Cochrane Training

Cochrane Learning live webinar: November 11th 2020
RoB2: Overall risk of bias

RoB 2: Overall risk of bias and incorporating RoB assessments into reviews

Jelena Savović
Population Health Sciences
Bristol Medical School

With special thanks to Julian Higgins, Jonathan Sterne, Matthew Page, Roy Elbers, Barney Reeves, Asbjørn Hróbjartsson, Isabelle Boutron, Luke McGuinness, Vincent Cheng and all RoB 2 collaborators

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Session outline

- Brief overview of RoB 2
- Reaching the overall RoB 2 judgement for the result
- Options for incorporating RoB 2 into synthesis
  - Primary analysis restricted to studies at low risk of bias
  - Present multiple (stratified) analyses and explore the impact of RoB
  - Present all studies and provide a narrative discussion
- Questions

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RoB 2 process

For each outcome (each key synthesis in the review)

For each study

Risk of bias assessment for a specific result

1. Specify result being assessed	2. Specify effect of interest	3. List sources of information used to inform assessment
4. Answer signalling questions	5. Judge risk of bias for each domain	6. Judge overall risk of bias for the result

For the synthesis

Integrate judgement(s) into results and conclusions

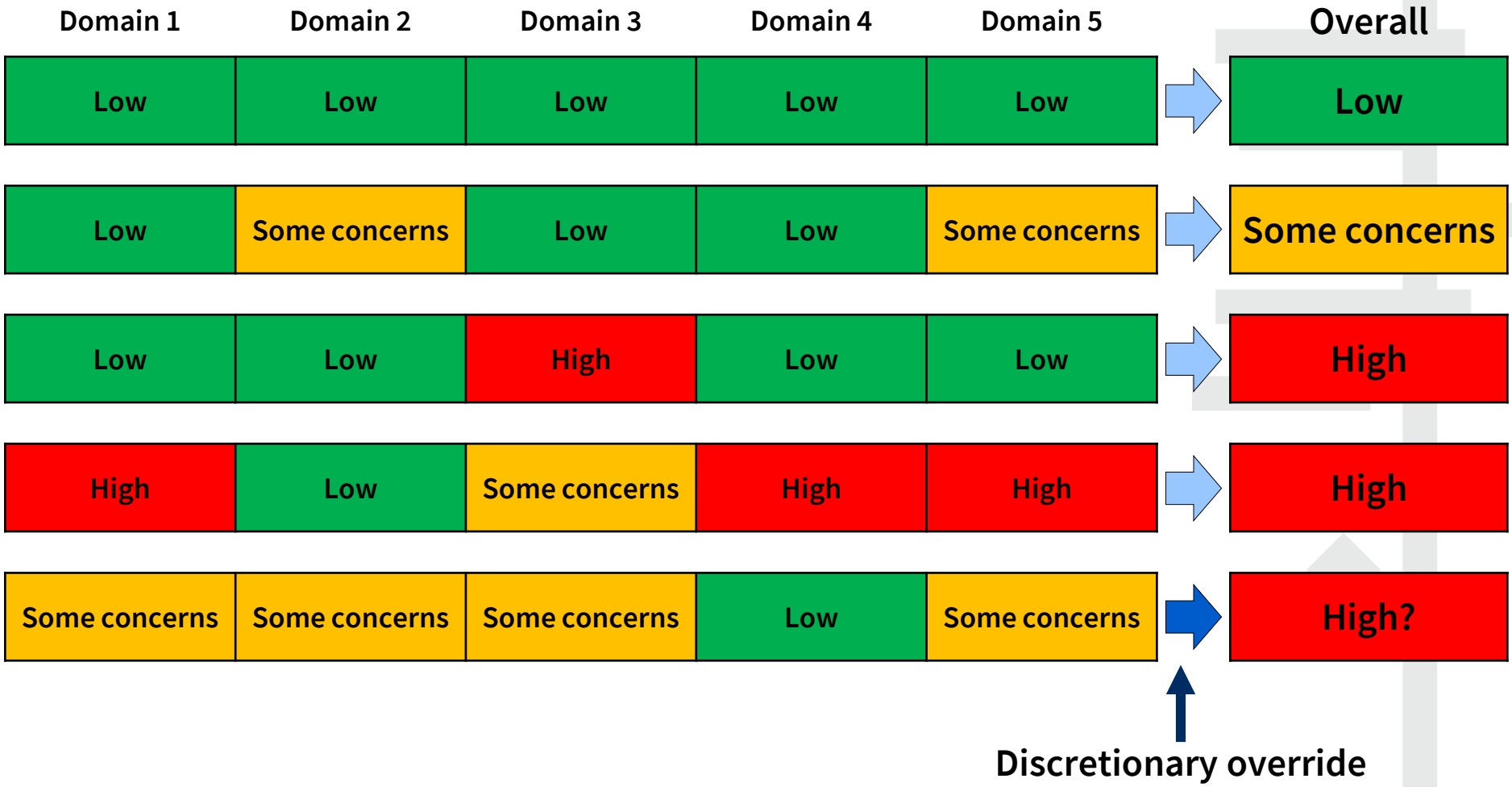
Risk of bias for a parallel group trial with interest in the effect of assignment to intervention

Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y/PY/PN/N/NI
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y/PY/PN/N/NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y/PY/PN/N/NI
	Risk of bias judgement	Low/High/Some concerns
	Optional: What is the predicted direction of bias arising from the randomization process?	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y/PY/PN/N/NI
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y/PY/PN/N/NI
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA/Y/PY/PN/N/NI
	2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	NA/Y/PY/PN/N/NI
	2.5. If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA/Y/PY/PN/N/NI
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y/PY/PN/N/NI
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA/Y/PY/PN/N/NI
	Risk of bias judgement	Low/High/Some concerns
	Optional: What is the predicted direction of bias due to deviations from intended interventions?	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y/PY/PN/N/NI
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA/Y/PY/PN/N
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA/Y/PY/PN/N/NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA/Y/PY/PN/N/NI
	Risk of bias judgement	Low/High/Some concerns
	Optional: What is the predicted direction of bias due to missing outcome data?	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y/PY/PN/N/NI
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y/PY/PN/N/NI
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y/PY/PN/N/NI
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA/Y/PY/PN/N/NI
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA/Y/PY/PN/N/NI
	Risk of bias judgement	Low/High/Some concerns
	Optional: What is the predicted direction of bias in measurement of the outcome?	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y/PY/PN/N/NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y/PY/PN/N/NI
	5.3 ... multiple eligible analyses of the data?	Y/PY/PN/N/NI
	Risk of bias judgement	Low/High/Some concerns
	Optional: What is the predicted direction bias due to selection of the reported results?	
Overall bias	**Risk of bias judgement**	Low/High/Some concerns
	Optional: What is the overall predicted direction of bias for this outcome?	

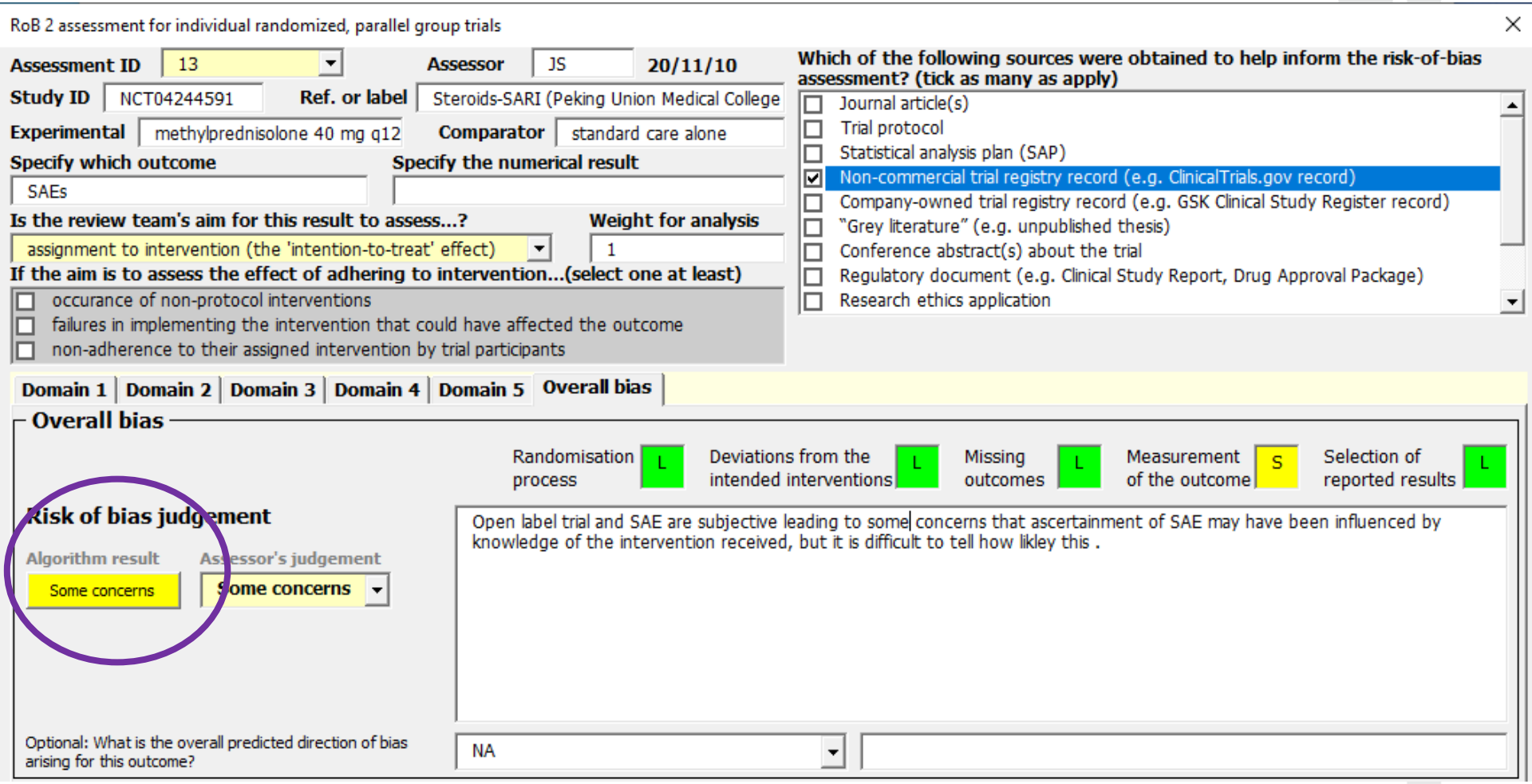
Overall risk of bias judgement

Low risk of bias	The study is judged to be at low risk of bias for all domains for this result.
Some concerns	The study is judged to be at some concerns in at least one domain for this result.
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result. OR The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Suggested overall risk of bias judgement



RoB 2 Excel tool includes a suggested overall judgement



Available to download from www.riskofbias.info

Cochrane risk of bias summary

Risk of bias for analysis 1.4 Submaximal cardiorespiratory fitness (gas exchange threshold) Open in table viewer

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Moalla 2006	~	✓	✓	~	~	~
Westhoff-Bleck 2013	~	✓	~	~	~	~
Duppen 2015	✓	✓	✓	~	~	~
Avila 2016	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~

Reproduced from: Williams et al. Physical activity interventions for people with congenital heart disease. *CDSR* 2020 (10): CD013400. DOI: 10.1002/14651858.CD013400.pub2.

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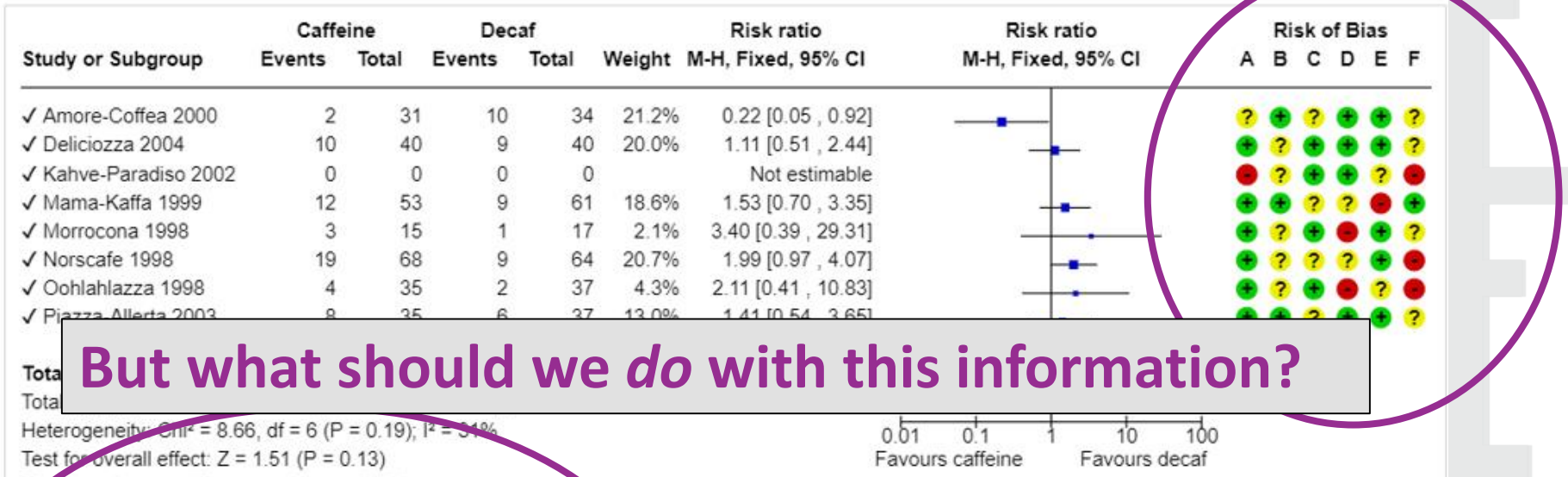
RevMan Web

Investigate sensitivity - 1.1 Headache

Odds ratio | **Risk ratio** | Risk difference | **Fixed effect** | Random effects | Scale 100 | Save image



Study or Subgroup	Caffeine Events	Caffeine Total	Decaf Events	Decaf Total	Weight	Risk ratio M-H, Fixed, 95% CI
✓ Amore-Coffea 2000	2	31	10	34	21.2%	0.22 [0.05 , 0.92]
✓ Deliciozza 2004	10	40	9	40	20.0%	1.11 [0.51 , 2.44]
✓ Kahve-Paradiso 2002	0	0	0	0		Not estimable
✓ Mama-Kaffa 1999	12	53	9	61	18.6%	1.53 [0.70 , 3.35]
✓ Morrocona 1998	3	15	1	17	2.1%	3.40 [0.39 , 29.31]
✓ Norscafe 1998	19	68	9	64	20.7%	1.99 [0.97 , 4.07]
✓ Oohlahlazza 1998	4	35	2	37	4.3%	2.11 [0.41 , 10.83]
✓ Piazza-Allerta 2003	8	35	6	37	13.0%	1.41 [0.54 , 3.65]

Risk ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours caffeine Favours decaf

Risk of Bias A B C D E F

But what should we *do* with this information?

Tota

Tota

Heterogeneity: Chi² = 8.66, df = 6 (P = 0.19); I² = 31%

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions: Headache

(C) Bias due to missing outcome data: Headache

(D) Bias in measurement of the outcome: Headache

(E) Bias in selection of the reported result: Headache

(F) Overall bias: Headache

https://documentation.cochrane.org/revman-kb/assessing-risk-of-bias/how-to-use-risk-of-bias-2-0-rob-2-0-tool-in-revman-web

\https://documentation.cochrane.org/revman-kb

Incorporating bias assessments in analyses

Cochrane Handbook, Chapter 7:

" It is not appropriate to present analyses and interpretations while ignoring flaws identified during the assessment of risk of bias"

Incorporating bias assessments in analyses: Suggested approaches

Cochrane Handbook, Chapter 7

Suggested approaches:

1) Primary analysis restricted to studies at low risk of bias (or low + some concerns)
2) Present multiple (stratified) analyses / Explore the impact of RoB
3) Present all studies and provide a narrative discussion

Incorporating bias assessments in analyses (1)

1) **Restrict primary synthesis to studies at low risk of bias / low risk & some concerns**

- based on overall risk of bias judgment for the result
- relatively simple with RoB 2 due to overall RoB judgment
- sensitivity analysis including all studies is encouraged

Incorporating bias assessments in analyses (1)

1) **Restrict primary synthesis to studies at low risk of bias / low risk & some concerns**

- based on overall risk of bias judgment for the result
- relatively simple with RoB 2 due to overall RoB judgment
- could also explore specific domains, if deemed useful
- sensitivity analysis including all studies is encouraged

What are the potential problems with this approach?

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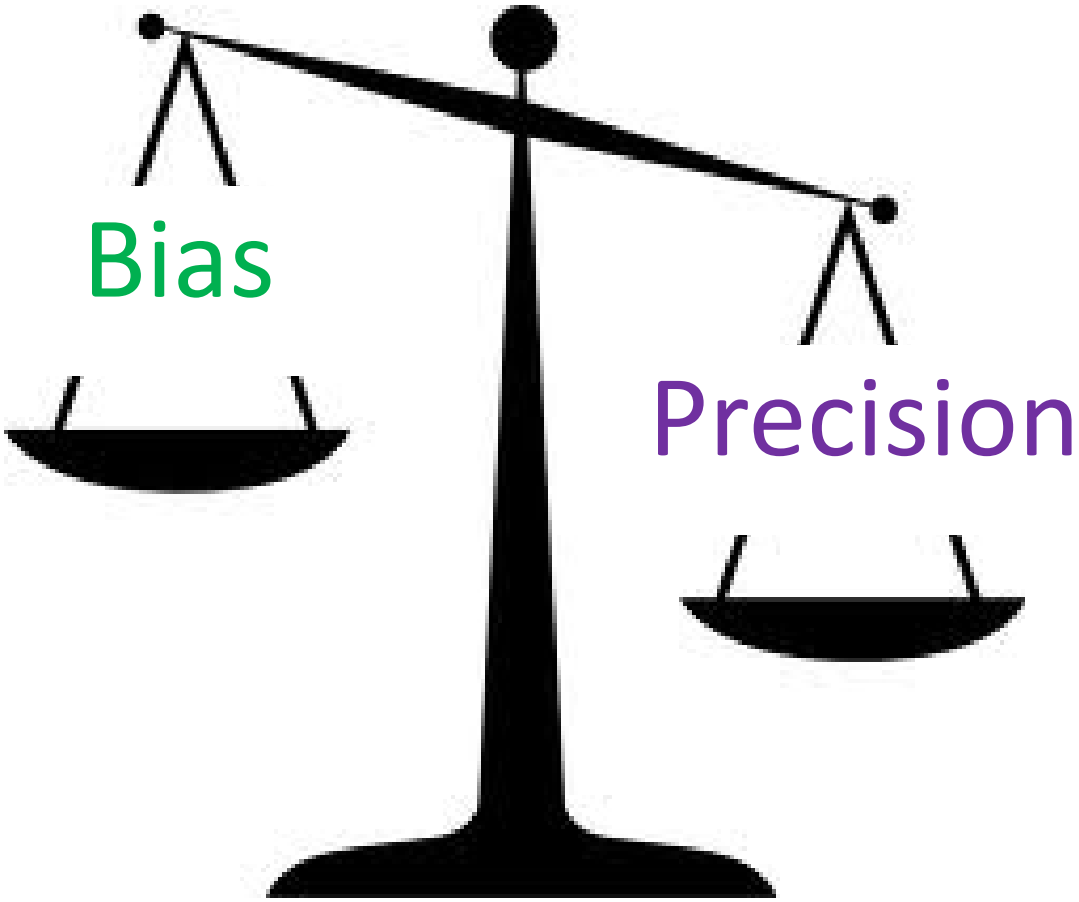


Incorporating bias assessments in analyses (2)

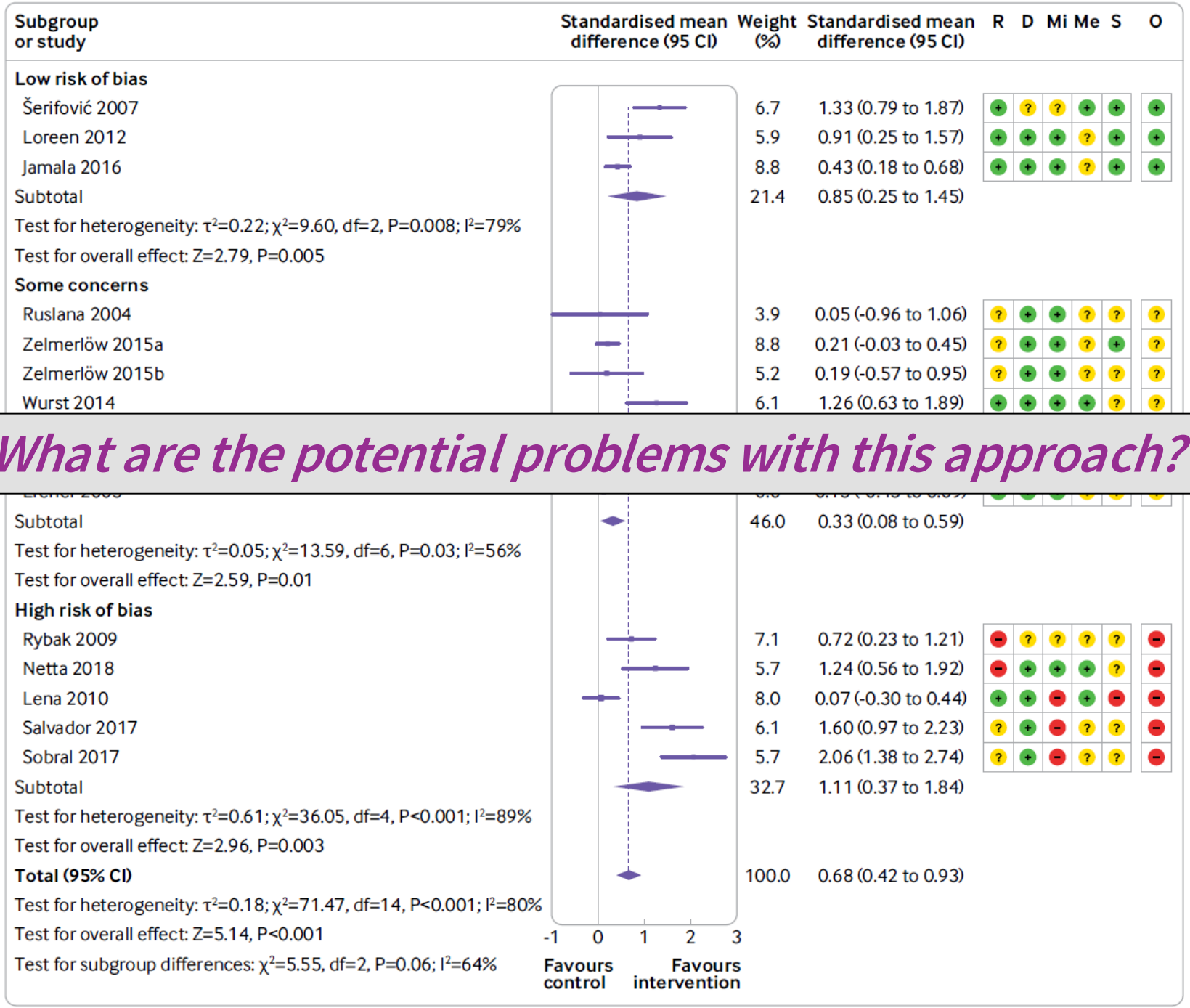
Bias is a key potential source of heterogeneity – we can use the same tools that are used to explore heterogeneity:

- *Subgroup analysis*
- Formal test for a difference between subgroups
- *Meta-regression (calculate difference or ratio of subgroup estimates and CI)*

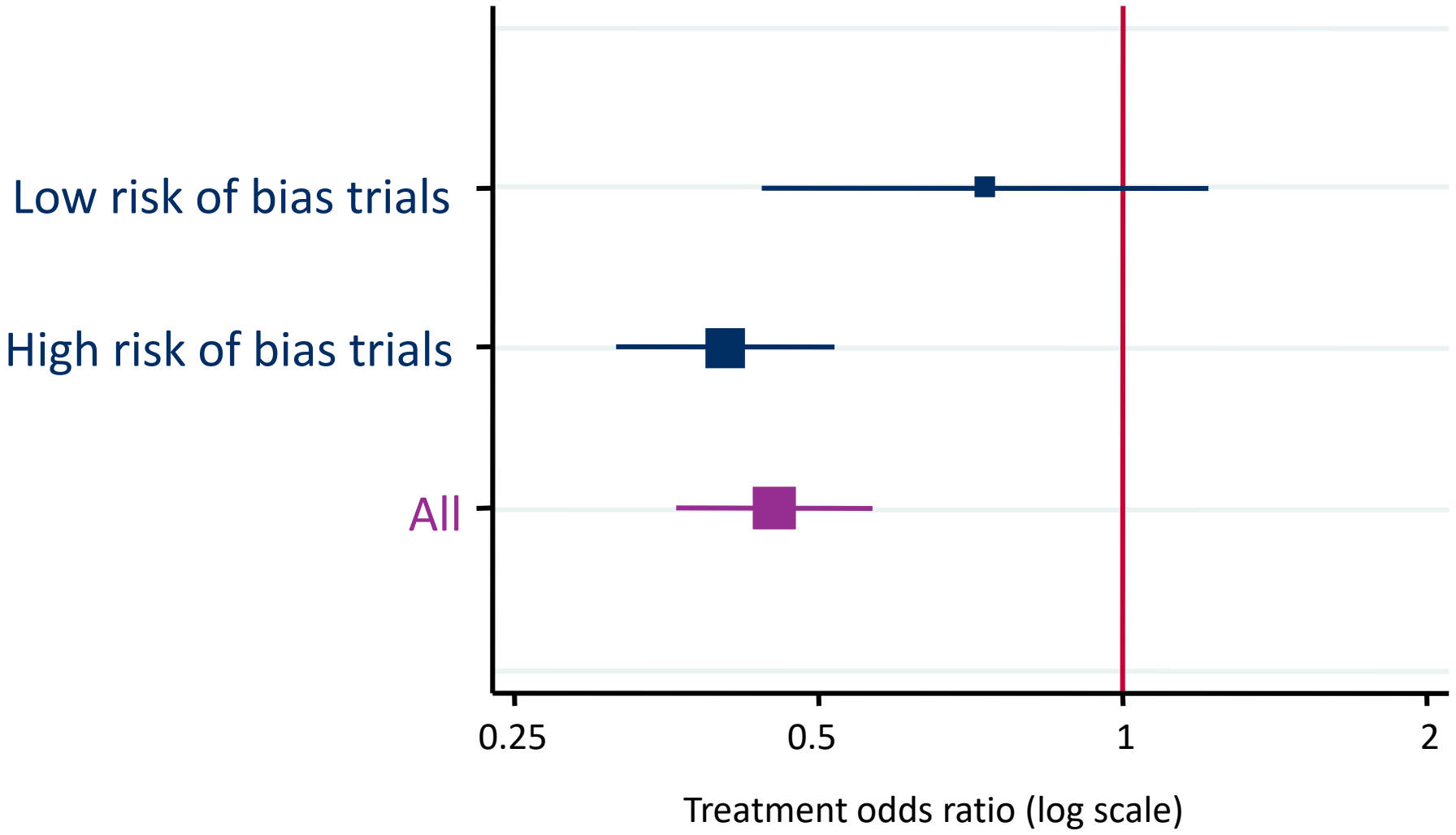
Incorporating bias assessments in analyses (2)

2) Provide multiple stratified analyses (subgroup analysis):

- Forest plot stratified by overall risk of bias
- Multiple estimates:
  - the ‘overall’ estimate (all studies)
  - Subgroup estimate for lower risk of bias studies
  - Subgroup estimate for higher risk of bias studies


Subgroup or study
Standardised mean difference (95 CI)
Weight (%)
Standardised mean difference (95 CI)
R D Mi Me S O
Low risk of bias
Šerifović 2007 6.7 1.33 (0.79 to 1.87)
Loreen 2012 5.9 0.91 (0.25 to 1.57)
Jamala 2016 8.8 0.43 (0.18 to 0.68)
Subtotal 21.4 0.85 (0.25 to 1.45)
Test for heterogeneity: τ²=0.22; χ²=9.60, df=2, P=0.008; I²=79%
Test for overall effect: Z=2.79, P=0.005
Some concerns
Ruslana 2004 3.9 0.05 (-0.96 to 1.06)
Zelmerlöw 2015a 8.8 0.21 (-0.03 to 0.45)
Zelmerlöw 2015b 5.2 0.19 (-0.57 to 0.95)
Wurst 2014 6.1 1.26 (0.63 to 1.89)
What are the potential problems with this approach?
Subtotal 46.0 0.33 (0.08 to 0.59)
Test for heterogeneity: τ²=0.05; χ²=13.59, df=6, P=0.03; I²=56%
Test for overall effect: Z=2.59, P=0.01
High risk of bias
Rybak 2009 7.1 0.72 (0.23 to 1.21)
Netta 2018 5.7 1.24 (0.56 to 1.92)
Lena 2010 8.0 0.07 (-0.30 to 0.44)
Salvador 2017 6.1 1.60 (0.97 to 2.23)
Sobral 2017 5.7 2.06 (1.38 to 2.74)
Subtotal 32.7 1.11 (0.37 to 1.84)
Test for heterogeneity: τ²=0.61; χ²=36.05, df=4, P<0.001; I²=89%
Test for overall effect: Z=2.96, P=0.003
Total (95% CI) 100.0 0.68 (0.42 to 0.93)
Test for heterogeneity: τ²=0.18; χ²=71.47, df=14, P<0.001; I²=80%
Test for overall effect: Z=5.14, P<0.001
Test for subgroup differences: χ²=5.55, df=2, P=0.06; I²=64%
-1 0 1 2 3
Favours control
Favours intervention

Example 1. Clozapine versus neuroleptic medication for schizophrenia



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Poll 1

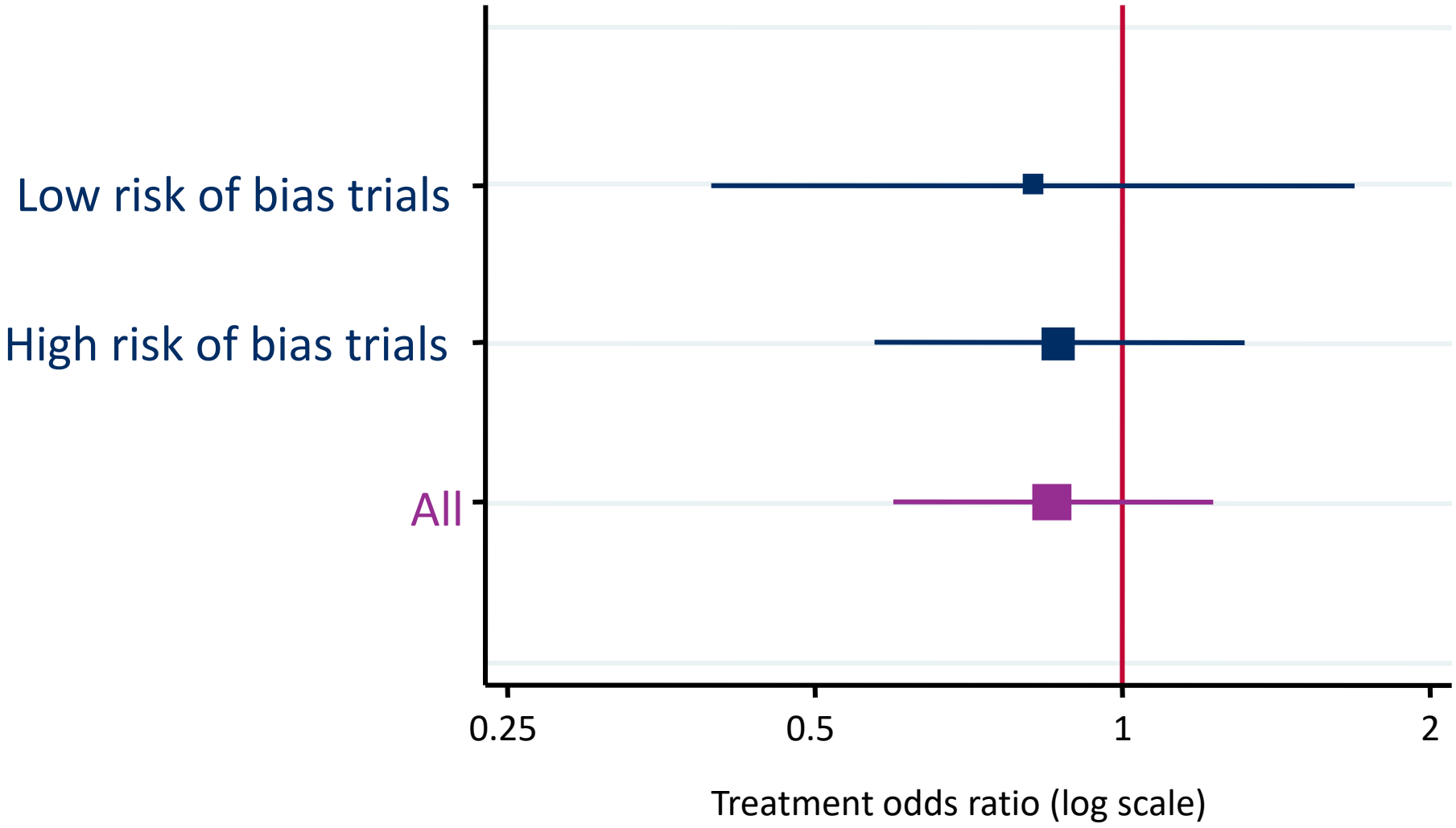
Should your main estimate (the one for SoF) be:

A. Based on low risk of bias trials only

B. Based on high risk of bias trials only

C. Based on all trials

Example 2. Ovulation suppression compared to Danazol for endometriosis



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Poll 2

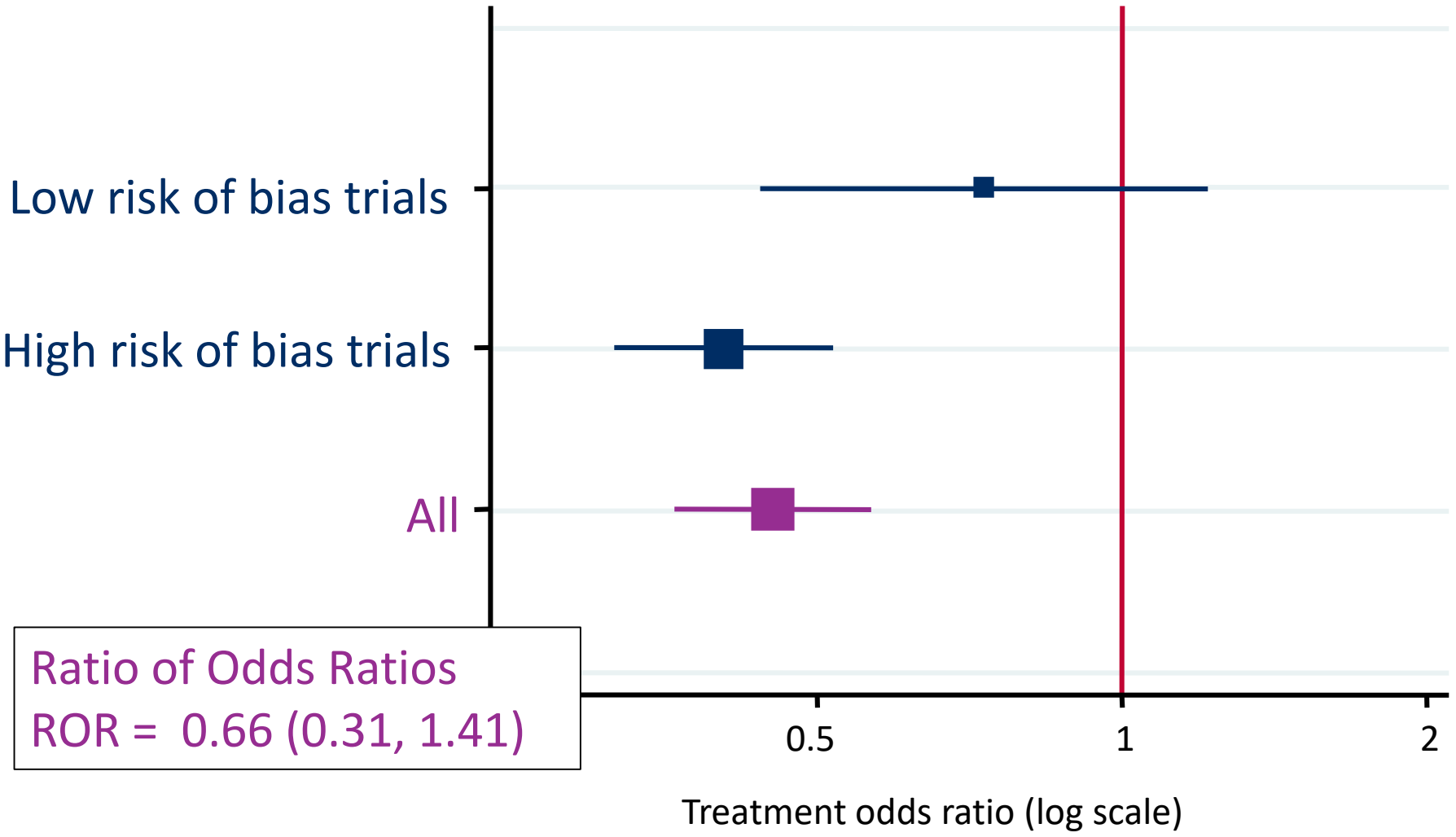
Should your main estimate (the one for SoF) be:

A. Based on low risk of bias trials only

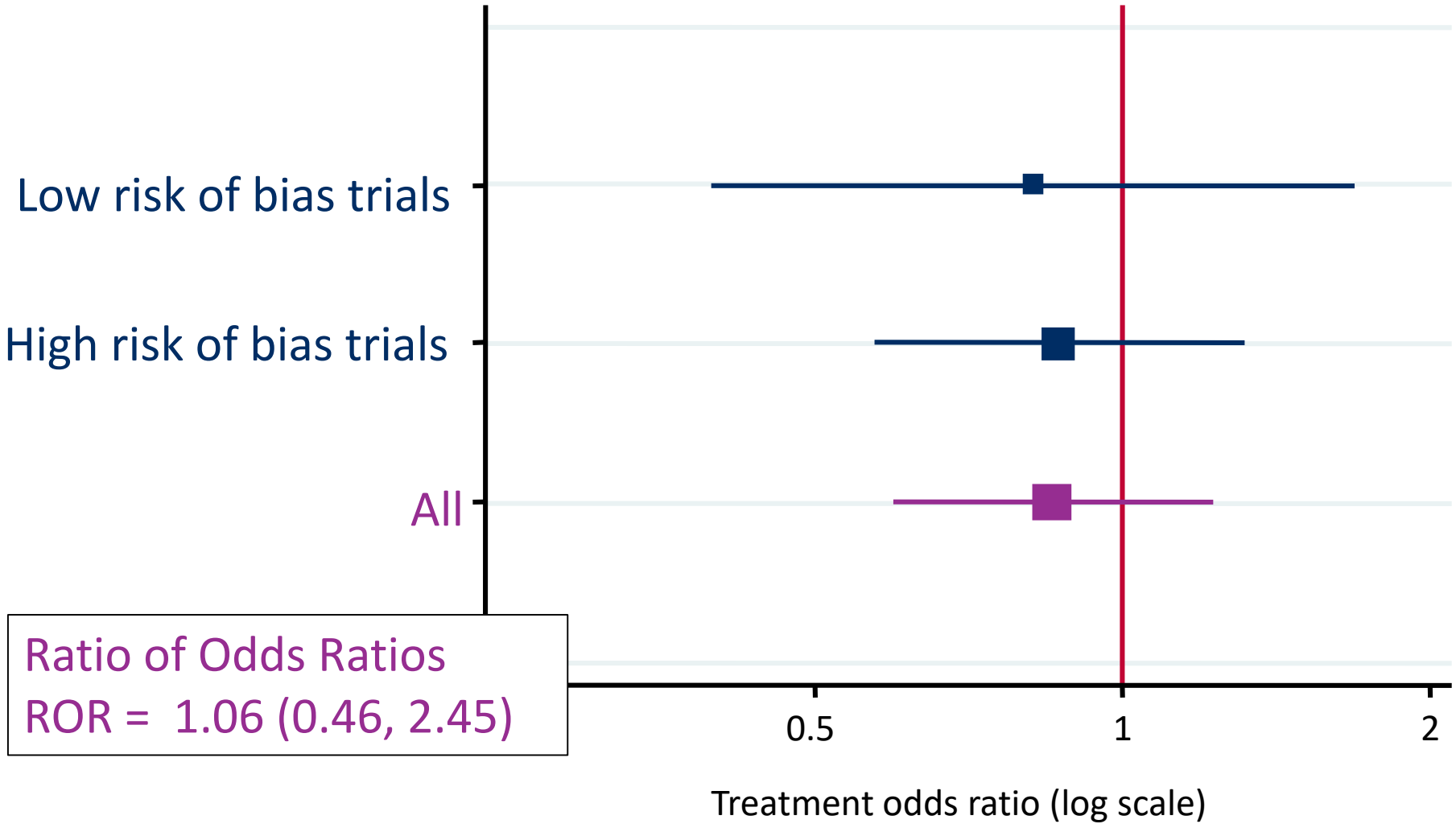
B. Based on high risk of bias trials only

C. Based on all trials

Example 1. Clozapine versus neuroleptic medication for schizophrenia



Example 2. Ovulation suppression compared to Danazol for endometriosis



Incorporating bias assessments in analyses (2)

Caution with test for differences and meta-regression:

- Low power
  - Individual review may not have enough studies in each ROB category to identify meaningful differences
  - Lack of a statistically significant difference between studies at high and low risk of bias does not mean absence of bias
- A significant difference between subgroups is not necessarily due to bias (there may be other sources of heterogeneity)

Incorporating bias assessments in analyses (2)

Other potential problems with approach 2:

- Three estimates per outcome: which one is the main result?
- May be confusing for readers
- Decision-makers want a single estimate of effect
- Summary of findings tables require single result per outcome

What are the main advantages?

- **Transparency**

How to choose the right approach for you?

Restricting to lower risk of bias results

vs

Presenting all subgroups and overall estimates

How to decide between these two main strategies ?

This decision should be made based on the balance between the potential for bias and the loss of precision resulting from exclusion of high risk of bias studies.

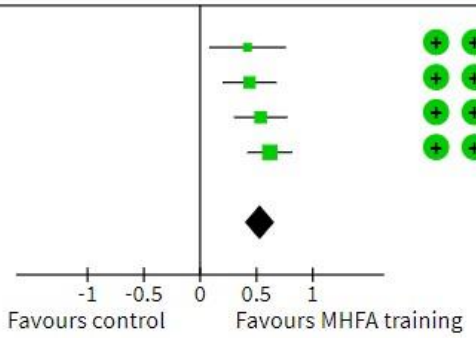
Incorporating bias assessments in analyses (3)

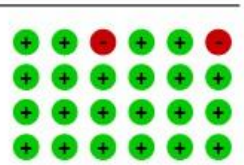
3) Include all studies in the meta-analysis and provide a narrative discussion of bias

- *Provide detailed description of RoB by individual domains*
- *Display and describe summary of RoB across studies*
- *Display all RoB judgements on forest plots*

Study or Subgroup	MHFA training Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Burns 2017	13.62	2.287	59	12.72	2.015	81	12.5%	0.42 [0.08 , 0.76]
Jensen 2016a	9.4	2.5	142	8.3	2.5	132	25.1%	0.44 [0.20 , 0.68]
Jensen 2016b	9.5	2.5	145	8.1	2.7	143	26.1%	0.54 [0.30 , 0.77]
Svensson 2014	8.7	2.1	199	7.3	2.4	207	36.3%	0.62 [0.42 , 0.82]
Total (95% CI)			**545**			**563**	**100.0%**	**0.53 [0.41 , 0.65]**

Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 8.61 (P < 0.00001)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported results
(F) Overall bias

Incorporating bias assessments in analyses (3)

3) Include all studies in the meta-analysis / synthesis and provide a narrative discussion of bias

- The simplest approach?
- Probably most common across literature

What are the potential problems with approach 3?

- Descriptions of RoB in Results/Discussion
- They get lost in Abstract / SoF / Conclusions (= potentially biased estimate gets used)
- Does not down-weight studies at high risk of bias → overall estimate is too precise (as well as potentially biased)

Incorporating bias assessments in analyses (3)

When is it acceptable to use strategy 3?

- When all studies are at the same risk of bias
- **Discouraged** when studies have different risk of bias
- Ensure summary RoB assessment incorporated into explicit measures of the certainty of evidence (GRADE)

Summary of methods for dealing with bias

Primary analysis

- all ‘at Low risk of bias overall’?
- stratified analyses?

Does RoB 2 explain heterogeneity?

- subgroup analyses
- meta-regression

Secondary analysis

- sensitivity analyses?

Certainty of the evidence

- RoB 2 will feed directly into GRADE

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Poll 3

Which method will you use in your next review?

a) Restrict to lower risk of bias results

b) Subgroups by risk of bias +/- meta-regression

c) Include all studies and describe RoB in text

d) Something else

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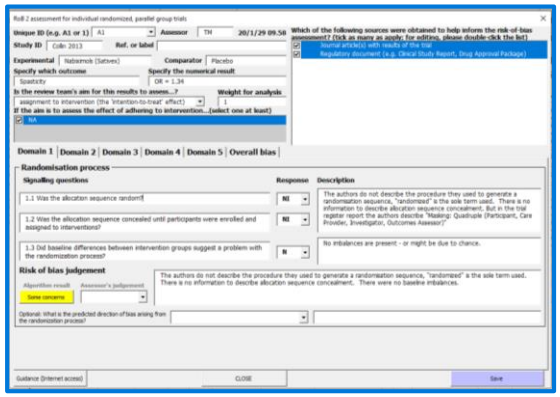
Resources available

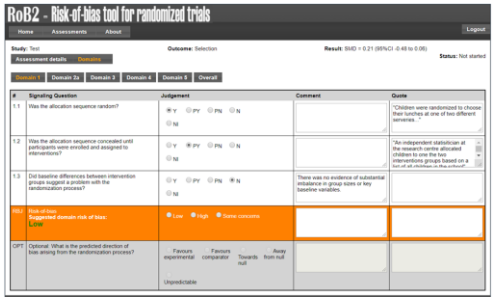
Implementation options

Excel tool

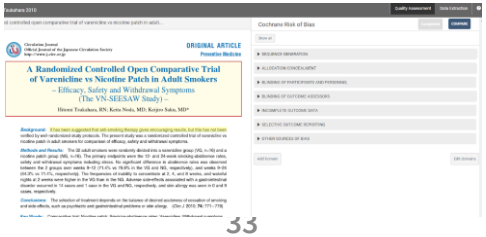


The recommended way to do RoB 2 assessments at the moment

Online platform (coming soon)



Covidence (in development)

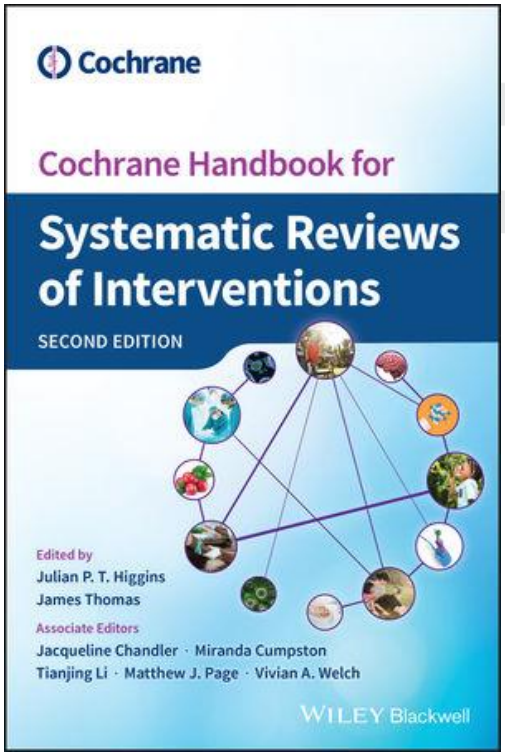


- RevMan 5
- RevMan Web

robvis

Cochrane Handbook (v 6)

- **Chapter 7** explains risk of bias issues in general
- **Chapter 8** provides a brief overview of the RoB 2 tool
- **MECIR** items summarize *Handbook* guidance



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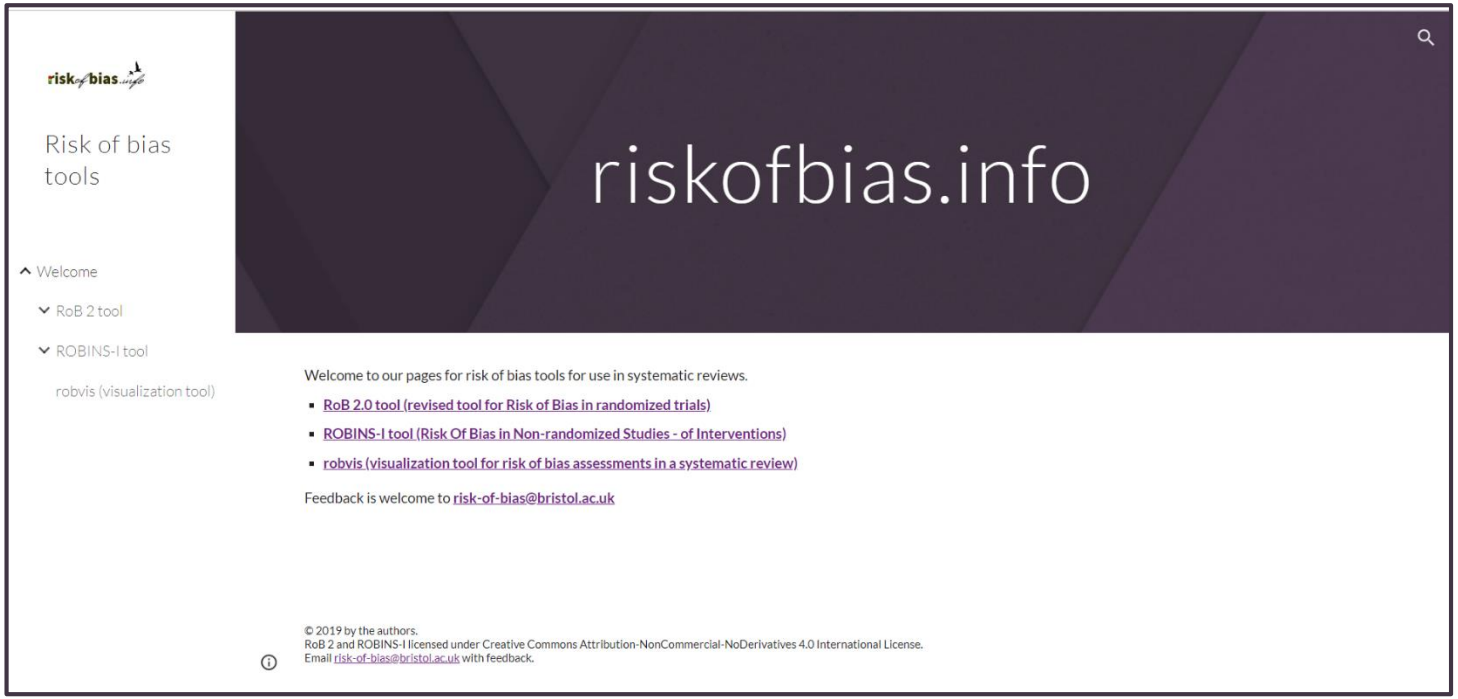

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

22 August 2019

Dedicated to Professor Douglas G Altman, whose contributions were of fundamental importance to development of risk of bias assessment in systematic reviews

Contents

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Questions

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