Preface

The quantity of research into the genetics of common diseases has exploded over the last 20 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 10 years, and applications now abound in current 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. 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 two main groups, Epidemiologists 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 ordinary least squares and logistic regression. Meanwhile, we have tried to make the perhaps alien terminology of econometrics accessible to our intended readership.

While we hope 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 hope 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.

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 in the first part of the book are marked with asterisks (*), and 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. This contains chapter summaries, paper summaries, web-based applications, and software code for implementing some of the statistical techniques discussed in the book.

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 and Adam Butterworth. 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 also grateful to the principal investigators of the studies in the CRP CHD Genetics Collaboration who have allowed us to use their data in this book, as well as to the study participants for giving their time and consent to participate in this 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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