Assessing risk of bias in non-randomized studies of exposures: ROBINS-E tool

Julian Higgins, University of Bristol

...on behalf of the ROBINS-E development team, led by Julian Higgins, Rebecca Morgan, Andrew Rooney, Kyla Taylor, Kristina Thayer and Jonathan Sterne
Welcome to the website for the ROBINS-E tool (Risk Of Bias In Non-randomized Studies - of Exposures)

Version 20 June 2023

We are pleased to make available a full version of ROBINS-E for follow-up studies.

A Word template is available for completing the tool.

The tool is also available in this ROBINS-E Excel implementation.

About ROBINS-E

Observational epidemiologic studies are key to evaluation of the effects of exposures (including environmental, occupational and behavioural exposures) on human health, because evaluation through randomized controlled trials (RCTs) is not usually feasible. Even when RCTs have been conducted, the evidence that they provide may suffer from limitations. Therefore, the best evidence to guide policymakers and the public will be from observational studies that implement appropriate methods to minimize the risk of bias in their results, and from systematic reviews of such studies.

The Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool provides a structured approach to assessing the risk of bias in observational epidemiological studies. ROBINS-E is designed primarily for use in the context of a systematic review. It should contribute to a thorough examination of the strength of evidence about the presence of, and/or nature of, a potential effect of an exposure on an outcome. A key feature of the ROBINS-E approach is the specification, for each study, of the causal effect estimated by the result under consideration.

ROBINS-E shares many characteristics with the RoB 2 tool for randomized trials and the ROBINS-I tool for non-randomized studies of interventions, and is informing the further development of ROBINS-I. ROBINS-E includes seven domains of bias, each of which is addressed using a series of signalling questions that aim to gather important information about the study and the analysis being assessed. After the relevant signalling questions have been completed, three judgements are made:

1. The risk of bias in the result that arises from this domain.
ROBINS-E: a tool to assess risk of bias in non-randomized studies – of exposures

• ROBINS-E concerns the risk of bias (RoB) in the results of a non-randomized study (observational study) that is...
  • quantitative
  • estimating the effect (harm or benefit) of an exposure
  • making comparisons of exposure groups or exposure levels

- Follow-up (cohort) studies
- Before/after or time series studies
- Case-control studies
- Cross-sectional studies
Intervention vs exposure

A continuum

• Interventions
  • by a health professional
  • legislation

• Personal choices
  • type of toothbrush
  • taking a vitamin supplement
  • dietary intake
  • lifestyle, e.g. smoking, exercise

• Exposures
  • occupational
  • environmental

• Traits
  • socioeconomic status
  • biomarkers
  • genetic
Risk-of-bias assessment

A. Specify result being assessed

B. Determine whether to proceed with full assessment → Stop

C. Describe study / analysis being assessed

D. Define causal effect of interest

Determine which signalling questions need to be addressed

E. Examine how important confounders were addressed

Risk-of-bias assessment

1. Bias due to confounding
2. Bias arising from measurement of the exposure
3. Bias in selection of participants into the study (or analysis)
4. Bias due to post-exposure interventions
5. Bias due to missing data
6. Bias arising from measurement of the outcome
7. Bias in selection of the reported result

Overall bias
A. Specify result being assessed

B. Determine whether to proceed with full assessment

C. Describe study / analysis being assessed

D. Define causal effect of interest

Establishing the causal effect being evaluated

Risk of bias

The study

Applicability

Target experiment

Research question
A. Specify result being assessed

B. Determine whether to proceed with full assessment → Stop

C. Describe study / analysis being assessed

D. Define causal effect of interest

Risk-of-bias assessment

1. Bias due to confounding
2. Bias arising from measurement of the exposure
3. Bias in selection of participants into the study (or analysis)
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6. Bias arising from measurement of the outcome
7. Bias in selection of the reported result

Overall bias

E. Examine how important confounders were addressed

Determine which signalling questions need to be addressed
As for ROBINS-I
We use the WN/SN (or WY/SY) construct for some questions

<table>
<thead>
<tr>
<th>Yes (Y)</th>
<th>Yes (Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably yes (PY)</td>
<td>Probably yes (PY)</td>
</tr>
<tr>
<td>Probably no (PN)</td>
<td>Weak no (WN) (no, but …)</td>
</tr>
<tr>
<td>No (N)</td>
<td>Strong no (SN) (no, and …)</td>
</tr>
<tr>
<td>No information (NI)</td>
<td>No information (NI)</td>
</tr>
<tr>
<td>Judgement</td>
<td>Interpretation</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Low risk of bias</strong></td>
<td>There is little or no concern about bias with regard to this domain</td>
</tr>
<tr>
<td><strong>Some concerns</strong></td>
<td>There is some concern about bias with regard to this domain, although it is not clear that there is an important risk of bias</td>
</tr>
<tr>
<td><strong>High risk of bias</strong></td>
<td>The study has some important problems in this domain: characteristics of the study give rise to a high risk of bias</td>
</tr>
<tr>
<td><strong>Very high risk of bias</strong></td>
<td>The study is very problematic in this domain: characteristics of the study give rise to a very high risk of bias</td>
</tr>
<tr>
<td><strong>Low risk of bias (except for concerns about uncontrolled confounding)</strong></td>
<td>There is little concern about bias with regard to confounding, but risk of bias due to uncontrolled confounding cannot be excluded in an observational study</td>
</tr>
</tbody>
</table>
ROBINS-E: Threat to conclusions

• Whether the risk of bias (arising from each domain) is sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome.

• Take into account
  • finding of the study (including its magnitude and the strength of evidence around it)
  • broad assessment of bias (through the likelihood of it being present, its likely direction and its likely magnitude)

• Challenging, and detailed guidance has not been developed for this.

• Response options: Yes / No / Can’t tell
Define research question for the synthesis

Specify eligibility criteria

List important **confounding factors**

Identify studies and eligible results

**Perform ROBINS-E assessment**
for each result contributing to the synthesis

Integrate ROBINS-E judgements into the synthesis
*e.g. stratification, sensitivity analysis, triangulation*

Draw conclusions, including certainty in the evidence
*e.g. using GRADE*
ROBINS-E contributors to date

Assessing risk of bias in non-randomized studies of interventions: ROBINS-I tool

Jonathan Sterne or Julian Higgins, University of Bristol

...with special thanks to Miguel Hernán, Barney Reeves, Jelena Savović, Matt Page and other ROBINS-I collaborators
• Initial development of the tool for non-randomized studies (ROBINS-I) was funded by the Cochrane Methods Innovation Fund

• Further work on ROBINS-I was funded by the UK Medical Research Council Methodology Panel (MR/M025209/1)
Meeting in Paris agreed to establish working groups on individual bias domains.

Face to face meeting of all collaborators agreed main features of the new tool.

Revision following initial piloting.

Launched at Hyderabad, posted at www.riskofbias.info.

Further funding from MRC.

Paper submitted.

Initial scoping meeting at the Madrid Colloquium.

Online survey of review groups.

Working groups established and briefing document circulated.

Initial version of the tool presented at Quebec Colloquium.

Piloting and cognitive interviews.

Training/piloting event with key Cochrane personnel in Paris.

Co-Eds decide not to adopt it.

Changes to improve understanding and usability.

Changes to improve understanding and usability.
ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions


Non-randomised studies of the effects of interventions are critical to many areas of healthcare evaluation, but their results may be biased. It is therefore important to understand and appraise their strengths and weaknesses. We developed ROBINS-I (“Risk Of Bias In Non-randomised Studies - of Interventions”), a new tool for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did such as cohort studies and case-control studies in which intervention groups are allocated during the course of usual treatment decisions, and quasi-randomised studies in which the method of allocation falls short of full randomisation. Non-randomised studies can provide evidence additional to that available from randomised trials about long term outcomes, rare events, adverse effects and populations that are typical of real world practice.12 The availability of linked databases and compilations of electronic health records has enabled NRSI to be conducted in large representative population cohorts.3 For many types of organisational or public health interventions, NRSI are the main source of evidence about the likely impact of the intervention because randomised trials are difficult or impossible to conduct on an area-wide basis. Therefore systematic reviews addressing the
ROBINS-I: development chronology

- Paper published
- Extension to other study designs
- RoB 2 changes incorporated
- RoB 2 published
- Proposed revision nearly completed

2016
- Paper published
- Cochrane Scientific Committee recommends as preferred tool

2017
- Extension to other study designs

2018
- RoB 2 changes incorporated
- Joint development of ROBINS-E
- Piloting of web implementation begins

2019
- RoB 2 published
- Revision discussed with ROBINS-I collaboration

2020
- Proposed revision nearly completed
- ROBINS-E finalization

2023
Welcome to our pages for risk of bias tools for use in systematic reviews.

- Rob 2 tool (revised tool for Risk of Bias in randomized trials)
- NEW! ROB ME (Risk Of Bias due to Missing Evidence in a synthesis)
- ROBINS-I tool (Risk Of Bias in Non-randomized Studies - of Interventions)
- robvis (visualization tool for risk of bias assessments in a systematic review)

Feedback is welcome to risk-of-bias@bristol.ac.uk
Overview of the tool

- Preliminary considerations at protocol stage
  - Identify key confounding factors (& co-interventions)
- For each study:
  - Triage questions:
    - decide if a full assessment is warranted
    - determine which version of the Confounding domain to use
  - Target (idealized) randomized trial to match the study
    - PICO; effect estimate of interest (ITT vs per-protocol)
  - Examine key confounding factors (& co-interventions)
  - For each bias domain (result-level assessment)
    - Signalling questions
    - Free text descriptions
    - Risk of bias judgements, proposed by an algorithm
  - Overall risk of bias judgement (result-level assessment)
    - feed into (e.g.) GRADE
Main changes from 2016 version

• Preliminary considerations at protocol stage
  • Identify key confounding factors (& co-interventions)

• For each study:
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Rewritten, with more issues considered
<table>
<thead>
<tr>
<th>Domain</th>
<th>Related terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias due to confounding</td>
<td><strong>Pre- or peri-intervention</strong> features, for which considerations of bias in NRSI are mainly distinct from those in RCTs</td>
</tr>
<tr>
<td>Bias in classification of interventions</td>
<td></td>
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<tr>
<td>Bias in selection of participants into the study</td>
<td></td>
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<tr>
<td>Bias due to departures from intended interventions</td>
<td></td>
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<tr>
<td>Bias due to missing data</td>
<td><strong>Post-intervention</strong> features, for which many considerations of bias in NRSI are similar to those in RCTs</td>
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<tr>
<td>Bias in measurement of outcomes</td>
<td></td>
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<tr>
<td>Bias in selection of the reported result</td>
<td></td>
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<tr>
<td>Domain</td>
<td>Related terms</td>
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<tr>
<td>---------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bias due to confounding</td>
<td>Versions for (a) baseline confounding only and (b) baseline and time-varying</td>
</tr>
<tr>
<td></td>
<td>confounding</td>
</tr>
<tr>
<td>Bias in classification of interventions</td>
<td>New consideration of immortal time bias arising from definition of intervention</td>
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<tr>
<td></td>
<td>groups; More specific consideration of non-differential classification bias</td>
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<tr>
<td>Bias in selection of participants into the study</td>
<td>New consideration of immortal time bias</td>
</tr>
<tr>
<td>Bias due to departures from intended interventions</td>
<td>Similar</td>
</tr>
<tr>
<td>Bias due to missing data</td>
<td>Much more detailed consideration of when bias arises, including consideration</td>
</tr>
<tr>
<td></td>
<td>of (i) whether missingness depends on the true value of the outcome and (ii)</td>
</tr>
<tr>
<td></td>
<td>imputation</td>
</tr>
<tr>
<td>Bias in measurement of outcomes</td>
<td>Similar</td>
</tr>
<tr>
<td>Bias in selection of the reported result</td>
<td>Additional consideration of analysis plans</td>
</tr>
</tbody>
</table>
ROBINS-I: contributors

- Core group:
  - Jonathan Sterne, Barney Reeves, Jelena Savović, Julian Higgins

- Wider development team and other contributors: