Use of the ROBINS-I tool for assessing risk of bias in systematic reviews: a protocol for a meta-epidemiological study

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Revision history

This protocol was initially submitted to PROSPERO[1] on 8 March, 2020. Amendments were requested on 10 March and 31 March to clarify the clinical relevance of the review topic, in accordance with PROSPERO's guidelines on methodological reviews. A final amended version was submitted on 24 April. The amendments did not substantially alter the planned review questions or methodology.

Introduction

Review question

This review will examine how the "Risk Of Bias In Non-randomised Studies – of Interventions" (ROBINS-I) tool[2] has been used in recently published systematic reviews (SRs). ROBINS-I is widely used and officially recommended by Cochrane for assessing risk of bias in non-randomised studies,[3] but to date the use of the tool within existing SRs has not been systematically investigated.

The aim of this review is to assess whether this widely used risk-of-bias tool is being applied with sufficient rigour in the current SR literature, and identify factors that might influence its misapplication (such as conflicts of interest or sources of funding), in order to help clinicians and researchers to carry out more effective SRs and produce more robust clinical guidelines based on the results of existing SRs.

This study will be framed around the following questions:

1. What is the distribution of risk of bias ratings made using ROBINS-I in recently published systematic reviews that have used the tool?
2. How does the distribution of ratings vary depending on the characteristics of the systematic review?
3. What characteristics (of individual studies and of systematic reviews) are associated with low risk of bias ratings?

Condition or domain being studied

This is a meta-epidemiological study examining risk of bias assessments made using the ROBINS-I in published SRs.

Assessing the risk of bias in primary research is an essential part of the SR process,[4] and is crucial for ensuring that the conclusions of the SR are accurate and based on the best available evidence. In turn, clinicians rely

on high-quality, unbiased SRs to inform clinical decisions and guidelines, based on up-to-date evidence of the effectiveness of individual healthcare interventions and treatments.

Assessing risk of bias in non-randomised studies of interventions is more complex than in randomised trials, but non-randomised studies remain essential in many areas of health research, and often need to be included in SRs.[5] If risk of bias is not assessed in a sufficiently rigorous way, this can lead SRs to draw biased and incorrect conclusions about the available evidence. This may in turn lead to patients receiving harmful treatments, or not benefiting from effective treatments, as these SRs inform clinical decisions and guidelines.

Methods

Types of study to be included

Inclusion criteria:

- Must be described as a systematic review
- Must state that ROBINS-I has been used to assess risk of bias
- Must be available in English

Exclusion criteria:

- Review protocols
- Primary research articles
- Reviews where ROBINS-I has not been used to assess risk of bias
- Methodological reviews aiming to ascertain the validity of ROBINS-I as a risk of bias assessment tool
- Reviews only available in languages other than English

Search strategy

The search aims to identify a broad range of recently published systematic reviews that have used the ROBINS-I tool to assess risk of bias.

The databases to be searched are: MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Database of Systematic Reviews.

Search terms:

- Publications that cite the ROBINS-I tool[2] (where supported by the database), **OR**
- Title or abstract contains: "robins-i" **OR** "risk of bias in non-randomized studies of interventions" (with wildcards to account for variations in spelling and hyphenation, depending on the database)

Publication date: 1 January 2020 onwards.

Publication status: peer-reviewed publications.

Main outcome(s)

The main outcome in this study is risk of bias in studies of healthcare interventions, when assessed in SRs using ROBINS-I, a widely used tool for assessing risk of bias in non-randomised studies. Clinicians and researchers rely heavily on SRs to inform clinical decisions and guidelines, and risk-of-bias tools such as ROBINS-I are essential for ensuring that their conclusions are supported by the best available evidence.

By investigating whether ROBINS-I, an official Cochrane risk-of-bias tool, is being correctly applied in the current SR literature, and what factors may predict or indicate misuse, this study will help clinicians and researchers to critically appraise existing SRs, carry out new SRs more effectively, and consequently make more robust and evidence-supported clinical decisions.

Measures of effect

ROBINS-I ratings are categorical. The officially recommended categories are "Low", "Moderate", "Serious", "Critical" and "No information". According to the authors of ROBINS-I, a "Low" risk of bias rating "corresponds to the risk of bias in a high quality randomised trial", and is expected to be exceptionally rare. The proportion of "Low" ratings in the included SRs will be reported, and the estimated effects of predictors of interest (e.g. sources of funding) on the proportion of low ratings will be reported as odds ratios.

Additional outcome(s)

This study also aims to identify common errors in the application of ROBINS-I, as well as exemplars of correct, rigorous use, through a narrative review of the included SRs. This will help clinicians and researchers make decisions about how far to rely on individual SRs that use ROBINS-I, to appraise whether the tool has been used appropriately, and to avoid common pitfalls when using ROBINS-I to critically appraise primary research.

Study selection

Database searches will be carried out by the lead reviewer (EI). The results will be independently screened by both reviewers based on title and abstract, with reference to the inclusion and exclusion criteria. Where a decision about inclusion cannot be made based on title and abstract alone, full-text PDFs will be retrieved and independently screened by both reviewers. Disagreements between the reviewers will be resolved by consensus.

Data extraction

Data extraction for all included systematic reviews will be performed by the lead reviewer (EI) and independently checked by a second reviewer (SVK), using Excel spreadsheets. For each included systematic review, the following data will be extracted:

- Population, Intervention, Comparator and Outcome (PICO) for the review
- Aims or research questions as described by the authors
- Whether a review protocol is available
- Whether narrative synthesis, meta-analysis, or both were used
- Whether a framework for assessing certainty of evidence (e.g. GRADE) was used
- Whether the review is a Cochrane Review
- Whether ROBINS-I assessments were performed in duplicate
- In what form ROBINS-I ratings were reported
- The number of included studies (randomised and non-randomised)
- Any declared funding sources for the systematic review (classified as industry/private sector, academic, government, foundation/NGO, other, or none)
- Any competing interests declared by the first author, last author, or other authors (classified as industry/private sector, other, or none) of the systematic review

For each study within a systematic review, the following data will be extracted:

- ROBINS-I risk of bias ratings (per domain and overall)
- Bibliographical information (title, author, journal, year, and DOI)

Risk of bias (quality) assessment

The AMSTAR 2 tool will be used to assess the methodological quality of a sample of the included reviews. This will be limited to reviews with high proportion of low risk of bias ratings, and a random control group of the remaining reviews; see "Strategy for data synthesis".

Strategy for data synthesis

Summary statistics will be produced to show the characteristics of all included SRs, including what proportion of the SRs assigned a low ROBINS-I rating to any included study and what proportion assigned a low ROBINS-I rating to a majority of included studies. For each individual SR, summary statistics for the ROBINS-I ratings of included studies will be calculated. Intraclass correlation coefficients will be calculated to assess how far the risk of bias ratings are clustered by SR, i.e. how much of the variability is attributable to variation between SRs rather than between studies. Since the individual risk of bias ratings are nested within SRs, multilevel logistic regression will be used to investigate whether any characteristics of SRs (e.g. funding sources and conflicts of interest) are associated with low ROBINS-I ratings.

In addition to analysing the entire dataset, SRs with a high proportion of low ROBINS-I ratings will be investigated in more detail. For these SRs, and a control group randomly selected from the remaining SRs, methodological quality will be assessed using AMSTAR 2, and study design characteristics of the included studies will be extracted. A narrative review will also be carried out to identify common errors in the application of ROBINS-I, as well as exemplars of correct, rigorous use.

The aim of this synthesis is to identify ways that ROBINS-I may be misapplied in SR literature and how they affect the resulting risk-of-bias judgements, as well as to investigate whether there is evidence that characteristics of an SR (such as funding sources and conflicts of interests) may influence the quality of its conduct. This will help clinicians and researchers to interpret and critically appraise the results of SRs that have used ROBINS-I, and to avoid common pitfalls when using ROBINS-I to critically appraise primary research.

Analysis of subgroups or subsets

Data allowing, reviews that have been appraised with AMSTAR 2 will be stratified by methodological quality.

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