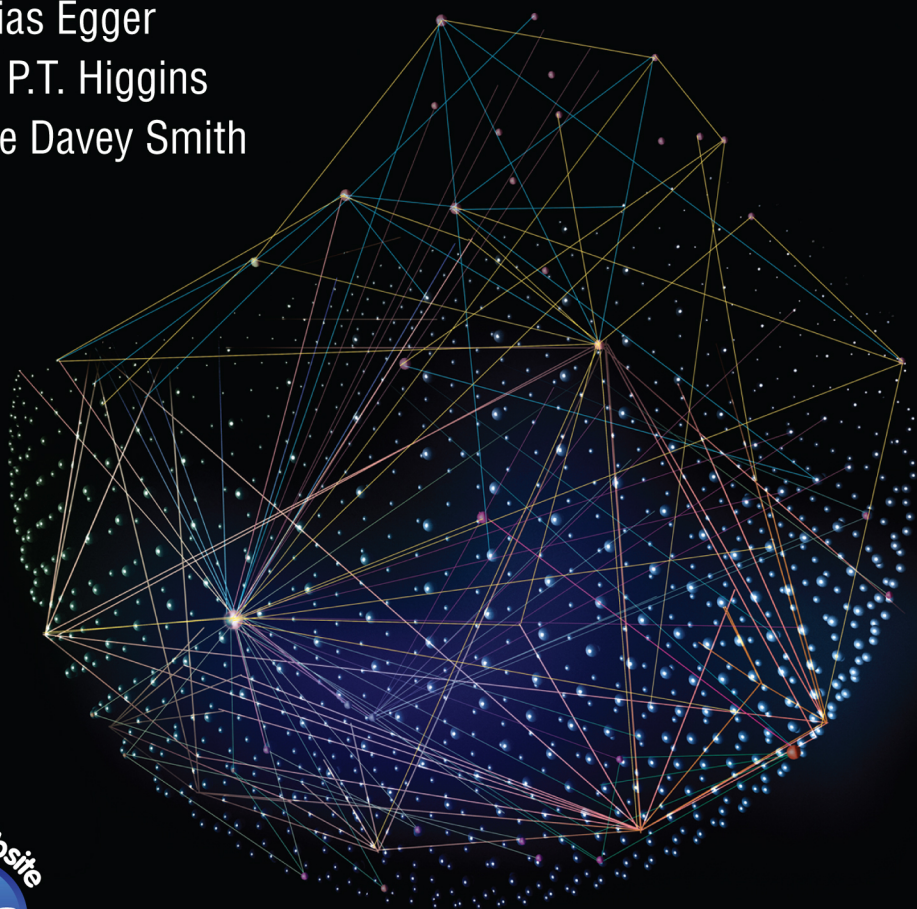


Third Edition

Systematic Reviews in Health Research

Meta-Analysis in Context

Edited by
Matthias Egger
Julian P.T. Higgins
George Davey Smith



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Preface

Iain Chalmers and Doug Altman edited the first edition of this book, which was published in 1995 and called simply *Systematic Reviews*. Their foreword focused on the “poor scientific quality of [traditional] reviews of clinical research” and the “disregard of scientific principles,” which may harm decision-making and patient outcomes [1]. Systematic reviews allow a more objective appraisal by systematically identifying, scrutinizing, and synthesizing the relevant studies. Today, more than a quarter of a century and two editions later [1, 2], systematic reviews and meta-analyses have become widely established, with thousands of such studies published every year. Also, their function has broadened, from the scientific synthesis of evidence to inform clinical practice, the main concern in 1995, to becoming part of the methods toolkit to address a wide range of questions, including evaluation of interventions, diagnosis and prognosis, prevalence and burden of disease, and discovery research.

This broader role is reflected in the current third edition. Of the 27 chapters, 12 are new, covering systematic reviews of prediction models, genetic association studies, and prevalence studies. The focus on methods has become stronger too, with new chapters dealing with missing data, network meta-analysis, and dose-response meta-analysis. These changes explain the book’s new title (*Systematic Reviews in Health Research*, rather than in Health Care) and revised structure. The first chapter discusses the rationale, history, and strengths and limitations of systematic reviews and meta-analysis. This introductory chapter is followed by a section on principles and procedures (six chapters), a section on meta-analysis (seven chapters), and one on systematic reviews and meta-analysis of specific study designs (six chapters). Two chapters cover Cochrane (formerly the Cochrane Collaboration) and systematic reviews and meta-analyses in guideline development and the *GRADE* approach (Grading of Recommendations Assessment, Development and Evaluation). The book ends with an outlook on innovations in and the future of systematic reviews and meta-analysis (two chapters) and a section on software (three chapters). The 15 chapters that made the journey from the second to the third edition have all been thoroughly updated. Nevertheless, all chapters will age, some more quickly than others. The book’s website (www.systematic-reviews3.org) will be our antidote to premature aging, by offering updates of some chapters (for example, those on software packages) and highlighting references to recent critical articles and instruments, new software, and other developments.

The intended audience will be similar to that for the popular second edition [2]: methodologically inclined clinicians, epidemiologists, health services researchers, and public health specialists interested in conducting high-quality systematic reviews and meta-analyses. The book will also be of interest to doctoral and other students in the

health sciences. Indeed, we see this book as an excellent resource for teaching and will provide exercises and computer practicals on the companion website.

On the long journey from the second to the third edition, we lost our dear friend, collaborator, and co-editor, Douglas Graham Altman. Doug sadly died, aged 69, on June 3, 2018. He made essential contributions to this third edition, helping define focus and content and co-authoring several chapters. On the following pages, we reprint Iain Chalmers' wonderful tribute to Doug's visionary role in developing systematic reviews and clarifying the role of meta-analysis [3]. We miss you very much, Doug, and dedicate this book to you.

Last but not least, huge thanks to all contributors to this book. They made it possible by patiently and stoically updating their chapters over several years. Many thanks to our project managers and editors in Bern, Carole Dupont, Chris Ritter, and Geraldine Wong, who supported us so well on this long journey. A big thank-you also to the editors at Wiley, Jennifer Seward, Samras Johnson V, and Ella Elliot, for their brilliant help and their patience.

The first edition of this book was applauded for its “simple and often humorous” discussion and its “intuitively appealing explanations” [4]. We hope you will agree that the third edition continues in this tradition.

Bern and Bristol, April 2022
Matthias Egger, Julian P.T. Higgins, George Davey Smith

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Tribute

Professor Doug Altman (1948–2018) co-edited the first and second editions of this book. Here, Sir Iain Chalmers, founder of The Cochrane Collaboration and the James Lind Alliance, reflects on Altman’s seminal contributions to the concept of systematic reviews and the role of meta-analysis.

Doug Altman’s Prescience in Recognizing the Need to Reduce Biases before Tackling Imprecision in Systematic Reviews

Iain Chalmers

RECOGNITION OF SHARED INTERESTS AND THE ORIGINS OF A FRIENDSHIP

I came to know Doug Altman during the 1980s when we were both members of the editorial team at the *British Journal of Obstetrics and Gynaecology*. I was working at the National Perinatal Epidemiology Unit at that time; Doug was at the Division of Medical Statistics at the Medical Research Council’s Clinical Research Centre. Our meeting at the *BJOG* was the beginning of what became a very close friendship.

Doug and I shared an interest in trying to improve the quality of the manuscripts submitted to the *BJOG*. We commissioned three papers providing reporting guidelines for those submitting reports of controlled trials, assessments of screening and diagnostic tests, and observational studies – early examples of an interest that would become manifested in Doug’s creation of the *EQUATOR* Network (Enhancing the QUALity and Transparency Of health Research).

We also discovered that we had both become interested in the scientific quality of reviews of research evidence, and the potential for statistical synthesis of estimates derived from several similar studies. I had used this approach in a review of four randomized comparisons of different ways of monitoring fetuses during labour [1], the results of which prompted a very large further controlled trial that confirmed the results of the meta-analysis [2].

Doug’s interest in the scientific quality of reviews of research evidence had been stimulated by two papers published in the late 1970s by Richard Peto [3, 4]. These led Doug to prepare a seven-page typescript entitled “Evaluating a series of clinical trials

of the same treatment” for presentation at the 1981 meeting of the International Epidemiological Association in Edinburgh [5]. Over the next two years Doug extended the material in the 7-page typescript to a 40-page typescript with the same title [6].

DOUG’S PIONEERING CONCEPTUALIZATION OF SYSTEMATIC REVIEWS AND THE ROLE OF META-ANALYSIS

Doug’s 1983 paper is important in the history of systematic reviews because of his prescience of what is important in the science of research synthesis. Unfortunately, it has been hidden from view because it was never formally published. I think Doug first showed me “the almost final version of [his] 1983 paper (complete with handwritten corrections)” at the end of 1986. He said he intended to finalize and submit it for publication, but that did not happen. As he admitted more than two decades later, “I wish I had published my ideas back in 1983” [7]. Since 2011, the typescripts of both papers [5, 6] have been available in the James Lind Library, and the shorter paper, with an accompanying commentary by Doug, is also available in the *Cochrane Methods* supplement to the *Cochrane Database of Systematic Reviews* [8].

In both these papers Doug touched on issues that would become more widely recognized as important by the 1990s. In particular, he made clear that techniques of statistical synthesis – “meta-analysis” – were but one element in a science of research synthesis, and usually not the most important. He made clear that, although statistical synthesis could address those elements of between-study variability due to random variation, it could not deal with other sources of variability – differences in entry criteria, study populations, the methods used to generate comparison groups, baseline differences between treatment groups, degrees of blindness achieved, and variations in and deviations from treatment protocols. Doug comments at the beginning of a nine-page section on “Combining the data” in the longer paper that “Since the main purpose of the paper is to discuss the whole issue of whether or not to combine trials rather than to carry out a comparison of the available methods, not all of the possible statistical methods will be described” [6]. Both his papers stressed the likely importance of publication bias and he regretted the lack (then) of hard evidence of the bias and the challenges this posed. He makes the important and too often neglected point:

Although the problem of possible publication bias may appear to be a major restriction on the validity of combining the results from several trials, it is important to realise that any such bias applies to the interpretation of individual studies, although this is always ignored and each study’s results taken at face value. ([6], p. 25)

Toward the end of his 1983 paper, Doug presciently identified two desirable developments that would become widely appreciated by the end of the decade. First, the use of individual patient data:

In view of the non-statistical problems in the combination of results from different trials, the choice of statistical method is unlikely to matter greatly, but methods

which make use of the raw data are definitely preferable to the combination of probabilities. The pooled estimate of relative risk should be presented with its confidence interval. ([6], p. 33)

Secondly, there is a paragraph in a section of the paper entitled “Ethical considerations” that anticipates developments in thinking and practice during the 1980s and 1990s, which Doug selected for attention after re-reading his paper over 30 years after drafting it [8]. Here’s the paragraph that had struck him:

[it] is important to consider whether the results of a series of studies of the same treatment should be accumulated on a regular basis in order to monitor the current state of knowledge about those treatments. Further trials might then be dependent on the combined significance of already completed trials but using a stricter level of statistical significance (say $P < 0.001$) than is usually applied in single trials. Even without such information trials should perhaps not be given ethical committee approval unless the researchers had analysed the results of published trials in the way suggested in order to demonstrate that there was still uncertainty about the efficacy of the treatment, and the range of uncertainty encompassed clinically relevant benefit. Further, power calculations for a new trial could be conditional on the results of published trials. ([6], p. 27)

THE ORIGINS OF SYSTEMATIC REVIEWS IN HEALTH RESEARCH: META-ANALYSIS IN CONTEXT

Following wider recognition of the need to improve the scientific quality of reviews [9–11], the opening of the Cochrane Centre in Oxford in October 1992 helped to generate interest in the science of research synthesis [12]. I was delighted that Richard Smith, editor of the *British Medical Journal*, recognized this and proposed an all-day meeting run jointly by the *BMJ* and The Cochrane Centre. I was very glad that he accepted that the title of the meeting would refer to systematic reviews, and not to meta-analysis, as had been proposed originally. The meeting was held at the Royal Institution on 7 July 1993. Eight presentations covered the development of systematic reviews; doubts about them and the challenge of finding relevant studies; rationale and practicalities; and assessing, updating, and disseminating systematic reviews.

Based on the presentations made at the meeting, a series of articles about systematic reviews began in the 3 September 1994 issue of the *BMJ*. In his “Editor’s Choice” column, Richard Smith noted that systematic review was “one of the most valuable tools in assessing new treatments and technologies” [13]. He was even more supportive in his Editor’s Choice column a few weeks later:

Systematic reviews provide the highest quality evidence on treatment. . . The author of a systematic review poses a clear question, gathers all relevant trials (whether published or not), weeds out the scientifically flawed, and then

amalgamates the remaining trials to reach a conclusion. Every stage in the process is crucial, and an article in the journal by Kay Dickersin and her colleagues shows how a careful Medline search for randomised controlled trials will not detect all such trials even in the journals indexed in Medline. [14]

Richard Smith went on to point out that systematic reviews are also important because – by amalgamating data from similar trials – they can increase the statistical power of treatment comparisons [14]. These succinct explanations of the rationale for systematic reviews made by the Editor-in-Chief of one of the world's most prominent medical journals were heartening to those of us calling for improvements in the scientific quality of reviews of research.

The *BMJ*'s series of articles on systematic reviews was well received and Richard Smith proposed that I should edit a compilation of the articles as a book. I accepted, on condition that Doug Altman would co-edit it with me, and I was very glad that both Richard and Doug agreed [15]. The contents and contributors to the book are shown in Figure T.1 and in the James Lind Library at <https://www.jameslindlibrary.org/chalmers-i-altman-dg-1995>. The book introduces and illustrates systematic reviews; discusses data collection for them; presents contrary stances on the value of using meta-analysis to generate overall summary statistics; provides guidelines for assessing the trustworthiness of reviews; describes how systematic reviews are being prepared, updated, and disseminated by the international network of people who together constitute the Cochrane Collaboration; and concludes with a classified bibliography for further reading. The book is dedicated to Thomas C. Chalmers, “in appreciation of his many pioneering contributions to the science of reviewing health research, and in particular, for the first clear demonstration of the dangers of relying on traditional reviews of research to guide clinical practice.”

Doug's and my Preface in the book provided an opportunity to explain why we had used the term “systematic review” rather than the more technical neologism “meta-analysis”:

Use of the term ‘systematic review’ implies only that a review has been prepared using some kind of systematic approach to minimising biases and random errors, and that the components of the approach will be documented in a materials and methods section. Other terms – particularly ‘meta-analysis’ – have caused confusion because of the implication that a systematic approach to reviews must entail quantitative synthesis of primary data to yield an overall summary statistic (meta-analysis). As we hope this book will help to make clear, this is not the case. In addition to those circumstances in which statistical synthesis (meta-analysis) of results of primary research is not advisable, there will be others in which it is quite simply impossible. It is just as important to take steps to control biases in reviews in these circumstances as it is to do so in circumstances in which meta-analysis is both indicated and possible. [15]

Doug reiterated this point in his 2013 commentary on “Twenty years of meta-analysis and evidence synthesis methods.” He wrote:

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CYNTHIA D MULROW, <i>associate professor, Divisions of General Medicine and Geriatrics, University of Texas Health Science Center, San Antonio, Texas, USA</i>	
2 Some examples of systematic reviews	9
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KAY DICKERSIN, <i>director, Baltimore Cochrane Center, Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA</i>	
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IAIN CHALMERS, <i>director, UK Cochrane Centre, NHS Research and Development Programme, Oxford</i>	
BRIAN HAYNES, <i>director, Canadian Cochrane Centre, Health Information Research Unit, McMaster University Medical Centre, Hamilton, Ontario, Canada</i>	
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FIGURE T.1 The contents and contributors to the first edition of the book on systematic reviews

As time went on we have realized that there are many hidden problems, nuances, extensions, and so on. And there have been big changes in strategy. The biggest impact probably came from the early realization that the statistical analysis is a relatively simple part of a rather complex set of actions which we now label as a systematic review. [8]

The issue was dealt with nicely in the title chosen for the second edition of the book, namely *Systematic Reviews in Health Care: Meta-Analysis in Context* [16]. I am grateful to the editors of the third edition of the book (Egger, Davey Smith, and Higgins) for inviting me to draw attention to the pioneering thinking and unpublished writing about research synthesis by their and my much-loved, late-lamented co-editorial colleague, Doug Altman.

Note

This text was published previously as Chalmers I. Doug Altman's prescience in recognising the need to reduce biases before tackling imprecision in systematic reviews. *Journal of the Royal Society of Medicine* 2020; 113:119–122.

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