

Clinical Epidemiology

Principles, Methods,
and Applications
for Clinical Research

SECOND EDITION

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PREFACE

In the current era of evidence-based medicine, with an abundance of published information and a clear need for relevant applied clinical research, clinical epidemiology is increasingly being recognized as an important tool in the critical appraisal of available evidence and the design of new studies.

This text is intended for those who are currently practicing medicine and related disciplines (such as pharmacy, health sciences, nursing sciences, veterinary medicine, and dentistry) as well as those involved in the design and conduct of applied clinical research. Apart from these “users,” “doers” of applied clinical research, notably undergraduate students and PhD fellows in medicine and related disciplines, will also benefit from the information provided. Clinical epidemiology instructors will find the text to be a valuable resource for their classes.

The purpose of the text is to teach both the “users” and “doers” of quantitative clinical research. Principles and methods of clinical epidemiology are used to obtain quantitative evidence on diagnosis, etiology, and prognosis of disease and on the effects of interventions. The content of this text reflects our teaching experience on the methodology of applied clinical research over the last 25 years. It was the ever-advancing development of clinical epidemiologic methodology, the increasing discrepancies between our teaching material and existing textbooks of epidemiology, and the many requests from students and practicing physicians for a concise text reflecting our courses that fueled our decision to prepare this novel text.

We hope that our text will contribute to a better understanding of the strengths of clinical epidemiology as well as help both researchers and users of quantitative clinical research in their endeavors to further improve patient care in daily clinical practice.

This edition has been revised and updated extensively. In doing so we benefited enormously from the comments given to us by many readers, specifically the PhD fellows and staff members at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, and in the Department of Epidemiology, Radboud University Medical Center Nijmegen.

As more than three thousand copies of the first edition and reprints have found their way to readers across the globe, we are confident that this text is well appreciated by all those engaged in clinical epidemiologic research or using the results of such studies in clinical practice. We hope this new edition will be similarly appreciated and welcome any comments or suggestions for further improvement.

Diederick E. Grobbee and Arno W. Hoes



FOREWORD

Clinicians often think of epidemiology as distinct from clinical research. As a consequence, epidemiologic methods, disease causation, and preventive medicine, as well as strategic public health issues, have been taught chiefly in epidemiology departments and at schools of public health. Many of these institutions, however, have become too isolated from the practice of medicine and the conduct of clinical research. And both camps—epidemiologic research and clinical research—have suffered from this mutual isolation. Epidemiology would be fertilized by close interaction with clinical medicine, while offering a powerful toolbox derived from advanced methodologic developments to clinical researchers. Epidemiologic principles and methods are not only integral to public health, but also highly relevant to clinical research. However, this fundamental fact is still not adequately appreciated by many clinical investigators.

Could epidemiologic methods and clinical epidemiology indeed revolutionize clinical research? Would methodologic rigor, adequate sample size, and skilled statistical analyses allow more rapid progress and quicker implementation of important discoveries? This bold and perhaps naïve idea came to my mind some 30 years ago and my initial hunch that it is true has grown ever since. Still a practicing surgeon at the time, my own research forced and encouraged some familiarity with the fundamental principles of epidemiology. And this familiarity truly changed my perspective on my professional performance in the operating room, clinical ward, outpatient departments, emergency units, and in the classroom where I lectured to medical students.

Foremost, my slowly growing familiarity with epidemiologic methodology helped me understand the fundamental prerequisites for causal inference—after all, a successful treatment is little more than a cause of a good outcome. This insight made me increasingly uncertain about the real benefit of our therapeutic, chiefly surgical, interventions and the performance of our diagnostic technologies. This was a time when hip replacement, coronary bypass surgery, breast-conserving surgery, laparoscopic cholecystectomy, kidney transplantation, vascular reconstruction, and radical prostatectomy (just to mention a few examples) transformed our work in the operating room—often without the support of benefit of new technologies from randomized trials. At the same time, computerized tomography, ultrasound, PET scans, and, subsequently, magnetic resonance revolutionized our ability to visualize organs and assess bodily functions. Today, the flow of novel therapeutic and diagnostic techniques is even more intense.

As a practitioner, I navigated through these years with two competing feelings. One was a growing frustration with how haphazardly clinical methods were used and combined; that novel surgical procedures—unlike the strictly regulated approval of new drugs—could be introduced overnight, often with no strategy to quantify risks versus benefits. As a corollary, decisions influencing the life and health of our patients were based on little scientific evidence. But another feeling grew too—a fascination with epidemiologic theory and methodology as directly relevant to advancing the evidence base for clinical practice. After 17 years, I left the operating room peacefully, permanently, and with no subsequent regret to become a full-time epidemiologist.

Persuading clinicians that methods of extraordinary relevance for their research are readily available in the epidemiologic toolbox can be challenging. But it is trickier still to provide an accessible text that helps them see the light and the opportunities. It is in this context that *Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research, Second Edition* becomes such a tremendously useful addition to the existing literature. I wish that this text had been available to me 30 years ago. I congratulate all those younger colleagues who now receive a firm and stable helping hand in their necessary endeavor to study a wide variety of clinical phenomena in human populations. And I hope that the text will also be read by the growing number of practitioners who need to understand the sophisticated methods used in cutting-edge clinical research.

Hans-Olov Adami

Hans-Olov Adami, MD, PhD, is Adjunct Professor of Epidemiology and former Chairman of the Department of Epidemiology at the Harvard School of Public Health, Associate Director of Populations Sciences at the Dana Farber/Harvard Cancer Center, and Professor Emeritus of Cancer Epidemiology at the Karolinska Institute, Stockholm, Sweden.

THE JULIUS CENTER

The Julius Center for Health Sciences and Primary Care (<http://www.juliuscenter.nl>) was established at the University Medical Center Utrecht in December 1996. The Julius Center was built upon previously existing small departments of epidemiology, public health, and clinical epidemiology, and was subsequently expanded to include primary care, biostatistics, and medical humanities.

The name was chosen to serve as a symbol for innovative health sciences rather than to specify the disciplines assembled in the center. Hendrik Willem Julius (1901–1971) was a professor of health sciences and hygiene at Utrecht University during the first half of the 20th century and an early advocate of the clinical trial. Julius was not affiliated with the center, but we are honored to use his name with the consent of his children and grandchildren.

Since its start, the Julius Center has continuously grown in its main domains of research, education, and patient care. A few principles have guided the decisions that shaped the center. One is that epidemiology is a basic medical discipline. This is reflected in the research agenda of the center and the background of its staff, who comprise a fair number of physicians working in productive harmony with epidemiologists from many other biomedical backgrounds. A second principle is the view that clinical epidemiology flourishes best in close approximation and interaction with clinical medicine. Consequently, the center is located in a hospital environment and provides clinical care in primary healthcare centers within a large, newly built area of the city of Utrecht, while joint appointments of staff further support the continuous interaction with other clinical departments. Finally, a leading principle is that the quality of research by junior fellows as well as by experienced staff is determined by the level of understanding of the principles and methods of epidemiology. To achieve this goal, good education is essential.

When the center had just opened and was still small in size, we began with the development of a common theoretical basis through teaching each other, harmonizing, and updating our views along the way. This has formed the basis for the current epidemiologic curriculum in Utrecht, including the content of the international Master of Science in Epidemiology program offered at Utrecht University (<http://www.mscepidemiology.eu>) and of our teaching of clinical epidemiology to medical students, clinicians, and other health professionals in the Netherlands and abroad.

We believe that a common and consistent set of principles and methods are the strongest assets of epidemiology and the true value clinical epidemiology has to offer to today's applied clinical research.

Much of the content of this text reflects our teaching to numerous students. We and our staff continue to provide courses on a wide range of topics in epidemiology and health sciences. Online versions of these courses may be found at Elevate (www.elevatehealth.eu), an academic educational e-learning platform.

ABOUT THE AUTHORS

Diederick (Rick) E. Grobbee, MD, PhD (1957) was trained in medicine in Utrecht and, after doing a residency in internal medicine, he obtained a PhD in epidemiology at Erasmus University in Rotterdam. His education was continued at McGill University in Montreal and as a visiting Associate Professor at the Harvard University School of Public Health. He spent nearly a decade at Erasmus, where he headed the cardiovascular epidemiology group and was appointed Professor of Clinical Epidemiology. He subsequently moved to the University Medical Center in Utrecht to become Professor of Clinical Epidemiology. Here he founded the Julius Center for Health Sciences and Primary Care in 1996. He served as Chairman for the Center for the next 14 years. He holds honorary appointments at Sydney University and the University of Malaya in Kuala Lumpur. In 2010, he was appointed Distinguished University Professor of International Health Sciences and Global Health at Utrecht University, where he is also Program Director of the international MSc and PhD Epidemiology Program. He is a fellow of the Royal Netherlands Academy of Sciences and chairs its Medical Section and Medical Advisory Council. He is Editor-in-Chief of the *European Journal of Preventive Cardiology*. His teaching experience includes courses on clinical epidemiology and clinical research methods to various audiences in several countries.

Arno W. Hoes, MD, PhD (1958) studied medicine at the Radboud University in Nijmegen. He obtained his PhD degree in clinical epidemiology at the Erasmus Medical Center in Rotterdam. He was further trained in clinical epidemiology at the London School of Hygiene and Tropical Medicine. In 1991, he was appointed Assistant Professor of Clinical Epidemiology and General Practice in the Department of Epidemiology and the Department of General Practice at the Erasmus Medical Center. In the latter department, he headed the research line, “cardiovascular disease in primary care.” In 1996, he moved to the Julius Center for Health Sciences and Primary Care of the University Medical Center in Utrecht, where he was appointed Professor of Clinical Epidemiology and Primary Care in 1998. Since 2010, he has been the Chair of the Julius Center. Most of his current research activities focus on the (early) diagnosis, prognosis, and therapy of common cardiovascular diseases. His teaching experience includes courses on clinical epidemiology, diagnostic research, case-control studies, drug risk assessment, and cardiovascular disease. He is a member of the Dutch Medicines Evaluation Board, the Health Council of the Netherlands, and is on the editorial boards of several medical journals.



CONTRIBUTORS

We thank the following colleagues and friends for their invaluable contributions and critical comments on several of the chapters of this text.

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Ale Algra has extensive experience with the design, conduct, and analysis of randomized clinical trials in neurovascular disease. His experience and attention to detail shaped Chapter 10.

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Huibert Burger has a strong interest in the theoretical basis of prediction research. He made important contributions to Chapter 4 on prognostic research.

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Yolanda van der Graaf is one of the most experienced “hands-on” clinical epidemiologists in our group and therefore the best equipped to address data analysis from a practical perspective, as is demonstrated in Chapter 12.

Rolf H.H. Groenwold, MD, PhD

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Rolf Groenwold is a talented clinical epidemiologist who specializes in confounding adjustment. He contributed significantly to Chapters 3 and 11.

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Geert van der Heijden is an evidence-based medicine aficionado and a literature search expert. His knowledge is shared in Chapter 11 on meta-analysis.

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Jacobus 'Koos' Lubsen is a longtime teacher and friend. Some of his provocative and lucid ideas can be found in Chapter 11.

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Carl Moons is an expert on prediction research, as he explores the conceptual and theoretical foundations utilizing his extensive practical experience. His views are expressed in Chapter 2 on diagnostic research and he has further contributed to Chapter 4 on prognostic research.

Yvonne T. van der Schouw, PhD

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Yvonne van der Schouw has a strong track record in etiologic epidemiologic research. Her work includes cohort studies and randomized trials on the effects of various nutritional factors on health. She provided the examples in Chapter 3.

ACKNOWLEDGMENTS

We are indebted to all current and former members of the scientific staff of the Julius Center for their crucial role in advancing the center's conceptual ideas of clinical epidemiology and the conduct of applied clinical research. The development of a joint teaching program shortly after the founding of the Julius Center marked an important first step in the process that eventually resulted in this text. Many staff members contributed to specific sections of this text, and their expertise, devotion, and hard work are greatly appreciated.

We thank our former colleagues at the Department of Epidemiology at Erasmus Medical Center Rotterdam for their role in the development of our epidemiologic thinking through many stimulating discussions (even when we disagreed).

We thank the many students, PhD fellows, clinicians, and participants in our teaching programs in the Netherlands and abroad for their criticism, discussions, and wit that continues to encourage us to further develop our understanding of clinical epidemiology and improve our teaching methods.

Our thinking about clinical epidemiology was influenced by many scientists. We would like to mention three in particular.

Hans A. Valkenburg laid the foundation for clinical epidemiology in the Netherlands by combining his clinical expertise and knowledge of epidemiology with his entrepreneurship, designing large-scale studies and laboratory facilities in close collaboration with clinical departments. We are proud that we were trained in clinical epidemiology at his department in Rotterdam. His ideas still serve as a role model for the Julius Center and other clinical epidemiology departments in the Netherlands.

We were profoundly influenced by the wealth of ideas on clinical epidemiology articulated by Olli S. Miettinen. Our many provocative discussions shared with him around the globe not only encouraged us to remain modest about our own contributions to the discipline, but strongly stimulated us to further explore the foundations of clinical epidemiology and their application in clinical research. We have no doubt that his reading of our text will induce further stimulating interaction and future adaptations.

We are grateful to Albert Hofman for his friendship and support in a crucial phase of our scientific development. He is at least partly "guilty" for our choice to pursue a career in clinical epidemiology. His contagious

enthusiasm about epidemiology and dedication to scientific excellence had a major impact on our work.

Without the relentless efforts of Monique den Hartog and Giene de Vries in the preparation of the manuscript, this text would never have been published. We truly thank them for their important secretarial contributions.

QUICK START

Throughout this text, we explore the challenges clinicians face in daily practice and the quantitative knowledge required to practice medicine. To serve both readers who mainly use clinical research findings as well as (inexperienced or more advanced) clinical researchers, the text is divided into three parts.

Part One (Overview) provides an introduction to the principles and theoretical background of clinical epidemiologic research and its interplay with clinical practice. In Part Two (Principles of Clinical Research), the four major types of clinical research (diagnostic research, etiologic research, prognostic research, and intervention research) are discussed in much more detail. In Part Three (Tools for Clinical Research), several methods that are often applied in clinical research are presented to assist the reader in the design, conduct, and understanding of specific studies.

The text starts with a theoretical and philosophical overview of the origins and nature of clinical epidemiology (Chapter 1). You may wish to read that at a later stage if your immediate interest is a specific type of research question or study.

The second part of the text emphasizes the design of clinical research, with major emphasis on the type of research question and theoretical design. In each of the chapters we gave ample attention to phrasing the research question. The question should be clear, unequivocal, and relevant in view of the clinical problem. Clinically relevant research questions are categorized with a view to the four types of challenges clinicians are faced with in daily practice and in the hierarchical order in which they occur naturally: (1) diagnostic questions, dealing with the challenge of efficiently setting the diagnosis underlying the patient's signs and symptoms (Chapter 2); (2) etiologic questions, dealing with the challenge of determining the cause(s) of disease (Chapter 3); (3) prognostic questions, dealing with the challenge of efficiently predicting the natural history of disease in a patient, answering the question: "What would happen if I do not intervene?" (Chapter 4); and (4) questions about the beneficial ("intended") and adverse ("unintended") effects of interventions on the course of a disease, dealing with the challenge of determining the effects of a particular therapy on a patient's prognosis (Chapters 5 and 6). We find this distinction between the four clinical domains very useful, both in our teaching of evidence-based medicine and clinical epidemiology and in our clinical research activities. This approach can be summarized as the DEPTH model, where *D* stands for Diagnosis, *E* for Etiology, *P* for Prognosis, and *Th* for Therapy (or intervention).

A clinically relevant research question, stemming from a problem encountered in clinical practice in one of the 4 DEPT_H areas, is leading in the research design. The design of a study should always start with the theoretical design. By theoretical design we mean the formulation of the occurrence relation as it follows from the research question and the subsequent conceptual definition of outcome, determinants, and possible extraneous determinants (confounders). In the theoretical design, a distinction is made between research that addresses causality (etiologic research), and descriptive research that does not address causality (diagnostic and prognostic research). Research on the benefits and risks of interventions is discussed as a separate case because it primarily deals with causality but also has non-causal aspects.

We find the distinction between causal and descriptive research extremely useful to arrive at the best results of a study. We realize that these terms have also been used with different meanings. In our use of the terms, *causal research* is research in which a causal question is addressed. *Descriptive research* is research where causality is not important, such as in diagnostic studies where the value of laboratory measurements to set a diagnosis is studied. While, for example, high blood glucose identifies a patient with diabetes, elevated glucose is a consequence and not a cause of the disease. Consequently, the research is descriptive and not causal. We do not claim that our use of terminology is right. We do believe, however, that our use of terminology provides a model that will help readers better understand the principles of research. Our terminology provides the reader with a consistent and robust framework to design, interpret, and apply clinical research.

The third part of the text is really about the practicalities of empirical clinical research. Data can be collected (Chapter 7) and analyzed (Chapter 12) in a number of ways. Chapters on cohort studies (Chapter 8), case-control studies (Chapter 9), clinical trials (Chapter 10), and meta-analyses (Chapter 11) should prepare the reader to be involved in setting up and carrying out applied clinical research with confidence and will help the reader in critically appraising the work of other researchers. In each chapter, the principles of the design are discussed as well as operational aspects. Worked-out examples should help the reader to understand how the research is actually conducted, analyzed, and interpreted.

In the text we have tried to be as consistent as possible in using epidemiologic terminology. There are different schools of thought and views on common epidemiologic terms. Some will call case-control studies retrospective studies, but we argue that in both cohort and case-control studies the outlook is typically longitudinal and in both types of studies data can be collected retrospectively. In general, we explain why we prefer certain

terms. For example, we use the term *extraneous determinant* when speaking about a confounder because it immediately tells us that the determinant is extraneous to the occurrence relationship of interest. The text is essentially self-contained. Extensive knowledge on epidemiology or statistics is not needed to benefit from its contents. References are given to more detailed and advanced texts.

This can be viewed as a comprehensive text covering everything you always wanted to know about clinical epidemiologic research. Alternatively, the reader can immediately zoom in on a topic that has acute relevance in view of the research he or she is engaged in. The chapter titles clearly indicate the content of the chapters and the extensive index at the end of the text should enable a reader to quickly find a topic or method of interest. We had several types of readers in mind when writing the text: students working on their master's or PhD degree should learn the background methodology for the studies they conduct, readers of research papers should be able to distinguish between studies that are relevant and valid and those that are flawed, and clinicians will find tools to assess whether certain findings from clinical research are applicable to their patients. Seasoned investigators should find food for thought and feel challenged to further refine their research approach. We are always eager to receive critical comments and suggestions for improvement that will help to further sharpen our thinking about clinical research.

