnical primer for conducting a meta-analysis to synthesize correlational data. Front. Psychol. 6:1549. doi: 10.3389/fpsyg.2015.01549

Abstract

Meta-analysis synthesizes a body of research investigating a common research question. Outcomes from meta-analyses provide a more objective and transparent summary of a research area than traditional narrative reviews. Moreover, they are often used to support research grant applications, guide clinical practice and direct health policy. The aim of this article is to provide a practical and nontechnical guide for psychological scientists that outlines the steps involved in planning and performing a meta-analysis of correlational datasets. I provide a supplementary R script to demonstrate each analytical step described in the paper, which is readily adaptable for researchers to use for their analyses. I also emphasise the importance of meta-analysis protocols and pre-registration to improve transparency and help avoid unintended duplication. While the worked example is the analysis of a correlational dataset, the general meta-analytic process described in this paper is applicable for all types of effect sizes. An improved understanding this tool will not only help scientists to conduct their own meta-analyses but also improve their evaluation of published meta-analyses.

Front. Psychol., 08 October 2015 | https://doi.org/10.3389/fpsyg.2015.01549

From pre-registration to publication: a non-technical primer for conducting a meta-analysis to synthesize correlational data

Daniel S. Quintana*

Kingston University London

Meta-analysis in R

Statistics in practice

How to perform a meta-analysis with R: a practical tutorial

Sara Balduzzi, Gerta Rücker, Guido Schwarzer

ABSTRACT

Objective Meta-analysis is of fundamental importance to obtain an unbiased assessment of the available evidence. In general, the use of meta-analysis has been increasing over the last three decades with mental health as a major research topic. It is then essential to well understand its methodology and interpret its results. In this publication, we describe how to perform a meta-analysis with the freely available statistical software environment R, using a working example taken from the field of mental health.

Methods R package meta is used to conduct standard meta-analysis. Sensitivity analyses for missing binary outcome data and potential selection bias are conducted with R package metasens. All essential R commands are provided and clearly described to conduct and report analyses.

Results The working example considers a binary outcome: we show how to conduct a fixed effect and random effects meta-analysis and subgroup analysis, produce a forest and funnel plot and to test and adjust for funnel plot asymmetry. All these steps work similar for other outcome types.

Conclusions R represents a powerful and flexible tool to conduct meta-analyses. This publication gives a brief glimpse into the topic and provides directions to more advanced meta-analysis methods available in R.

Dataset used

R code

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Meta-analysis in R

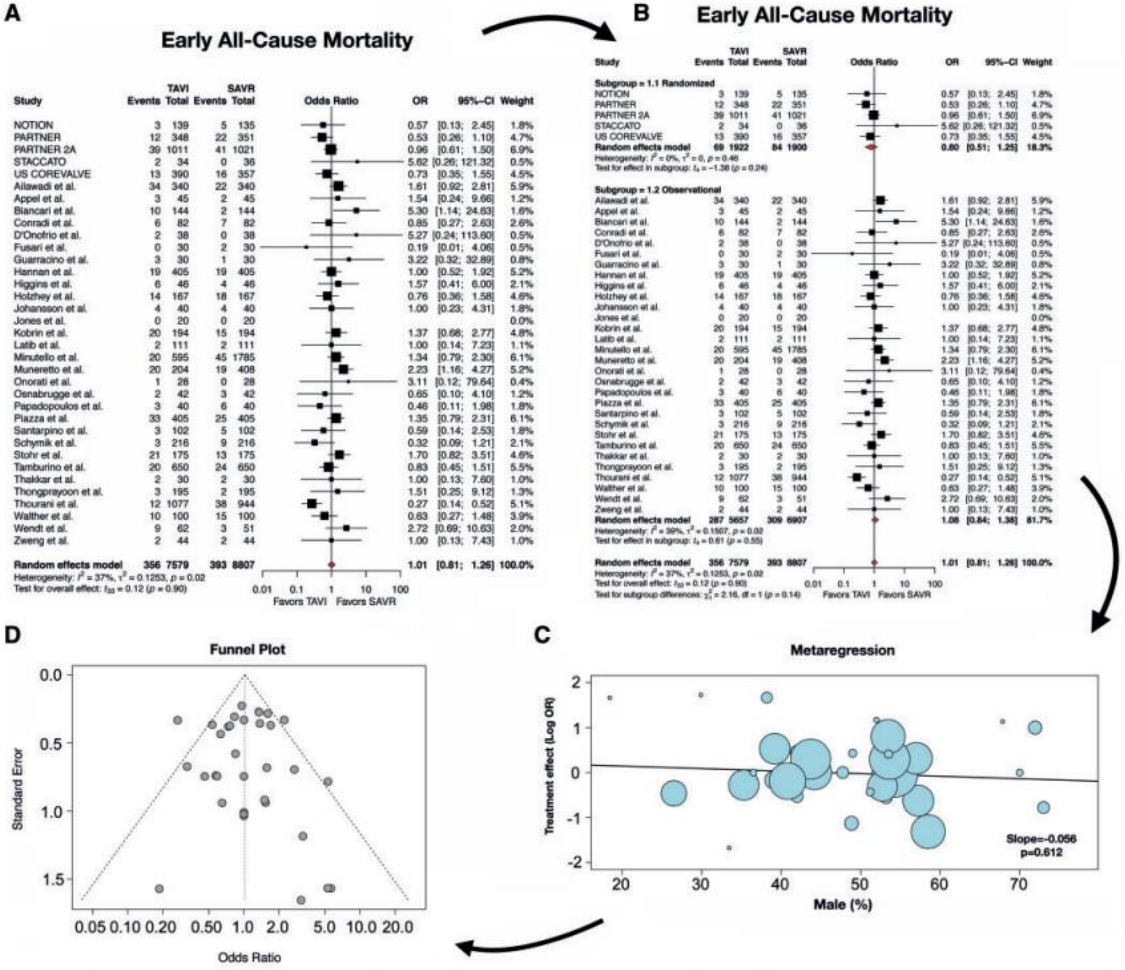

Figure 2: A practical example of a comparative meta-analysis of early mortality in TAVI versus surgery studies. (**A**) The pooled results of RCTs and observational studies are shown. (**B**) The results are consistent between RCTs and observational studies. (**C**) A bubble plot from meta-regression analysis exploring whether the percentage of male patients included in each study acts as a treatment effect modifier. (**D**) The funnel plot with symmetrical distribution of studies and no concerns as regards publication bias are shown. CI: confidence interval; OR: odds ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

The R command used for analysis is provided in the Supplementary Material, Appendix S1.

Cite this article as: Buccheri S, Sodeck GH, Capodanno D. Statistical primer: methodology and reporting of meta-analyses. Eur J Cardiothorac Surg 2018;53:708–13.

Statistical primer: methodology and reporting of meta-analyses†

Sergio Buccheri[a], Gottfried H. Sodeck[b] and Davide Capodanno[a,*]

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Meta-analysis in R

Meta-Analysis Programs & Datasets

Field, A. P. & Gillett, R. (2010). How to do a meta-analysis. *British Journal of Mathematical and Statistical Psychology, 63*, 665-694.

Getting Started	Basic Meta-Analysis	Moderator Variable Analysis	Sensitivity to Publication Bias	Links

Effect-Size Measure	Symbol	Program	Dataset
Correlation	r	Pub_Bias_r.R (Windows) Pub_Bias_r.R (Mac)	Cartwright-Hatton_et_al_2004.sav
Standardised Difference Between Two Means	d	Pub_Bias_d.R (Windows) Pub_Bias_d.R (Mac)	Else-Quest_et_al_2006.sav
Difference Between Two Proportions	D or h	Pub_Bias_D_h.R (Windows) Pub_Bias_D_h.R (Mac)	Pozzulo_&_Lindsay_1998.sav

Expert tutorial

How to do a meta-analysis

Andy P. Field[1]* and Raphael Gillett[2]*

British Journal of Mathematical and Statistical Psychology (2010), 63, 665–694

The British Psychological Society
www.bpsjournals.co.uk

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Meta-analysis in R

Meta-analysis in

using metafor, meta and MAd

Edward Purssell, Senior Lecturer, King's College London

Tutorial On Meta-Analysis In R

R useR! Conference 2013

Stephanie Kovalchik
Research Fellow, National Cancer Institute

Meta-analysis course (in R)

Thomas Pollet (Northumbria University)

Meta Analysis In R

Example of Meta-Analysis using R and meta library

George Pipis Follow

Software Review

Journal of Educational and Behavioral Statistics
2017, Vol. 42, No. 2, pp. 206–242
DOI: 10.3102/1076998616674315

A Review of Meta-Analysis Packages in R

Joshua R. Polanin
Development Services Group, Inc.

Emily A. Hennessy
Emily E. Tanner-Smith
Vanderbilt University

CRAN Task View: Meta-Analysis

Maintainer: Michael Dewey
Contact: lists at dewey.myzen.co.uk
Version: 2021-07-24
URL: https://CRAN.R-project.org/view=MetaAnalysis

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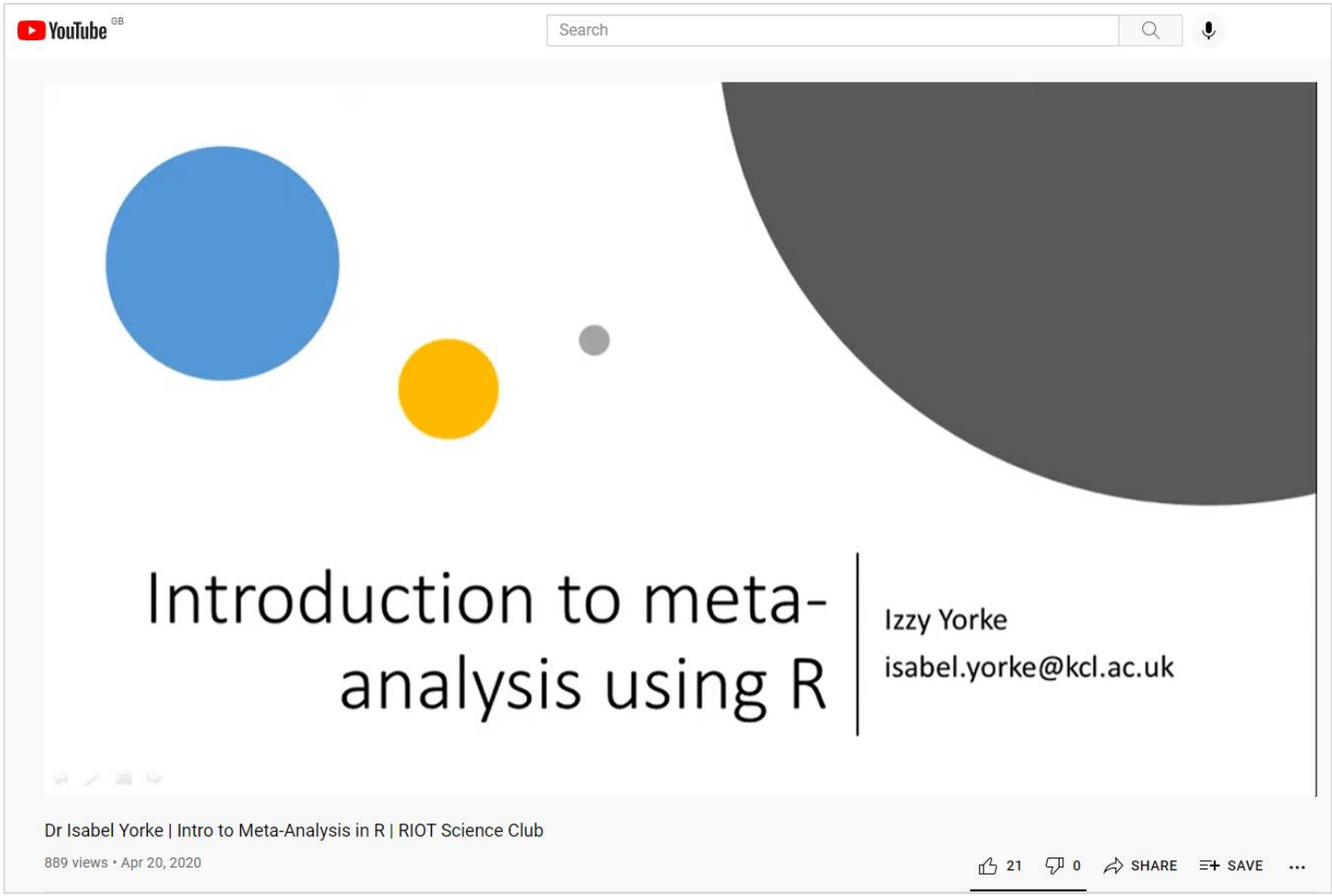
Meta-analysis in R



Link for this YouTube video: https://www.youtube.com/watch?v=OtuNtK02yaQ
Link for PPTx: https://osf.io/b84vk/download

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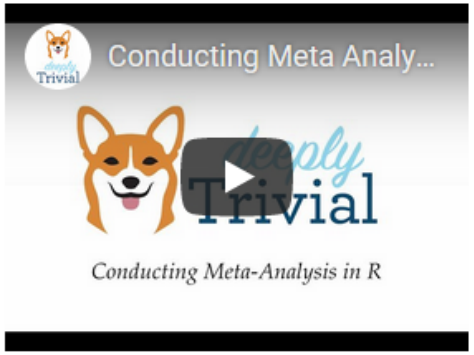
Meta-analysis in R

Sunday, April 29, 2018

Statistics Sunday: Conducting Meta-Analysis in R

Here it is, everyone! The promised 4th post on meta-analysis, and my second video for Deeply Trivial! In this video, I walk through conducting a basic meta-analysis, both fixed and random effects, in the metafor package:



See these previous posts and links for more information:

- Effect sizes
- Meta-Analysis Variance
- Meta-Analysis Weights
- the BMJ Open article mentioned in the video
- Finally, the homepage for the metafor package

You can access the code I used in the video here as well as code to do similar analysis with the or_meta dataset here.

Meta-analysis in R

Script:
meta_analysis.R @ http://www.dorak.info/r

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GOODBYE!


Good Luck