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## *Preface to the second edition*

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The volume of research into the genetics of common diseases has exploded over the last 25 years. While many genetic variants related to various diseases have been identified, their usefulness may lie more in what they offer to our understanding of the biological mechanisms leading to disease rather than to, for example, predicting disease risk. To understand mechanisms, we need to separate the relationships of risk factors with diseases into those that are causal and those that are not. This is where Mendelian randomization can play an important role.

The technique of Mendelian randomization itself has undergone rapid development, mostly in the last 15 years, and applications now abound in medical and epidemiological journals. Its basis is that of instrumental variable analysis, which has a much longer history in statistics and particularly in econometrics. Relevant papers on Mendelian randomization are therefore dispersed across the multiple fields of genetics, epidemiology, statistics and econometrics – and increasingly bioinformatics. The intention of this book is to bring together this literature on the methods and practicalities of Mendelian randomization, especially to help those who are relatively new to this area.

In writing this book, we envisage the target audience comprising three main groups, Epidemiologists, Bioinformaticians, and Medical Statisticians, who want to perform applied Mendelian randomization analyses or understand how to interpret their results. We therefore assume a familiarity with basic epidemiological terminology, such as prospective and case-control studies, and basic statistical methods, such as linear and logistic regression. While Mendelian randomization methods can be applied in a diverse range of areas, we concentrate on applications in epidemiology, and hope that researchers in other areas will still find the content relevant.

While we have tried to ensure that this book will be accessible to a wide audience, a geneticist may baulk at the simplistic explanations of Mendelian inheritance, a statistician may yearn for a deeper level of technical exposition, and an epidemiologist may wonder why we don't just cut to the chase of how to perform the analyses. Our aim is that enough detail is given for those who need it, references are available for those who want more, and a section can simply be glossed over by those for whom it is redundant. We have also tried as far as possible to allow each chapter to be read in isolation. The price of this is that we may introduce a topic in one chapter, only to return to it in more detail in a later chapter.

While we have included relevant statistical methodology available up

to the publication date of the book, our focus has been on methods and issues which are of practical relevance for applied Mendelian randomization analyses, rather than those which are of more theoretical interest, or ‘cutting-edge’ developments which may not stand the test of time. As such, to a research statistician, the book will provide a background to current areas of methodological debate, but it will generally not offer opinions on controversial topics which are likely to become out-of-date quickly as further investigations are performed. Where possible, sections with technical content are written in such a way that they can be omitted without interrupting the flow of the book.

A website to complement this book, as well as the authors’ ongoing research on this topic, is available at [www.mendelianrandomization.com](http://www.mendelianrandomization.com). This contains chapter summaries, paper summaries, web-based applications, and software code for implementing some of the statistical techniques discussed in the book.

In preparing this second edition of this book, we substantially re-wrote and re-ordered the book to account for new developments in summarized data and two-sample Mendelian randomization, to emphasize the practical implications of methodological issues rather than their technical aspects, and to include a wider range of examples of the technique.

We would like to express our thanks to all those who commented on chapters of this book, whether in chapter or book form. We thank Frank Dudbridge, Brandon Pierce, Dylan Small, Maria Glymour, Stephen Sharp, Mary Schooling, Tom Palmer, George Davey Smith, Debbie Lawlor, John Thompson, Jack Bowden, Shaun Seaman, Lucas Tittmann, Daniel Freitag, Peter Willeit, Edmund Jones, Angela Wood, Adam Butterworth, Apostolos Gkatzionis, Andrew Grant, Verena Zuber, Eric Slob, and Dipender Gill. Further individuals commented as anonymous referees, and so we cannot thank them by name. We also thank Rob Calver, our editor, for being knowledgeable, supportive, and open to our ideas. We are grateful to the those who have allowed us to use their data in this book, either by allowing figures to be reprinted or by making summarized data publicly available, as well as to the study participants who gave their time and consent to participate in research.

In short, while we realize that we will not be able to please all of our readers all of the time, we hope that this book will enable a wide range of people to better understand what is an important, but complex and multidisciplinary, area of research.

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