CHAPTER 32

Theoretical Perspectives on Biodemography of Aging and Longevity

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Biodemography of aging represents an area of research that integrates demographic and biological theory and methods and provides innovative tools for studies of aging and longevity. Biodemography of aging conducts comparative studies of aging and mortality in different species and addresses some key questions about aging, life course, and health. Biodemography of aging is the science of the mechanisms that determine the life span of organisms. Among its most interesting problems is the problem of the heritability and variability of lifetimes, the problem of sex differentials in lifetimes, and the problem of the changing life span of organisms in the process of evolution. Thus one of the objectives of the biodemography of aging is to explain the causes of individual differences in lifetimes, as well as the causes of interspecies differences. The practical interest of these studies is to open up the possibility of predicting and controlling the aging and longevity of organisms, and most importantly, to discover ways of extending the lives of human beings.

BIODEMOGRAPHY OF AGING AND LONGEVITY: A HISTORICAL REVIEW

Biodemography of aging and longevity was developed as an independent scientific discipline at the beginning of the 20th century, thanks to the classic investigations of the American scientist Raymond Pearl (Pearl, 1922; Pearl & Pearl, 1934). At this time, researchers used the term “biology of life span,” which was suggested by one of Raymond Pearl’s students, Professor Vladimir Alpatov (Alpatov, 1930). Because the study of the mechanisms that determine the length of life is closely linked with investigations into the processes of aging, biodemography of aging owed its subsequent development to the biology of aging and gerontology. It is worth noting that such famous gerontologists as Alex Comfort, Bernard L. Strehler, and George Sacher also made an invaluable contribution to the study of life span and biodemography of aging (Comfort, 1979; Sacher, 1977; Strehler, 1978). The ideas and methods of the biodemography of aging are so widely used in gerontology that some gerontologists regard it as one of the branches of their own discipline. However, the biodemography of aging and longevity, in distinction to gerontology, is just as much interested in the mechanisms that determine mortality and aging in wild animal populations (which are of great importance for ecology and the theory of evolution), and effects of external factors on mortality (which are of special interest also for toxicology and radiobiology). Thus, although the biodemography of aging and longevity is close to biogerontology, it nevertheless has its own specific goals and cannot be reduced to this latter science.
Moreover, the biodemography of aging has its own historical roots, which connect it with demography and population biology. The result is that the biodemography of aging and longevity has developed its own characteristic style of research: the use of precise quantitative methods, a probabilistic approach to natural phenomena, and a desire to explain the mechanisms of particular processes by their external manifestations in the population under investigation.

The beginnings of the field are straddled by such great scientists as Christian Huygens (1629–1695), Gottfried Wilhelm Leibniz (1646–1716), Edmund Halley (1656–1742), Leonard Euler (1707–1783), and Pierre Simon Laplace (1749–1827). The contribution of these men was basically related to the collection of statistical information concerning human mortality in the form of life tables. The well-known Belgian scientist, Adolphe Quetelet (1796–1874), became one of the founders of the modern method of constructing life tables. This initial historical stage in the development of the subject can be described as the “period of descriptive human mortality statistics.”

The biodemography of aging and longevity was further developed in the works of a well-known English expert on mathematical statistics, one of the founders of biometry, Karl Pearson (1857–1936). In 1901, Pearson founded the journal *Biometrika*, remaining its editor until he died. In the first issue of this journal, Pearson published his article “On the Inheritance of the Duration of Life and on the Intensity of Natural Selection in Man” (Beeton & Pearson, 1901). This work signifies the beginning of truly biological research into life span. Nevertheless, the remarkable American scientist Raimond Pearl must be considered the real founder of the biodemography of aging. In our opinion, the biodemography of aging was born as an independent discipline in 1922 with the appearance of Pearl’s book *The Biology of Death* (Pearl, 1922). This book is in fact not concerned at all with problems of death (the dying process), but is totally dedicated to problems of the biology of life span. Pearl published a total of several dozen works on this problem, including a large series of articles entitled “Experimental Studies on the Duration of Life.” In his studies, Pearl dealt with practically all the problems in the biology of life span, including the genetic, ecological, physiological, and comparative-evolutionary aspects. Many of these works have preserved their importance and relevance to the present day, and methodologically almost all of Pearl’s works can serve as a model for contemporary researchers. One of his famous studies is represented by the book *The Ancestry of Long-Lived* where he showed for the first time that longevity runs in families (Pearl & Pearl, 1934).

Because the biodemography of aging and longevity was founded by scholars having a strong background in mathematics (mathematicians, physicists, astronomers, statisticians), it is a discipline that, from the start, unlike most of the other areas of biology, began to take the shape of an exact science. In this regard it is related to such areas of biology as biometry, quantitative genetics, and biokinetics. Whereas in many areas of biology exceptional attention is paid to experimental techniques in the search for clear qualitative effects, in biodemography of aging primary importance is attached to the method of quantitative observation with subsequent mathematical analysis of the results. This approach, which is less “aggressive” toward the natural environment, may seem at first glance to be too indirect, formal, and unconvincing. However, its value has been demonstrated many times in the history of the natural sciences. For example, all the basic notions of genetics (the concept of genes and their mutations, the concept of allelic forms of genes and their pair-wise association [the diploid concept], the conclusion that genes are linearly ordered and organized into cohesive groups, chromosomes) were the result of this “formal” method, a statistical
The desire to discover scientific truths “by pen and paper” was a characteristic feature of the founders of the biodemography of aging, and this tradition has been maintained to the present day. The historical development of the biodemography of aging is closely interwoven with the historical development of statistics, demography, and even the technical aspects of life insurance. This led to the discipline being formed as a statistical, population-based area of biology, which easily borrows the methods and ideas of other sciences. The biology of aging, like most of the other divisions of modern biology, is characterized by a “bottom-up” approach, while the biodemography of aging finds a “top-down” approach more natural, an explanation of mechanisms as they are revealed at the level of populations of organisms. Of course, these two approaches are not mutually exclusive. They complement each other, as the historical experience of the science development shows.

In the 1960s–1980s, the biodemography of aging studies seems to be scattered among a multitude of disciplines: gerontology and the biology of aging (Comfort, 1979; Strehler, 1978), demography (Bourgeois-Pichat, 1979; Manton, Stallard, & Vaupel, 1981; Olshansky & Carnes, 1997), ecology (Caughley, 1966; Hutchinson, 1978), radiobiology (Lindop, 1961; Sacher, 1956, 1966), and other disciplines. We need to acknowledge significant contributions by Bernard Strehler and George Sacher into the field. They not only established and analyzed existing mortality regularities, but also suggested mathematical theories of aging explaining these regularities (Sacher, 1977; Strehler & Mildvan, 1960). At that time, the biodemography of aging and longevity had suffered above all from the disconnectedness of biological and demographic studies. The clearest manifestation of this is the fact that the colossal archive of data on the human life span (hundreds of demographic life tables from a wide variety of the world’s population groups) has been almost unused in human biology, despite the acute deficiency of factual information in the field. For a long time many biologists had no idea of the scale of this archive of accumulated demographic data, and of how it might be used to investigate the biology of life span.

The temporary loss of contact with demography has had the consequence that many researchers—biologists working on life span—lacked the necessary minimum demographic and statistical knowledge for the task. As a result, some biologists strongly believed in the concept of the species-specific life-span limit beyond which survival is impossible even for a second. It was also maintained that the species-specific human life-span limit “has remained unchanged across time, races and civilizations” (Economos, 1985). The theoretical unsoundness of this dogma has been frequently pointed out by demographers (Sauvy, 1961), by experts in probability theory (Feller, 1968), and by biologists who are qualified in statistical methods (Caughley, 1977). The failure of this concept to agree with the observed mortality data in humans was demonstrated in the book *The Biology of Life Span* (Gavrilov & Gavrilova, 1991). Publication of this book was considered as “the birth of modern biodemography” by renowned American demographer, S. J. Olshansky, in his thoughtful review essay on the history of biodemography (Olshansky, 1998). In this book the authors overviewed existing mortality laws; tested the validity of the Gompertz law of mortality using data on more than 100 life tables for humans, fruit flies, and other species; compared mortality across different species and historical periods; analyzed sex differentials in mortality among various species; suggested reliability theory of aging; and provided references for hundreds of published life tables. S. J. Olshansky himself (together with Bruce Carnes) was among the founders of contemporary biodemography of aging and made a significant contribution to
the field (Carnes & Olshansky, 1997; Carnes, Olshansky, & Grahn, 1996; Olshansky & Carnes, 1997). In particular, the researchers tested the Gompertz law of mortality using data on humans and mice (Carnes et al., 1996). They also conducted a biologically motivated partitioning of mortality into endogenous and exogenous parts using cause-of-death data on humans and rodents (Carnes & Olshansky, 1997). Methodological studies of demographic indicators, which take into account health status of population (healthy life expectancy and active life expectancy), were another direction of research initiated during the 1980s and 1990s (Crimmins, Hayward, & Saito, 1996; Laditka & Laditka, 2009).

Publication of the monograph “Between Zeus and Salmon” in 1997 was a significant event in the history of biodemography of aging (Wachter & Finch, 1997). Besides topics already described earlier in The Biology of Life Span book (mortality laws, limit to individual life span, reliability theory of aging) this monograph established new research directions for biodemography of aging: evolutionary and ecological models of aging (Tuljapurkar, Partridge, Rose); intergenerational relations (Lee); evolution of the human life course (Kaplan); comparative biodemography (Austad, Finch, Carey); and biomarkers in population-based surveys (Wallace). The latter topic was further developed in other editions: Biosocial Surveys published in 2007 (Weinstein, Vaupel, & Wachter, 2007) and Conducting Biosocial Surveys: Collecting, Storing, Accessing, and Protecting Biospecimens and Biodata published in 2010 (Hauser, Weinstein, Pool, & Cohen, 2010). Study of biomarkers in population-based surveys is now one of the most rapidly developing areas of biodemographic research (Crimmins & Seeman, 2000; Crimmins & Vasunilashorn, 2011).

The scope of biodemography research is exceptionally broad and continues to expand. In recent years, especially intensive work has been carried out in genetics (Boardman, Barnes, Wilson, Evans, & Mendes de Leon, 2012; Gögele et al., 2011; Yashin et al., 2015), and comparative biodemography (Austad, 2009; Weinstein & Lane, 2014). Significant attention is paid to the effects of early-life conditions on late-life mortality, and to the problem of the evolution of life span (Hayward, Rickard, & Lummaa, 2013). Another promising area of research in biodemography of aging is related to biomarkers as predictors of health and longevity (Crimmins et al., 2014; Crimmins & Seeman, 2000; Karlamangla, Merkin, Crimmins, & Seeman, 2010).

### BIODEMOGRAPHIC THEORIES ANSWERING THE “WHY DO WE AGE?” QUESTION

It is generally believed that evolutionary theory of aging is able to answer the question: Why do we age? (Le Bourg, 2014). Traditional evolutionary theory of aging explains aging as a result of declining force of natural selection (Robins & Connelly, 2014). According to this theory, death rates are increasing with age because a selection against deleterious mutations is weaker for later-acting mutations, thus shifting the mutation-selection balance to a higher equilibrium frequency of later-acting deleterious mutations. Evolutionary explanations of aging and limited longevity of biological species are based on two major evolutionary theories: the mutation accumulation theory (Medawar, 1958) and the antagonistic pleiotropy theory (Williams, 1957). These two theories can be briefly summarized as follows:

1. According to the mutation accumulation theory, aging is an inevitable result of the declining force of natural selection with age. For example, a mutant gene
that kills young children will be strongly selected against (will not be passed to the next generation) while a lethal mutation that affects only old people will experience no selection because people with this mutation will have already passed it to their offspring by that age. Over successive generations, late-acting deleterious mutations will accumulate, leading to an increase in mortality rates later in life.

2. According to the antagonistic pleiotropy theory, late-acting deleterious genes may even be favored by selection and be actively accumulated in populations if they have any beneficial effects early in life.

Note that these two theories of aging are not mutually exclusive, and both evolutionary mechanisms may operate at the same time. The main difference between the two theories is that, in the mutation accumulation theory, genes with negative effects at old age accumulate passively from one generation to the next, while in the antagonistic pleiotropy theory these genes are actively kept in the gene pool by selection (Le Bourg, 2014).

The evolutionary “disposable soma theory” (Kirkwood & Holliday, 1979) postulated a special class of gene mutations with the following antagonistic pleiotropic effects: These hypothetical mutations save energy for reproduction (positive effect) by partially disabling molecular proofreading and other accuracy-promoting devices in somatic cells (negative effect). The authors of the disposable soma theory argued that “it may be selectively advantageous for higher organisms to adopt an energy saving strategy of reduced accuracy in somatic cells to accelerate development and reproduction, but the consequence will be eventual deterioration and death” (Kirkwood & Holliday, 1979). Most researchers (including the authors themselves) agree that the disposable soma theory is a special, more narrowly defined variant of the antagonistic pleiotropy theory of aging.

Currently, some researchers started to challenge traditional evolutionary theories of aging pointing to the diversity of age-specific trajectories of mortality and fertility and suggesting the development of broader perspectives on the evolution of aging (Jones et al., 2014).

It should be noted that one of the first explanations of aging with evolutionary arguments was proposed by August Weismann (1834–1914), the great German theorist and experimental biologist of the 19th century. His initial idea was that there exists a specific death mechanism designed by a natural selection to eliminate the old, and therefore worn-out, members of a population (Gavrilov & Gavrilova, 2002). The purpose of this programmed death of the old is to clean up the living space and to free up resources for younger generations. Later the idea of programmed aging was abandoned by Weismann himself and criticized by gerontologists (Gavrilov & Gavrilova, 1991; Kirkwood, 1998; Kirkwood & Melov, 2011). One of the principal arguments against the theory of programmed death is a paucity of old individuals in the wild, so that the aging program could not evolve during evolution (Kirkwood & Melov, 2011). However, recent studies demonstrated that the process of senescence is nearly ubiquitous in the living world (Lemaître et al., 2015). Senescence patterns are highly variable among species and current evolutionary theories of aging propose that such variation can be accounted for by differences in allocation to growth and reproduction during early life rather than by programmed aging (Lemaître et al., 2015). Nevertheless, the question of whether aging is programmed was debated by gerontologists (Austad, 2004; Bredesen, 2004) and some of them recognized the possibility of both programmatic and nonprogrammatic
components of aging (Bredesen, 2004). Recently, more researchers have begun to consider aging as a programmed process (Mittendorf & Martins, 2014; Skulachev, 2011), although the majority of gerontologists does not support this view.

The problem of the biological evolution of aging was initially studied in a purely theoretical, nonexperimental way by August Weismann, Ronald Fisher, Peter Medawar, George Williams, William Hamilton, Brian Charlesworth, and other researchers. The resulting evolutionary theories of aging were then partially tested by direct evolutionary experiments on laboratory fruit flies (Rose, 1991; Stearns, Ackermann, Doebeli, & Kaiser, 2000). Specifically, the researchers found that aging and life span do evolve in subsequent generations of biological species in a theoretically predicted direction, depending on particular living conditions. For example, a selection for later reproduction (artificial selection of late-born progeny for further breeding) produced, as expected, longer-lived fruit flies (Rose, 1991), while placing animals in a more dangerous environment with high extrinsic mortality redirected evolution, as predicted, to a shorter life span in subsequent generations (Stearns et al., 2000). Therefore, the early criticism of the evolutionary theory of aging, as merely theoretical speculation with limited and indirect supporting evidence obtained from retrospective and descriptive studies, has been overturned. On the contrary, the evolutionary plasticity of aging and longevity is now an established experimental fact.

TESTING EVOLUTIONARY THEORIES OF AGING WITH HUMAN DATA

Many biodemographic studies use human data to test predictions of evolutionary theories of aging. We consider here some of the most promising directions of research. Both antagonistic pleiotropy theory (Williams, 1957) and the disposable soma theory of aging (Westendorp & Kirkwood, 1998) argue that genetic investments in somatic maintenance increase longevity at the cost of reproductive success. According to these theories, one may expect that long-lived individuals should have less children on average compared to their shorter-lived peers. Some studies found support for these theories (Doblhammer & Oeppen, 2003; Lycett, Dunbar, & Voland, 2000; Westendorp & Kirkwood, 1998), while others found no relation between longevity and reproduction (Gavrilova, Gavllov, Semyonova, & Evdokushkina, 2004), or even higher fertility among long-lived individuals (Goegele et al., 2011). This issue still remains to be resolved. For example, a recent study of Ashkenazi Jews found that centenarians have less children on average than controls (Tabatabaie et al., 2011) and the analysis of Framingham Heart Study data found negative phenotypic correlation between number of children ever born and life span (Wang, Byars, & Stearns, 2013). On the other hand, study of Swedish twins found no support for the disposable soma theory (Chereji, Gatz, Pedersen, & Prescott, 2013). Thus, more research is needed to resolve the existing controversies as suggested by the experts in this area (Gagnon, 2015).

Disposable soma theory of aging (Kirkwood, 1998) predicts a trade-off between investment in reproduction and a woman’s own survival. An alternative approach, also supported by empirical findings from human populations, speculates that selection for increased reproductive success simultaneously may drive the selection of longevity (Müller, Chiu, Carey, & Wang, 2002; Perls, Alpert, & Fretts, 1997; Smith, Gagnon et al., 2009; Smith, Mineau, & Bean, 2002). It was postulated that postreproductive life extension is triggered by late births (reproductive potential hypothesis; Muller et al., 2002). Existing studies support the reproduction potential hypothesis: Women
bearing children at advanced ages have been shown to have better postmenopausal survival (Grundy & Kravdal, 2008; Helle, Lummaa, & Jokela, 2005; Müller et al., 2002; Sun et al., 2015). In testing this hypothesis, it is important to consider the direction of causality between longevity and late reproduction: it could be a genuine causation effect (late childbirth extends maternal life) or a selection effect (longer-lived mothers lose their fertility later). Some insights into these issues can be gained by studying late reproduction in relatives (mothers or sisters) of long-lived women (Smith, Mineau, Garibotti, & Kerber, 2009).

Another interesting approach is to study sex composition of offspring and parental mortality and longevity. The trade-off between longevity and reproduction is often investigated by relating the total number of children to the total life span (Doblhammer & Oeppen, 2003). However, delivering sons compared with daughters is likely to be energetically more costly for the mothers (Helle, Lummaa, & Jokela, 2002). Indeed, maternal longevity was negatively related to having sons (Harrell, Smith, & Mineau, 2008; Helle & Lummaa, 2013; Helle et al., 2002; Jasienska, Nenko, & Jasienski, 2006; Van de Putte, Matthijs, & Vlietinck, 2004) and positively related to having daughters (Beise & Voland, 2002; Helle et al., 2002). Some studies found that having daughters increased paternal life span (Jasienska et al., 2006). This gender effect may be due to the lower direct physiological costs of daughters and to the fact that daughters more often become caregivers for older parents. These results demonstrate that both the direct effects of reproductive investment and the social effects of gender-biased family structure appear to be important in determining female life span.

■ BIODEMOGRAPHY OF AGING AND LIFE HISTORY THEORY

The evolutionary theory of aging may be considered as part of a more general life history theory (Stearns, 1992), which tries to explain how evolution designs organisms to achieve reproductive success (i.e., avoid extinction). Life history theory is based on mathematical methods of optimization models with specific biological constraints. Among the questions posed and answered by life history theory are (Stearns, 1992): Why are organisms small or large? Why do they mature early or late? Why do they have few or many offspring? Why do they have a short or a long life? Why must they grow old and die? The latter two questions represent the entire scientific agenda of the evolutionary theory of aging. Therefore, it could be said that the evolutionary theory of aging is a subset of the life history theory (Le Bourg, 2001). On the other hand, the evolutionary theory of aging is considered to be the intellectual core of the biodemography of aging and longevity (Carnes & Olshansky, 1993).

The “grandmother hypothesis” is one of the most widely known concepts among the life history topics. It suggests that the evolution of human life history proposes that grandmother effects promoted increase in life span without changes in the age of female fertility decline (Hawkes & Smith, 2010). Similar conclusions were made by using computer simulations of intergenerational transfers from postreproductive humans to their descendants. As a result, the growth and survival of descendants is enhanced, which in turn promotes selection for postreproductive survival (Lee, 2014). Effects of stressful environments characterized by high extrinsic mortality on life history evolution are another direction of research. It was shown that the speed of life histories is associated with family-level effects rather than with individual-level mortality experiences and that exposure to higher levels of mortality in the family leads to earlier marriage and reproduction (Störmer & Lummaa, 2014).
THEORIES ANSWERING THE “HOW DO WE AGE?” QUESTION

Theories of aging providing specific explanations of age-related changes attempt to answer the “How do we age?” question. Among these theories are the free radical theory, cell membranes theory, oxidative stress and mitochondria theory, cell communication theory, immunological theory, and others (Robert & Fulop, 2014). Many of these theories are focused on specific chemical processes that are damaging to the organism’s organs and tissues, such as free radical damage or protein cross-linkage. In view of the existing numerous types of damage, Gladyshev suggested a model explaining aging through an imperfectness-driven nonrandom damage process pointing out that physicochemical properties preclude ideal biomolecules and perfect biological functions (Gladyshev, 2013). It should be noted that some aging theories are very general (e.g., free radical theory), while others may explain aging in a limited number of species (e.g., immunological theory). Discussing all existing specific explanations of aging is beyond the scope of this chapter, so we focus our review on some theories that are more specific for humans.

Neuroendocrine Theory of Aging

One theory, which has support from experiments on lower organisms, is the neuroendocrine theory of aging (Weinert & Timiras, 2003). This theory proposes that aging occurs due to changes in neural and endocrine functions. A particular emphasis in this theory is given to the hypothalamo–pituitary–adrenal (HPA) axis as the master regulator that signals the onset and termination of each life stage (Weinert & Timiras, 2003). One of the first versions of the neuroendocrine theory of aging was proposed by Vladimir Dilman who suggested that the key process in development and aging is a gradual elevation of the threshold of sensitivity of the hypothalamus to feedback suppression (Dilman, 1971; Dilman & Dean, 1992). More recent studies emphasize the role of lifelong exposure to stress, which can weaken the ability to adapt and lead to so-called diseases of adaptation. According to these studies, aging should be considered as a result of declining ability to resist stress (Weinert & Timiras, 2003).

Most studies now are focused on insulin/insulin-like growth factor I (IGF-I) signal response pathway as an evolutionarily conserved mechanism of longevity from yeast to humans. Animal experiments demonstrated that insulin/IGF-like signaling pathway controls aging in worms, insects, and mammals and that genetic down regulation or interruption of this signaling pathway can lead to significant life extension (Anisimov & Bartke, 2013). Biologists believe that rapid growth may be harmful, while delayed maturation would be beneficial for longevity and health (Rollo, 2002). Animal studies of different strains and breeds within biological species of dogs, rats, and mice showed that smaller animals live on average longer within a given species (Michell, 1999; Miller, Chrisp, & Aitchley, 2000; Samaras, Elrick, & Storms, 2003). It is also well known that caloric restriction is a powerful way of life extension in animals (Finch, 2007). These biological findings agree with the recent studies of adverse effects of obesity on human mortality (Flegal, Kit, Orpana, & Graubard, 2013), particularly at younger ages (Wang, 2015). However, these biological data do not agree with the results obtained by historical demographers. Studies of demographers showed that an individual’s height at a young adult age seems to be a good indicator of a person’s nutritional and infectious disease history in the past (Alter, 2004; Alter, Neven, & Oris, 2004; Elo & Preston, 1992). Most studies, starting with Waaler’s pioneer work, found a negative relationship...
between body height and mortality later in life (Elo & Preston, 1992; Waaler, 1984). A study of the Union Army veterans found that the relationship between height and subsequent mortality was negative, findings similar to a study of modern Norwegian males (Costa & Lahey, 2005; Fogel & Costa, 1997). Infectious diseases (and diarrhoeal diseases in particular) can result in growth retardation leading to shorter adult height. For example, conscripts from high-mortality districts of antebellum New York were shorter than those from healthier districts (Haines, Craig, & Weiss, 2003). Based on existing historical information, Crimmins and Finch hypothesized that both the decline in old-age mortality and the increase in height were promoted by a declining burden of infections and inflammatory causes rooted in the external environment (Crimmins & Finch, 2006). However, recent data on contemporary Japanese men demonstrated that height in midlife is positively associated with mortality and it was also associated with fasting insulin level pointing to the involvement of insulin/IGF signaling pathway in both aging and growth regulation (He et al., 2014). Similarly, higher longevity was found for shorter Sardinian men compared to their taller peers (Salaris, Poulain, & Samaras, 2012). It appears that environmental factors are able to modulate the existing biological link between height and life span.

**LIFE-COURSE PERSPECTIVE IN AGING THEORIES**

Early-life programming theory and cumulative risk theory apply life-course perspective for explaining old age diseases and mortality. A growing body of evidence documents that adverse early-life conditions negatively affect survival and health in later life (Ben-Shlomo & Kuh, 2002; Bengtsson & Mineau, 2009; Blackwell, Hayward, & Crimmins, 2001; Hamil-Luker & O’Rand, 2007; Hayward & Gorman, 2004). Two major explanations of these effects now exist in the scientific literature. The first explanation is related to direct effects of adverse childhood conditions on the human organism resulting in “scarring” (Elo & Preston, 1992; Preston, Hill, & Drevenstedt, 1998) or biological imprint in a way that makes it more susceptible to late-life diseases (Hamil-Luker & O’Rand, 2007). This theory, also known as the “latency model,” suggests that early-life exposures can program permanent changes in an organism’s physiology. A variant of this theory is the fetal origin hypothesis suggested by Barker (Barker, 1998) that the fetus may adapt to malnutrition or metabolic changes of maternal organism, but these changes may be accompanied with permanent damage of physiological systems resulting in premature chronic diseases (Hamil-Luker & O’Rand, 2007). Another variant of this theory is the idea of early-life inflammatory exposure (Finch, 2007; Finch & Crimmins, 2004).

The second theory explaining early-life effects on later-life mortality is the cumulative risk theory (Galobardes, Lynch, & Davy Smith, 2004), or pathway model (Hamil-Luker & O’Rand, 2007; Kuh & Ben-Shlomo, 1997), also called a theory of “cumulative disadvantage” in sociology (Ferraro & Kelley-Moore, 2003). For example, early-life social disadvantage may result in poor education and unhealthy behaviors and eventually limited job opportunities and low socioeconomic status in adulthood, which are known risk factors for poor health and mortality (Hamil-Luker & O’Rand, 2007). This theory considers an indirect mechanism among death risks across the life cycle that is attributable to their joint association with other variables (Preston et al., 1998). Both theories are not mutually exclusive.

Childhood exposure to infections (as a factor of elevated mortality later in life) deserves special attention. Finch and Crimmins (Finch & Crimmins, 2004) proposed
a hypothesis that historical decline in chronic inflammation (due to decreasing exposure to early-life infections) has led to a decrease in morbidity and mortality resulting from chronic conditions in old age. Studies of rural 18th-century Sweden (Bengtsson & Lindstrom, 2000, 2003), U.S. Civil War veterans (Costa, 2000, 2002), and Americans in their 50s (Blackwell et al., 2001) demonstrated that exposure to infections early in life is associated with elevated mortality from chronic diseases at older ages. Existing historical evidence suggests that disease load in the early-20th-century United States was high (Preston & Haines, 1991). Many factors related to child mortality in 1900 (Preston & Haines, 1991) were found to be significant predictors of survival to advanced ages (Ferrie & Rolf, 2011; Preston et al., 1998; Stone, 2003). It was demonstrated that early-life mortality that is linked to exposure to infection and poor nutrition predicts both the estimated cohort mortality level at age 40 years and the subsequent Gompertz rate of mortality acceleration during aging (Beltrán-Sánchez, Crimmins, & Finch, 2012). This suggests that early childhood infections in the late 19th and early 20th centuries represented a significant health hazard with potential harmful effects later in life.

Currently, studies of early-life predictors of longevity have become an important direction of research in biodemography of aging. It was demonstrated that such biodemographic factors as maternal age at person’s birth (Gavrilov & Gavrilova, 2012; Gillespie, Russell, & Lummaa, 2013; Jarry, Gagnon, & Bourbeau, 2013); season of birth and ambient temperature (Bruckner, van den Berg, Smith, & Catalano, 2014; Gavrilov & Gavrilova, 2014); longevity of relatives (Gavrilov & Gavrilova, 2014; Sebastiani et al., 2013); and transgenerational responses to early-life experience (Pembrey, Saffery, & Bygren, 2014) are important predictors of longevity and health. In addition to that, research in the area of developmental psychology shed light on the relationships between personality, well-being, and health. Specifically, it was found that the basic five-factor personality dimensions (particularly conscientiousness, neuroticism, and extraversion, but also often agreeableness and openness) do predict multiple diseases and longevity (Friedman & Kern, 2014; Shanahan, Hill, Roberts, Eccles, & Friedman, 2014). Study of early-life factors of aging and longevity is an important area of biodemographic research, which continues to grow.

NEW DEVELOPMENTS IN BIODEMOGRAPHY OF AGING: STUDIES OF OLD-AGE MORTALITY

Attempts to develop a fundamental quantitative theory of aging, mortality, and life span have deep historical roots. In 1825, the English actuary (life insurance specialist), Benjamin Gompertz (1779–1865), published a work (Gompertz, 1825), which became the keystone of the biodemography of aging (see reviews in Gavrilov & Gavrilova, 1991; Kirkwood, 2015). Gompertz provided a theoretical foundation for the idea (and used concrete examples to demonstrate it) that the hazard rate (the relative rate at which a population dies out) increases with age according to the geometric progression law. Moreover, he noted that, alongside this mortality, there must also exist a chance mortality that does not depend on age. Gompertz’s observation was taken into account in 1860 by another English actuary, William Makeham (1823–1891), who presented the age-related change in mortality as the sum of a constant (the Makeham term) and an exponential (the Gompertz function). This was the birth of the well-known Gompertz-Makeham equation, which has great importance for biodemography of aging to this day (Makeham, 1860). Currently, the Makeham term of the equation is called the “background mortality” (Gavrilov, Gavrilova, 1991) and the Gompertz term is called...
the “senescent mortality” (Bongaarts, 2009). An exponential (Gompertzian) increase in death rates with age is observed for many biological species including fruit flies *Drosophila melanogaster*, nematodes, mosquitoes, human lice *Pediculus humanus*, flour beetles *Tribolium confusum*, mice, rats, dogs, horses, mountain sheep, and baboons (see reviews in Gavrilov & Gavrilova, 1991, 2006).

It was also believed that exponential growth of mortality with age (Gompertz law) is followed by a period of deceleration, with slower rates of mortality increase at extreme old ages (Gavrilov & Gavrilova, 1991; Greenwood & Irwin, 1939). This mortality deceleration eventually produces the “late-life mortality leveling-off” and “late-life mortality plateaus” at extreme old ages. Greenwood and Irwin (Greenwood & Irwin, 1939) provided a detailed description of this phenomenon in humans and even made the first estimates for the asymptotic value of the upper limit to human mortality. The same phenomenon of “almost nonaging” survival dynamics at extreme old ages was described for other biological species, and in some species, like medfly and housefly, the mortality plateau can occupy a sizable part of their lives (Carey, Liedo, Orozco, & Vaupel, 1992; Gavrilov & Gavrilova, 2006).

According to some researchers, the late-life mortality plateau represents a distinct phase of life when the aging slows down or stops. They called the discovery of late-life mortality deceleration “a revolution for aging research” (Rose, Rauser, Mueller, & Benford, 2006). Evolutionary biologists suggest that aging is a result of declining forces of natural selection with age. When these forces eventually bottom up at extreme old ages, then the cessation of aging is expected according to this paradigm (Mueller, Rauser, & Rose, 2011). The lifelong heterogeneity theory is another, even more popular, explanation of mortality deceleration, which was first proposed by the British actuary Eric Beard in 1959 (Beard, 1959). As George Sacher explained, “sub-populations with the higher injury levels die out more rapidly, resulting in progressive selection for vigour in the surviving populations” (Sacher, 1966). Another explanation of this phenomenon comes from the reliability theory of aging that explains mortality leveling-off by an exhaustion of organism’s redundancy (reserves) at extremely old ages, so that every additional random hit of damage results in death (Gavrilov & Gavrilova, 1991). There is also an opinion that lower (than predicted) risks of death for older people may be due to their less risky behavior (Greenwood & Irwin, 1939).

The existence of mortality plateaus is well described for a number of lower organisms, including medfly, house fly *Musca domestica*, fruit flies *Anastrepha ludens*, *Anastrepha obliqua*, *Anastrepha serpentine*, parasitoid wasp *Diachasmimorpha longicaudatis*, and bruchid beetle *Callosobruchus maculates* (see review in Gavrilov & Gavrilova, 2006). In the case of mammals, however, data are much more controversial. Some researchers reported short-term periods of mortality deceleration in mice at advanced ages (Sacher, 1966). However, Austad later argued that rodents do not demonstrate mortality deceleration even in the case of very large samples with many animals surviving to old ages (Austad, 2001). Study of baboons found no mortality deceleration at older ages (Bronikowski et al., 2002). Longitudinal study of mortality among seven wild primate species failed to find mortality deceleration at older ages (Bronikowski et al., 2011). Thus, we may suggest that mortality deceleration is observed for many invertebrate species, but the evidence for mammals is controversial.

Due to painstaking efforts of Kannisto, Thatcher et al., it became possible to pool together and analyze data on mortality after age 80 years for Japan and 13 Western European countries. These data formed the basis of the Kannisto-Thatcher Database
on Old Age Mortality. Analysis of these data demonstrated that mortality decelerates after age 80 years, reaching a maximum or ceiling around age 110 years (Horiuchi & Wilmoth, 1998; Thatcher, Kannisto, & Vaupel, 1998).

Recently, new developments happened in this research area thanks to the use of more detailed and more accurate data. In particular, the U.S. Social Security Administration Death Master File (DMF) was used to estimate hazard rates at extremely old ages using a more accurate method of extinct generations. Availability of month-of-birth and month-of-death information in this data source provides a unique opportunity to obtain more accurate hazard-rate estimates for every month of age. The study of 20 single-year extinct birth cohorts with good data quality found that mortality deceleration at advanced ages is negligible up to the advanced age of 106 years (Gavrilov & Gavrilova, 2011). This finding was further supported by additional studies of mortality in 22 single-year U.S. birth cohorts based on data from the Human Mortality Database (Gavrilova & Gavrilov, 2015). The same conclusion was made after analysis of mortality trajectories in 8 cohorts of laboratory mice, and 10 cohorts of laboratory rats (Gavrilova & Gavrilov, 2015). Thus, it turned out that for all three mammalian species, the Gompertz model fits mortality data significantly better than the “mortality deceleration” Kannisto model. Another recent study confirmed that mortality in the U.S. birth cohorts is compatible with the Gompertz-like mortality. The same results were obtained for Canada and Australia, although old-age mortality in European countries were more compatible with models predicting mortality deceleration with the onset of mortality deceleration occurring later in more recent birth cohorts (Bebbington, Green, Lai, & Zitikis, 2014).

It is not surprising why earlier studies (Gavrilov & Gavrilova, 1991; Horiuchi & Wilmoth, 1998; Thatcher et al., 1998) reported mortality deceleration and mortality leveling-off at advanced ages as early as at age 80 years. Most empirical studies of mortality trajectories were conducted in the 1990s when age reporting among aging cohorts was not as accurate as it is now. It was demonstrated that the age misreporting at older ages leads to mortality underestimation, which contributes to mortality deceleration (Preston, Elo, & Stewart, 1999). Also, it was found that mortality deceleration is more expressed in the case of data with poor quality compared to data with better quality (Gavrilov & Gavrilova, 2011). During the last decade, age reporting has significantly improved due to better registration and education in developed countries including large countries such as the United States and Canada.

These results suggest that mortality deceleration at advanced ages is not a universal phenomenon, and survival of many mammalian species follows the Gompertz law up to very old ages. This new finding represents a challenge to many aging theories, including the evolutionary theory that explains senescence by declining force of natural selection with age. New ideas are needed to explain why exactly the same exponential pattern of mortality growth is observed not only at reproductive ages, but also at very old post-reproductive ages (up to 106 years), long after the force of natural selection becomes negligible (when there is no room for its further decline). A new finding on wide applicability of the Gompertz law to adult ages leads to another burning research question: How is it possible for different diseases and causes of death to “negotiate” with each other in order to produce a simple exponential function for all-cause mortality (given that contribution of different causes of death in all-cause mortality changes dramatically with age)? Further biodemographic studies should provide an answer to this question.
IN SEARCH OF GENERAL BIODEMOGRAPHIC THEORY OF AGING

There is a growing interest in scientific explanations of aging and in the search for a general theory that can explain what aging is and why and how it happens. There is also a need for a general theoretical framework that would allow researchers to handle an enormous amount of diverse observations related to aging phenomena. To transform these numerous and diverse observations into a comprehensive body of knowledge, a general theory of species aging and longevity is required.

The quest for a general explanation of aging (age-related increase in failure rates), applicable both to technical devices and to biological systems, invites us to consider the general theory of systems failure known as “reliability theory” (Barlow & Proschan, 1975). Reliability theory was historically developed to describe failure and aging of complex electronic (military) equipment, but the theory itself is a very general theory based on mathematics (probability theory) and systems approach (Barlow & Proschan, 1975). It may therefore be useful to describe and understand the aging and failure of biological systems too. Reliability theory may be useful in several ways: first, by providing a kind of scientific language (definitions and cross-cutting principles) that helps to create a logical framework for organizing numerous and diverse observations on aging into a coherent picture. Second, it helps researchers to develop an intuition and an understanding of the main principles of the aging process through consideration of simple mathematical models, having some features of a real world. Third, reliability theory is useful for generating and testing specific predictions, as well as deeper analyses of already collected data. In this chapter, we review some applications of reliability theory to the problem of biological aging.

The reliability theory was first applied in the 1970s to explain aging of biological species (Abernethy, 1979; Gavrilov, 1978). Since that time, the reliability theory of aging has been developed further (Gavrilov & Gavrilova, 1991, 2001, 2006) leading to the following conclusions: (a) Redundancy is a key notion for understanding aging and the systemic nature of aging in particular. Systems, which are redundant in numbers of irreplaceable elements, do deteriorate (i.e., age) over time, even if they are built of nonaging elements. (b) An apparent aging rate or expression of aging (measured as age differences in failure rates, including death rates) is higher for systems with higher redundancy levels. (c) Redundancy exhaustion over the course of life explains the observed compensation law of mortality (mortality convergence at later life) as well as the observed late-life mortality deceleration, leveling-off, and mortality plateaus. (d) Living organisms seem to be formed with a high load of initial damage, and therefore their life spans and aging patterns may be sensitive to early-life conditions that determine this initial damage load during early development. The idea of early-life programming of aging and longevity may have important practical implications for developing early-life interventions promoting health and longevity.

There may be several different research strategies in attempts to understand the nature of the aging process. The prevailing research strategy now is to focus on the molecular level in the hope of understanding the proverbial nuts and bolts of the aging process. In accordance with this approach, many aging theories explain aging of organisms through aging of organisms’ components. However, this circular reasoning of assuming aging in order to “explain” aging eventually leads to a logical dead end, because moving in succession from the aging of organisms to the aging of organs, tissues, and cells, we eventually come to atoms, which are known not to age. A good example of a broad vision of the aging problem is provided by the evolutionary theories.
of aging (Kirkwood & Holliday, 1979; Rose, 1991). Evolutionary perspective helps us to stay focused on a bigger picture, and to avoid being overwhelmed by billions of tiny details. Evolutionary theories demonstrate that taking a step back from too close consideration of the details over “the nuts and bolts” of the aging process helps to gain a broader vision of the aging problem. The remaining question is whether the evolutionary perspective represents the ultimate general theoretical framework for explanations of aging. Or perhaps there may be even more general theories of aging, one step further removed from the particular details. The main limitation of evolutionary theories of aging is that they are applicable to reproducing organisms only, because these theories are based on the idea of natural selection and on the declining force of natural selection with age. However, aging is a very general phenomenon—it is also observed in technical devices (such as cars), which do not reproduce and that are, therefore, not subject to evolution through natural selection. Thus, there may exist a more general explanation of aging, beyond the evolutionary theories.

The quest for a general explanation of aging (age-related increase in failure rates) applicable both to technical devices and biological systems invites us to consider the general theory of systems failure known as “reliability theory” (Gavrilov & Gavrilova, 2001, 2006). Interestingly, the reliability theory suggests that we need to reevaluate the old belief that aging is somehow related to limited economic or evolutionary investments in systems’ longevity. The theory provides a completely opposite perspective on this issue: Aging is a direct consequence of investments into systems’ reliability and durability through enhanced redundancy. This is an important statement, because it helps to explain why the expression of aging (age-associated differences in failure rates) might be more profound in more complicated redundant systems, designed for higher durability (Gavrilov & Gavrilova, 2006). For example, reliability approach may help to explain general mechanisms underlying lower mortality of women and their poorer health compared to men, which some researchers consider “elusive” (Austad & Bartke, 2015). Mortality patterns of men and women suggest that a female organism is more reliable because it has higher redundancy. However, organisms with higher redundancy are able to accumulate more damage and still stay alive. Hence women on average are able to survive with more diseases, which is a payment for higher redundancy of female organism. The theory also suggests that research on aging should not be limited to the studies of qualitative changes (e.g., age-related changes in gene expression), because changes in quantity (numbers of cells and other functional elements) could be an important driving force of the aging process. In other words, aging may be driven largely by a process of redundancy loss (de Grey, 2003; Gavrilov & Gavrilova, 2006).

Reliability theory of aging provides theoretical arguments explaining the importance of early-life conditions in later-life health outcomes (Gavrilov & Gavrilova, 2006). According to this theory, biological species (including humans) start their lives with extremely high initial damage load (HIDL hypothesis) and therefore should be sensitive to early-life conditions affecting the level of this damage. In this regard, reliability theory of aging is compatible with life-course theories (discussed earlier), which emphasize the role of childhood adversity on late-life health and mortality.

Reliability theory of aging is perfectly compatible with the idea of biological evolution, and it helps to identify key components that may be important for evolution of species reliability and durability (longevity): initial redundancy levels; initial damage load; rate of redundancy loss; and repair potential (Gavrilov & Gavrilova, 2006). Moreover, reliability theory helps evolutionary theories explain how the age of onset
of diseases caused by deleterious mutations could be postponed to later ages during the evolution (as suggested by the mutation accumulation theory of aging)—this could be easily achieved by simple increase in the initial redundancy levels (e.g., initial cell numbers). From the reliability perspective, the increase in initial redundancy levels is the simplest way to improve survival at particularly early reproductive ages (with gains fading at older ages). This exactly matches with the higher fitness priority of early reproductive ages emphasized by evolutionary theories. Evolutionary and reliability ideas also help to understand why organisms seem to “choose” a simple but short-term solution of the survival problem through enhancing the system’s redundancy, rather than more permanent but complicated solution based on rigorous repair (with a potential for negligible senescence).

Laird and Sherratt attempted to reconcile reliability and evolutionary models (Laird & Sherratt, 2009, 2010). They showed how a degree of redundancy (and more broadly an ability to deal with damage to system components) can evolve by natural selection, and that the resulting population equilibrium is sufficiently diverse to generate mortality trajectories with attributes that are observed in natural populations, but are not as readily understood by the late-acting deleterious effects of functioning genes (Laird & Sherratt, 2009). Another study applied a top-down approach to aging research and illustrated the potential of reliability-based models to investigate aging using an insect model (Boonekamp, Brigà, & Verhulst, 2015). Researchers found that these models were able to fit data on flies subjected to food or temperature manipulations and provided new insights in the experimental results.

Aging is a complex phenomenon, and a holistic approach using reliability theory may help to analyze, understand, and perhaps control it. We suggest therefore that reliability theory should be added to the arsenal of methodological approaches applied in biodemographic research on aging.

## CONCLUSION

Finding mechanisms of aging and longevity of organisms is an important task that will help to reduce morbidity and mortality and diminish the burden of care of the elderly in society. Biodemography that emerged at the intersection of biology and demography is a priority area of science and provides researchers with innovative methods for understanding the mechanisms of aging, mortality, and life span. During the last decade, biodemography of aging has broadened its scope and incorporated studies of longevity predictors (including biomarker studies), psychological measures, and research on morbidity and the disablement process. In addition to classic studies of mortality laws and regularities, a new research in genetic markers has been developed. Once emerged as a science analyzing mortality patterns at population level, biodemography of aging now incorporates studies at individual level with risk factor analysis.

In this chapter we reviewed biodemographic theories of aging that attempt to answer the proverbial “why” and “how” questions in gerontology. Evolutionary theories provide an answer to the “Why do we age?” question through the mechanisms of natural selection. They are able to make testable predictions regarding human longevity, mortality, and reproduction, which were discussed in this chapter. More specific theories attempt to answer the “How do we age?” question. Neuroendocrine theory of aging is particularly promising for explaining mechanisms of aging in view of recent findings that insulin/IGF-like signaling pathway controls aging in worms, insects, and mammals (Anisimov & Bartke, 2013). Life-course perspective offers another approach
to unraveling the causes and mechanisms of aging that is more specific to humans. Reliability theory of aging provides a more general explanation of the aging process and suggests answers to both the “why” and the “how” questions about aging. It explains why aging occurs by identifying the key determinant of aging behavior: system redundancy in numbers of irreplaceable elements. Reliability theory also explains how aging occurs, by focusing on the process of redundancy loss over time as the major mechanism of aging.

Biodemographic theories advance our understanding of biological, social, and environmental factors that favor healthy aging and longevity, including early-life childhood conditions, which has implications for public health policy, population forecasting, and health planning. The growing number of persons living beyond age 80 years underscores the need for accurate studies of mortality at advanced ages and understanding the biosocial mechanisms of aging and longevity. These are important issues not only for demographic forecasts of mortality and population aging, policy implications on health care and pension expenditures, but also for improving our understanding of the fundamental mechanisms of human aging and longevity.

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