

Bias due to missing results in a synthesis

Trusted evidence.
Informed decisions.
Better health.



Steps of a Cochrane Review

1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. assess studies for risk of bias
8. **analyse and present results**
9. **interpret results and draw conclusions**
10. improve and update review



Session outline

- **understanding non-reporting biases**
- minimising risk of bias due to missing results in a synthesis
- assessing risk of bias due to missing results in a synthesis



The dissemination of evidence

unavailable
(unpublished)

**available in
principle**
(thesis, journal
not indexed by
major
databases)

**easily
available**
(MEDLINE-
indexed)

**actively
disseminated**
(news, drug
company)

Non-reporting biases

- dissemination of research findings is influenced by the P value, magnitude or direction of the study's results
- statistically significant results that suggest an intervention works are more likely than statistically non-significant results to be available...
- ...therefore more likely to be included in your review
- two main types:
 - selective non-publication of studies or 'publication bias'
 - selective non-reporting of results or 'outcome reporting bias'

Evidence for selective non-publication of studies

Time of inception (12 cohorts)

Positive studies (n=1555)

Null or negative studies (n=976)

OR 2.9 (95% CI 2.4-3.5)

Regulatory submissions (4 cohorts)

Positive studies (n=615)

Null or negative studies (n=240)

OR 5.0 (95% CI 2.0-12.5)

Abstract presentation at conference (27 cohorts)

Positive studies (n=6109)

Null or negative studies (n=4180)

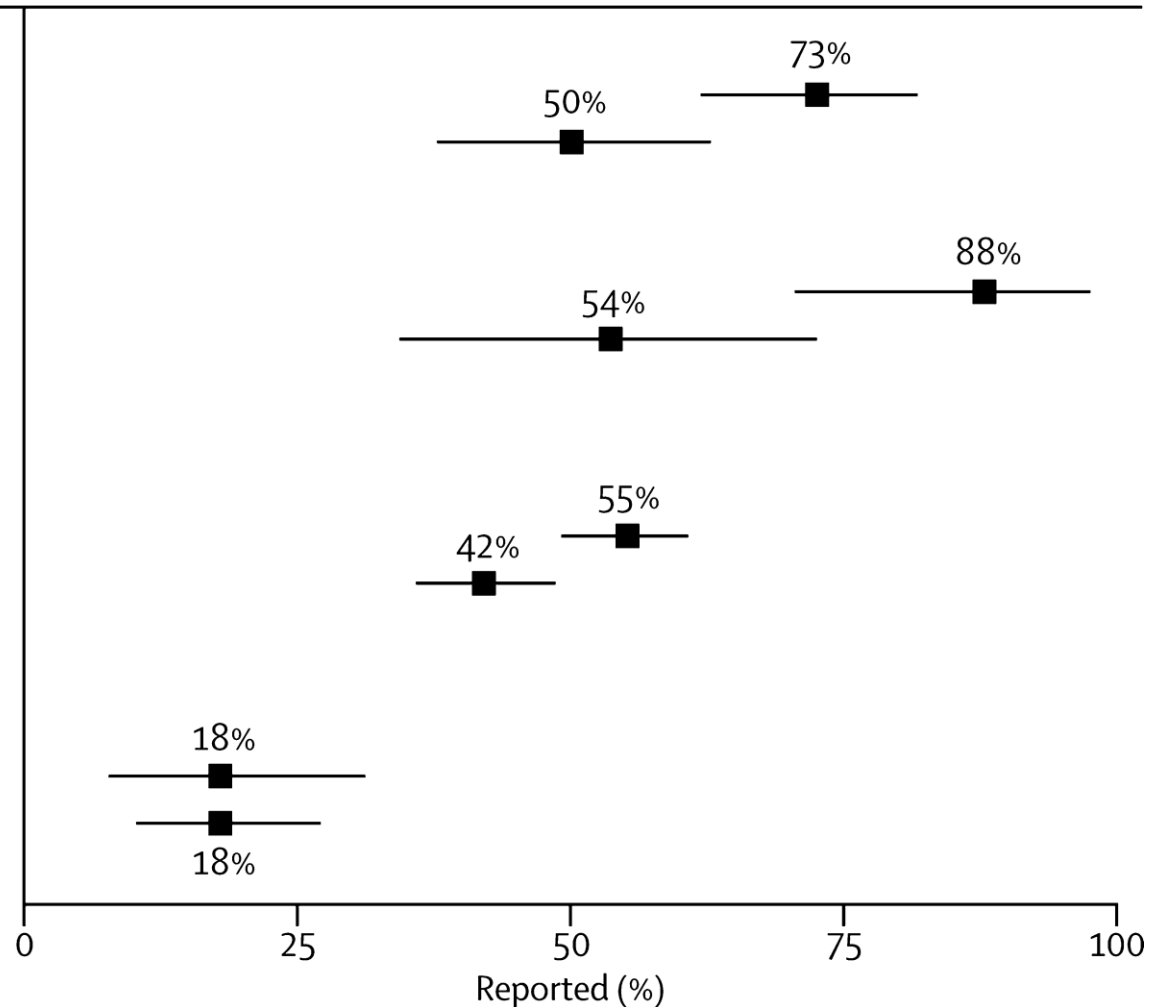
OR 1.7 (1.4-2.0)

Manuscripts submitted to journals (4 cohorts)

Positive studies (n=1869)

Null or negative studies (n=767)

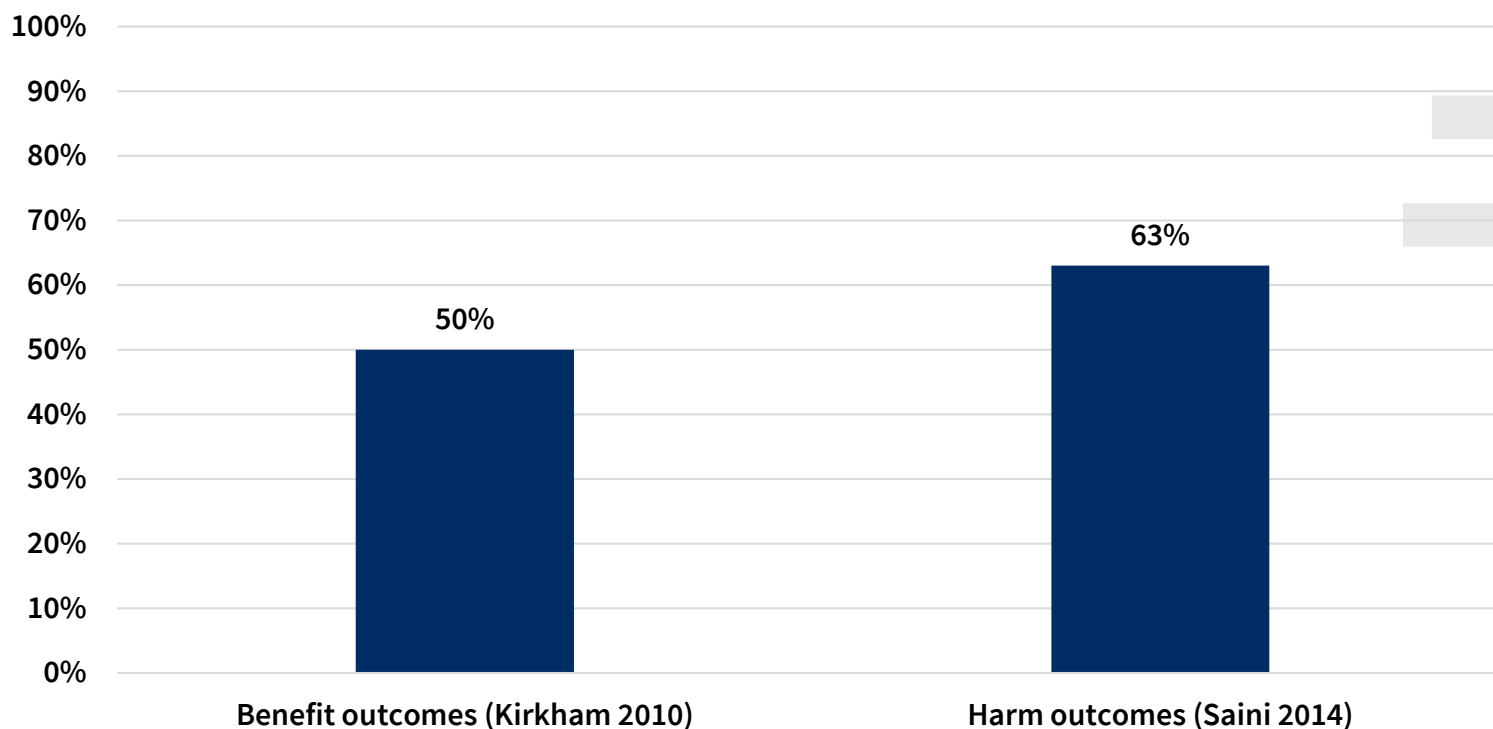
OR 1.1 (0.8-1.4)



Source: Chan A-W, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC, et al. Increasing value and reducing waste: addressing inaccessible research. *The Lancet*. 2014;383(9913):257-66.

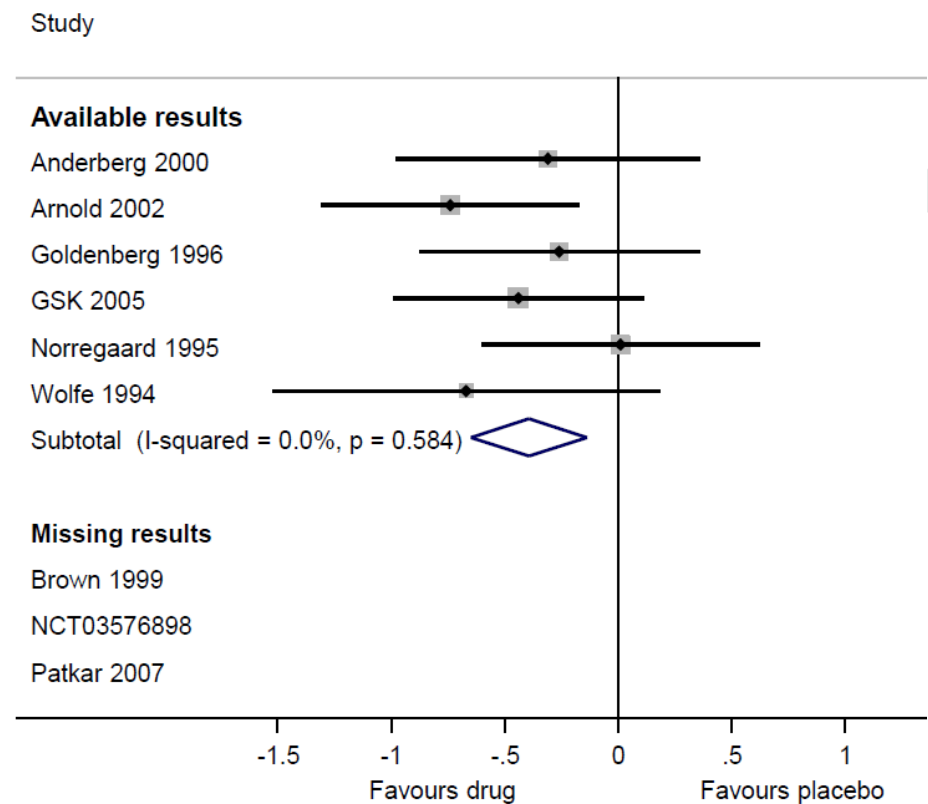
Evidence for selective non-reporting of results

% studies with results missing for the primary outcome of a review that are suspected to be missing due to selective non-reporting of results



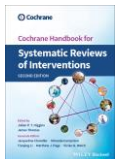
Non-reporting biases

- selective non-publication of studies or selective non-reporting of study results can lead to **bias due to missing results in a synthesis** (e.g. meta-analysis)
- may lead to overestimated or underestimated effects



Session outline

- understanding non-reporting biases
- **minimising risk of bias due to missing results in a synthesis**
- assessing risk of bias due to missing results in a synthesis



See Chapter 13, Section 13.2 of the Handbook

Minimising risk of bias

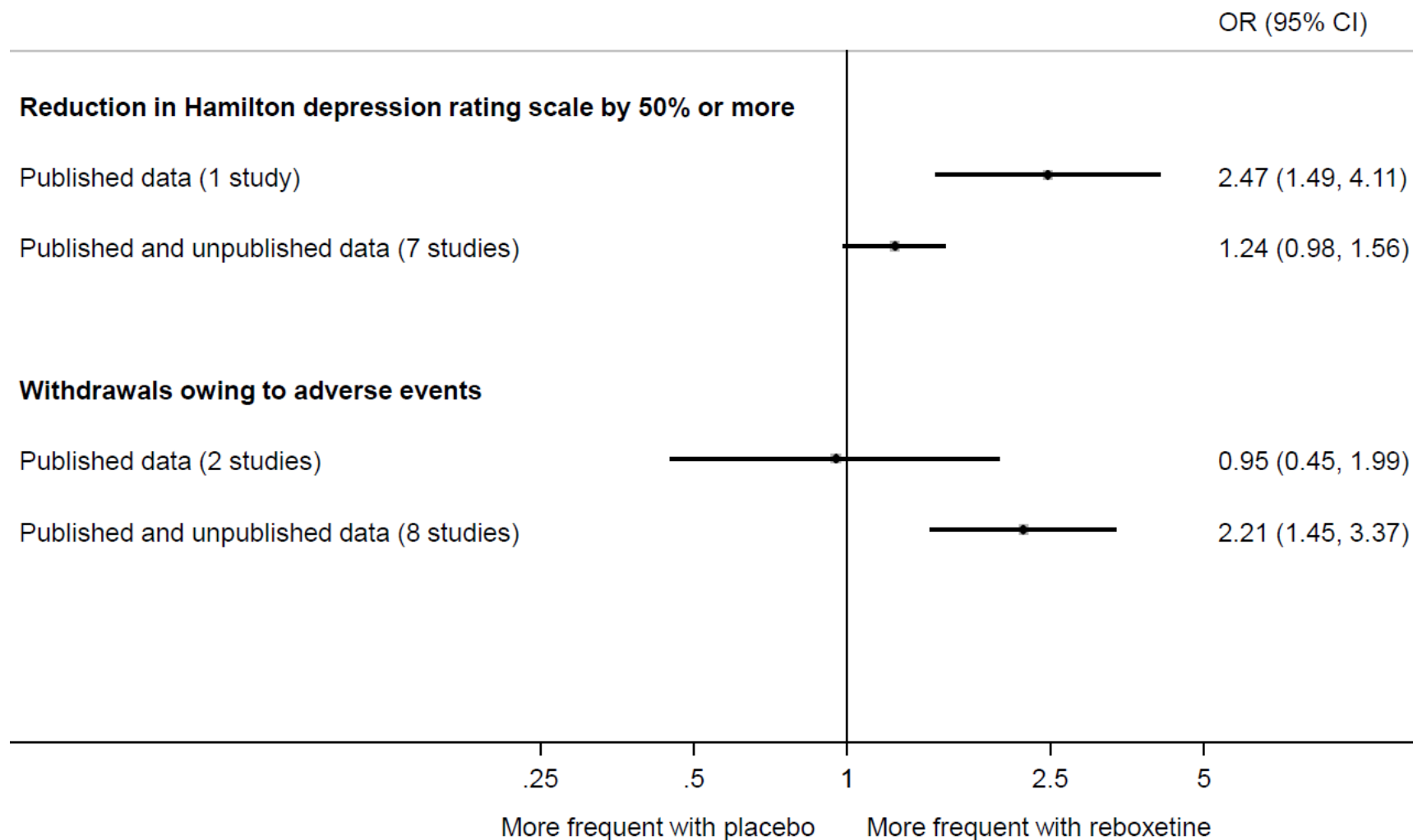
Include results from sources other than published reports

- comprehensive search to identify published articles, trials register entries, clinical study reports, dissertations, preprints, government reports, non-English literature

Restrict syntheses to studies that could be identified before their results became known (e.g. prospective meta-analysis)

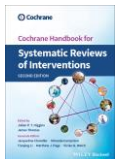
- enables identification of all eligible studies regardless of the P value, magnitude or direction of any result
- avoids possibility of missing *eligible* studies, but there is still potential for missing results in these studies, so an assessment of risk of bias is still necessary

Value of adding unpublished data to a meta-analyses of reboxetine versus placebo for acute treatment of major depression (data from Eyding et al. BMJ 2010)



Session outline

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- **assessing risk of bias due to missing results in a synthesis**



See Chapter 13, section 13.3 of the Handbook

ROB-ME framework

ROB-ME = “Risk Of Bias due to Missing Evidence”, a new framework for integrating assessment of risk of bias in syntheses due to:

- missing studies (selective non-publication of studies)
- missing study results (selective non-reporting of results)

Development informed by

- review of existing tools (Page et al. BMJ Open 2018)
- expert consensus

Only a framework at this stage (see Chapter 13 of the Handbook for more details). A structured tool is currently in development.

ROB-ME framework

1. Select which syntheses will be assessed for risk of bias
2. Consider which study results would be eligible for inclusion in each synthesis
3. Record whether any of the studies identified are missing from each synthesis because results known (or presumed) to have been generated are unavailable: the ‘known unknowns’
4. Consider whether each synthesis is likely to be biased because of the missing results in the studies identified
5. Consider whether results from additional studies are likely to be missing from each synthesis: the ‘unknown unknowns’
6. Reach an overall judgement about risk of bias due to missing evidence in each synthesis

ROB-ME framework: Step 1

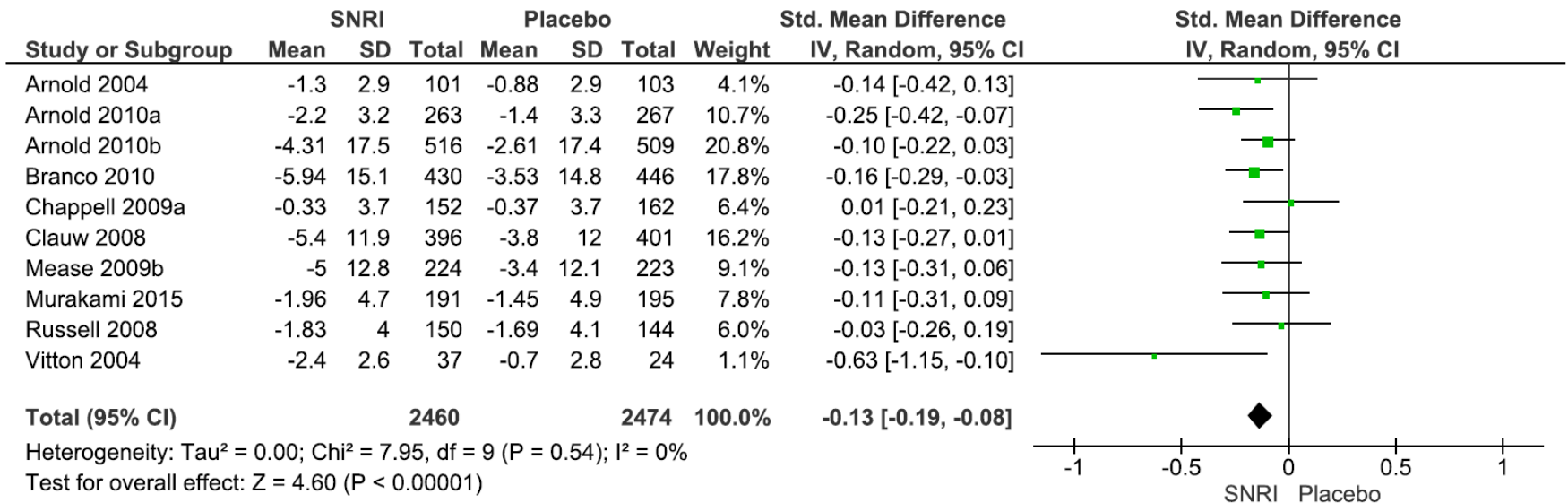
Select which syntheses (e.g. meta-analyses) will be assessed for risk of bias

- May not be feasible to assess all syntheses in the review
- Strive to assess syntheses of patient-important outcomes (typically those in ‘Summary of findings’ tables)



Synthesis 1: A meta-analysis of self-reported fatigue at the end of treatment

SMD -0.13, 95% CI -0.19, -0.08; 10 trials



Adapted from Welch P, et al. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database of Systematic Reviews 2018(2):CD010292

ROB-ME framework: Step 2

Consider which study results would be eligible for inclusion in each synthesis. That is, indicate whether the synthesis is restricted to particular:

- Intervention comparisons
- Measurement instruments
- Time points
- Methods of analysis (e.g. final versus change from baseline values; adjusted versus unadjusted estimates)
- Sources (e.g. journal articles, register entries)



Eligible study results for the meta-analysis of fatigue

Between-group comparisons of any SNRI versus placebo

Any instrument measuring fatigue. Common scales include:

- Fibromyalgia Impact Questionnaire (FIQ) fatigue subscale score
- Multidimensional Fatigue Inventory (MFI)

Mean change from baseline to end of treatment

Any source (e.g. journal articles, register entries, etc.)

ROB-ME framework: Step 3

Assemble various sources of information about each study meeting the inclusion criteria of the review

- trials register entry
- protocol
- journal articles
- clinical study reports (CSRs) and other regulatory documents
- info from authors or sponsors



ROB-ME framework: Step 3

For each study meeting the inclusion criteria of the review:

1. Compare information about what outcomes were measured with results that were available
2. Record whether the particular results sought were available for the study
3. If unavailable, consider whether this is because of the nature of the findings (e.g. statistical non-significance, unfavourable direction of effect)

ROB-ME framework: Step 3

May be reasonable to suspect selective non-reporting if:

- outcome was pre-specified yet no result is available, and no explanation for its absence is provided
- results were incompletely reported when the between-group difference was statistically non-significant
- outcome is almost certain to have been recorded but no results are available (refer to core outcome sets)
- authors have conflicts of interest that might have led them to withhold unfavourable results (refer to TACIT)

ROB-ME framework: Step 3

Results might be unavailable for a reason other than selective non-reporting, e.g.

- the outcome was clearly not measured (based on an examination of the protocol or statistical analysis plan)
- the instrument or equipment needed to measure the outcome were not available at the time the study was conducted
- the outcome was measured but data were not analysed owing to a fault in the measurement instrument, or substantial missing data

ROB-ME framework: Step 3

Results Matrix (add/delete rows and columns where necessary)

Study ID*	Number of participants analysed**	Availability of results for Synthesis 1	Availability of results for Synthesis 2	Availability of results for Synthesis 3

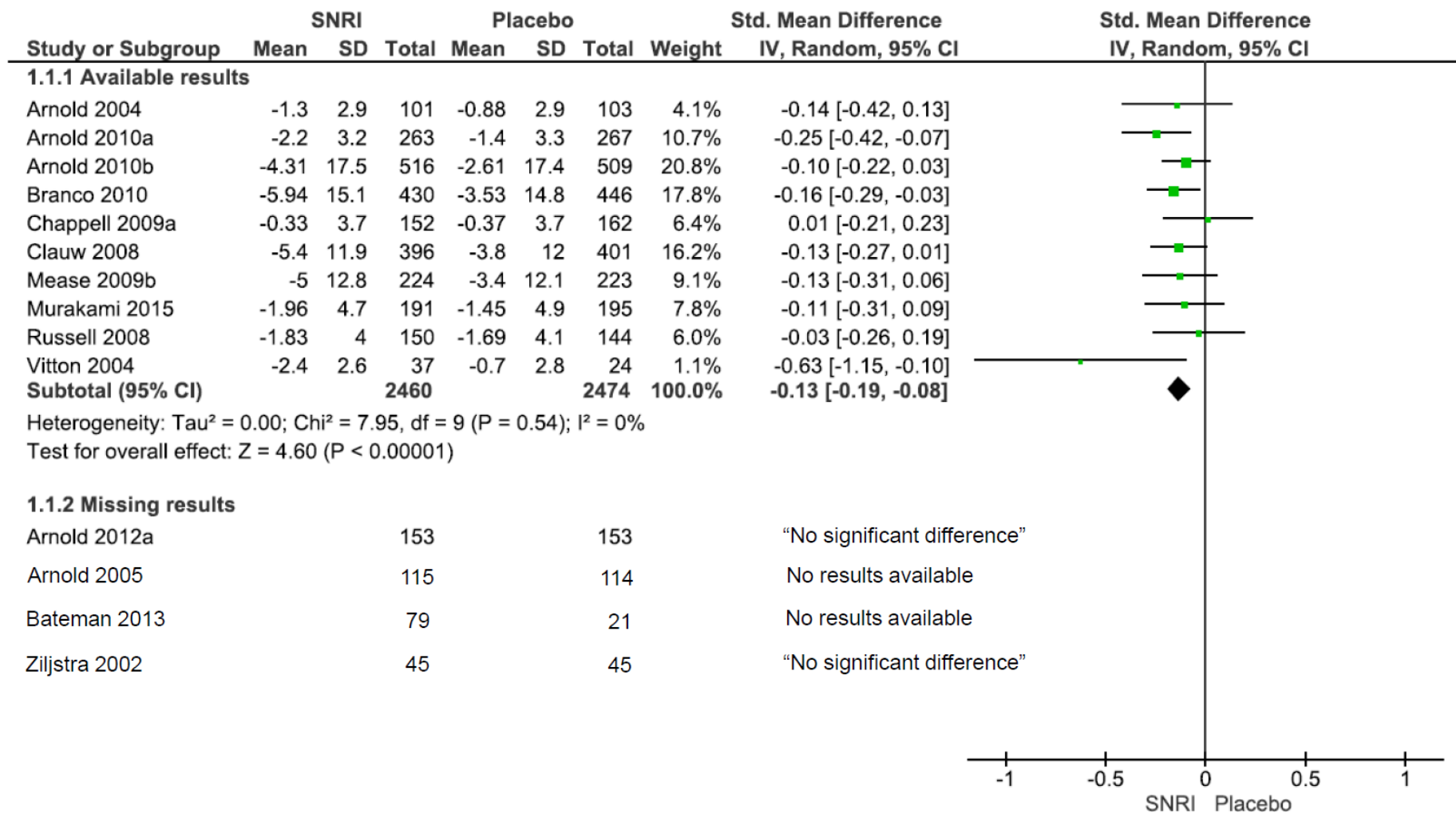
*List all studies identified, regardless of whether a report of the results is available (e.g. include those identified from trials registers only)

**If it is not clear how many participants were analysed, record the total number of participants assigned to the relevant intervention and control groups

Key for availability of results

✓	A study result is available for inclusion in the synthesis.
X	No study result is available for inclusion in the synthesis, likely because of the P value, magnitude or direction of the result generated (select if any of the relevant scenarios in Box 1 apply).
–	No study result is available for inclusion in the synthesis, for a reason unrelated to the P value, magnitude or direction of the result (select if any of the relevant scenarios in Box 1 apply).
?	Unclear whether an eligible study result was generated.

Study ID	Sample size (SNRI)	Sample size (placebo)	Synthesis assessed for risk of bias		
			Mean fatigue scores	Pain relief ≥50%	Mean anxiety scores
Arnold 2004	101	103	✓	✓	✓
Arnold 2005	115	114	X	✓	–
Arnold 2010a	263	267	✓	✓	✓
Arnold 2010b	516	509	✓	✓	✓
Arnold 2012a	153	153	X	✓	✓
Bateman 2013	79	21	X	✓	–
Branco 2010	430	446	✓	✓	✓
Chappell 2009a	152	162	✓	✓	–
Clauw 2008	399	401	✓	✓	–
Clauw 2013	100	50	–	–	–
Mease 2009b	224	223	✓	✓	–
Murakami 2015	191	195	✓	✓	✓
NCT00697787	42	43	–	–	–
Russell 2008	150	144	✓	✓	–
Trugman 2014	181	93	–	–	–
Vitton 2004	37	24	✓	✓	✓
Ziljstra 2002	45	45	X	X	?



ROB-ME framework: Step 4

Impact of known missing results:

- Data from 4934 participants included in the meta-analysis
- Data from 725 participants missing
- $725/(4934+725) = 13\%$ of total participant data known to be missing from the meta-analysis
- Consider performing sensitivity analysis (see Chapter 13 of the Handbook for more details)

ROB-ME framework: Step 5

There may be no evidence of selective non-reporting of results in the studies meeting the inclusion criteria...

...but that doesn't guarantee the synthesis is free of bias.

Additional results may be missing from the synthesis

- studies that have been undertaken but not reported in any form
- classic 'publication bias'

ROB-ME framework: Step 5

Consider whether circumstances indicate potential for there to be additional studies that were not identified because of the P value, magnitude or direction of results generated

Less concerned when reviewing set of studies known to have been initiated, irrespective of their results (e.g. prospective meta-analysis)

More concerns if:

- research area is not one for which all studies are expected to have been prospectively registered
- no trials registers were searched
- search strategy designed to retrieve studies only if they *reported* a particular outcome



ROB-ME framework: Step 5

Consider findings of graphical and statistical methods,
when appropriate

- contour-enhanced funnel plots
- tests for funnel plot asymmetry
- sensitivity analyses

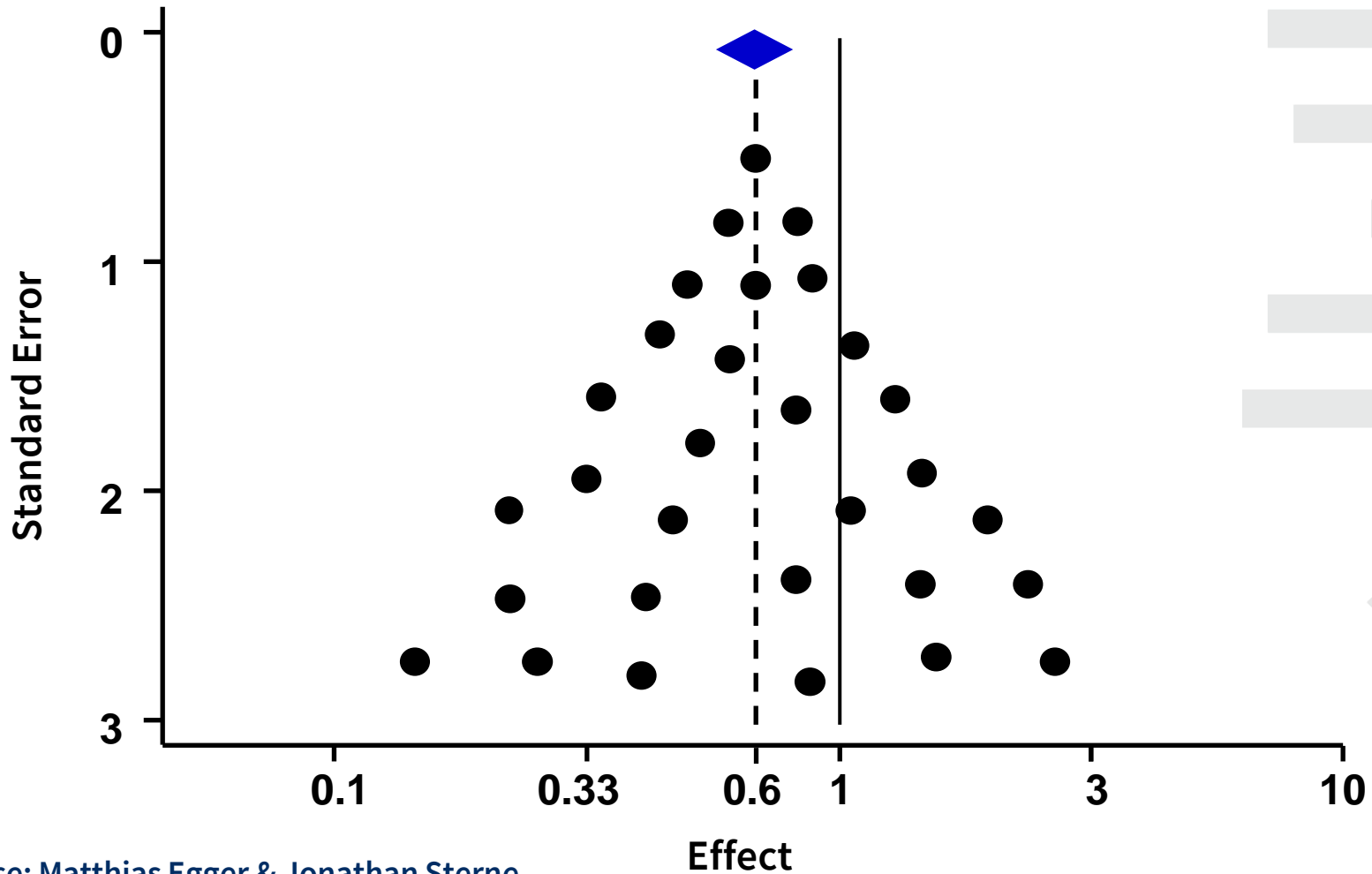


Funnel plots

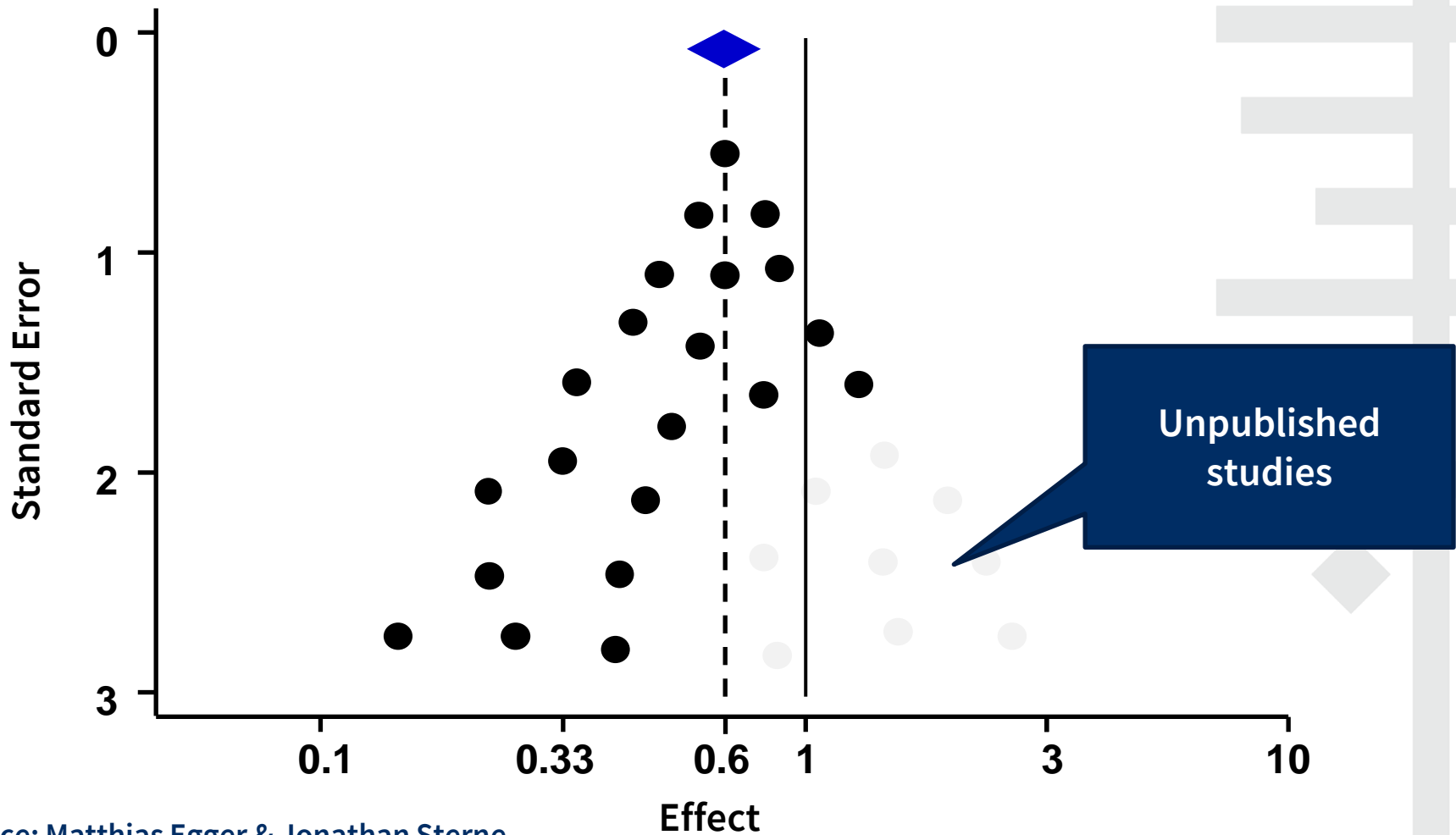
- plot effect size against study size
 - study size usually indicated by a measure like standard error
- studies will be scattered around the effect estimate
 - larger studies at the top, smaller studies further down
 - small studies expected to scatter more widely
- a symmetrical plot will look like an inverted funnel or triangle



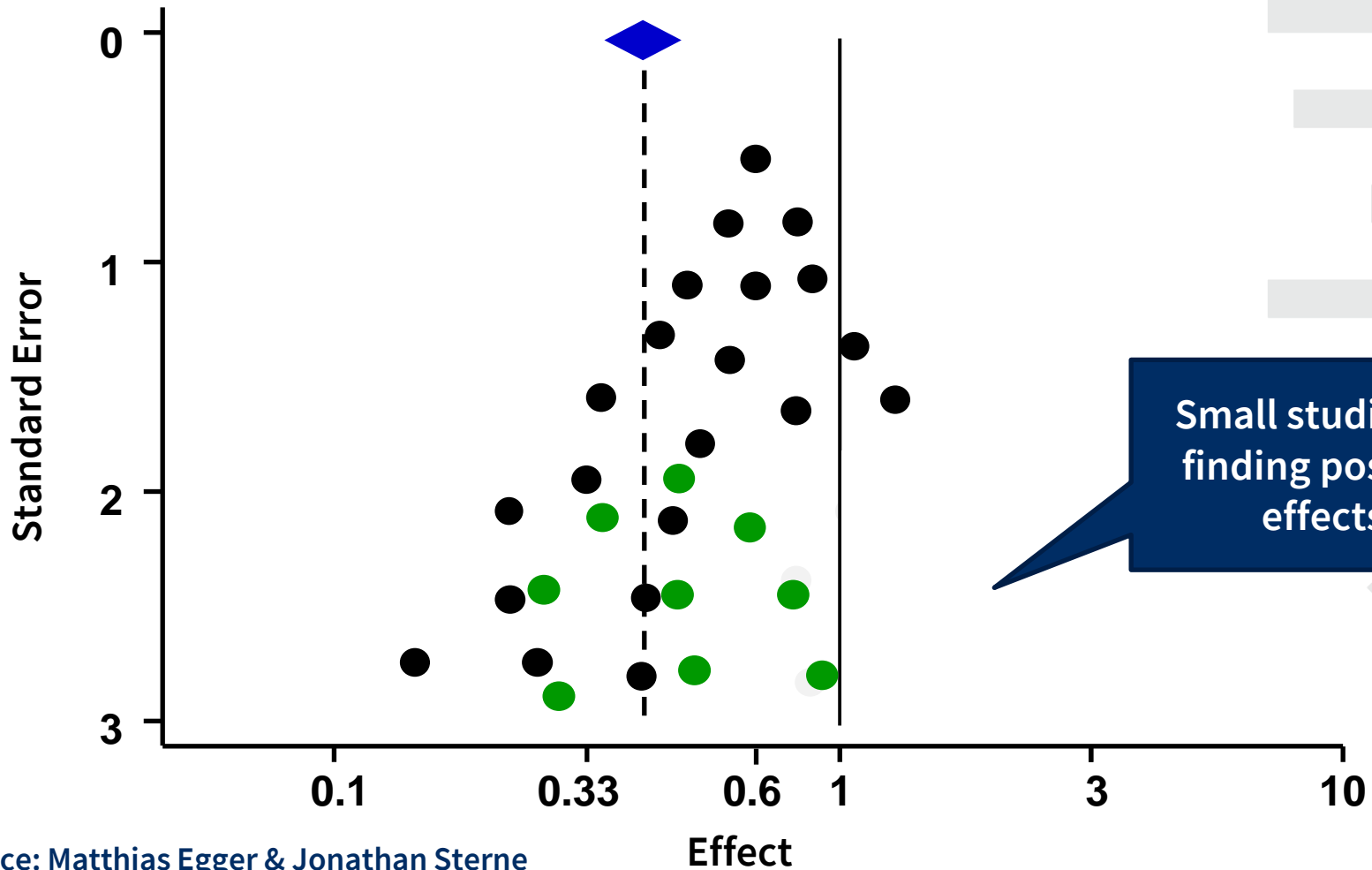
Symmetrical funnel plot



Asymmetrical funnel plot



Asymmetrical funnel plot



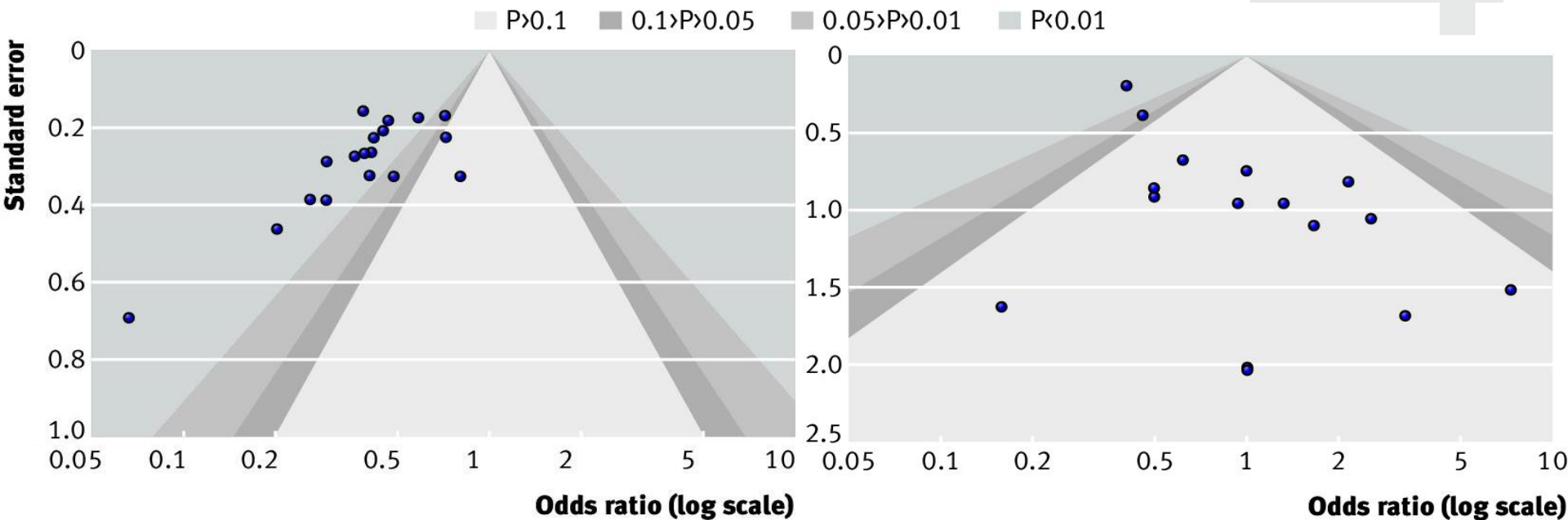
Small studies all finding positive effects

Reasons for funnel plot asymmetry

- chance
- artefact
 - some statistics are correlated to SE, e.g. OR
- clinical diversity
 - different populations different in small studies
 - different implementation different in small studies
- methodological diversity
 - greater risk of bias in small studies
- reporting biases



Contour-enhanced funnel plots



Source: Sterne JAC, Sutton AJ, Ioannidis JPA et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*2011;342:d4002 doi: 10.1136/bmj.d4002

ROB-ME framework: Step 5

Consider findings of graphical and statistical methods,
when appropriate

- contour-enhanced funnel plots
- tests for funnel plot asymmetry
- sensitivity analyses

Consult a statistician before proceeding with tests and sensitivity analyses



ROB-ME framework: Step 6

Consider the findings of each approach to reach an overall judgement of risk of bias due to missing results. For example, if:

- selective non-reporting of results was not detected in any of the studies identified...
- ...but the search for evidence was not comprehensive, or a contour-enhanced funnel plot suggests the synthesis is likely to be missing results that were systematically different from those observed...
- ...there may be reason for concern

What to include in your protocol

- planned methods for *minimizing* risk of bias due to missing results
- planned methods for *assessing* risk of bias due to missing results



Take home message

- Clear evidence of non-reporting biases in health research
- ROB-ME provides a framework for considering risk of bias due to missing results in syntheses included in your review
- A structured ROB-ME tool (in development) will integrate with other risk of bias tools (RoB 2) and facilitate appropriate interpretation of results

References

Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.0 (updated July 2019). Available from <https://training.cochrane.org/handbook>: Cochrane; 2019.

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