CHAPTER 3

Malleability of Human Aging

The Curious Case of Old-Age Mortality in Japan

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ABSTRACT

Steady growth in human life expectancy has been a key feature of the last century, with projected further increases likely to have enormous impacts on societies worldwide. Despite the significance of these changes, our understanding of the factors shaping this trend is incomplete. During most of the historical increase, by far, the major influence was progressive decline in early and midlife death rates because of the reduction in premature deaths, caused chiefly by infection. Recent decades have seen the emergence of a new driver of increasing longevity—declining mortality among those who are old already, pointing to greater malleability in human aging than had been foreseen. There is still debate, however, as to how much of this decrease in old age mortality is caused by a better early-life environment and how much is caused by improved conditions in late life. A unique resource exists in the case of Japan, where material circumstances for the general population were consistently adverse through the early decades of the 20th century but improved rapidly after 1950. Here, we compare the Japanese birth cohorts of 1900, 1910, and 1920 and follow their period and cohort mortality trends. The results show that cohorts with similar environments early in life have very different mortality trajectories in old age. This strengthens the

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expectation that preventive measures in later life can deliver great benefit, while not contradicting the importance of life course approaches, to improving health and well-being.

INTRODUCTION

Over the last century, mortality in developed countries has decreased at all ages (Christensen, Doblhammer, Rau, & Vaupel, 2009; Oeppen & Vaupel, 2002; Vaupel, 2010). Initially, the largest decrease was in child mortality, and only in recent decades has the decrease been predominantly at old age (Kannisto, Lauritsen, Thatcher, & Vaupel, 1994; Vaupel, 1997). The determinants of the decrease in child mortality are well known and include improved hygiene, vaccinations, and other preventive measures. Exposures to infectious diseases and to poor nutrition early in life, including the period in utero, have been linked with mortality in old age (Barker, 2004, 2007; Bateson et al., 2004; Bengtsson & Lindstrom, 2003; Blackwell, Hayward, & Crimmins, 2001; Sayer et al., 1998). In the unusual case of individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–1945—when, for about six months, average daily adult intake was reduced to around 700 kcal—persistent epigenetic differences have been detected six decades later (Heijmans et al., 2008). Individuals exposed periconceptionally to famine displayed, in their 60s, significantly less DNA methylation of the imprinted IGF2 gene that is involved in human growth and development. In this accident of history, the timing of the nutritional stress could be determined with precision, and it is striking that individuals similarly exposed to famine, but during late gestation, did not show persistent epigenetic differences. Although the evidence that developmental and early life events can influence long-term health in rodents and humans is incontrovertible (Gluckman & Hanson, 2004; Gluckman, Hanson, & Beedle, 2007; Tarry-Adkins, Chen, Jones, Smith, & Ozanne, 2010; Tarry-Adkins, Martin-Gronert, Chen, Cripps, & Ozanne, 2008), much remains to be learned about the extent and scale of such effects within the broader context of increasing human life expectancy. Furthermore, intervention strategies based solely on targeting developmental factors are of little use to the growing numbers of older adults.

Establishing the contribution of factors acting directly on mortality in later life is challenging. In most countries, improvements in living conditions have occurred relatively smoothly over time, so that the cohorts now reaching old age will have benefited from changes that have occurred throughout the life course. There are, however, instances where changes have been more sudden. A study of changes in old-age mortality in East Germany after reunification with West

Germany has shown rapid convergence of death rates in the two populations—rates in the East falling within little more than two decades to match those in the West (Scholz & Maier, 2003; Vaupel, Carey, & Christensen, 2003). However, this was only seen at very high age, when mortality rates always converge, and there are still some who argue that old-age mortality is biologically fixed (e.g., Carnes & Olshansky, 2007; Carnes, Olshansky, & Hayflick, 2012; Hayflick, 2000). Data from smoking cessation in old age does suggest, however, that health benefits can still be achieved even when the antismoking intervention was introduced in old age (Vetter & Ford, 1990).

A striking instance of transition to a long-living population structure is seen in Japan, which in recent years has led the world in life expectancy. Although many countries that experienced development through the 20th century have witnessed some features of the same transition, the case of Japan is exceptional because of the relative uniformity of living conditions for the general population during the first half of the 20th century, as evidenced by mortality statistics, followed by the rapid pace of improvements after 1950. Aspects of Japanese longevity are notably different from that in other countries, specifically the relatively small range of socioeconomic differences and the greater prominence of stroke as compared to heart disease (Ikeda et al., 2011). Nevertheless, Japan provides an intriguing "natural experiment" to examine impacts of health improvements at different stages in the life course, which can reasonably be expected to have general relevance for the broader biology of human aging and longevity.

METHODS

We used Japanese period and cohort mortality data for this study. Period mortality data and cause-specific mortality data were retrieved from the publicly available *Historical Statistics of Japan* of the Japanese Ministry of Health, Labour and Welfare. Period mortality data were accessible for the years 1899–1903, 1909–1913, and 1921–1925, with a 1×5 age-year interval. We employed these mortality data as an approximation to 1900, 1910, and 1920 period mortality data. We recognized issues on these official mortality data and studies revising these mortality data, notably by Mizushima (1962). However, the patterns of revised age-specific mortality rates were not significantly different from the official mortality data when the three periods were compared. The cohort mortality data were obtained from a study conducted by Nanjo and Yoshinaga (2003) and were available with a 1×1 age-year interval.

All calculations were performed on publicly available population data. No participants were recruited for this study. Ethical approval was therefore not considered necessary to study population mortality and morbidity statistics.

RESULTS

Figure 3.1 shows age-specific period and cohort mortality rates for the Japanese birth cohorts of 1900, 1910, and 1920 using publicly available data from the Historical Studies of Japan (Japan, 2011). Looking at period mortality, the profiles in 1900, 1910, and 1920 were almost identical for all age categories.

We can thus use these data to compare period and cohort mortality rates of three populations that were similarly exposed to an adverse environment early in life and which began to experience a rapidly improving environment at age 30, 40, and 50 years, respectively. These three birth cohorts had similar mortality rates at younger ages; only around the age of 10 years, the mortality in 1910 and 1920 was lower compared to 1900. The trends started to follow complete separate trajectories at middle age as conditions improved, and these differences persisted into old age. On closer observation, the 1920 birth cohort showed a mortality peak around the age of 25 years because of World War II, followed by a subsequent decrease of mortality before a steady increase with age. The 1910 and 1900 birth cohorts showed similar patterns, with war-related mortality peaks around ages 35 and 45 years, respectively.

To study further the mortality differences at middle and old age as found in the cohort mortality data, we plotted the differences in cohort mortality rates of the 1910 and 1920 cohorts compared to the mortality rates of the 1900 cohort, as shown in Figure 3.2. With the exception of infant mortality (age 0), the mortality rates of the 1910 and 1920 birth cohorts were very similar to the mortality rates of the 1900 cohort at younger ages for both females and males. However, from 1950 onward, with the improvement of the environment after the war, the mortality rates were considerably lower for the more recent birth cohorts. For the 1910 cohort, the mortality difference started at age 40 years and persisted up to old age. The 1920 birth cohort started to diverge at age 30 years and shows the strongest mortality decrease at old age.

In addition to the all-cause mortality data, it is important to consider changes in causes of death. Table 3.1 presents the cause-specific death rates of the age group 65–75 years for the periods 1965–1974, 1975–1984, and 1985–1994, respectively, corresponding to the cohorts born in 1900, 1910, and 1920. For individuals born in 1920, most cause-specific death rates (cerebrovascular disease, heart disease, tuberculosis, peptic ulcer, accidents, and suicides) were lower than in the 1900 birth cohort. The reduction in mortality was most pronounced for deaths caused by cerebrovascular disease. Only the mortality rates caused by smoking-related malignancies (trachea, bronchus, and lung) were higher for the 1920 cohort. Nevertheless, the overall mortality of malignancies was lower for the 1920 birth cohort.

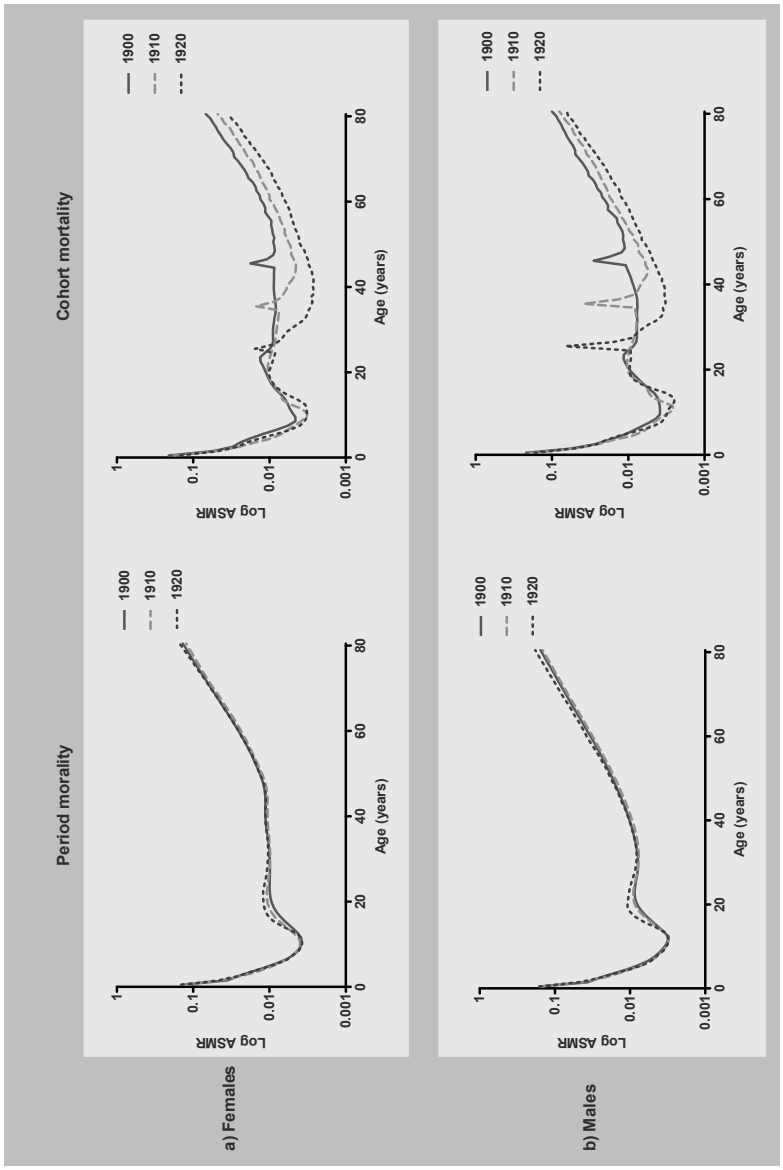

FIGURE 3.1 Period and cohort annual mortality rates for (a) females and (b) males. ASMR = age-specific mortality rate.

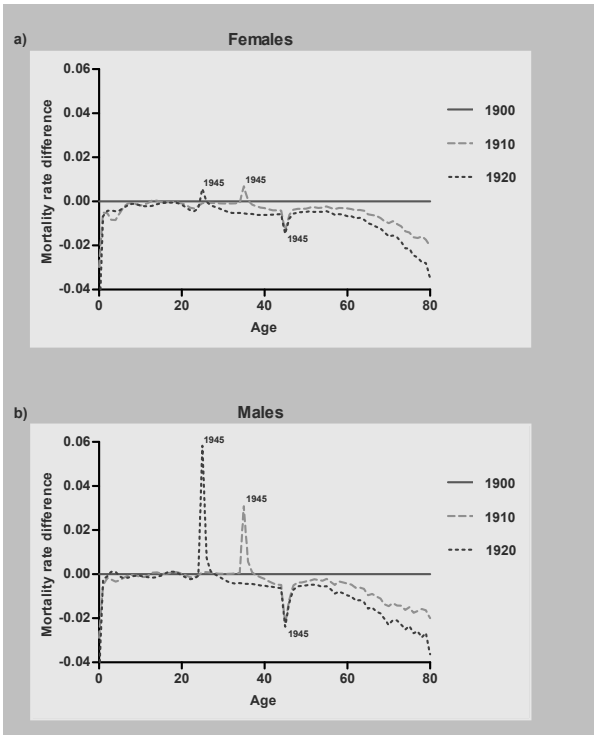

FIGURE 3.2 Cohort mortality rate differences of the 1910 and 1920 birth cohorts when compared to the 1900 birth cohort for (a) females and (b) males.

DISCUSSION

Our analysis of these Japanese data reveals that cohorts with similar environmental conditions early in life had very different old-age mortality trajectories when exposed to environmental improvements at middle age. Mortality of the 1920 cohort was significantly lower compared to the cohorts from 1900 and 1910. This difference was mainly because of large reductions in cerebrovascular disease, which was the major cause of death in Japan. These findings strongly suggest that a large part of the mortality benefit is through old-age plasticity supporting growing recognition of the malleability of human aging (Kirkwood, 2008). The contrary view—that old-age mortality is essentially fixed—is still held, however, and underlies, for example, the concept of "compression of morbidity," which suggests that the goal of age-related medicine should be to postpone as far as possible the onset of diseases within the fixed human lifespan (Fries, 2002), at least until such time as science can slow down the aging process itself (Carnes

TABLE 3.1
Cause-Specific Mortality Rates at Age 65–75 Years

Causes of Death	1900 Cohort	1910 Cohort	1920 Cohort
Cerebrovascular disease	1,142	610	277
Heart disease[a]	464	411	314
Malignant neoplasm	744	719	688
Smoking related[b]	86	152	141
All other	658	567	547
Tuberculosis	86	33	11
Peptic ulcer	47	21	8
Accidents	84	59	58
Suicides	44	39	29

Mortality rates are per 100,000 per year, including hypertension,[a] trachea,[b] bronchus, and lung. Table 3.1 is generated from cause-specific mortality rates for the birth cohorts born in 1900, 1910, and 1920 at the age of 65–75 years. Consequently, it consists of period mortality data from 1965 to 1974, 1975 to 1984, and 1985 to 1994 for the 1900, 1910, and 1920 cohorts, respectively. The cause-specific death rates were calculated per 100,000 persons per year by dividing the total number of deaths caused by a specific cause, by the population size of that age group in that year, and then multiplied by 100,000.

& Olshansky, 2007; Carnes et al., 2012; Le Bourg, 2012; Olshansky, Carnes, & Cassel, 1990; Olshansky, Carnes, & Desesquelles, 2001).

In view of the scale of the societal impacts of increasing human life expectancy, it remains important to establish the mechanisms that underlie the ongoing declines in death rates at the oldest ages, which, in general, show associations both at international level with wealth as measured by gross domestic product (Janssen, Kunst, & Mackenbach, 2006) and intranationally with socioeconomic status (Jakab & Marmot, 2012). In Japan, it is clear that socioeconomic conditions improved rapidly after 1950, but the "proximate" causes that mediate between wealth and health in reducing mortality are less clear. One possibility is simply that better medical care interventions became available, as in the example of cardiovascular disease management (Ford et al., 2007). Improvements in health care could explain the observed reduction in cerebrovascular disease, which has been suggested by others as well (Ikeda et al., 2011). The potential importance of medical care to falling mortality is, however, commonly overstated (Olshansky et al., 2005). In addition, in the case of Japan, a significant step in reducing social inequalities was the introduction of the universal coverage of health insurance

in 1961 (Fukawa, 2002). It can be argued that more universal access to existing medical care and preventive interventions may have played a part.

An alternative possibility is that improved living conditions act systematically on the array of factors that either exacerbate or improve the progressive accumulation of various forms of damage. That is, the improvement might arise not because diseases are treated better or more universally but because diseases themselves progress more slowly or are ameliorated by improved general conditions. For example, many deaths attributed to heart disease and stroke can be identified as proximate consequences of cold exposure in winter (Eurowinter Group, 1997). Amelioration of cold exposures with improving social conditions may thus have an impact on many specific causes of death without any change in the classical risk factors or treatments of those specific causes. Older people also suffer extensive comorbidity—for example, in one detailed study of a 1921 birth cohort of 85-year-olds in Newcastle upon Tyne, most participants had between four and six age-related diseases (Collerton et al., 2009). It would not be at all surprising to see environmental and social improvements impacting upon several or all such comorbidities simultaneously.

Finally, it is possible that a general improvement in environment, living conditions, and social well-being might impact upon the accumulation of molecular and cellular damage that is thought to constitute the intrinsic aging process (Kirkwood, 2005). That is, aging itself might be slowed from different ages in the different cohorts considered. Such an explanation, which involves the diverse effects of nutrition, lifestyle, occupation, and so forth, interacting with biochemical stresses and repair mechanisms could be compatible with the strong socioeconomic gradients seen in health and life expectancy. However, although not undisputed (Koopman et al., 2011; Rozing & Westendorp, 2008), it is considered that the slope of log mortality rates is an indicator of the population rate of aging (Finch, 1990), and it should be noted that the progressive reductions of risk between the cohorts reported here bring about either a parallel reduction or a small increase in the gradient of the log-mortality slope.

In conclusion, cohorts with similar early life environments have very different mortality trajectories in old age, indicating that old age mortality is much more malleable than commonly thought. This strengthens the expectation that interventions in later life, which include lifestyle (especially exercise), nutrition, and proactive health screening with preventive medical treatments such as statins and control of moderate hypertension, can deliver great benefit.

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