MONASH University

School of Public Health and Preventive Medicine

ROB-ME: a new tool for assessing risk of non-reporting biases in evidence syntheses

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ROB-ME contributors

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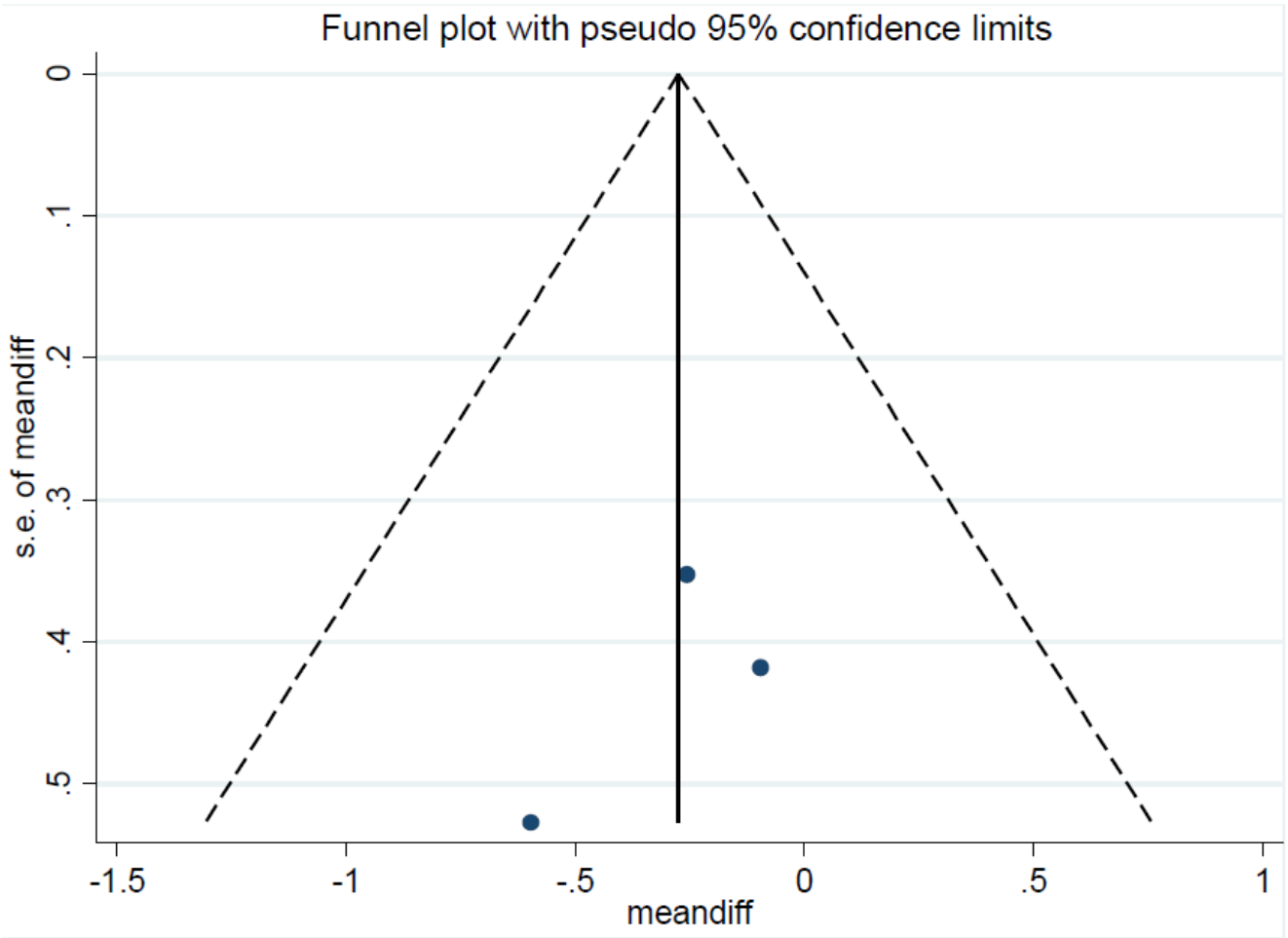
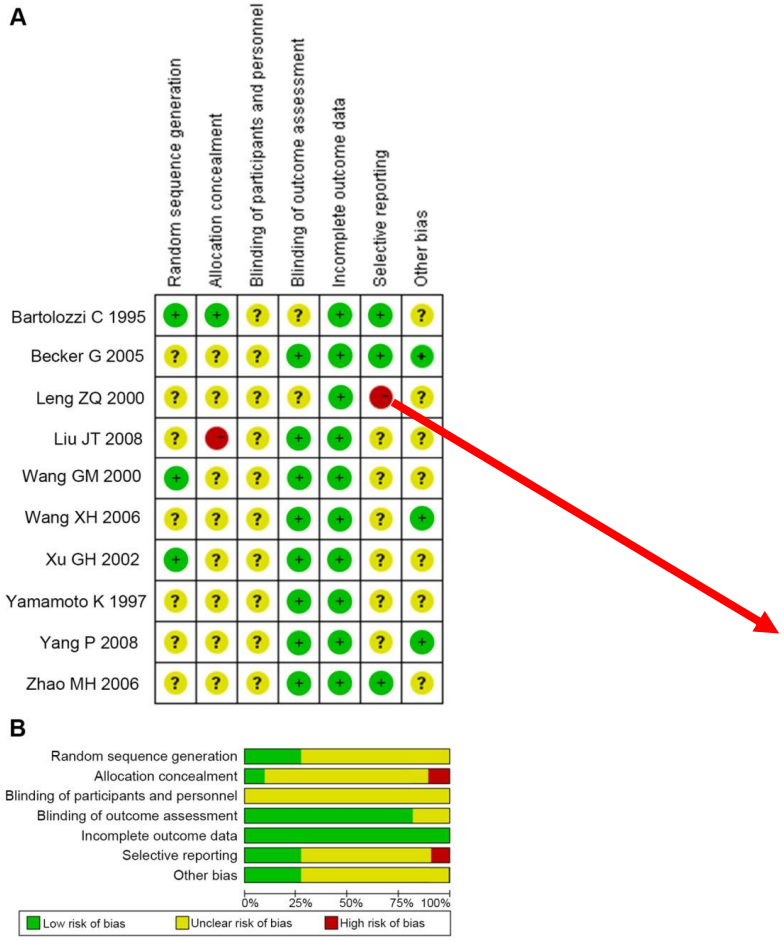
Non-reporting bias

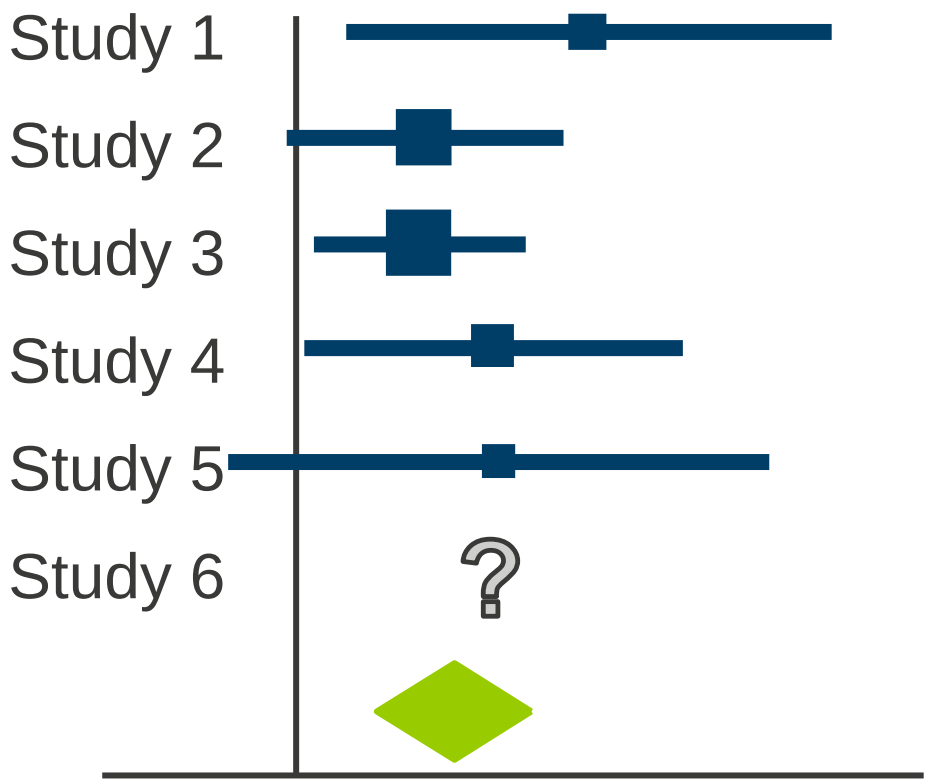
- Arises when decisions about *whether*, *when*, *where* or *how* to report results of eligible studies are influenced by the P value, magnitude or direction of the results
- Typically suppression of non-significant studies or results
- Can lead to bias in a synthesis

Current practice: too much focus on funnel plots



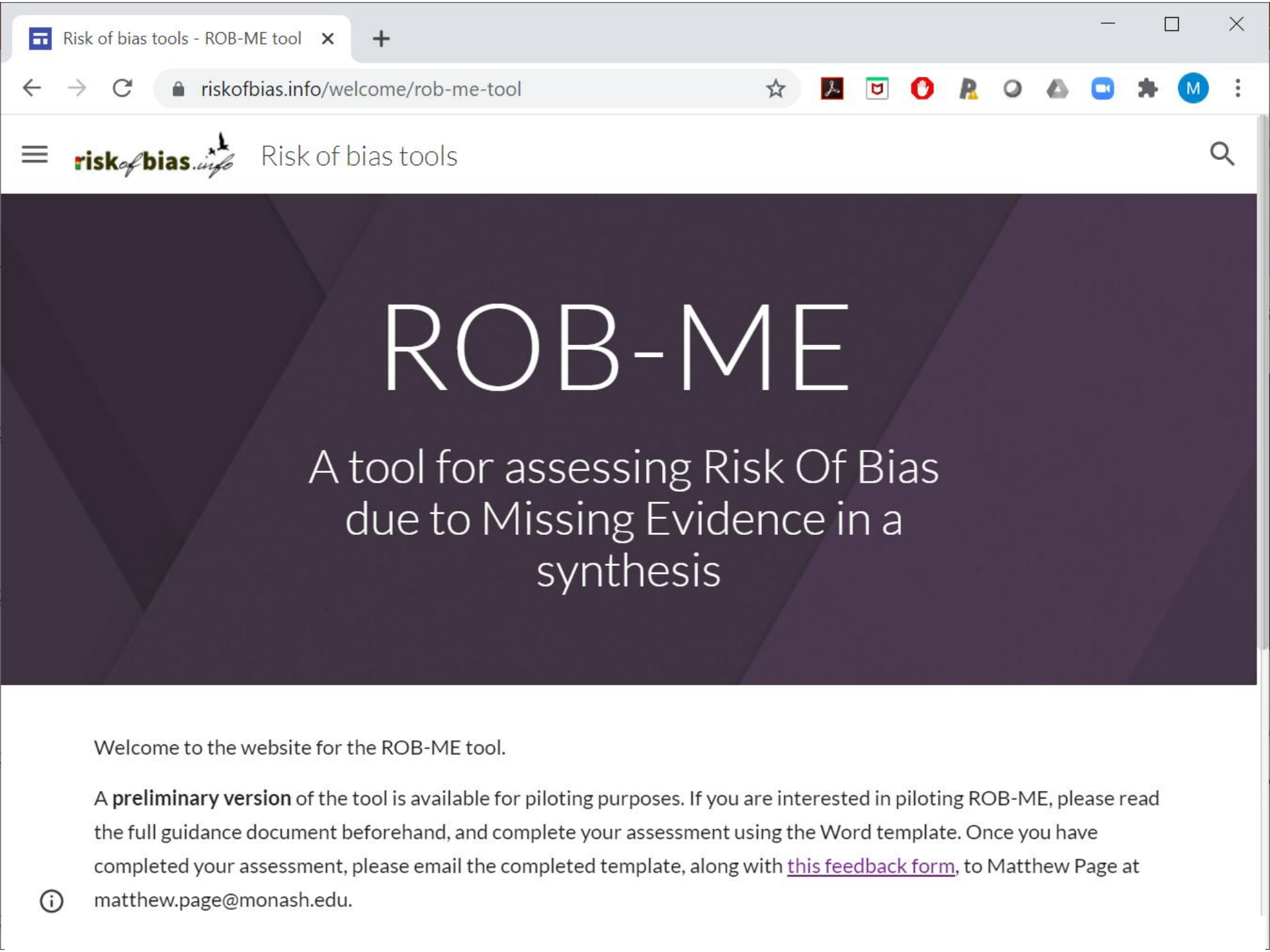
Current practice: too little focus on assessments of selective non-reporting





ROB-ME tool

- ROB-ME = “Risk Of Bias due to Missing Evidence”, a new tool for integrating assessment of risk of bias in syntheses due to:
  - missing studies (‘publication bias’)
  - missing study results (‘selective reporting bias’)
- Primarily designed to assess meta-analyses of the effects of interventions
- Development informed by
  - review of existing tools (Page et al. BMJ Open 2018)
  - expert consensus


Risk of bias tools - ROB-ME tool
riskofbias.info/welcome/rob-me-tool
Risk of bias tools
ROB-ME
A tool for assessing Risk Of Bias due to Missing Evidence in a synthesis
Welcome to the website for the ROB-ME tool.
A **preliminary version** of the tool is available for piloting purposes. If you are interested in piloting ROB-ME, please read the full guidance document beforehand, and complete your assessment using the Word template. Once you have completed your assessment, please email the completed template, along with this feedback form, to Matthew Page at matthew.page@monash.edu.

Risk of bias tools - ROB-ME tool

riskofbias.info/welcome/rob-me-tool

Risk of bias tools

PRELIMINARY VERSION

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ROB-ME tool

1. Select and define which syntheses will be assessed for risk of bias due to missing evidence

2. Determine which studies meeting the inclusion criteria for the review have missing results

3. Consider the potential for missing studies across the review

4. Assess risk of bias due to missing evidence in each synthesis

ROB-ME tool: 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)

Specify which study results would be eligible for inclusion in each synthesis (e.g. eligible measurement instruments, time points, methods of analysis)

ROB-ME tool: Step 1

List each synthesis

Define eligible results for each synthesis

Step 1. Select and define syntheses that will be assessed for risk of bias due to missing evidence		
No.	List all syntheses that will be assessed for risk of bias (e.g. random-effects meta-analysis of the effect of ibuprofen versus placebo on pain intensity at short-term (0-12 weeks) (add/delete rows where necessary)	For each synthesis, specify which results were eligible for inclusion, indicating whether the synthesis was restricted to particular: • outcome definitions (e.g. measures, metrics, time points), and; • methods of analysis (e.g. analysis populations, crude or adjusted estimates). If such information is reported elsewhere in the systematic review, either indicate the relevant section of the review or copy the information here.
1		
2		
3		

ROB-ME tool: Step 2

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 tool: Step 2

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 results of interest 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) or some other reason (e.g. outcome not measured)

ROB-ME tool: Step 2

Record availability of results for each study

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

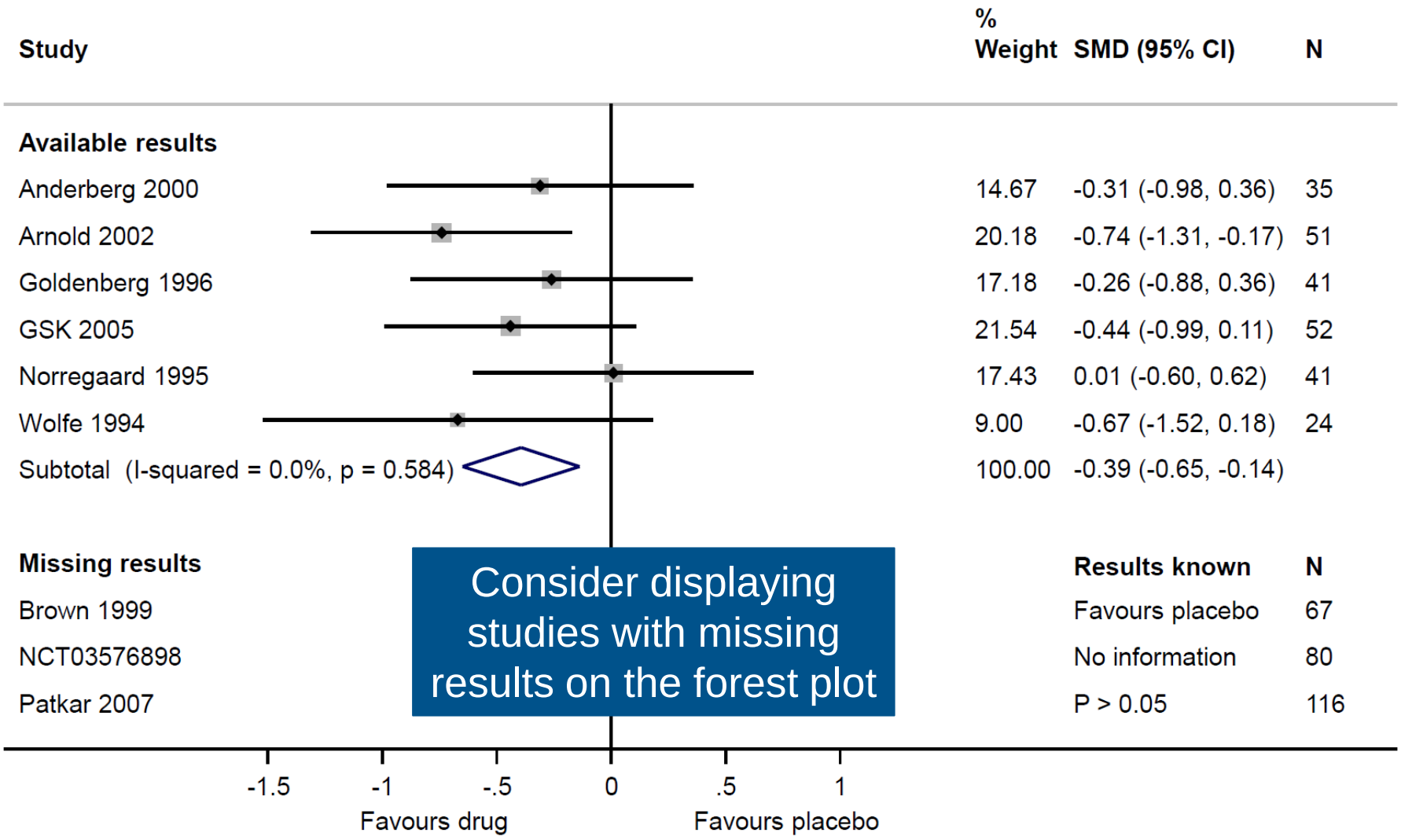
✓	A study result is available for inclusion in the synthesis.
X	No study result is available for inclusion in the synthesis, likely because of the P value, magnitude or direction of the result generated (select if any of the relevant scenarios in Box 1 apply).
–	No study result is available for inclusion 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.

Matrix template modified from Kirkham et al. BMJ 2018;362:k3802

Study ID	Number of participants analysed	Synthesis assessed for risk of bias		
		Mean fatigue scores	Pain relief ≥50%	Mean anxiety scores
Anderberg 2000	35	✓	✓	✓
Arnold 2002	51	✓	–	X
Brow		X	✓	–
Goldenberg 1996	41	✓	✓	✓
GSK 2005	52	✓	✓	✓
NCT03576898	80	X	✓	–
Norregard 1995	41	✓	✓	✓
Patkar 2007	116	X	X	?
Wolfe 1994	24	✓	–	–

Results not reported, likely because P>0.05

ROB-ME tool: Step 2



ROB-ME tool: Step 3

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

ROB-ME tool: Step 3

More concerns about additional missing studies 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 tool: Step 3

Answer questions

Step 3. Consider the potential for missing studies across the review

Answer the following questions to determine whether circumstances indicate potential for some eligible studies not being identified because of the P value, magnitude or direction of the results generated (answer these questions once, in relation to the systematic review as a whole).

3.1. Were prospectively registered studies or studies identified for a prospective meta-analysis the only type of study eligible for inclusion in the review? Y / N

3.2. If N to 3.1: Would you expect information about every eligible study to be made publicly available regardless of their results? NA / Y / PY / PN / N

3.3. If Y/PY to 3.2: Were you likely to have found all eligible studies regardless of their results? NA / Y / PY / PN / N

Check the box below if the response to 3.1 was 'No' and the response to 3.2 or 3.3 was 'No' or 'Probably no'

☐ Circumstances indicate potential for some eligible studies not being identified because of the P value, magnitude or direction of the results generated

Provide any relevant information to support responses

Draw conclusion about potential for missing studies

ROB-ME tool: Step 4

Assess risk of bias due to missing evidence in each synthesis

- Similar structure as RoB 2 and ROBINS-I
- Signalling questions to facilitate risk of bias judgements
  - Yes', 'Probably yes', 'Probably no', 'No', 'No information'
- Risk of bias judgements follow from answers to signalling questions (can be over-ridden)
  - 'Low risk of bias', 'Some concerns', 'High risk of bias'

ROB-ME tool: Step 4

Answer signalling questions

Details of the synthesis being assessed for risk of bias	
Specify the synthesis	
Specify the synthesized result (e.g. estimate and 95% CI)	
Specify the number of included studies and participants	
Risk of bias assessment	
Signalling questions	**Response options**
The following questions relate to the within-study assessment of non-reporting bias ('known unknowns')	
4.1. Of the studies identified, was there any for which no result was available for inclusion in the synthesis, likely because of the P value, magnitude or direction of the result generated (refer to Step 2)?	Y / N
4.2. If Y to 4.1: Is it likely that there would be a notable change to the synthesized effect estimate if the omitted results had been included?	NA / Y / PY / PN / N / NI
4.3. Of the studies identified, was there any for which it was unclear whether an eligible result was generated (refer to Step 2)?	Y / N
4.4. If Y to 4.3: Is it likely that there would be a notable change to the synthesized effect estimate if the potentially omitted results had been included?	NA / Y / PY / PN / N / NI
The following questions relate to the across-study assessment of non-reporting bias ('unknown unknowns')	
4.5 Do circumstances indicate potential for eligible studies not being identified because of the P value, magnitude or direction of the results generated (refer to Step 3)?	Y / PY / PN / N
4.6. If Y/PY to 4.5: Is it likely that studies not identified had results that were eligible for inclusion in the synthesis?	NA / Y / PY / PN / N
4.7. If Y to 4.1 or 4.3 or Y/PY to 4.5: Does the pattern of observed study results suggest that the synthesis is likely to be missing results that were systematically different (in terms of P value, magnitude or direction) from those observed?	NA / Y / PY / PN / N
4.8. If Y/PY/NI to 4.2, 4.4, 4.6 or 4.7: Did sensitivity analyses suggest that the synthesized result was biased due to missing results?	NA / Y / PY / PN / N
Risk of bias judgement	Low / High / Some concerns
Optional: What is the predicted direction of bias for this synthesis?	

Reach risk-of-bias judgement

Y: 'Yes'; PY: 'Probably yes'; PN: 'Probably no'; N: 'No'; NA: 'Not applicable'; NI:

ROB-ME tool: Step 4 signalling questions

- Are any studies included in the review missing or potentially missing from the synthesis because of the P value, magnitude or direction of effect? *(refer to Step 2)*
- If so, is a notable change to the synthesized result likely?
- Do circumstances indicate potential for additional missing studies? *(refer to Step 3)*
- If so, are missing studies likely to have eligible results?
- Does the pattern of results suggest the synthesis is missing studies/results that are different from those observed?
- Do sensitivity analysis suggests the synthesis is biased?

ROB-ME tool: Step 4 signalling questions

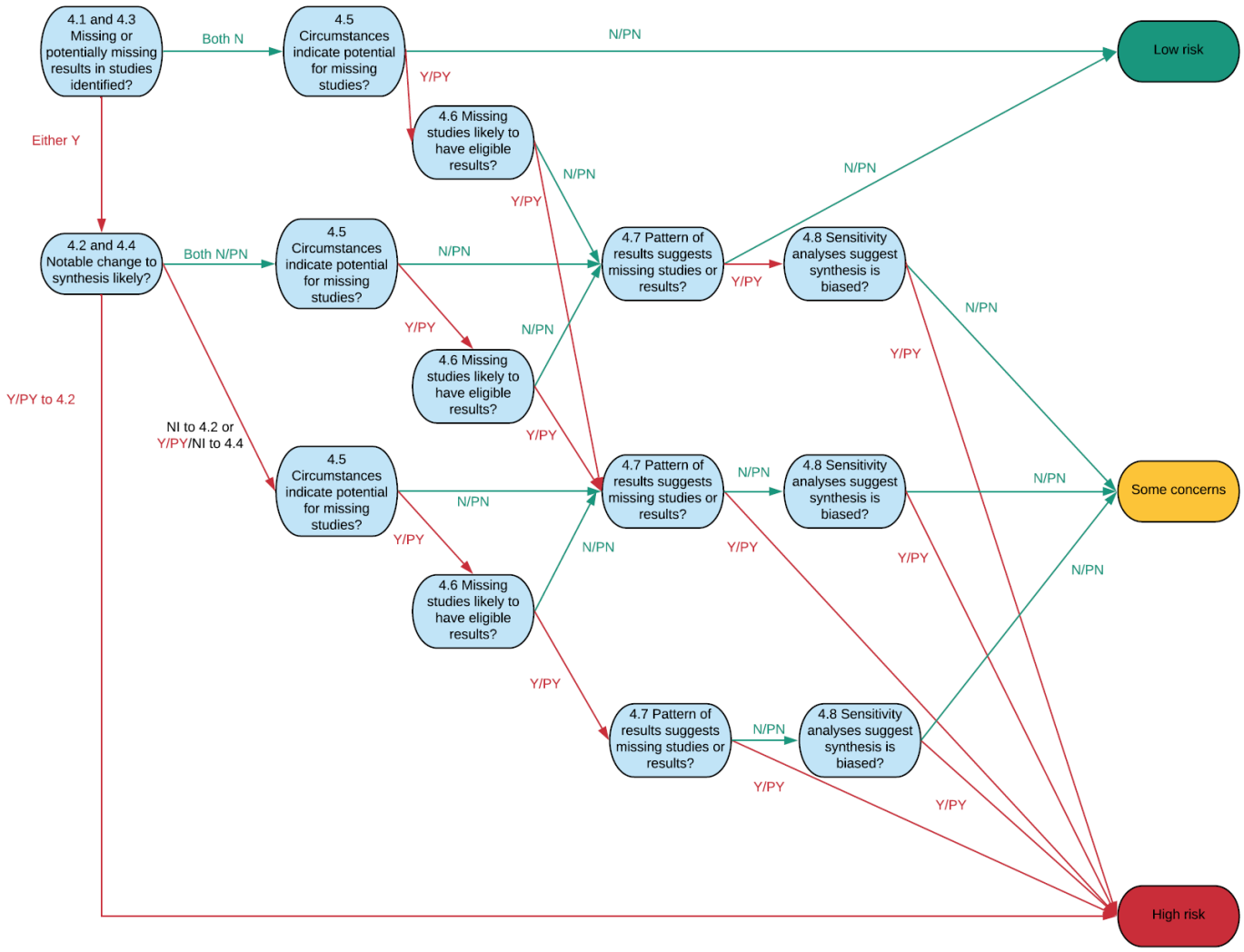
Step 4. Assess risk of bia

Responses underlined in

Guidance for answering signalling questions available in full guidance document and cribsheet

Details of the synthesis		
Specify the synthesis	For example, "Random effects meta-analysis of the effect of ibuprofen versus placebo on pain intensity at short-term (0-12 weeks)"	
Specify the synthesized result (e.g. estimate and 95% CI)	For example, "Mean difference -15.00, 95% CI -23.99, -6.01"	
Specify the number of included studies and participants	For example, "10 studies (4,934 participants)"	
Risk of bias assessment		
Signalling questions	**Elaboration**	**Response options**
The following questions relate to the within-study assessment of non-reporting bias ('known unknowns')		
4.1. Of the studies identified, was there any for which no result was available for inclusion in the synthesis, likely because of the P value, magnitude or direction of the result generated (refer to Step 2)?	***Note: In software to be developed to implement the tool, responses to this question will be prefilled automatically based on what users enter into the Results Matrix (Step 2).*** **Answer 'Yes'** if any of the studies in the Results Matrix were marked with an 'X' for this particular synthesis.	Y / N
4.2. If Y to 4.1: Is it likely that there would be a notable change to the synthesized effect estimate if the omitted results had been included?	First, consider whether the amount of missing evidence is large enough that its omission is likely to lead to a notable change in the synthesized point estimate observed (regardless of how large the observed estimate is). Second, if known, consider the direction of effect (e.g. favours experimental intervention versus favours control) for any studies missing from the synthesis. It may be helpful to append any known studies that are missing from the synthesis to a forest plot, for example using the template presented in Figure 1. **Answer 'Yes / Probably yes'** if the amount of missing information is non-trivial and, if known, the direction of effect in omitted studies differs from the direction of effect for the synthesis, and hence the omission is likely to lead to a notable change in the magnitude of the synthesized point estimate. If the meta-analysis was estimated using a fixed-effect model, consider the total weight of the studies missing from the synthesis. If the weight of missing studies was comparable to that of the available studies, there is reason for concern (even more so if the direction of effect in omitted studies differs from	NA / Y / PY / PN / N / NI

Algorithm for ROB-ME judgement



Piloting

- Preliminary guidance and tool template for ROB-ME available at riskofbias.info
- Piloting phase open
  - seeking improvements to wording and clarity, which sections need more guidance
  - piloters are requested to email their assessments and a feedback form to matthew.page@monash.edu
- We discourage use of the tool in systematic reviews or methodological studies until the final version is released.

Take home message

- ROB-ME provides a framework for considering risk of bias due to missing evidence in syntheses included in your review

- ROB-ME tool will integrate with other risk of bias tools (e.g. RoB 2) and facilitate appropriate interpretation of results

- See riskofbias.info for more detail