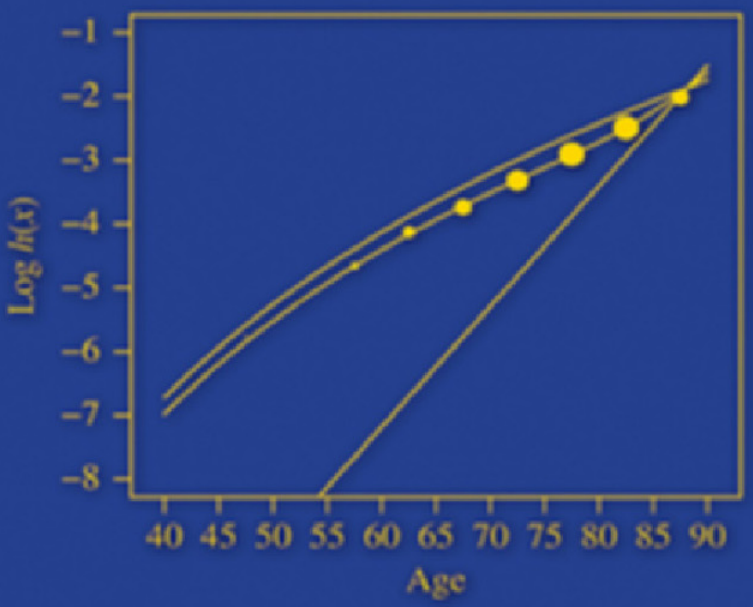
The Biostatistics of Aging

From Gompertzian Mortality to an Index of Aging-Relatedness



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From Gompertzian Mortality to an Index of Aging-Relatedness

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To my parents Menache and Norma Levy
G.L.

To my wife Betty
B.L

The decay of vitality with age is a biological fact most recognize in themselves and none fail to recognize in others; but the biometry of the subject is a difficult undertaking.

Greenwood, M. and Irwin, J. O. (1939). The biostatistics of senility. *Human Biology*, **11**, 1–23.

CONTENTS

PREFACE AND ACKNOWLEDGMENT

The purpose of this book is to describe a new quantitative method to examine the relative contributions of genetic factors and lifetime exposures to rates of mortality and disease incidence in a population. The book is highly multidisciplinary. The theoretical foundations of the work presented here involve the fields of statistics, evolutionary biology, demography, and epidemiology and should be of interest to those in these fields. Moreover, in its applications the work is broadly relevant to medicine, aging, and public health. Researchers and practitioners in these areas are also target audiences. We expect readers to comprise a spectrum from the more mathematically inclined to the more biologically inclined, though of course there will be readers who have expertise in both domains. This made the choice of level of presentation especially difficult. We chose to tilt the balance in favor of reaching a wide audience, at the cost of possibly making some (though hopefully not all) of the material in a field seem basic for an expert in that field. We also endeavored to make the book more widely appealing by keeping the denser mathematical material in a separate section in Chapter 2 and in a few appendices, and by providing summary pictures and statements after a series of mathematical results and at the end of some elaborate arguments. We bring the results and arguments from different areas of knowledge together starting in Section 2.2.1, and we hope the reader's forbearance will be rewarded with some interesting synergies.

On a personal note, we have enjoyed collaborating on this project immensely and have learned a great deal from each other. From one perspective, the statistical modeling required was of the most precious kind as it derived from careful evolutionary and causal thinking, leading inexorably to consideration of one special model, rather than a plethora of them. From another perspective, the evolutionary arguments benefited from giving them a sound statistical underpinning and the clarity that mathematics

can bring to an argument. In the interchange of ideas, we could hardly have had more fun.

The book greatly benefited from an illustrative application of the proposed method using data from the Israeli Ischemic Heart Disease (IIHD) study (Section 4.5). This was possible thanks to a collaboration with Uri Goldbourt, Ph.D., of the Division of Epidemiology and Preventive Medicine at the Sackler Faculty of Medicine of Tel Aviv University. The IIHD study collected mortality information on more than 10,000 subjects over a 43-year follow-up period (1963–2006), and Dr. Goldbourt has been involved with the study for nearly half a century. We deeply appreciate his invaluable help and responsiveness and are grateful for his graciousness in allowing us to report some of our analytic results from these data here.

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INTRODUCTION

The so-called aging-related diseases currently constitute a major public health concern, and their importance only tends to increase with the increase in absolute and relative numbers of older people in the population. The qualification "aging-related" is commonly used in the medical literature for diseases or disorders in a wide range of categories (e.g., neurodegeneration, cardiovascular, metabolic, neoplasia) and affecting virtually every organ system. In addition to *aging-related*, other terms that are often used with the same meaning are *age-related*, *age-dependent*, and *age-associated*. Although usually no formal definition is given, these terms are generally employed as referring to diseases whose age-specific point incidence rates (or, briefly, "incidence") increase with increasing age.

However, some authors have drawn a fundamental distinction among these terms. While considerations about the relation between disease and aging go back a long way (Blumenthal, 2003), perhaps one of the earliest discussions specifically pointing to that terminological distinction is to be found in Kohn (1963), who noted, "it is useful to make two categories of the bad things that happen to people with increasing age—basic aging processes and age-related diseases, and to consider that the latter may be conditioned by, or dependent on, the former." He then distinguished between a category of diseases that shows an increasing incidence with increasing age and a category that shows "a less clear-cut, age-related increase in incidence." Two decades later, Kohn (1982) proposed that age-related diseases could be categorized in three ways: diseases that are normal aging processes themselves, diseases in which the

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incidence increases with increasing age, and diseases that have more serious consequences the older the affected persons. The more precise distinction that is most relevant to this work was given by Brody and Schneider (1986), who described two classes of "chronic diseases and disorders of old age" as follows: "Age-dependent diseases and disorders are defined as those whose pathogenesis appears to involve the normal aging of the host. Mortality and morbidity from age-dependent diseases and disorders (e.g. coronary artery disease and Alzheimer's disease) increase exponentially. Age-related diseases and disorders, on the other hand, have a temporal relationship to the host but are not necessarily related to aging processes. They occur at a specific age and then decline in frequency or continue at less than an exponential rate of increase (e.g. multiple sclerosis and amyotrophic lateral sclerosis)."[1]

Particularly relevant to this work, Brody and Schneider (1986) suggested that the group of diseases related to the aging process is characterized by an exponential increase in age-specific incidence or mortality rates, as opposed to "less than an exponential rate of increase." However, they did not provide a basis rooted in biological or statistical principles for that notion. Similarly, Kohn (1963) had considered, without justification from first principles, that an exponential increase in cause (disease)-specific (DS) mortality rates with age "is characteristic of deaths due to basic age-related processes and suggests the extent to which a disease is related to such processes." Brody and Schneider (1986) illustrated such notion by plotting DS mortality rates by age for cardiovascular disease and cancer, representing the groups with and without exponential increase in age-specific rates, respectively (Fig. 1.1).

In the context of a meta-analysis of dementia prevalence, Ritchie and Kildea (1995) distinguished between an "ageing-related disorder" ("caused by the ageing process itself") and an "age-related disorder" ("occurring within a specific age range"). Thus, they suggested that one category had a causal relation to the aging process and the other did not (labeled "ageing-related" and "age-related," respectively), as Brody and Schneider (1986) had done before but instead labeling the first category "age-dependent." As an example that this distinction continues to provoke and underlie the debate about the relation between diseases and aging in the twenty-first century, even if the causality notion is not always explicitly conveyed, Blumenthal (2003) offered the following "note on terminology" in his article titled "The aging-disease dichotomy: true or false?": "In this essay I have used the term aging-associated disease rather than age-related disease. This choice is to emphasize that the primary focus here has been on diseases with age at onset in the senescent period of the life span, the oldest old, rather than through progressive periods of the total life span."[2]

Yet, in a sense, the relation between diseases and aging has eluded medical thinking. While employing separate terms or categories for qualitatively different relations between diseases and aging seems warranted, it may not be clear under which

[1] Reproduced from *Journal of Chronic Diseases*, **39**, Brody, J. A. and Schneider, E. L., Diseases and disorders of aging: An hypothesis, pages 871–876, Copyright 1986, with permission from Elsevier.
[2] Reproduced from *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, **58**, Blumenthal, H. T., The aging–disease dichotomy: True or false? pages M138–M145, Copyright 2003, with permission from Oxford University Press.

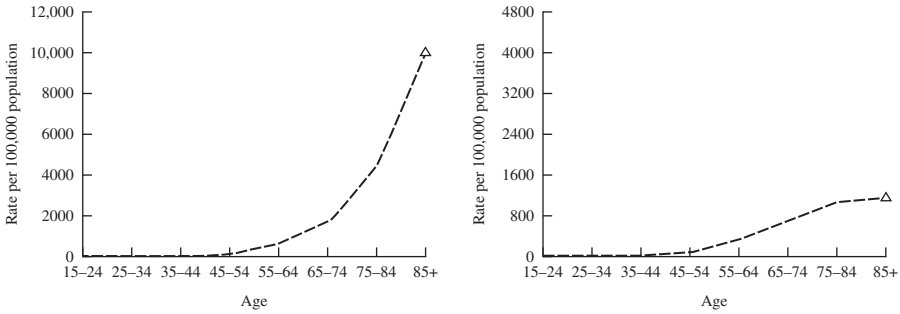

FIGURE 1.1 Cause (disease)-specific mortality rates by age for cardiovascular disease (left) and all cancers (right), data from the United States, 1978 (reproduced from *Journal of Chronic Diseases*, **39**, Brody, J. A. and Schneider, E. L., Diseases and disorders of aging: An hypothesis, pages 871–876, Copyright 1986, with permission from Elsevier).

category a disease falls given how its incidence increases with age. On the other hand, diseases considered to be in the same category may show different rates of increase in incidence rates with age. This may be seen as reflecting the fact that the aforementioned distinction arises from an underlying relation on a continuous scale, which therefore might better be considered using a quantitative approach. Although the authors quoted in the preceding text have attempted to clarify the meaning of aging-relatedness, the quantification of aging-relatedness has not been addressed at all in the medical, biostatistical, epidemiological, or demographic literature. *Hence, we aimed to develop an index of aging-relatedness, as a means of quantifying and elucidating the underlying meaning of aging-relatedness*.

Since the increase of mortality rates with age is an expression of aging at the population level, the notion of aging-relatedness applies as well, and perhaps even more naturally, to mortality. Medawar (1955) distinguished between a personal measure of aging, which "purports to measure a process that takes place in the life history of an individual animal," and a statistical or actuarial measure of aging, "which is founded upon the mortality of a population of individuals and which bears only indirectly upon the changes that occur within the lifetime of anyone." The assumed relevance of the mortality experience of a population to the physiological process of aging of its members is reflected in other authors' definitions of aging or senescence. For instance, Maynard Smith (1962) stated, "Ageing processes may be defined as those which render individuals more susceptible as they grow older to the various factors, intrinsic or extrinsic, which may cause death." Similarly, Comfort (1979, p. 21) stated, "Senescence shows itself as an increasing probability of death with increasing chronological age: the study of senescence is the study of the group of processes, different in different organisms, which lead to this increase in vulnerability." More recent statements include Kirkwood's (1985): "The pattern of mortality experienced by human populations serves to illustrate what is most commonly understood by the term *aging*. Following the attainment of sexual maturity and a peak of vitality which occurs early in adulthood, a long period of progressive deterioration takes place during which