New guidance on reporting the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool

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Session outline

- Bias
- Introduction to ROBINS-I
- Protocol considerations
- Worked example
- Reporting considerations
- Visual displays
- Top tips!

Bias

“ the systematic difference between the study results obtained from an NRSI and a pragmatic randomized trial (both with a very large sample size), addressing the same question and conducted on the same participant group, that had no flaws in its conduct”

Sterne et al, 2022

ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions)

- The assessment is specific to a **single result**.

- **Seven** domains:
  Bias due to confounding;
  Bias in the selection of participants into the study;
  Bias in the classification of the intervention;
  Bias due to deviations from intended interventions;
  Bias due to missing outcome data;
  Bias in measurement of the outcome;
  Bias in selection of the reported result.

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ROBINS-I

- Signalling questions
  - Yes; probably yes; probably no, no or no information
- Risk of bias judgements: low risk of bias, moderate, serious, critical
- Overall risk of bias

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Protocol considerations

Methods section: Assessment of risk of bias in included studies

- State that **ROBINS-I** tool will be used and reference it (state the version of the tool that was used).
- State **who** will assess bias (initials), how many and whether independently and duplicate.
- State the **effect of interest** - effect of assignment or effect of adherence.
- List or refer to the **results** that will be assessed using ROBINS-I, including outcome(s), outcome measure(s) and timepoint(s).
- List the **confounders** that you would expect to be controlled for each type of outcome.
- List possible **cointerventions** that could differ between intervention groups and have an impact on outcome.
- List the **domains** of the tool
- List the **judgment options** (low, moderate, serious, critical) and how **overall risk of bias** is reached, e.g. using the signalling questions/tool algorithms

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Specifying the nature of the effect of interest

- the effect of assignment to the interventions at baseline
  - To inform a health policy question about whether to recommend an intervention in a particular health system

- the effect of starting and adhering to intervention
  - directly inform a care decision by an individual patient

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Confounding

- Confounding occurs when there are common causes of the choice of intervention and the outcome of interest.

- pre-intervention prognostic factor (i.e. a variable that predicts the outcome of interest) that also predicts whether an individual receives one or the other interventions of interest.

- For example: severity of pre-existing disease, presence of comorbidities and socio-economic status.

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Co-interventions

Relevant co-interventions are the interventions or exposures that individuals might receive after or with initiation of the intervention of interest, which are related to the intervention received and which are prognostic for the outcome of interest.

Protocol considerations continued

Data synthesis

- State whether the primary analysis will include all eligible studies or only those which have low risk of bias, or low risk, moderate and serious risk of bias.
- State that you will exclude data from studies at critical risk of bias from your analyses.

Subgroup analysis and investigation of heterogeneity/ Sensitivity analysis

- (If applicable) Specify if subgroup analysis or sensitivity analysis is planned based on risk of bias

Summary of findings and assessment of the certainty of the evidence

- State how the ROBINS-I assessment will be used to assess the certainty of the evidence/ GRADE/ summary of findings

Other considerations:

- Authors should not make any changes to the tool
- State how detailed ROBINS-I data will be stored and presented

Word document template

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / PN / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI

Domain 1: Bias due to confounding

Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline

Domain 1: Bias due to confounding

- 1.1 Is there potential for confounding of the effect of intervention in this study?
- 1.2 Was the analysis based on splitting participants' follow up time according to intervention received?
- 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?
- 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?
- 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
- 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?
- 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?
- 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?

Serious risk of bias

They measured confounding variables, but used an analysis (Mann Whitney U) that does not allow for adjustment.

Domain 2: Bias in selection of participants into the study

When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical

This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention

Domain 2: Bias in selection of participants into the study

- 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?
- 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?
- 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?
- 2.4. Do start of follow-up and start of intervention coincide for most participants?
- 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?

Low risk of bias

Prospectively recruited study. Consecutive series of participants selected. Later 12 participants were excluded based on outcome. However we deal with these in Domain 5.

Domain 3: Bias in classification of the intervention

Bias introduced by either differential or non-differential misclassification of intervention status

- Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null
- Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias

Domain 3: Bias in classification of the intervention

- 3.1 Were intervention groups clearly defined?
- 3.2 Was the information used to define intervention groups recorded at the start of the intervention?
- 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?

Serious risk of bias
Intervention status is not well defined – 8 used both protocols.

Domain 4: Bias due to deviations from intended interventions

- Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s)

Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).

Domain 4: Bias due to deviations from intended interventions

If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2

- 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?
- 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?

If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6

- 4.3. Were important co-interventions balanced across intervention groups?
- 4.4. Was the intervention implemented successfully for most participants?
- 4.5. Did study participants adhere to the assigned intervention regimen?
- 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?

Serious risk of bias

There were deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. We don't know anything about the 8 people that used both protocols (i.e. which groups they were from).

Domain 5: Bias due to missing data

Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders

Domain 5: Bias due to missing data

- 5.1 Were outcome data available for all, or nearly all, participants?
- 5.2 Were participants excluded due to missing data on intervention status?
- 5.3 Were participants excluded due to missing data on other variables needed for the analysis?
- 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?
- 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?

Serious risk of bias

A large proportion 21% of participants were missing because they had no outcome data, we don't know which groups they were in. No analysis was done to assess the effect of missing data.

Domain 6: Bias in measurement of the outcome

- Bias introduced by either differential or non-differential errors in measurement of outcome data.

- Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects

Domain 6: Bias in measurement of the outcome

- 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? **N**
- 6.2 Were outcome assessors aware of the intervention received by study participants? **PN**
- 6.3 Were the methods of outcome assessment comparable across intervention groups? **Y**
- 6.4 Were any systematic errors in measurement of the outcome related to intervention received? **N**

Moderate risk of bias
(i) The methods of outcome assessment were comparable across intervention groups; and (ii) The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and (iii) Any error in measuring the outcome is only minimally related to intervention status.

Domain 7: Bias in selection of the reported result

Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

Domain 7: Bias in selection of the reported result

Is the reported effect estimate likely to be selected, on the basis of the results, from...

- 7.1. ... multiple outcome *measurements* within the outcome domain? **PY**
- 7.2 ... multiple *analyses* of the intervention-outcome relationship? **PN**
- 7.3 ... different *subgroups*? **PN**

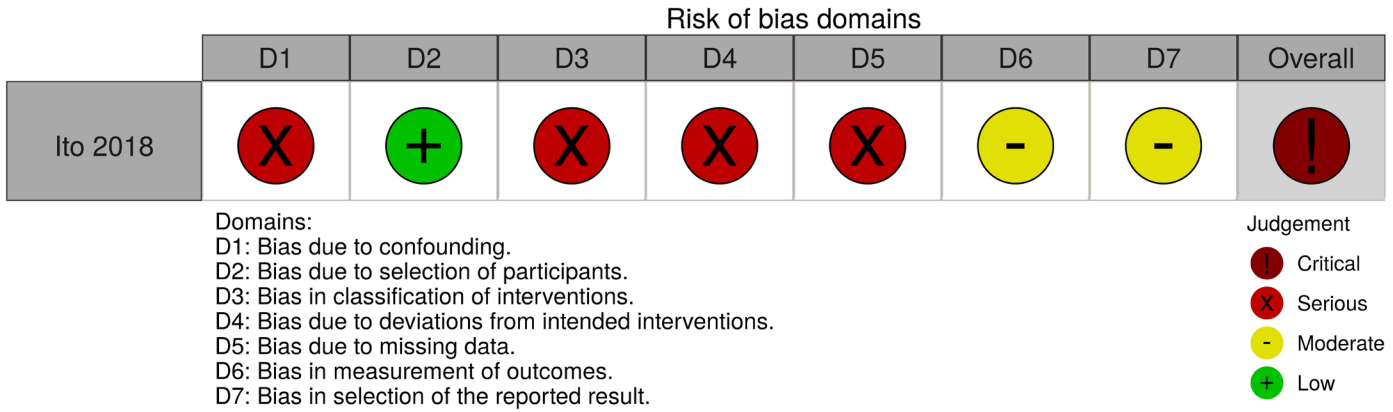
Moderate risk of bias

There was no apriori protocol. Selection based on outcome could be possible as they have not used Thyroglobulin level (measured at time of whole body scan)and we would expect that for a study in this time period. There appear to be no issues with, intervention, multiple analyses or different subgroups.

Overall risk of bias

- **Low risk of bias**: The study is judged to be at low risk of bias for all domains for this result.
- **Moderate risk of bias**: The study is judged to be at low or moderate risk of bias for all domains.
- **Serious risk of bias**: The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.
- **Critical risk of bias**: The study is judged to be at critical risk of bias in at least one domain.

Overall risk of bias



Analysis did not adjust for confounding. Intervention status poorly defined. Important deviations from intervention. Over 20% of participants missing.

Reporting considerations

Results: Risk of bias in included studies

- Refer to results-level ROBINS-I tables, which includes the support for judgement for each domain assessment.
- State how to access detailed risk of bias assessments data (with consensus responses to the signalling questions).
- Provide a brief overview of the risk of bias assessments.

Results: Describing the effects of interventions

- Refer to visual representations of the risk of bias assessments in relation to each result.

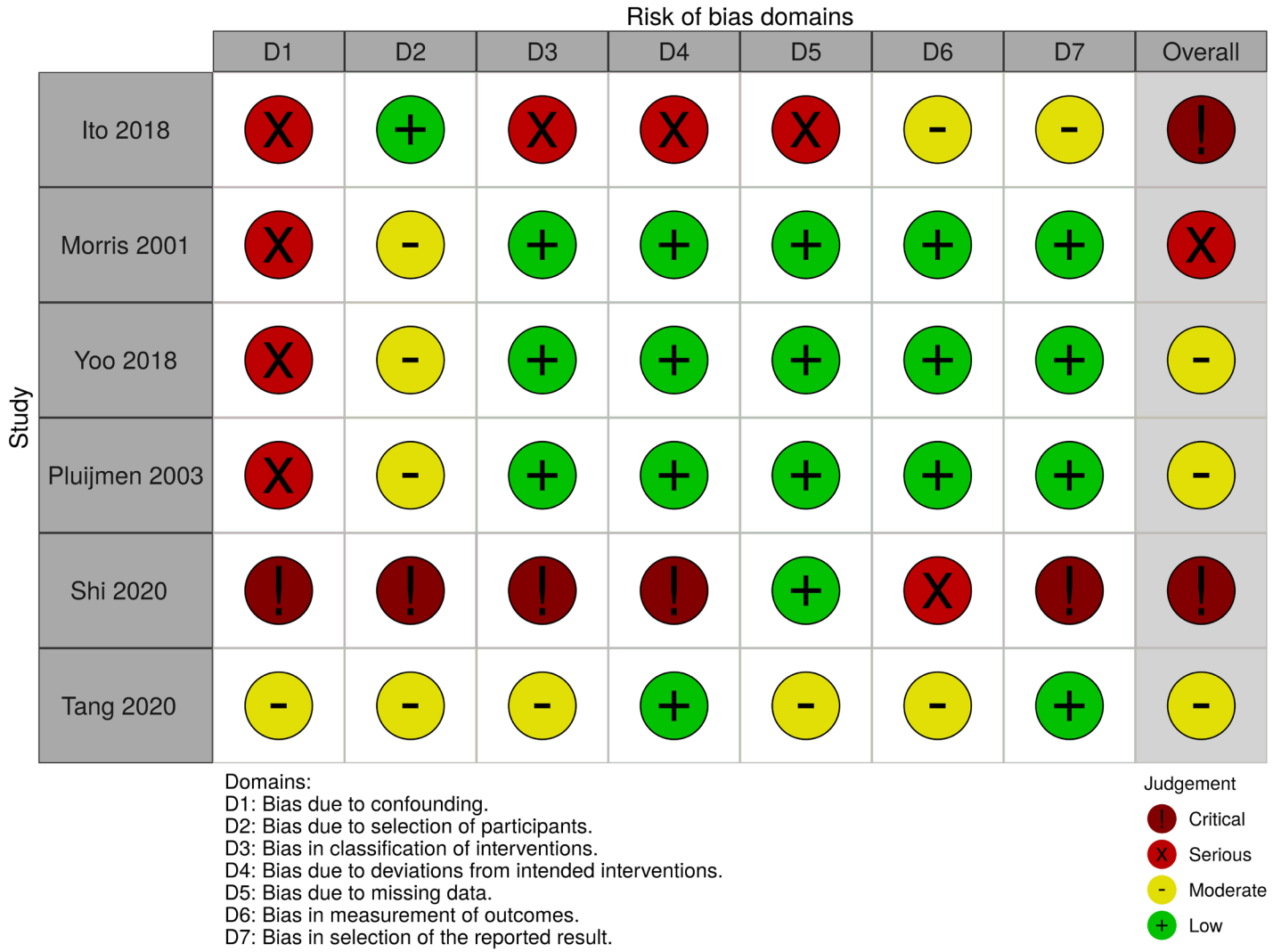
Results: Subgroup analysis/ Sensitivity analysis

- (If applicable) Discuss any subgroup analysis/ sensitivity analysis conducted that relates to the overall risk of bias judgments.

Discussion: Certainty of the evidence

- Discuss any risk of bias judgements that affect the certainty of the evidence along with all other GRADE considerations.

Visual displays of risk of bias information



Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Ito 2018	Serious	Low	Serious	Serious	Serious	Moderate	Moderate	Critical
Rationale for judgement	They measured confounding variables. But used an analysis (Mann Whitney U) that does not allow for adjustment.	Prospectively recruited study. Consecutive series of participants selected. Later 12 participants were excluded based on outcome. However, we deal with these in Domain 5.	Intervention status is not well defined – 8 participants used both protocols.	There were deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. We do not know anything about the 8 people that used both protocols (i.e. which groups they were from).	A large proportion 21% of participants were missing because they had no outcome data, we do not know which groups they were in. No analysis was done to assess the effect of missing data.	(i) The methods of outcome assessment were comparable across intervention groups; and (ii) The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and (iii) Any error in measuring the outcome is only minimally related to intervention status.	There was no a priori protocol. Selection based on outcome could be possible as they have not used Thyroglobulin level (measured at time of whole-body scan) and we would expect that for a study in this time period. There appear to be no issues with, intervention, multiple analyses, or different subgroups.	Four domains at "Serious" risk of bias therefore bias overall judged to be "Critical". Analysis did not adjust for confounding. Intervention status poorly defined. Important deviations from intervention. Over 20% of participants missing.
Morris 2001	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Rationale for judgement	They measured confounding variables. But used an analysis (Chi square and Mann Whitney U) that does not allow for adjustment.	Selection into the study was based upon the outcome (results of ablation) but this is unlikely to be related to the intervention (advice for low diet).	Intervention status is well defined and based solely on what was collected at the time of intervention.	Any deviations from intended intervention reflected usual practice	Data were complete. But people selected were chosen based on outcome data. Bias for this dealt with in Selection bias (Domain2)	i) The methods of outcome assessment were comparable across intervention groups; and (ii) The outcome measure is unlikely influenced by knowledge of the intervention received by study participants; and (iii) Any error in measuring the outcome is only minimally related to intervention status	There was no a priori protocol however, based on clinical knowledge there appears to be no selection based on outcome, intervention, multiple analyses, or different subgroups.	Analysis did not adjust for confounding. Selection based on results of ablation (outcome).

Intervention type	Study name	Outcome measure	Timepoint	N Intervention/Control	Statistics as presented in the papers	Risk-of-bias Overall assessment	Direction of effect favours intervention control?	Re-analysis using summary data from studies Standardised difference in difference (95% Confidence intervals)
Improving green infrastructure	Green storm water Philadelphia	Single item question Stress	2 years	N/A	Adjusted difference in difference estimate for stress (SE)= -0.01 (0.05) p=ns	Moderate	No effect	Not able to calculate
	Greening vacant lots	Single item question Stress	7 years	4436/13308	Adjusted difference in difference estimate for Stress (SE)=-0.02 SE=0.12 R^2=0.68 p=ns	Moderate	No effect	Not able to calculate
Urban regeneration	Neighbourhoods Law	GHQ-12	Baseline	274/504	Intervention Proportion poor MH=0.180 SD=0.38 Control Proportion poor MH=0.138 SD=0.345	Critical	Favours intervention	-0.11 (95% CI -0.22 to 0.01)
		GHQ-12	11 years	398/823	Intervention Proportion poor MH=0.176 SD=0.38 Control Proportion poor MH=0.173 SD=0.378			
	Wythenshawe regeneration	GHQ-12	22 months	Total=1344	MD 0.273 (95% CI -0.134 to 0.481) p=0.27	Critical	No effect	0.01 (95% CI -0.06 to 0.09)

Common errors

- Authors apply ROBINS-I to studies not to specific results.
- Modification of the tool e.g., removal of a domain or creation of additional domains.
- Overall judgement does not include the worst domain-level judgement.
- Including data that is at critical risk of bias in analyses.
- Sensitivity analyses based on a judgement from a single domain.
- No support for domain-level or overall judgements in the tables.
- Long description of all aspects of bias in the results text section of the review.

ROBINS-I top tips !

- Don’t forget to complete all of the boxes
- Disagreements are no bad thing
- Early investment goes a long way
- Authors are not expected to assess risk of bias for all results from all included studies

For further information

Risk of bias website https://www.riskofbias.info/welcome of bias tools

Robvis https://mcguinlu.shinyapps.io/robvis/

References

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- McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411

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