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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

The Biostatistics of Aging: From Gompertzian Mortality to an Index of Aging-Relatedness,
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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

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[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.

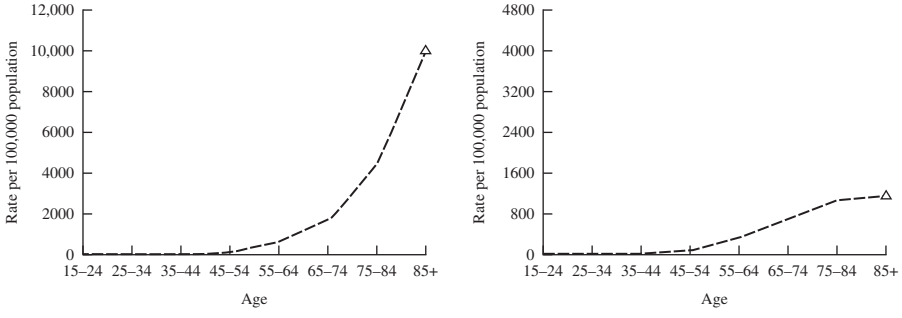

FIGURE 1.1 Cause (disease)-specific mortality rates by age for cardiovascular disease (left) and all cancers (right), data from the United States, 1978 (reproduced from *Journal of Chronic Diseases*, **39**, Brody, J. A. and Schneider, E. L., Diseases and disorders of aging: An hypothesis, pages 871–876,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

individuals become increasingly likely to die." Or Finch's (1990, p. 5): "Senescence is mainly used to describe age-related changes in an organism that adversely affect its vitality and functions, but most importantly, increase the mortality rate as a function of time." The implicit assumption in all these authors' definitions—that the pattern of age at death (or schedule of age-specific mortality rates) in a population parallels functional changes in the organism—is supported by experimental research with a variety of organisms (Austad, 2001).

Consistent with this premise, the index of aging-relatedness that we propose in this book is based on the schedule of age-specific mortality rates at a given point in time, through the use of time-to-event population-based data. Likewise, the index of aging-relatedness as applied to specific diseases is based on age-specific incidence rates or DS and age-specific mortality rates. The terms *aging-related* and *aging-relatedness* are used in this work without reference to the terminological distinctions in the preceding text. Indeed, developing a quantitative index of aging-relatedness would turn these distinctions moot. This is also to say that no claim of causality in the sense expressed by Brody and Schneider (1986) and Ritchie and Kildea (1995) is made in connection with the proposed index of aging-relatedness. Rather, in Chapters 2 and 3, we develop an extensive theoretical framework for the proposed index of aging-relatedness involving the statistical theory of extreme values and the evolutionary theory of aging, both of which rest on solid ground. We start by considering the biological basis of the Gompertz survival distribution, which is precisely characterized by the exponentially increasing hazard rate referred to by Kohn (1963) and Brody and Schneider (1986) and has long played a central role in demography for describing the survival time of human populations. The theoretical framework then includes (i) original mathematical results on the asymptotic behavior of the minimum of time-to-event random variables, extending those of the classical statistical theory of extreme values (Section 2.1.2); (ii) an account of the Gompertz pattern of mortality in human populations, using those results on the statistical theory of extreme values and arguments based on the evolutionary theory of aging (Section 2.2.1); and (iii) the development of the sufficient and component causes model of causation in epidemiology into an evolution-based model of causation, relevant to mortality and aging-related diseases of complex etiology (Section 3.2). While these are necessary steps toward devising the proposed index of aging-relatedness, each stands on its own as a theoretical contribution.

The index of aging-relatedness is presented in Chapter 4. The evolution-based model of causation provides the motivation for a statistical model for describing mortality and incidence of aging-related diseases of complex etiology involving a mixture of the Gompertz and Weibull distributions. This creates a framework for interpreting the index of aging-relatedness, which is defined as a parameter of this model (Sections 4.1 and 4.2). We describe the estimation procedures for obtaining the index and present an illustrative application to a real set of data (Sections 4.4 and 4.5). Although the overall presentation of this book proceeds from Gompertzian mortality to the index of aging-relatedness, we originally set out to develop an index of aging-relatedness. As we considered the theoretical basis for various proposals and found the mixture model index especially appealing from a theoretical viewpoint, the scope of the work

widened considerably—while remaining in essence a medically motivated quantitative/statistical pursuit—to involve other disciplines such as demography, epidemiology, evolutionary biology, and population genetics. With this widening scope came a deeper reach. Even as our motivation was at first sight purely conceptual, a practical biomedical and public health relevance of the index arises from its interpretation, in a special sense, in terms of genetic and environmental contributions to mortality or disease incidence in a population. As a consequence, despite an ostensibly narrow initial aim, there are widespread implications of our theoretical framework and the index of aging-relatedness. These are discussed in Chapter 5. In its implications, the work presented in this book is additionally relevant to the fields of gerontology and geriatrics (Sections 5.3 and 5.4), as well as any medical specialty whose practitioners deal with aging-related diseases, but the most direct and practical implications are for public health (Sections 5.5 and 5.6) now and into the future.