ELSEVIER

Journal of Clinical Epidemiology ■ (2018) ■

Journal of Clinical Epidemiology

COMMENTARY

Assessing risk of bias in studies that evaluate health care interventions: recommendations in the misinformation age

Matthew J. Page[a,*], Isabelle Boutron[b,c,d,e], Camilla Hansen[f], Douglas G. Altman[g], Asbjørn Hróbjartsson[f]

[a]*School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne, Victoria 3004, Australia*
[b]*METHODS team, Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), UMR 1153, INSERM, Paris, France*
[c]*Faculté de Médecine, Sorbonne Paris Cité, Paris Descartes University, Paris, France*
[d]*Centre d'Épidémiologie Clinique, AP-HP (Assistance Publique des Hôpitaux de Paris), Hôpital Hôtel Dieu, Paris, France*
[e]*Cochrane France, Cochrane, Paris, France*
[f]*Center for Evidence-Based Medicine, University of Southern Denmark & Odense University Hospital, Odense, Denmark*
[g]*UK EQUATOR Centre, Centre for Statistics in Medicine, NDORMS, University of Oxford, Oxford OX3 7LD, United Kingdom*

Accepted 10 January 2018; Published online xxxx

Abstract

Methods to assess the risk of bias in a way that is reliable, reproducible. and transparent to readers, have evolved over time. Viswanathan et al. recently provided updated recommendations for assessing risk of bias in systematic reviews of health care interventions. We comment on their recommendations and discuss new tools in development that we, as co-convenors and coordinators of the Cochrane Bias Methods Group, are leading, which complement the methods recommended.

Keywords: Bias; Methodology; Quality; Randomized trials; Nonrandomized studies; Systematic reviews

1. Introduction

There is empirical evidence that flaws in the design and conduct of intervention studies are associated with biased estimates of treatment benefits and harms [1,2]. Failure to consider potential biases can lead to the adoption of ineffective and unsafe interventions in clinical practice. The ability to assess the trustworthiness of research results is therefore an indispensable skill, which is becoming even more valuable in this age of misinformation and ''alternative facts'' [3,4]. International guidance for the conduct and reporting of systematic reviews suggests that the assessment of the risk of bias in the included studies is a key feature of a credible evidence synthesis [5−8]. However, the methods required to assess risk of bias in a way that is reliable, reproducible, and transparent to readers have evolved over time [9].

In this issue of the *Journal of Clinical Epidemiology*, Viswanathan et al. [10] describe recommendations for assessing risk of bias in randomized and nonrandomized studies that evaluate health care interventions. The guidance updates that provided in 2012 and included in the United States *Agency for Healthcare Research & Quality*

DOI of original article: 10.1016/j.jclinepi.2017.12.004.

Conflicts of interest: The authors read the journal's policy, and the authors of this manuscript have the following competing interests: M.J.P., I.B., and A.H. were members of the core group who developed the RoB 2.0 tool for assessing risk of bias in randomized trials. I.B., D.G.A., and A.H. participated in the development of the ROBINS-I tool for assessing the risk of bias in nonrandomized studies of interventions. M.J.P., I.B., and A.H. are leading or contributing to the development of new tools for assessing risk of reporting biases in systematic reviews, and conflicts of interest in randomized trials. M.J.P., I.B., D.G.A., and A.H. are co-convenors of the Cochrane Bias Methods Group, and C.H. is coordinator of the Group. The views expressed in this manuscript are those of the authors and not necessarily those of Cochrane or its registered entities, committees, or working groups. All authors declare that they meet the ICMJE conditions for authorship. M.J.P. wrote the first draft of the manuscript. All authors contributed to revisions of the manuscript. All authors approved the final version of the submitted manuscript. Funding: There was no direct funding for this manuscript. M.J.P. is supported by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship (1088535). The funders had no role in decision to publish or preparation of the manuscript.

* Corresponding author. Tel.: +61 9903 0248.
E-mail address: matthew.page@monash.edu (M.J. Page).

https://doi.org/10.1016/j.jclinepi.2018.01.004
0895-4356/

(AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews [11]. We comment on the recommendations and discuss new tools in development that we, as co-convenors and coordinators of the Cochrane Bias Methods Group, are leading, which complement the methods recommended.

2. Summary of the recommendations by Viswanathan et al

Viswanathan et al. [10] provide the following key suggestions for assessing risk of bias in randomized trials and nonrandomized studies of interventions (NRSIs). Risk of bias assessment should be separated from assessment of other issues, such as precision of effect estimates, applicability, and conflicts of interest in included studies. Methods for assessing the risk of bias should be prespecified in the review protocol. When selecting the risk of bias domains to assess, systematic reviewers should consider domains included in the framework underpinning the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [12]. That is, reviewers should consider problems arising from the randomization process in randomized trials, and bias due to confounding, selection of participants and misclassification of interventions in NRSI, along with bias due to deviations from intended interventions, missing data, measurement of outcomes, and selective outcome reporting in both randomized trials and NRSI. Methods to reduce uncertainty in assessments should be used, such as assessment of studies by two authors independently, or some combination of human effort with machine automation (e.g., human review of assessments made by machine learning methods). Domain-level judgments with supporting details (e.g., quotes of methods reported) should be presented in lieu of numerical ''quality scores'', to aid transparency and reproducibility of assessments [10].

3. Comparison with the approach advocated by the Cochrane Bias Methods Group co-convenors

To a considerable extent, Viswanathan et al. [10] provide an endorsement of generally accepted principles for the risk of bias assessment that have been developed and refined by methodological researchers often associated with Cochrane. The recommendations described previously are largely consistent with the 2011 Cochrane Handbook recommendations [7] and the frameworks used to develop the ROBINS-I tool [12] and the revised Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) [13]. However, there are several areas where we propose alternative recommendations.

Viswanathan et al. [10] suggest that systematic reviewers consider assessing risk of bias on a per-outcome basis, given that some outcomes in a study may be more prone to bias than others (e.g., the risk of bias in effect estimates for all-cause mortality and patient-reported pain are likely to differ in a trial that cannot blind participants to the assigned intervention). We agree with this sentiment but think it should go one step further in recommending result-level assessments, which are even more specific than outcome-level assessments. For example, if two results are available for a single outcome, such as pain, one adjusted for confounders and the other not, the risk of bias may differ for the two results. Therefore, consistent with the ROBINS-I [12] and RoB 2.0 [13] tools, we encourage reviewers to make assessments specific to a particular result.

In addition, we have some concerns with the suggestion that systematic reviewers should select "… the most important categories of bias for the outcome(s) and topic at hand" [10]. This suggests that domains already included in existing tools could be modified on a per-review basis, with particular domains added or removed based on the preference of the systematic reviewer. Modification of existing tools occurs frequently in practice; for example, in an audit of 100 Cochrane reviews published in 2014, the domains, "blinding of participants and caregivers" and "blinding of outcome assessors" had been omitted from the Cochrane risk of bias tool [14] in 38% and 35% of reviews, respectively [15]. In our view, such modifications are inadvisable; allowing users to remove certain domains that they deem not applicable (e.g., because it is not possible to blind participants to the intervention) means that important bias domains are ignored inappropriately. Likewise, review authors should not add additional domains to these tools. Both ROBINS-I [12] and RoB 2.0 [13] include a fixed set of mechanistically defined bias domains, selected based on empirical evidence, and wide consultation with methodologists, statisticians, epidemiologists, trialists and systematic reviewers. The included domains are intended to cover all issues that might lead to risk of bias in all NRSI and trials, respectively.

4. Unresolved issues in risk of bias assessment

There are several unresolved issues in assessing risk of bias in studies. The suggested move from study-level to result-level assessments begs several questions, including how many results in each study should be assessed? And if not all results need to be assessed, which should be prioritized? And how can this new approach to risk of bias assessment be incorporated into the data collection process? In addition, systematic reviewers are advised to consider not only the risk of bias but also the direction of the bias (i.e., which of the interventions being compared is the bias predicted to favor). However, there is currently very little guidance as to how to reach such judgments. Also, whether and if so, how, to take account of the risk of bias in meta-analyses, is an issue of ongoing research [2,16]. We anticipate that guidance for risk of bias assessment will need to be updated in future once these issues are resolved.