Research Techniques Made Simple: Assessing Risk of Bias in Systematic Reviews

Aaron M. Drucker[1], Patrick Fleming[2] and An-Wen Chan[3]

Systematic reviews are increasingly utilized in the medical literature to summarize available evidence on a research question. Like other studies, systematic reviews are at risk for bias from a number of sources. A systematic review should be based on a formal protocol developed and made publicly available before the conduct of the review; deviations from a protocol with selective presentation of data can result in reporting bias. Evidence selection bias occurs when a systematic review does not identify all available data on a topic. This can arise from publication bias, where data from statistically significant studies are more likely to be published than those that are not statistically significant. Systematic reviews are also susceptible to bias that arises in any of the included primary studies, each of which needs to be critically appraised. Finally, competing interests can lead to bias in favor of a particular intervention. Awareness of these sources of bias is important for authors and consumers of the scientific literature as they conduct and read systematic reviews and incorporate their findings into clinical practice and policy making.

Journal of Investigative Dermatology (2016) **136,** e109–e114; doi:10.1016/j.jid.2016.08.021

CME Activity Dates: October 22, 2016
Expiration Date: October 21, 2017
Estimated Time to Complete: 1 hour

Planning Committee/Speaker Disclosure: All authors, planning committee members, CME committee members and staff involved with this activity as content validation reviewers have no financial relationship(s) with commercial interests to disclose relative to the content of this CME activity.

Commercial Support Acknowledgment: This CME activity is supported by an educational grant from Lilly USA, LLC.

Description: This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

Objectives: At the conclusion of this activity, learners should be better able to:
- Recognize the newest techniques in biomedical research.
- Describe how these techniques can be utilized and their limitations.
- Describe the potential impact of these techniques.

CME Accreditation and Credit Designation: This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of William Beaumont Hospital and the Society for Investigative Dermatology. William Beaumont Hospital is accredited by the ACCME to provide continuing medical education for physicians.
William Beaumont Hospital designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Method of Physician Participation in Learning Process: The content can be read from the Journal of Investigative Dermatology website: http://www.jidonline.org/current. Tests for CME credits may only be submitted online at https://beaumont.cloud-cme.com/RTMS-Nov16 – click 'CME on Demand' and locate the article to complete the test. Fax or other copies will not be accepted. To receive credits, learners must review the CME accreditation information; view the entire article, complete the post-test with a minimum performance level of 60%; and complete the online evaluation form in order to claim CME credit. The CME credit code for this activity is: 21310. For questions about CME credit email cme@beaumont.edu.

INTRODUCTION

Systematic reviews are comprehensive overviews of the existing evidence on a specific research question. If appropriate, they can include a pooled statistical summary of available data called a meta-analysis. Systematic reviews and meta-analyses are becoming increasingly prevalent in medical journals; a PubMed search using "systematic reviews" as a publication type filter in the *Journal of Investigative Dermatology*, *Journal of the American Academy of Dermatology*, *JAMA Dermatology*, and *British Journal of Dermatology* returned 7 results published in 2010 compared with 27 in 2015, although these figures may capture some narrative reviews as well. The results of systematic reviews can help guide clinicians, patients, and policy makers by providing more precise and comprehensive information than individual studies alone. They can also be used to identify gaps in knowledge and suggest areas for future research. A previous paper in the *Research Techniques Made Simple* series

[1]*Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA;* [2]*Division of Dermatology, University of Toronto, Toronto, Ontario, Canada; and* [3]*Division of Dermatology, University of Toronto and Women's College Research Institute, Toronto, Ontario, Canada*

Correspondence: Aaron M. Drucker, Department of Dermatology, Brown University, Box G-D, Providence, Rhode Island 02903, USA.E-mail: aaron_drucker@brown.edu

Abbreviation: PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol

SUMMARY POINTS

- It is important for authors of systematic reviews to:
  - Register a protocol before conducting the review and explain any deviations from it
  - Utilize the PRISMA-P and PRISMA guidance
  - Search comprehensively beyond the published literature
  - Assess risk of bias in included primary studies
  - Disclose competing interests.
- It is important for consumers of systematic reviews to be aware of those same issues when reading review reports and when interpreting the implications of their findings on clinical practice and policy.

discussed the methodology and utility of systematic reviews and meta-analyses in dermatology (Abuabara et al., 2012). In this article, we discuss the various types of bias that can occur in systematic reviews so that they can be avoided or acknowledged by review authors, and critically assessed by users of the dermatology literature.

REPORTING BIAS AND THE IMPORTANCE OF PROTOCOLS

Reporting bias refers to the selective dissemination of research findings based on the nature of the results (Kirkham et al., 2010). For example, the choice of review outcomes or included studies might be changed to highlight significant findings. The selective inclusion of outcomes or studies with more significant results after exploring the data will bias the results of the review toward positive findings.

To help identify and deter reporting bias, it is critical for systematic reviews to be conducted in accordance with a protocol written before beginning the review. As with other types of research, the protocol defines the research question—including the population, intervention or exposure, and outcomes of interest—and describes the methodology in sufficient detail to allow replication by others. To avoid a data-driven hypothesis, the research question should be formulated in advance based primarily on clinical relevance rather than knowledge of available evidence. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement is a valuable evidence-based resource that defines the key content of a review protocol, including a description of search strategies and data sources, eligibility criteria, method of study screening and selection, primary and secondary outcomes, data extraction, and any planned analyses (Shamseer et al., 2015). Similarly, it is recommended that authors adhere to the comprehensive PRISMA guidance when actually preparing reports of systematic reviews (Moher et al., 2009). The PRISMA statement contains an evidence-based checklist of items to address in the manuscript itself and has been endorsed by many medical journals.

Public availability of the review protocol facilitates critical appraisal of the methods and identification of protocol deviations and selective reporting of results. It is important that protocols be prospectively registered online at PROSPERO—an online database of systematic reviews (http://www.crd.york.ac.uk/prospero/). Alternatively, protocols may be published in their entirety (as with Cochrane reviews). Subsequent publications of systematic reviews should state where the protocol was registered and where a copy of the protocol can be found. Protocol deviations do not necessarily lead to bias but must be explained in the Methods section of the systematic review report. For example, the search strategy might be modified if the results obtained from the original search were too broad or narrow. A recently published meta-analysis by Atzmony et al. (2015) concerning adjuvant

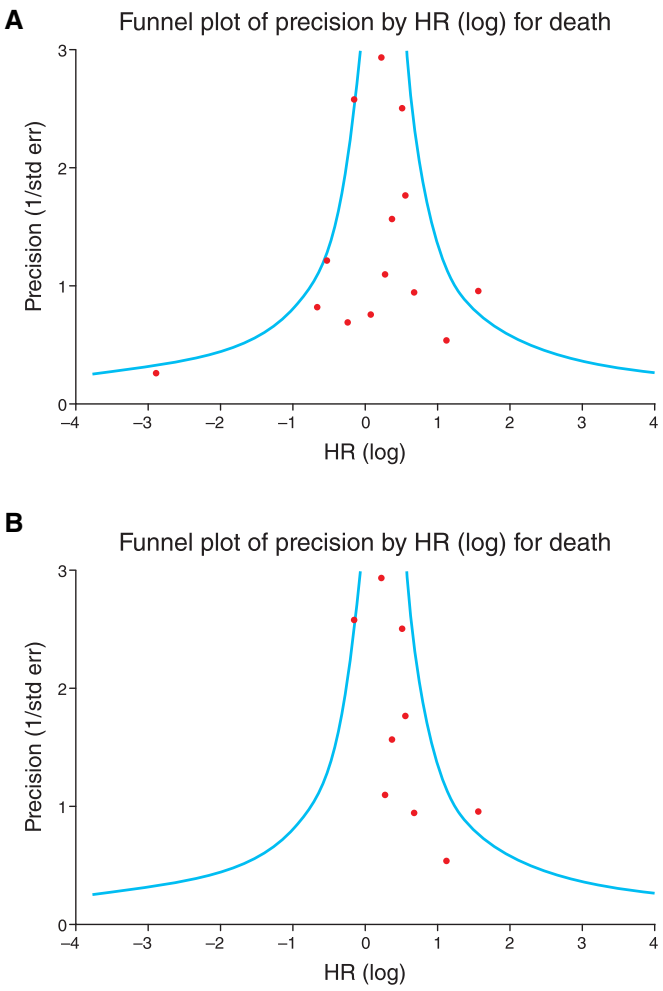

Figure 1. Representative examples of funnel plots. Funnel plots are scatter plots representing effect estimates on the *x*-axis compared with study precision (often the standard error of effect estimates) on the *y*-axis. (**a**) A symmetrical funnel plot adapted from a meta-analysis on the use of sirolimus in renal transplant recipients (Knoll et al., 2014). In this plot, the *x*-axis (log hazard ratio [HR]) is a proxy for effect estimates and the *y*-axis (standard error) is inversely related to the study sample size. The data points (red circles) each refer to a specific study. In a symmetrical funnel plot, the data points should be scattered symmetrically within the funnel (blue lines), suggesting a low risk of publication bias. (**b**) In this fictional plot (modified from Knoll et al., 2014), there is clear asymmetry within the funnel, with missing data points from unpublished trials in the lower-left portion of the funnel, suggesting a high risk of publication bias. Reproduced from Knoll et al., 2014 with permission from BMJ Publishing Group Ltd.