Journal of Gerontology: BIOLOGICAL SCIENCES
1997, Vol. 52A, No. 1, B78–B92

Postmenopausal Acceleration of Age-Related Mortality Increase

Shiro Horiuchi

Laboratory of Populations, Rockefeller University, New York City.

The force of natural selection to eliminate deleterious genes is attenuated with advancing age, allowing senescence to evolve. This suggests that a distinctly marked end of the reproduction period is likely to be followed by an acceleration of senescence. It is thus expected that menopause should trigger an acceleration of age-related mortality increase in human females. Such an abrupt initiation of mortality acceleration is not predicted for human males at the same ages, whose fecundity declines more gradually. Life table aging rate patterns for selected industrialized countries generally support this hypothesis. A cause-of-death decomposition analysis indicates that the sex differential in mortality acceleration is mainly due to cardiovascular diseases, which is consistent with the prevalent view that postmenopausal changes in the sex hormone status may affect lipoprotein metabolism, and in turn, raise the risk of arteriosclerosis.

IN the evolutionary biology of aging, the fundamental cause of senescence is considered to be the declining force of natural selection with age (Rose, 1991; Charlesworth, 1994). This notion is elaborated in two converging theories. The antagonistic pleiotropy theory postulates that if some genes enhance reproductive success early in life but have deleterious effects later, such genes still could proliferate in the population since the force of natural selection is weak or nonexistent after the reproductive period (Medawar, 1952; Williams, 1957). The disposable soma theory proposes that since resources are apportioned between reproduction and somatic maintenance, the optimum fitness strategy is to allocate sufficient energy to somatic maintenance for reproductive success but not necessarily for indefinite survival (Kirkwood, 1981).

It may be expected, in consideration of these theories, that an exhaustion of the reproductive potential of an organism tends to be followed by an accelerated deterioration of other major physiological functions. If a complete or near-complete depletion of reproductive capacity occurs at a certain time of life in a distinct manner, then even genes whose damaging effects materialize immediately after the depletion could have high chances of accumulation; and an adequate strategy of resource allocation is to keep a high level of somatic repair efficiency only up to the fixed end of the reproductive period, without additional investment for its continuation thereafter. On the other hand, if the reproductive potential declines slowly over a long time span, then a gradually increasing number of genes will exert their adverse effects as age advances; somatic repair machinery will evolve whose efficiency will decline with age progressively, without an abrupt breakdown.

The rate of decline in the reproductive capacity varies among species, differs between sexes of the same species, and changes with age in the life of an organism. The predicted association is clearly seen in broad interspecies differentials. Rapid, gradual, and negligible progressions of senescence are often found for species with semelparous, iteroparous, and vegetative modes of reproduction, respectively, although there are a number of exceptions (Finch, 1990).

The association between the decline in reproductive potential and the progression of senescence can be predicted for sex differentials as well. Although males and females in a population constitute essentially the same gene pool, sex differentials in senescence can be expected to evolve, since some genes on the X and Y chromosomes may have senescence-related effects and some genes on the autosomes may be expressed differently in the senescent processes of males and females. In human females, the end of the reproductive period is marked clearly as menopause: the production of new germ cells ceases after some point in fetal life, and the stock of oocytes and primordial follicles in the ovary is almost exhausted by the time of menopause (vom Saal and Finch, 1988), which is, on the average, around age 50 (Khaw, 1992). It is thus expected that menopause triggers an acceleration of senescence in females. In males, spermatogenesis in the seminiferous tubules continues from puberty on, at progressively declining rates but without any unambiguous endpoint except death. Accompanying changes in gonadal hormones are observed: production of estradiol and progesterone in the ovary virtually ceases after menopause, but the number of testosterone-producing Leydig cells in the testes decreases gradually (vom Saal and Finch, 1988).

It has been postulated that pathways for the evolution of senescence should be reflected in relationships between the age pattern of reproduction and the age trajectory of mortality in populations (Carnes and Olshansky, 1993; Carnes et al., 1996). Thus, the sex difference in fecundity decline for humans gives rise to a hypothesis that is testable with demographic data: the age-related mortality increase for females should start to accelerate around the average age of menopause; but this is unlikely to be seen for males in the same age range.

The concept of mortality acceleration needs further clarification in the following two aspects. First, the mortality *level,* mortality *increase,* and mortality *acceleration* (increase of increment) need to be carefully distinguished in the same way as the location, speed, and acceleration of a physical object. If senescence starts long before menopause, then mortality will continue to increase through adult ages. Therefore, the expected impact of menopause on senescence should not simply be an *increase* of mortality, which proceeds at any adult age whether menopause occurs or not, but should be an *acceleration* of the mortality increase.

Second, age-related mortality increase and mortality acceleration can be measured in either absolute or relative terms. This study will focus on relative changes, since clear patterns of age variations, trends, and risk factor effects are usually found in the logarithms of death rates. Hereafter, "mortality increase" and "mortality acceleration" mean increase and acceleration, respectively, of the logarithmic death rate with respect to age.

Some data on age patterns of sex mortality differentials have already been published. Age variations in the ratio of male to female death rate, obtained for a number of countries in different periods, are generally consistent with the above hypothesis (Lopez, 1983; United Nations Secretariat, 1988a, 1988b). The typical trajectory of the sex ratio of all-cause mortality in industrialized countries during recent decades is that the ratio rises with age in the person's 50's, reaches a peak in the early 60's, and falls thereafter without ever reaching unity. An example of such a pattern is shown in Figure 1A for Sweden. The decrease in the sex mortality ratio after ages 60–64 implies that the rate of relative mortality increase with age is faster for females than males around age 65 and above. The slope of the sex mortality ratio curve changes from upward in the 50's to moderately downward in the late 60's and to steeply downward in the 70's. This slope change suggests that the acceleration of age-related relative increase in mortality is greater for females than males through the 50's to 70's. As for the male-to-female ratio of cause-specific mortality, the decline at old ages is pronounced for heart disease (Waldron, 1985; United Nations Secretariat, 1988b; Wingard and Cohn, 1990).

The sex mortality ratios, however, do not show whether the sex difference in mortality acceleration results from an acceleration in female mortality, or a deceleration in male mortality, or both. Nor do they indicate clearly the ages at which such an acceleration or deceleration starts and ends. Therefore, in order to fully describe sex differences in the age pattern of mortality, it is not sufficient to calculate the sex mortality ratio by age: it is important to examine first the age trajectory of the death rate for each sex and then compare the male and female curves.

Age variations in mortality are usually examined by plotting death rates against age in a semi-logarithmic graph. Significant menopausal effects on mortality patterns are hardly noticed in such a graph. Both male and female mortality curves appear fairly straight and nearly parallel (Figure 1B). Neither male nor female curve shows any significant changes of the slope around age 50 (Nelson, 1995). Mortality accelerations, however, should not be detected indirectly from visual convexities of the logarithmic mortality curve. Trigonometry suggests that the mortality curve could appear almost straight even in the presence of considerable slope changes, except for the usually less steep segment of the curve at very old ages (Horiuchi and Wilmoth, 1997). Therefore, mortality accelerations should be measured directly from age differences in the rate of mortality increase.

Mortality accelerations were shown in several demographic and actuarial studies. Evidence for postmenopausal acceleration of female mortality is seen sporadically (Horiuchi, 1983; Pakin and Hrisanov, 1984; Ekonomov et al., 1989; Horiuchi and Coale, 1990; Himes et al., 1994). However, their research designs were not necessarily adequate for examining menopausal impacts on mortality, since these studies were conducted for other purposes. The research design problems include lack of control of a strong confounding factor (Horiuchi, 1983), too long age intervals (Pakin and Hrisanov, 1984), use of local-level data from a single country (Ekonomov et al., 1989), lack of comparison between sexes (Horiuchi and Coale, 1990), and use of sex-specific model life tables instead of national vital statistics (Himes et al., 1994). Menopause is mentioned only in Pakin and Hrisanov (1984), and very briefly. Moreover, these studies do not use any cause-of-death (COD) data, which may provide some clues on physiological pathways through which postmenopausal mortality acceleration occurs.

The present study is designed to test the hypothesis on postmenopausal mortality acceleration. Mortality accelerations will be measured directly from vital statistics in selected countries and compared between males and females. Sex differences of all-cause mortality acceleration will then be decomposed in terms of cause of death.

METHOD

Measurement of mortality acceleration. — The major tool of this analysis is the rate of relative mortality increase with age, which is defined as:

$$k(x) = \frac{1}{\mu(x)} \frac{d\mu(x)}{dx} = \frac{d \ln \mu(x)}{dx}, \qquad (1)$$

where $\mu(x)$ is the force of mortality (instantaneous death rate per person-year of exposure) at exact age x. This may be briefly called the life table aging rate, or LAR (Carey and Liedo, 1995). A LAR of .08, for example, means that the death rate is rising at the exponential rate of 8% per year of age (which is equivalent to the geometric rate of about 8.3% in a year). The LAR rises with age if the relative mortality increase accelerates. The LAR remains constant over age if the mortality pattern follows an exponential function. The LAR approach is discussed in more detail elsewhere in this issue (Horiuchi and Wilmoth, 1997).

Since data tabulated by 5-year age groups are used, the LAR is estimated by

$$\hat{k}(x) = [\ln M(x,5) - \ln M(x-5,5)] / 5, \qquad (2)$$

where $M(x,5)$ is the death rate (number of deaths per person-year) between exact ages x and $x+5.0$ years. This approximation has been shown to be sufficiently accurate (Horiuchi and Coale, 1990). These definitions (1) and (2) can be extended to each cause of death and each sex.

The cumulated acceleration of mortality between ages x_1 and x_2 is $k(x_2)$-$k(x_1)$ and the sex difference (female minus male) in the mortality acceleration (SDMA) can be measured by

$$g(x_1,x_2) = [k_f(x_2) - k_f(x_1)] - [k_m(x_2) - k_m(x_1)] \quad (3)$$

where subscripts f and m denote female and male, respectively. This definition can also be applied to each cause. The statistical significance of the sex difference in Eq. (3) can be tested using the formula for the standard error of LAR (Wilmoth, 1995).

The sex difference in acceleration of mortality from all causes, defined by Eq. (3), can be decomposed into cause-specific factors. Then each cause-specific factor (or the total effect, denoted by TT) can be decomposed further into: (a) the mortality acceleration (MA) effect, which is derived from sex differences in cause-specific mortality acceleration (i.e., LAR slope); (b) the mortality increase (MI) effect, which comes from sex differences in cause-specific mortality increase (i.e., LAR level); and (c) the residual (RS) effect, which is interactions of these two effects. Details of the decomposition methodology are given in the Appendix.

Data. — The World Health Organization (WHO) maintains and updates a machine-readable data base containing deaths by sex, age, and cause and population by sex and age for most countries in the world that have nationwide systems of death registration. International mortality data for this study were drawn from the data base. At first, several countries, preferably with large population sizes in middle and old ages, were needed to be selected for the analysis. However, an international comparison of sex differences in the age pattern of adult mortality during recent decades suffers from substantial variations in male cohort mortality. In a number of countries in which not only the armed forces but also the general population was deeply involved in World War I (e.g., Austria, France, Germany, Hungary, and Poland) or World War II (e.g., France, Germany, Italy, Japan, and the former USSR), relatively high mortality at middle and old ages was found for the male cohorts who were adolescents at the end of the war (Okubo, 1981; Horiuchi, 1983; Boleslawski, 1985; Caselli et al., 1985; Tango and Kurashima, 1987; Anderson and Silver, 1989; Wilmoth et al., 1990). Such a pattern of cohort mortality variations was not seen for females. Unfortunately, the list of these countries overlaps to some extent with the list of populous industrialized countries.

This limitation could be partly moderated by using data from the period when causes of deaths in the civil registration were recorded according to the Eighth Revision of the International Classification of Diseases (ICD8). This period typically began in 1968 or 1969 and ended in 1978 or 1979, during which the cohorts who had been adolescents at the end of World War II did not reach the focal age range of this study, which will be 55–75. However, countries deeply involved in World War I had to be entirely excluded from the analysis. Thus, mortality data during the ICD8 period in seven countries (England and Wales, Italy, Japan, the Netherlands, Spain, Sweden, and the United States) were selected for the general comparison of all-cause mortality patterns.

Out of the seven countries, three countries that have very different COD structures from each other (England and Wales, Italy, and Japan) were selected further for more detailed breakdown by COD. The most common COD (in terms of broad categories) between exact ages 55 and 75 during the ICD8 period of 1968–1978 was different among these three countries: heart disease in England and Wales (34%), malignant neoplasm in Italy (27%), and cerebrovascular disease in Japan (29%).

CODs in the WHO mortality data base during the ICD8 period are a short list (called List A) of 150 relatively broad categories, supplemented with some additional detailed categories, which vary with year and differ among countries. CODs selected for this analysis are listed in Table 1. Most of them satisfy the following condition: the proportion of all deaths between exact ages 55 and 75 in 1968–1978 that were attributed to the COD exceeds 1% in at least one of the three countries or 0.5% in at least two countries. Exceptions to this condition are sex-specific cancers, residual categories such as "other cardiovascular diseases" and "other external injuries," and influenza, which almost met the condition. Note that "chronic rheumatic heart disease," "hypertensive disease," "other forms of heart disease," and "nephritis and nephrosis" are not directly comparable to similar categories in ICD9 because their definitions changed significantly between ICD8 and ICD9 (Klebba and Scott, 1980).

It should also be noted that "infective and parasitic diseases" do not include all infectious diseases. This ICD category mainly consists of highly contagious diseases that are common in developing countries, but does not include some infectious diseases, which are classified according to the organ system to which the infected organ belongs. "Hypertensive disease" is essentially a "remainder" category after exclusion of most deaths due to hypertension-induced ischemic heart disease or cerebrovascular disease.

Possible confounding factors. — The above data set was supplemented with some historical Swedish data in order to examine if the observed sex difference in all-cause mortality acceleration was some type of statistical artifact. One possibility is that if the age pattern of mortality varies with the level of mortality, then the sex difference in mortality pattern may simply be a result of the sex difference in the mortality level. Some linkages between the level and pattern of mortality have been found: for example, lower mortality levels are associated with steeper mortality curves in the international data analyzed by Strehler and Mildvan (1960). Thus, LAR patterns will be compared between Swedish males and females in different periods but at similar mortality levels.

Another possibility is that male and female cohorts may follow different mortality trends, thereby distorting sex differences in period mortality patterns. This seems to merit attention, since considerable cohort variations are observed for smoking-related cancer mortality (Case, 1956; Devesa et al., 1989), and smoking is an important behavioral factor of sex mortality difference (Waldron, 1986). Furthermore, significant impacts of nutritional improvement since the mid-19th century on adult mortality decline have been shown (Fogel, 1994). In particular, nutritional status in childhood and adolescence affects adult mortality in later years,

Table 1. Causes of Death, ICD8 Detailed List Numbers, and Distribution of Deaths in England and Wales, Italy, and Japan, 1968–1978

Cause of Death	ICD8 Detailed List Number	Proportion of Deaths Between Ages 55 and 75 (%)		
		England and Wales	Italy	Japan
All causes	000–E999	100.00	100.00	100.00
Infective and parasitic diseases	000–136	0.51	1.19	2.89
Tuberculosis	010–019	0.31	0.82	2.22
Other infective and parasitic diseases	[a]	0.20	0.38	0.67
Malignant neoplasms	140–209	27.72	27.22	26.49
Of esophagus	150	0.73	0.57	1.16
Of stomach	151	2.75	4.31	10.27
Of rectum and large intestine	153, 154	3.35	2.85	1.96
Of pancreas	157	1.24	0.90	1.19
Of lung, bronchus, and trachea	162	8.93	5.38	3.12
Of female breast	174	2.33	1.70	0.42
Of uterus	180–182	0.81	1.17	1.18
Of ovary, Fallopian tube, and broad ligament	183	0.84	0.38	0.22
Of prostate	185	0.79	0.87	0.21
Leukemia	204–207	0.54	0.77	0.37
Of all other and unspecified sites	[a]	5.40	8.32	6.39
Diabetes mellitus	250	0.94	3.00	1.73
Cardiovascular diseases	390–458	50.03	44.25	44.95
Chronic rheumatic heart disease	393–398	1.38	1.07	0.64
Hypertensive disease	400–404	1.60	2.67	2.25
Ischemic heart disease	410–414	29.56	15.69	7.03
Other forms of heart disease	420–429	2.91	9.43	5.63
Cerebrovascular disease	430–438	11.12	13.23	28.59
Cerebral hemorrhage	431	2.84	3.09	13.66
Cerebral infarction	432–434	3.32	4.34	3.48
Other cerebrovascular diseases	[a]	4.95	5.81	11.45
Diseases of arteries, arterioles, and capillaries	440–448	2.18	1.82	0.62
Venous thrombosis and embolism	450–453	1.21	0.26	0.03
Other cardiovascular diseases	454–458	0.07	0.08	0.15
Influenza	470–474	0.48	0.40	0.19
Pneumonia	480–486	4.78	1.99	2.95
Bronchitis, emphysema, and asthma	490–493	5.95	4.51	1.89
Peptic ulcer	531–533	0.74	0.95	1.15
Cirrhosis of liver	571	0.40	4.79	2.43
Nephritis and nephrosis	580–584	0.49	0.57	1.09
External injuries	E800–E999	2.32	3.74	5.03
Accidents	E800–E949	1.50	3.07	3.18
Suicide and self-inflicted injury	E950–E959	0.61	0.59	1.72
Other external injuries	[a]	0.21	0.09	0.13
All other causes	[a]	5.63	7.38	9.22

[a]Comprises residual codes of the larger category.

thereby producing pronounced cohort effects. This may produce notable differences between period and cohort mortality patterns. The present analysis, therefore, will include a comparison of LAR pattern between Swedish male and female cohorts.

RESULTS

Mortality from all causes. — Figure 1C and Figure 2 display the all-cause LARs for males and females from age 35 to 80 in the seven selected countries during their respective ICD8 periods. (In the tables of this article, LARs are multiplied by 100 and shown in percent, and accordingly, so are SDMAs.) A notable sex difference is seen between ages 55 and 75. The LAR increases steeply with age for females in all of the countries except the U.S.; typically, the mortality increment per year of age rises from about 8 to 9% around age 55 to about 12 to 13% around age 75. In contrast, the LAR does not rise significantly with age for males at the same ages: it remains relatively flat for males in Italy, Japan, Spain, and Sweden, declines moderately for males in the United States, and declines steeply for males in England and Wales and the Netherlands. The U.S. female LAR curve appears exceptional: the LAR rise between ages 55 and 75 is relatively small and limited to the short age range of 65–70.

Figure 3 suggests that the sex difference in all-cause mortality acceleration is neither an artifact of a sex difference in mortality level nor that of a sex difference in cohort mortality trend. The contrast between a relatively flat male

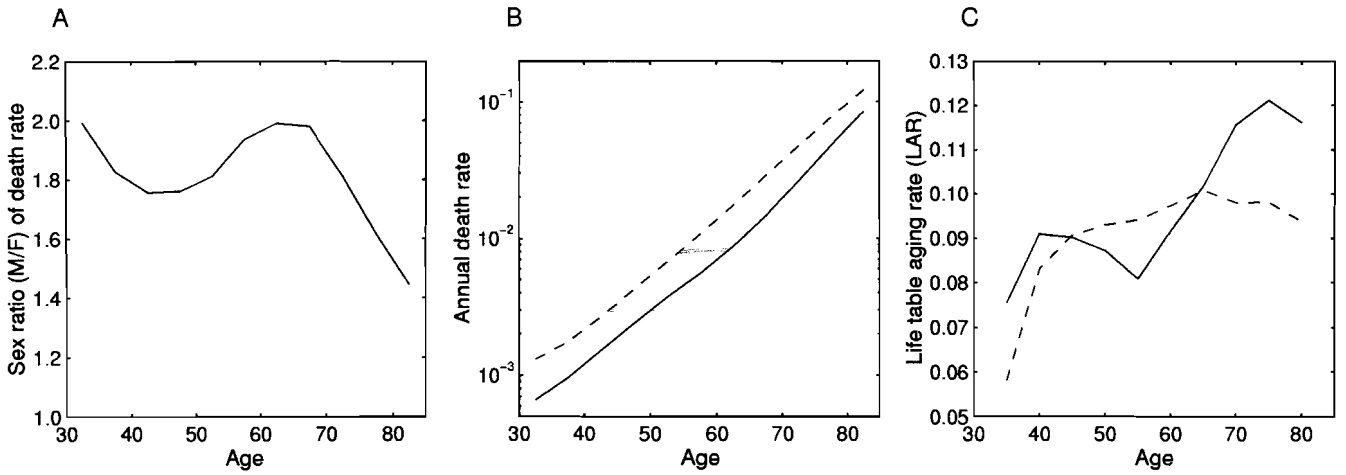


Figure 1. Mortality in Sweden, 1969–1986 (ICD8 period). **(A)** Ratio of male death rate to female death rate. **(B)** Natural logarithm of death rate for males (dashed line) and females (solid line). **(C)** Life table aging rate for males (dashed line) and females (solid line).

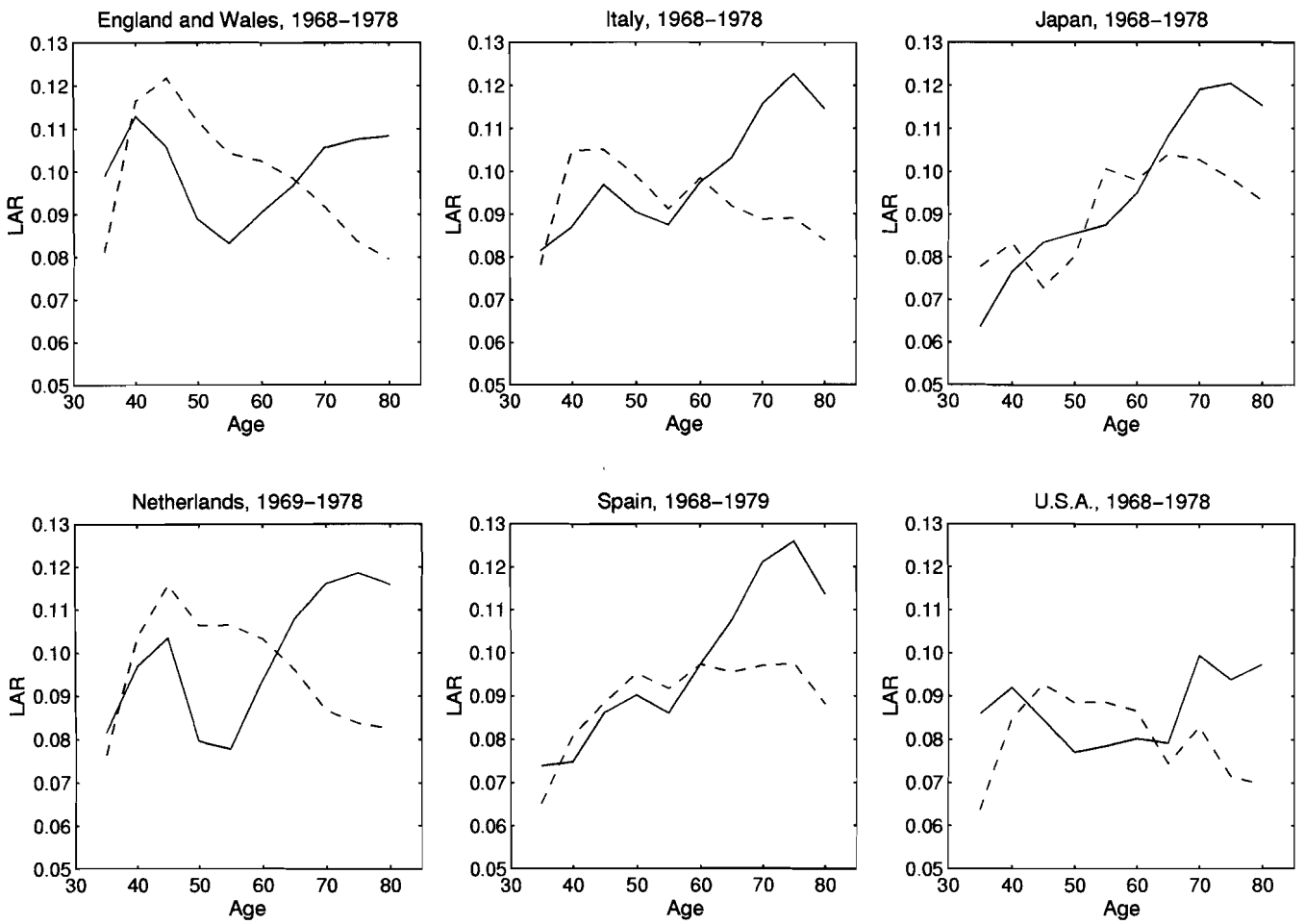


Figure 2. Life table aging rate for males (dashed line) and females (solid line) in selected countries during the ICD8 periods: England and Wales, 1968–1978; Italy, 1968–1978; Japan, 1968–1978; the Netherlands, 1969–1978; Spain, 1968–1979; and the U.S.A., 1968–1978.

Figure 3. Life table aging rate in Sweden. **(A)** Males in 1986–1990 (dashed line) and females in 1951–1955 (solid line). **(B)** Male (dashed line) and female (solid line) cohorts born in 1901–1905.

LAR curve and a steeply rising female LAR curve is seen again between Swedish males in 1986–1990 and Swedish females in 1951–1955, both of whom have the life expectancy at age 55 of about 23 years, and between Swedish male and female cohorts born in 1901–1905. The crossover point of the male and female cohort LAR curves in Figure 3B is at a higher age than those in Figures 1C, 2, and 3A, since the LAR curve for the Swedish female cohort is substantially lower than the period curves for females. It can be shown that a declining mortality level tends to make the cohort LAR lower than the period LAR, and it is known that Swedish females achieved considerably greater mortality reduction than Swedish males during the last several decades.

Cause-of-death structure. — Table 2 exhibits results of the COD decomposition, of the sex difference (female minus male) in mortality acceleration (SDMA) for all causes combined from age 55 to 75 in England and Wales, Italy, and Japan. The total (TT), mortality acceleration (MA), mortality increase (MI), and residual (RS) effects of the CODs are shown as percentages of the all-cause SDMA, although some effects are negative. A positive effect means a contribution to the female excess over male in all-cause mortality acceleration. The effects of a COD are strongly influenced by the proportion of all deaths in the age range that are attributable to the cause. Table 2 presents, in addition, cause-specific LARs ($\times 100$) by sex at ages 55 and 75 as well as cause-specific SDMAs ($\times 100$) between the two ages. The SDMA of a COD shows the direction and extent of sex difference in acceleration of mortality due to the cause.

The SDMA of all cardiovascular diseases combined is positive, and their total effect is 85% of all-cause SDMA in England and Wales, 69% in Italy, and 56% in Japan. These effects are large even in comparison with the proportion of all deaths in this age range that are due to cardiovascular diseases, which is 50% in England and Wales, 44% in Italy, and 45% in Japan (Table 1).

This analysis used 10 mutually exclusive categories of cardiovascular diseases (not counting "cerebrovascular disease," which comprises three categories). Particularly important is ischemic heart disease, the total effect of which is the strongest among all CODs in England and Wales (52% of all-cause SDMA) and Italy (34%), but not in Japan (only 11%). In all three countries, however, the profile of contribution differs between ischemic heart disease and the other nine categories of cardiovascular diseases: ischemic heart disease exercises mainly the mortality increase effect, and the other cardiovascular diseases the mortality acceleration effect.

The mortality *increase* of ischemic heart disease in this age range is substantially faster for females than for males (Figure 4B). On the other hand, the extent of ischemic heart disease mortality *acceleration* does not differ notably between the sexes. On the contrary, the other nine categories of cardiovascular diseases generally exhibit greater female than male mortality acceleration. In particular, "diseases of arteries, arterioles, and capillaries" has a markedly high SDMA, which is greater than 5.0 in all three countries. Major components of this category are arteriosclerosis (excluding arteriosclerotic disease in the heart, brain, or lung) and aortic aneurysm.

Malignant neoplasms exhibit another pattern. The increase of cancer mortality tends to slow down for both males and females. However, the deceleration is more pronounced for males than for females (Figure 4A), which makes the all-cancer SDMA significantly positive.

Most of the other CODs can be divided into two groups. The SDMA is greater than 2.0 for tuberculosis, other infective and parasitic diseases, influenza, pneumonia (Figure 4D), "bronchitis, emphysema, and asthma," peptic ulcer, and accidents in all three countries, with two exceptions in England and Wales. In contrast, the SDMA is negative or nearly zero for diabetes mellitus, cirrhosis of the liver, and nephritis and nephrosis (Figure 4E) in all three countries.

Table 2. Cause-of-Death Decomposition of Sex Difference in Mortality Acceleration Between Ages 55 and 75

Causes of Deaths	Percent of All-Cause SDMA				LAR (×100)				SDMA (×100)
	TT	MA	MI	RS	M 55	M 75	F 55	F 75	
	England and Wales, 1968–1978								
All causes	99.76[ab]	38.89[b]	27.81[b]	33.06[b]	10.43	8.37	8.32	10.76	4.50*
Infective and parasitic diseases	0.35[b]	0.33[b]	–0.19[b]	0.21[b]	7.87	4.68	5.58	5.74	3.35**
Tuberculosis	0.59	0.40	–0.03	0.22	8.16	3.39	3.01	3.63	5.38**
Other infective and parasitic diseases	–0.24	–0.07	–0.15	–0.01	7.30	7.81	8.12	7.28	–1.35
Malignant neoplasms	6.80[b]	10.76[b]	–20.67[b]	16.72[b]	11.84	4.76	6.59	5.01	5.50*
Of esophagus	0.44	0.22	0.12	0.10	11.52	6.91	10.03	6.84	1.42
Of stomach	3.87	2.21	0.98	0.69	12.55	4.92	11.86	8.38	4.15*
Of rectum and large intestine	–2.39	0.83	–2.44	–0.78	11.29	7.81	10.32	7.94	1.09
Of pancreas	0.48	0.63	–0.04	–0.12	11.33	4.75	10.06	5.89	2.41**
Of lung, bronchus, and trachea	23.03	6.57	–0.09	16.55	12.98	1.41	7.97	0.43	4.03*
Of female breast	–9.14	–1.83	–7.30	N.A.	N.A.	N.A.	4.00	2.93	–1.07*
Of uterus	–2.94	–0.61	–2.33	N.A.	N.A.	N.A.	3.80	2.76	–1.04
Of ovary, Fallopian tube, and broad ligament	–4.47	–2.77	–1.70	N.A.	N.A.	N.A.	4.63	–0.07	–4.70*
Of prostate	–3.57	2.47	–6.04	N.A.	21.77	12.70	N.A.	N.A.	9.08*
Leukemia	0.40	0.60	–0.25	0.06	9.19	5.60	5.56	6.63	4.66*
Of all other and unspecified sites	1.09	2.46	–1.59	0.22	9.40	5.30	7.80	5.68	1.99*
Diabetes mellitus	0.02	–0.59	0.86	–0.26	10.31	8.68	12.86	8.25	–2.98**
Cardiovascular diseases	85.40[b]	14.24[b]	59.28[b]	11.88[b]	10.00	8.75	11.46	12.05	1.85*
Chronic rheumatic heart disease	–1.79	0.86	–1.60	–1.05	8.26	3.63	7.33	5.05	2.35**
Hypertensive disease	2.75	0.77	1.82	0.16	9.49	8.39	10.30	11.41	2.21**
Ischemic heart disease	51.82	–5.38	46.17	11.03	9.35	6.61	13.81	10.18	–0.90*
Other forms of heart disease	6.20	1.62	3.21	1.36	11.97	14.33	12.19	16.87	2.33*
Cerebrovascular disease	20.48[b]	11.09[b]	8.75[b]	0.65[b]	12.72	11.41	9.73	13.39	4.98*
Cerebral hemorrhage	3.51	2.66	1.11	–0.26	11.50	8.52	9.24	10.43	4.18*
Cerebral infarction	8.78	2.73	5.96	0.09	17.60	12.76	16.46	15.38	3.76*
Other cerebrovascular diseases	8.20	5.70	1.67	0.82	11.49	11.57	8.28	13.28	4.92*
Diseases of arteries, arterioles, and capillaries	4.37	3.84	0.47	0.06	15.25	13.08	11.66	17.48	7.99*
Venous thrombosis and embolism	1.39	1.21	0.50	–0.32	11.29	6.59	8.85	8.76	4.60*
Other cardiovascular diseases	0.18	0.24	–0.04	–0.02	13.95	4.39	3.57	8.02	14.01*
Influenza	0.19	0.24	–0.05	–0.00	10.36	10.43	8.51	10.84	2.25
Pneumonia	3.78	2.90	0.35	0.53	12.47	15.03	11.32	16.40	2.52*
Bronchitis, emphysema, and asthma	–0.60	7.49	–10.50	2.42	16.08	8.35	9.53	8.68	6.87*
Peptic ulcer	1.03	1.03	0.03	–0.03	10.82	8.16	7.66	11.54	6.54*
Cirrhosis of liver	–0.42	–0.29	–0.07	–0.06	4.97	1.28	5.71	–0.47	–2.49
Nephritis and nephrosis	–0.29	–0.31	–0.04	0.06	8.61	10.13	8.86	7.74	–2.63
External injuries	2.70[b]	0.43[b]	2.15[b]	0.12[b]	2.59	8.47	2.77	11.39	2.73*
Accidents	2.60	0.66	2.25	–0.31	3.22	10.80	4.93	13.99	1.47
Suicide and self-inflicted injury	–0.15	–0.19	–0.06	0.11	1.34	0.46	1.17	–0.64	–0.94
Other external injuries	0.25	–0.03	–0.04	0.32	2.38	3.18	–0.45	–0.10	–0.45
All other causes	0.81	2.67	–3.34	1.49	8.81	10.61	7.10	10.83	1.92*
	Italy, 1968–1978								
All causes	99.85[ab]	65.17[b]	18.01[b]	16.67[b]	9.11	8.91	8.74	12.27	3.74*
Infective and parasitic diseases	3.47[b]	2.56[b]	0.71[b]	0.19[b]	7.92	1.76	6.04	8.93	9.05*
Tuberculosis	3.31	2.06	0.95	0.30	8.38	–0.32	5.53	6.48	9.65*
Other infective and parasitic diseases	0.15	0.50	–0.23	–0.11	6.23	6.06	6.58	10.78	4.38**
Malignant neoplasms	12.21[b]	22.42[b]	–18.58[b]	8.36[b]	9.40	3.99	6.76	6.35	5.01*
Of esophagus	1.33	0.39	0.52	0.42	10.51	5.33	11.31	9.15	3.02
Of stomach	6.15	4.64	0.68	0.83	12.64	5.87	11.00	8.83	4.60*
Of rectum and large intestine	–1.37	2.42	–3.21	–0.59	10.74	7.09	9.56	9.12	3.20*
Of pancreas	–0.47	–0.54	0.32	–0.24	8.66	4.31	12.81	6.05	–2.41
Of lung, bronchus, and trachea	22.57	9.03	4.74	8.80	8.72	–2.82	7.36	3.65	7.83*
Of female breast	–6.34	1.38	–7.72	N.A.	N.A.	N.A.	3.24	4.11	0.86**
Of uterus	–6.78	–1.57	–5.21	N.A.	N.A.	N.A.	5.00	3.43	–1.57*
Of ovary, Fallopian tube, and broad ligament	–2.18	–1.15	–1.03	N.A.	N.A.	N.A.	3.83	0.50	–3.34*
Of prostate	–3.71	3.40	–7.11	N.A.	20.83	11.04	N.A.	N.A.	9.80*
Leukemia	–0.69	0.21	–0.73	–0.18	7.28	4.51	7.32	5.55	0.99
Of all other and unspecified sites	3.71	4.21	0.17	–0.68	8.16	3.67	8.48	5.93	1.94*
Diabetes mellitus	–1.36	–2.32	3.70	–2.74	12.43	7.24	16.76	8.29	–3.28*

Continued on next page

Table 2. Cause-of-Death Decomposition of Sex Difference in Mortality Acceleration Between Ages 55 and 75 *(Continued)*

Causes of Deaths	Percent of All-Cause SDMA				LAR (×100)				SDMA (×100)
	TT	MA	MI	RS	M 55	M 75	F 55	F 75	
Cardiovascular diseases	68.65[b]	22.90[b]	37.15[b]	8.59[b]	10.25	11.21	11.45	14.31	1.90*
Chronic rheumatic heart disease	−3.25	−0.10	−2.36	−0.79	4.21	3.32	4.99	3.87	−0.23
Hypertensive disease	4.47	1.18	2.57	0.71	11.72	11.21	12.24	13.40	1.67
Ischemic heart disease	33.64	0.20	29.12	4.33	8.72	8.99	13.26	13.58	0.05
Other forms of heart disease	16.65	8.66	5.96	2.03	14.57	12.28	13.98	15.20	3.52*
Cerebrovascular disease	13.62[b]	9.70[b]	2.52[b]	1.41[b]	12.11	12.08	11.17	13.90	2.76*
Cerebral hemorrhage	1.22	2.13	−0.66	−0.25	10.47	8.26	9.88	10.26	2.60*
Cerebral infarction	5.57	2.71	2.66	0.19	16.50	13.57	15.71	15.20	2.42*
Other cerebrovascular diseases	6.83	4.85	0.51	1.47	11.18	12.21	10.16	14.34	3.15*
Diseases of arteries, arterioles, and capillaries	3.62	3.18	−0.50	0.94	12.51	15.68	12.30	21.66	6.18*
Venous thrombosis and embolism	−0.08	0.05	−0.17	0.04	8.18	7.39	5.82	5.68	0.66
Other cardiovascular diseases	−0.02	0.04	0.02	−0.08	3.36	3.95	7.56	9.75	1.60
Influenza	0.47	0.63	−0.04	−0.13	16.18	11.38	11.50	12.90	6.19**
Pneumonia	1.38	1.73	−0.72	0.37	12.10	13.90	11.64	16.59	3.16*
Bronchitis, emphysema, and asthma	2.64	4.49	−7.00	5.15	16.45	8.29	16.00	12.49	4.64*
Peptic ulcer	1.89	0.60	1.01	0.28	9.30	5.59	11.97	10.89	2.62
Cirrhosis of liver	4.99	0.93	2.27	1.79	6.48	0.98	7.29	2.52	0.73
Nephritis and nephrosis	−0.86	−0.35	−0.56	0.05	6.26	7.26	6.80	5.76	−2.03
External injuries	7.48[b]	6.67[b]	6.71[b]	−5.90[b]	3.47	6.61	3.51	13.66	7.02*
Accidents	7.18	6.82	6.76	−6.40	3.57	7.22	4.28	14.83	6.89*
Suicide and self-inflicted injury	0.38	−0.16	−0.09	0.64	3.90	3.25	1.73	0.22	−0.85
Other external injuries	−0.09	0.02	0.04	−0.14	−1.23	3.09	−0.04	4.81	0.54
All other causes	−1.08	4.90	−6.64	0.66	8.15	11.47	7.90	13.50	2.28*
				Japan, 1968–1978					
All causes	99.18[ab]	73.79[b]	11.55[b]	13.84[b]	10.06	9.84	8.74	12.05	3.52*
Infective and parasitic diseases	4.95[b]	3.53[b]	0.56[b]	0.86[b]	8.79	7.26	5.51	9.71	5.73*
Tuberculosis	3.77	2.84	0.18	0.75	8.66	6.13	4.27	6.32	4.58*
Other infective and parasitic diseases	1.18	0.69	0.39	0.10	9.39	11.52	8.67	14.13	3.32*
Malignant neoplasms	17.04[b]	19.41[b]	−12.56[b]	10.19[b]	11.45	3.93	7.48	4.66	4.71*
Of esophagus	4.01	1.37	0.67	1.97	15.34	3.38	14.30	7.78	5.45*
Of stomach	14.44	13.52	−2.93	3.84	11.74	4.05	8.12	5.44	5.01*
Of rectum and large intestine	−1.29	0.48	−1.55	−0.23	8.84	6.71	8.17	6.89	0.85
Of pancreas	0.23	0.01	0.09	0.12	11.08	1.34	11.11	1.42	0.05
Of lung, bronchus, and trachea	6.28	3.67	−1.51	4.12	14.44	2.11	10.35	3.34	5.31*
Of female breast	−0.29	1.02	−1.31	N.A.	N.A.	N.A.	0.68	2.85	2.16*
Of uterus	−7.50	−3.29	−4.21	N.A.	N.A.	N.A	5.49	2.03	−3.46*
Of ovary, Fallopian tube, and broad ligament	−0.70	−0.49	−0.21	N.A.	N.A.	N.A	1.74	−0.48	−2.21**
Of prostate	−0.82	0.87	−1.69	N.A.	22.29	11.72	N.A.	N.A.	10.57*
Leukemia	−0.18	0.02	−0.13	−0.06	4.79	0.10	4.50	−0.07	0.12
Of all other and unspecified sites	2.88	2.23	0.22	0.43	10.23	3.89	9.68	4.62	1.28*
Diabetes mellitus	−2.25	−1.36	0.09	−0.98	11.62	5.72	14.03	4.85	−3.28*
Cardiovascular diseases	56.26[b]	32.64[b]	17.21[b]	6.42[b]	12.20	11.20	11.46	13.35	2.89*
Chronic rheumatic heart disease	−0.51	0.37	−1.21	0.33	6.91	6.87	5.05	6.67	1.66
Hypertensive disease	6.52	2.25	3.35	0.92	13.34	14.76	12.38	17.19	3.38*
Ischemic heart disease	11.16	1.43	7.74	1.99	12.98	9.67	14.09	11.59	0.80
Other forms of heart disease	4.91	2.84	−0.05	2.12	9.31	14.16	9.08	15.60	1.66*
Cerebrovascular disease	33.24[b]	24.69[b]	7.56[b]	0.99[b]	12.71	10.59	12.11	12.81	2.82*
Cerebral hemorrhage	16.96	9.85	7.07	0.04	11.54	7.26	11.37	9.84	2.76*
Cerebral infarction	3.32	3.86	−0.31	−0.23	16.96	11.89	14.68	13.88	4.28*
Other cerebrovascular diseases	12.96	10.99	0.80	1.17	14.11	12.79	12.77	14.95	3.50*
Diseases of arteries, arterioles, and capillaries	0.83	0.92	−0.12	0.02	11.13	13.78	9.84	17.58	5.08*
Venous thrombosis and embolism	0.05	0.06	−0.03	0.02	14.40	9.75	7.00	7.76	5.40
Other cardiovascular diseases	0.07	0.08	−0.03	0.02	8.14	9.65	7.82	10.86	1.53
Influenza	0.20	0.49	−0.17	−0.12	15.62	11.90	8.04	13.84	9.53*
Pneumonia	0.24	3.70	−3.20	−0.26	13.26	13.84	11.00	16.04	4.45*
Bronchitis, emphysema and asthma	−1.87	3.24	−4.34	−0.77	15.43	12.53	10.27	13.93	6.56*
Peptic ulcer	2.69	1.93	1.09	−0.34	9.96	9.13	8.76	14.28	6.35*
Cirrhosis of liver	0.97	−1.81	3.96	−1.18	4.95	4.71	8.51	5.93	−2.34*
Nephritis and nephrosis	−0.33	0.11	−0.58	0.15	7.77	8.55	7.27	8.37	0.31

Continued on next page

Table 2. Cause-of-Death Decomposition of Sex Difference in Mortality Acceleration Between Ages 55 and 75 *(Continued)*

Causes of Deaths	Percent of All-Cause SDMA				LAR (×100)				SDMA (×100)
	TT	MA	MI	RS	M 55	M 75	F 55	F 75	
External injuries	5.15[b]	3.42[b]	7.40[b]	–5.66[b]	3.17	5.25	3.78	7.99	2.12*
Accidents	4.73	3.07	7.36	–5.70	3.47	5.36	5.23	9.95	2.83*
Suicide and selected injury	0.40	0.28	–0.05	0.17	2.87	4.97	2.77	5.32	0.46
Other external injuries	0.03	0.06	0.09	–0.13	–0.76	5.47	–1.27	6.09	1.13
All other causes	16.13	8.50	2.09	5.53	8.60	15.43	7.72	17.38	2.83*

Notes: SDMA = sex difference (F minus M) in mortality acceleration; TT = total effect; MA = mortality acceleration effect; MI = mortality increase effect; RS = residual effect; M = males; F = females; N.A. = not applicable. LAR = life table aging rate. SDMA for a sex-specific cause is calculated by setting mortality acceleration for the other sex to be zero.

[a]Not 100% because of approximation errors.

[b]Sum over the subcategories.

*$p < .01$; **$p < .05$ by two-sided test.

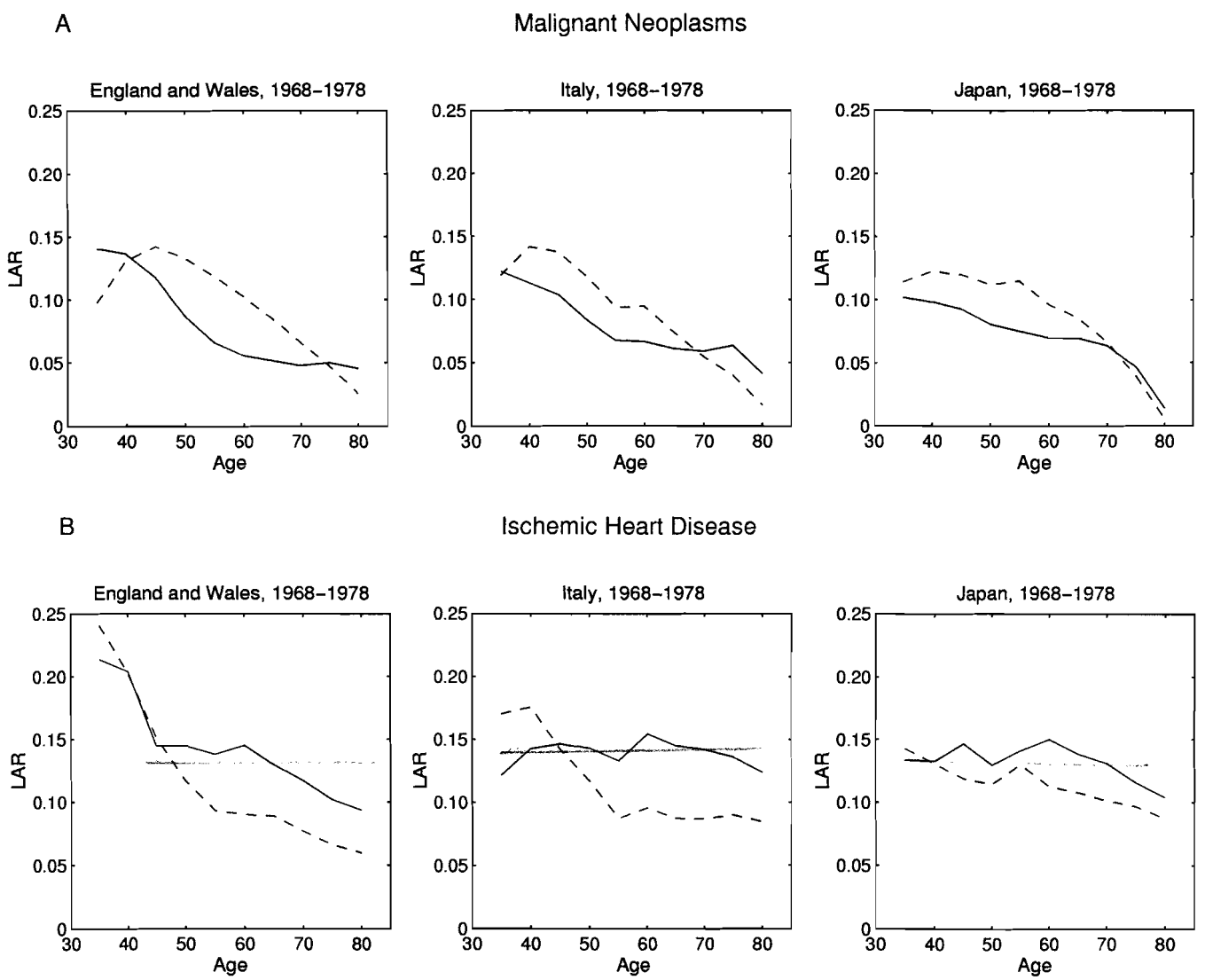
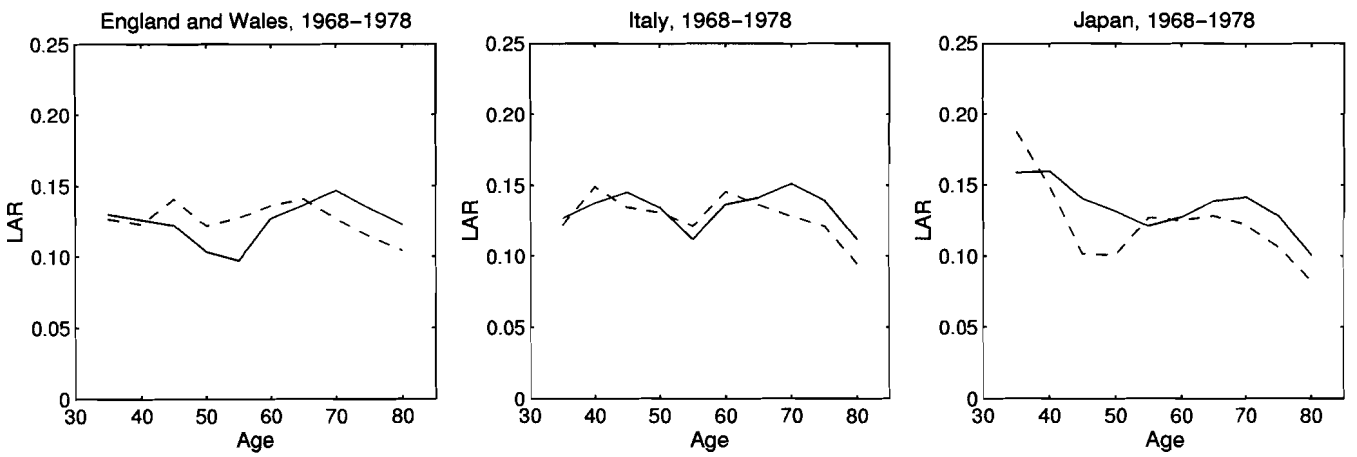


Figure 4. Life table aging rate for selected causes of death in England and Wales, 1968–1978, Italy, 1968–1978, and Japan, 1968–1978: **(A)** malignant neoplasms; **(B)** ischemic heart disease; **(C)** cerebrovascular disease; **(D)** pneumonia; and **(E)** nephritis and nephrosis. Dashed lines indicate males and solid lines, females.

Continued on next page

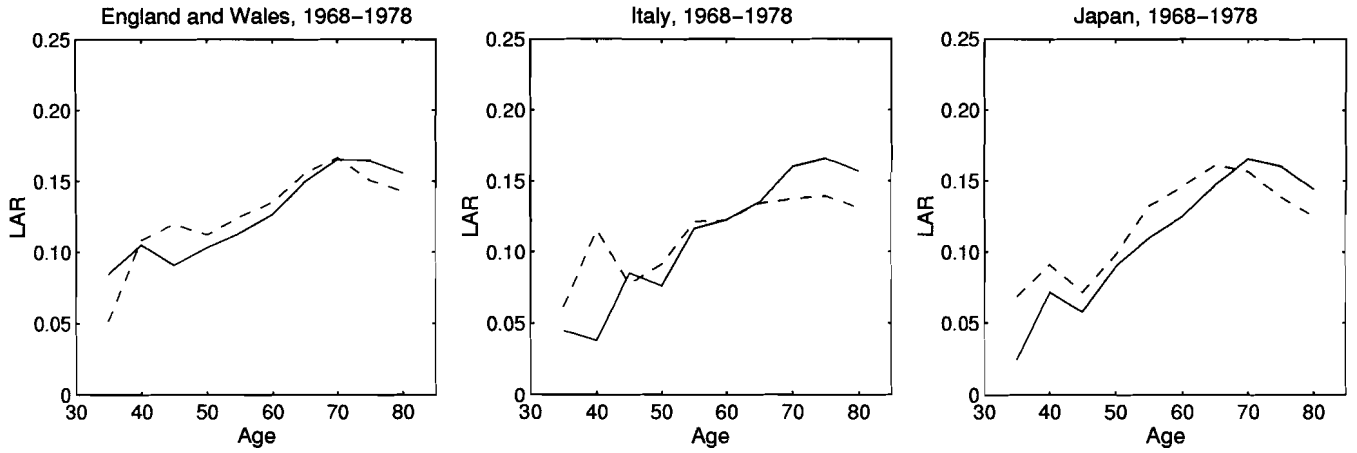
C

Cerebrovascular Disease



D

Pneumonia



E

Nephritis and Nephrosis

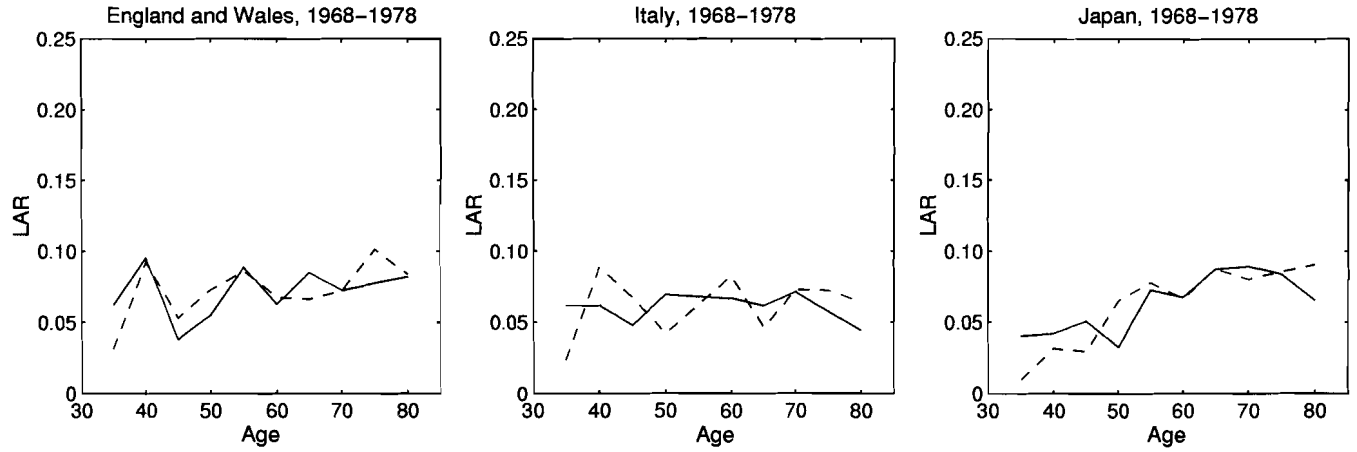


Figure 4 illustrates some typical patterns of sex difference in the cause-specific LAR between ages 55 and 75. Note that the vertical axis of Figure 4 covers a considerably broader LAR range than that of Figure 2. Cerebrovascular disease, pneumonia, and malignant neoplasms represent three types of sex-differential mortality acceleration. The LAR for cerebrovascular disease rises noticeably from age 55 to age 70 (with a decline after age 70) in females but not in males (Figure 4C). The LAR for pneumonia rises in both males and females but less steeply in males than in females (Figure 4D). On the contrary, the LAR for malignant neoplasms falls in both males and females but more steeply in males than in females (Figure 4A). Ischemic heart disease shows a pronounced sex difference in mortality increase: the LAR remains relatively flat between 55 and 75 for both males and females, but the LAR level in females is substantially higher than in males (Figure 4B). Lastly, nephritis and nephrosis do not exhibit notable sex LAR differences (Figure 4E).

DISCUSSION

Major results. — Mortality data from seven industrialized countries have shown postmenopausal mortality acceleration clearly, although the U.S. pattern was anomalous. It may seem rather surprising that this phenomenon, which appears fairly obvious in Figure 2, has not been captured by many researchers who visually inspected logarithmic mortality curves of males and females a number of times. The acceleration was usually overlooked because the curvature of a line is an insensitive indicator of the change of the slope of the line, unless the line is nearly flat or only moderately slanted. This fact has not drawn sufficient attention from users of semi-log mortality plots (Horiuchi and Wilmoth, 1997). The present results underscore the importance of measuring mortality acceleration directly by calculating LARs.

The effects of cardiovascular diseases amount to more than half of the sex difference in all-cause mortality acceleration. This is consistent with a prevalent view about sex differentials in longevity. Sex steroid hormones of females, in particular estrogens, may affect lipoprotein metabolism and, in turn, reduce the risk of arteriosclerosis (Kalin and Zumoff, 1990). This causal linkage is considered a major biological reason for the usually longer expectation of life of females over males (Hazzard and Applebaum-Bowden, 1989; Smith, 1993). However, the postmenopausal changes in the sex hormone status, in particular the decrease in the estrogen level, will diminish the special survival advantage of females (Gorodeski, 1994).

Another potential reason for the relatively low risk of cardiovascular diseases in premenopausal women is the iron depletion through menstruation (Sullivan, 1991). A high level of stored iron may cause some oxidative damage to the heart. Menstruation keeps the level of stored iron lower for females than for males, but menopause makes it start to increase in females.

There are reasons that somatic repair should be more efficient in females than in males as long as the females are reproductive. They include high risk of complications of pregnancy and childbirth, lactation and childcare, and the upper limit of the maximum number of children, which is much greater for males. Death rates in the 20's, 30's, and 40's are substantially lower for females than for males. Gonadal hormones may be a major physiological factor that enhances the somatic maintenance level of females relative to that of males.

Although the ovarian production of the sex hormones ceases shortly after menopause, the development of diseases affected by the hormonal changes (e.g., arteriosclerosis) could be lengthy. Therefore, whereas the mortality risk may start to accelerate abruptly, the risk level will increase gradually. Figures 1C and 2 show the female LAR tends to be lower than the male LAR (i.e., female mortality tends to rise more slowly than male mortality) in the 40's and early 50's of age. (The Japanese anomaly in Figure 2 is likely to be the war-cohort effect.) Then the acceleration starts around age 55, but it seems to take about a decade before the female rate of mortality increase overtakes the male rate of mortality increase (Figures 1C and 2). After about age 65, the female mortality level approaches the male level progressively on the logarithmic scale (Figure 1B), but never overtakes the male level, according to studies of centenarian mortality (Kannisto, 1994). It seems that the relative survival advantage of females over males is slowly attenuated at old ages but is not completely lost.

The female LAR upturn in Figures 1C and 2 may not be seen clearly in economically underdeveloped countries or historical data of industrialized countries. In these populations, nonsenescent forces of mortality (reflected strongly in such CODs as complications of pregnancy and childbirth, and infective and parasitic diseases of young and middle-aged persons) may keep premenopausal death rates at relatively high levels, thereby clouding the effects of menopause on mortality trajectories.

The acceleration of female mortality appears to stop around age 75 in the populations studied here. This does not necessarily suggest that the factors causing the mortality acceleration cease to work around age 75: it is possible that their effects continue beyond 75 but are overridden by factors causing mortality deceleration. The tendency for the age-related mortality increase to decelerate at very old ages has been found for many human populations (Manton, 1992) as well as some animal species (Smith, 1994), and can be explained as resulting from selective survival (Vaupel et al., 1979; Manton et al., 1994).

Lastly, the anomalous U.S. pattern is worthy of further investigation. The less pronounced and late-starting mortality acceleration of U.S. females may possibly be related to the wide use of estrogen replacement therapies among them (Hemminki et al., 1988).

Questions remaining. — The COD analysis leaves several questions unanswered. First, ischemic heart disease contributes to the all-cause SDMA through its mortality increase effect, but most of the rest of the cardiovascular disease categories do so mainly through their mortality acceleration effects. It remains unclear whether this difference suggests more than one physiological pathway through which menopause may affect cardiovascular diseases.

Second, the SDMA of all cancers combined is positive

and significant, and their joint total effect on all-cause SDMA is notably large. Reasons for the sex-differential cancer patterns are yet to be clarified. The positive effect of all cancers is mainly due to cancers of stomach and "lung, bronchus and trachea," but not sex-specific cancers (female breast, uterus, "ovary, Fallopian tube and broad ligament," and prostate). Actually, the total effects of sex-specific cancers tend to be negative because of their mortality increase effects: prostate cancer mortality increases with age at high rates and mortality of the three female-only cancers increases slowly in the age range. The slow increases of female-only cancers after the cessation of ovarian hormone production seem consistent with existing evidence for the raised risks of endometrial and breast cancers among women using exogenous estrogens (Hulka, 1994).

The slowdown, or even decrease, of breast cancer incidence rate has previously been observed at peri- and early postmenopausal ages (Clemmensen, 1948; Pathak and Whittemore, 1992). This incidence pattern is not repeated in mortality data of Clemmensen's time but is reflected clearly in recent mortality data (e.g., Chie et al., 1995). The breast cancer mortality, however, starts to accelerate after age 70 for England and Wales and Japan and after age 65 for Italy. These accelerations are not well captured by this decomposition analysis because they occur only late in the age range of 55–75.

The deceleration of age-related mortality increase for cancers of lung, bronchus, and trachea is less pronounced for females than for males. This may be partly due to sex differentials in smoking trends in industrialized countries, where the increase in tobacco consumption has slowed down among males but continues among females (Chollat-Traquet, 1992). Since a mortality increase through successive cohorts tends to lower period LARs (Horiuchi and Wilmoth, 1997), the smoking trends are likely to lower the female LARs for lung cancer to greater extents than the male LARS, particularly at younger ages. This makes the apparent deceleration of lung cancer mortality less pronounced for females than for males. In addition, the effects of the differential trends in smoking prevalence can be amplified further by greater lung cancer risks among females than among males at the same smoking level (Brownson et al., 1992; Harris et al., 1993; Risch et al., 1993). The lung cancer susceptibility is associated with the cytochrome p450 activity (Ikawa et al., 1995; Bouchardy et al., 1996), which tends to be higher in females than in males (Fletcher et al., 1994; Harris et al., 1995).

Third, positive SDMAs tend to be seen for tuberculosis, other infective and parasitic diseases, influenza, pneumonia, and "bronchitis, emphysema, and asthma." These diseases are closely related to immune functions. Immune reactivity, which is affected by the sex hormones, is generally stronger in females than in males (Paavonen, 1994). Sex hormone effects on autoimmune disorders have been found (Homo-Delarche et al., 1991), but menopausal impacts on immunosenescence await further research.

Fourth, SDMAs of cirrhosis of the liver, and nephritis and nephrosis are negative or negligible. The reasons for their difference from most of the rest of the CODs are unknown. The importance of distinguishing the effects of menopause from other aspects of senescence has been stressed by Kuller et al. (1994).

Finally, the negative SDMAs of diabetes mellitus in all of the three countries were not expected because there could be some causal channels linking menopause, sex steroids, obesity, and diabetes: weight gain and increase in the waist-to-hip ratio are observed for women in peri- and postmenopausal periods (Wing et al., 1991; Heymsfield et al., 1994); older women tend to have higher body mass index than older men (Morley, 1993); obesity is a major risk factor of non-insulin-dependent diabetes mellitus (Jarrett, 1989); and a moderate dose of exogenous estrogen reduces insulin resistance (Lindheim et al., 1993). It is also known that diabetes mellitus is an important risk factor of ischemic heart disease (Kannel et al., 1991), with greater effects on female than male mortality (Barrett-Conner, 1992).

This relationship between diabetes mellitus and ischemic heart disease may illustrate a fundamental problem in data on the underlying (primary) cause of death. Although the problem of multiple CODs may be less serious in the study age range of 55–75 than supposedly more comorbid ages of above 75, the "underlying cause" is a severely limited source of information on diseases that raise risks of other diseases that often become fatal. Among all U.S. death certificates mentioning diabetes mellitus as a contributing cause of death, only about a quarter identify it as the underlying cause (Steenland et al., 1992).

Limitations and future research directions. — A word of caution may be needed about the use of all-cause mortality data in Figures 1–3. Gompertz proposed a fundamental dichotomy of cause of death: senescence versus chance. The hypothesis of postmenopausal mortality acceleration should be applied to senescence-related deaths only, but not to deaths that are independent of senescent processes. Some researchers classified ICD codes into the senescent and nonsenescent types (Bourgeois-Pichat, 1978; Carnes et al., 1996). However, such a classification was not adopted in this study, since many deaths result from interactions of the two mortality forces: for example, infection with influenza virus may occur by chance, but the infection is more likely to cause death to older persons with weakened immune functions. Major COD categories that are usually considered nonsenescent are external injuries (E800–E999 in ICD8), infective and parasitic disease (000–136), and complications of pregnancy and childbirth (630–678). Table 1 indicates that only small proportions of deaths between ages 55 and 75 (thus only small effects on all-cause LARs) are attributed to these categories.

Two points seem noteworthy for further research on this subject. First, in this study, only mortality data are used. For further understanding of sex differentials in mortality acceleration, it seems essential to compare age trajectories of physiological variables between males and females and link them to sex-specific morbidity and mortality patterns (e.g., Manton et al., 1995).

The second issue is generalizability. It seems interesting to investigate if postreproductive mortality acceleration is found more explicitly for females than males in other species. For example, LAR trajectories of medflies exhibit

notable sex differences (Carey and Liedo, 1995). However, female medflies do not show greater acceleration than males of mortality after reproductive ages. The applicability of the hypothesis may be limited to species with similar reproductive mechanisms to those of humans.

ACKNOWLEDGMENTS

This research was supported by grants K01 AG-00554 and R01 AG-10518 from the National Institute on Aging. I am grateful to James Carey, Joel Cohen, Douglas Ewbank, Horton Johnson, Michael Young, and two anonymous reviewers for comments on earlier versions, John Wilmoth for suggestions on the standard error of the LAR, and Christine Himes for sending me some unpublished results of her data analysis.

Address correspondence to Dr. Shiro Horiuchi, Rockefeller University, 1230 York Avenue, Box 20, New York, NY 10021-6399. E-mail: horiush@rockvax.rockefeller.edu

REFERENCES

Anderson, B.A.; Silver, B.D. Patterns of cohort mortality in the Soviet Union. Popul. Dev. Rev. 15:471–501; 1989.

Barrett-Conner, E. Diabetes mellitus, hypertriglyceridemia, and heart disease risk in women. Int. J. Fertil. 37(Suppl.):72–82; 1992.

Boleslawski, L. Roznice w umieralnosci miedzy generacjami jako skutek wojen swiatowych (Differentiation of mortality between generations as a result of the world wars). Studia demograficzne 4:51–7; 1985 [In Polish].

Bourgeois-Pichat, J. Future outlook for mortality decline in the world. Popul. Bull. U.N. 11:12–41; 1978.

Bouchardy, C.; Benhamou, S.; Dayer, P. The effect of tobacco on lung cancer risk depends on CYP2D6 activity. Cancer Res. 56:251–253; 1996.

Brownson, R.C.; Chang, J.C.; Davis, J.R. Gender and histologic type variations in smoking-related risk of lung cancer. Epidemiology 3:61–64; 1992.

Carey, J.R.; Leido, P. Sex-specific life table aging rates in large medfly cohorts. Exp. Gerontol. 30:315–325; 1995.

Carnes, B.A.; Olshansky, S.J. Evolutionary perspectives on human senescence. Popul. Dev. Rev. 19:793–806; 1993.

Carnes, B.A.; Olshansky, S.J.; Grahn, D. Continuing the search for a fundamental law of mortality. Popul. Dev. Rev. 22:231–264; 1996.

Case, R.A.M. Cohort analysis of cancer mortality in England and Wales, 1911–1954, by site and sex. Brit. J. Prev. Soc. Med. 10:172–199; 1956.

Caselli, G.; Vaupel, J.W.; Yashin, A.I. Mortality in Italy: Contours of a century of evolution. Genus 41:39–55; 1985.

Charlesworth, B. Evolution in age-structured populations (2nd ed.). Cambridge, U.K.: Cambridge University Press, 1994.

Chie, W.C.; Chen, C.F.; Lee, W.C.; Chen, C.J.; Lin, R.S. Age-period-cohort analysis of breast cancer mortality. Anticancer Res. 15:511–515; 1995.

Chollat-Traquet, C. Women and tobacco. Geneva: World Health Organization, 1992.

Clemmensen, J. Carcinoma of the breast: results from statistical research. Br. J. Radiol. 21:583–590; 1948.

Devesa, S.S.; Blot, W.J.; Fraumeni, J.F. Declining lung cancer rates among young men and women in the United States: a cohort analysis. J. Natl. Cancer Inst. 81:1568–1571; 1989.

Ekonomov, A.L.; Rudd, C.L.; Lomakin, A.J. Actuarial aging rate is not constant within the human life span. Gerontology 35:113–120; 1989.

Finch, C.E. Longevity, senescence, and the genome. Chicago: The University of Chicago Press, 1990.

Fletcher, C.V.; Acosta, E.P.; Strykowski, J.M. Gender differences in human pharmacokinetics and pharmacodynamics. J. Adolescent Health 15:619–629; 1994.

Fogel, R.W. Economic growth, population theory, and physiology: the bearing of long-term processes on the making of economic policy. Am. Economic Rev. 84:369–395; 1994.

Gorodeski, G.I. Impact of the menopause on the epidemiology and risk factors of coronary artery heart disease in women. Exp. Gerontol. 29:357–375; 1994.

Harris, R.E.; Zang, E.A.; Anderson, J.I.; Wynder, E.L. Race and sex differences in lung cancer risk associated with cigarette smoking. Int. J. Epidemiol. 22:592–599; 1993.

Harris, R.Z.; Benet, L.Z.; Schwartz, J.B. Gender effects in pharmacokinetics and pharmacodynamics. Drugs 50:222–239; 1995.

Hazzard, W.R.; Applebaum-Bowden, D. Why women live longer than men: the biologic mechanism of the sex differential in longevity. Trans. Am. Clin. Climatol. Assoc. 101:168–189; 1989.

Hemminki, E.; Kennedy, D.L.; Baum, C.; McKinlay, S.M. Prescribing of noncontraceptive estrogens and progestins in the United States, 1974–86. Am. J. Public Health 78:1479–1481; 1988.

Heymsfield, S.B.; Gallagher, D.; Poehlman, E.T.; Wolper, C.; Nonas, K.; Nelson, D.; Wang, Z.M. Menopausal changes in body composition and energy expenditure. Exp. Gerontol. 29:377–389; 1994.

Himes, C.L.; Preston, S.H.; Condran, G.A. A relational model of mortality at older ages in low mortality countries. Popul. Stud. 48:269–291; 1994.

Homo-Delarche, F.; Fitzpatrick, F.; Christeff, N.; Nunez, E.A.; Bach, J.F.; Dardenne, M. Sex steroids, glucocorticoids, stress and autoimmunity. J. Steroid Biochem. Mol. Biol. 40:619–637; 1991.

Horiuchi, S. The long-term impact of war on mortality: old-age mortality of World War I survivors in the Federal Republic of Germany. Popul. Bull. U.N. 15:80–92; 1983.

Horiuchi, S.; Coale, A.J. Age patterns of mortality for older women: an analysis using the age-specific rate of mortality change with age. Math. Popul. Stud. 2:245–267; 1990.

Horiuchi, S.; Wilmoth, J.R. Age patterns of the life table aging rate for major causes of death in Japan, 1951–1990. J. Gerontol. Biol. Sci. 52A:B67–B77; 1997.

Hulka, B.S. Links between hormone replacement therapy and neoplasia. Fertil. Steril. 62:168S–175S; 1994.

Ikawa, S.; Uematsu, F.; Watanabe, K.; Kimpara, T.; Osada, M.; Hossain, A.; Sagami, I.; Kikuchi, H.; Watanabe, M. Assessment of cancer susceptibility in humans by use of genetic polymorphisms in carcinogen metabolism. Pharmacogenetics 5(Special Issue):S154–S160; 1995.

Jarrett, R.J. Epidemiology and public health aspects of non-insulin-dependent diabetes mellitus. Epidemiol. Rev. 11: 151–171; 1989.

Kalin, M.F.; Zumoff, B. Sex hormones and coronary disease: a review of the clinical studies. Steroids 55:330–352; 1990.

Kannel, W.B.; Wilson, P.W.F.; Zhang, T.J. The epidemiology of impaired glucose tolerance and hypertension. Am. Heart J. 121:1268–1273; 1991.

Kannisto, V. Development of oldest-old mortality, 1950–1990: evidence from 28 developed countries. Odense, Denmark: Odense University Press; 1994.

Khaw, K.T. Epidemiology of the menopause. Br. Med. Bull. 48:249–261; 1992.

Kirkwood, T.B.L. Repair and its evolution: survival versus reproduction. In: Townsend, C.R.; Calow, P., eds. Physiological ecology: an evolutionary approach to resource use. Sunderland, MA: Sinauer Associates, 1981:165–189.

Kitagawa, E.M. Components of a difference between two rates. J. Am. Stat. Assn. 50:1168–1194; 1955.

Klebba, A.J.; Scott, J.H. Estimates of selected comparability ratios based on dual coding of 1976 death certificates by the eighth and ninth revisions of the International Classification of Diseases. Monthly Vital Statistics Report 28(11):1–18; 1980.

Kuller, L.H.; Meilahn, E.N.; Cauley, J.A.; Gutai, J.P.; Matthews, K.A. Epidemiologic studies of menopause: changes in risk factors and disease. Exp. Gerontol. 29:495–509; 1994.

Lindheim, S.R.; Presser, S.C.; Ditkoff, E.C.; Vijod, M.A.; Stanczyk, F.Z.; Lobo, R.A. A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. Fertil. Steril. 60:664–667; 1993.

Lopez, A.L. The sex mortality differentials in developed countries. In: Lopez, A.L.; Ruzicka, L.T., eds. Sex differentials in mortality: trends, determinants and consequences. Canberra: Australian National University, 1983:53–120.

Manton, K.G. Mortality and life expectancy changes among the oldest old. In: Suzman, R.M.; Willis, D.P.; Manton, K.G., eds. The oldest old. New York: Oxford University Press, 1992:157–182.

Manton, K.G.; Stallard, E.; Woodbury, M.A.; Dowd, J.E. Time-varying

covariates in models of human mortality and aging: multidimensional generalizations of the Gompertz. J. Gerontol. Biol. Sci. 49:B169–B190; 1994.
Manton, K.G.; Woodbury, M.A.; Stallard, E. Sex differences in human mortality and aging at late ages: the effect of mortality selection and state dynamics. Gerontologist 35:597–608; 1995.
Medawar, P.B. Unsolved problems of biology. London: H.K. Lewis, 1952.
Morley, J.E. Nutrition and the older female: a review. J. Am. College Nutr. 12:337–343; 1993.
Nelson, J.F. The potential role of selected endocrine system in aging processes. In: Masoro, E.J., ed. Handbook of physiology. Section 11: Aging. New York: Oxford University Press, 1995:377–394.
Okumbo, M. Increase in mortality of middle-aged males in Japan. (NUPRI Research Paper Series No. 3). Tokyo: Nihon University Population Research Institute, 1981.
Paavonen, T. Hormonal regulation of immune responses. Ann. Med. 26:255–258; 1994.
Pakin, Y.V.; Hrisanov, S.M. Critical analysis of the applicability of the Gompertz-Makeham law in human populations. Gerontology 30:8–12; 1984.
Pathak, D.R.; Whittemore, A.S. Combined effects of body size, parity, and menstrual events on breast cancer incidence in seven countries. Am. J. Epidemiol. 135:153–168; 1992.
Risch, H.A.; Howe, G.R.; Jain, M.; Burch, J.D.; Holowaty, E.J.; Miller, A.B. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. Am. J. Epidemiol. 138:281–293; 1993.
Rose, M.R. Evolutionary biology of aging. New York: Oxford University Press, 1991.
Smith, D.W.E. Human longevity. New York: Oxford University Press, 1993.
Smith, D.W.E. The tails of survival curves. BioEssays 16:907–911; 1994.
Steenland, K.; Nowlin, S.; Ryan, B.; Adams, S. Use of multiple-cause mortality data in epidemiologic analyses: U.S. rate and proportion files developed by the National Institute for Occupational Safety and Health and the National Cancer Institute. Am. J. Epidemiol. 136:855–862; 1992.
Strehler, B.L.; Mildvan, A.S. General theory of mortality and aging. Science 132:14–21; 1960.
Sullivan, J.L. Antioxidants and coronary heart disease. Lancet 337:432–433; 1991.
Tango, T.; Kurashima, S. Age, period and cohort analysis of trends in mortality from major diseases in Japan, 1955 to 1979: peculiarity of the cohort born in the early Showa Era. Stat. Med. 6:709–726; 1987.
United Nations Secretariat. Sex differentials in survivorship in the developing world: levels, regional patterns and demographic determinants. Popul. Bull. U.N. 25:51–64; 1988a.
United Nations Secretariat. Sex differentials in life expectancy and mortality in developed countries: an analysis by age groups and causes of death from recent and historical data. Popul. Bull. U.N. 25:65–106; 1988b.
Vaupel, J.W.; Manton, K.G.; Stallard, E. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography 16:439–454; 1979.
vom Saal, F.S.; Finch, C.E. Reproductive senescence: phenomena and mechanisms in mammals and selected vertebrates. In Knobil, E.; Neil, J.; Ewing, L.L.; Greenwald, G.S.; Markart, C.L.; Pfaff, D.W., eds. The physiology of reproduction. New York: Raven Press, 1988:2351–2413.
Waldron, I. What do we know about causes of sex differences in mortality? A review of the literature. Popul. Bull. U.N. 18:59–76; 1985.
Waldron, I. The contribution of smoking to sex differences in longevity. Public Health Reports 101:163–173; 1986.
Williams, G.C. Pleiotropy, natural selection and the evolution of senescence. Evolution 11:398–411; 1957.
Wilmoth, J.R. Are mortality rates falling at extremely high ages? An investigation based on a model proposed by Coale and Kisker. Popul. Stud. 49:281–295; 1995.
Wilmoth, J.; Vallin, J.; Caselli, G. When does a cohort's mortality differ from what we might expect? Population [English ed.] 2:93–126; 1990.
Wing, R.R.; Matthews, K.A.; Kuller, L.H.; Meilahn, E.N.; Plantinga, P.L. Weight gain at the time of menopause. Arch. Intern. Med. 15:97–102; 1991.
Wingard, D.L.; Cohn, B.A. Variations in disease-specific sex morbidity and mortality ratios in the United States. In: Ory, M.G.; Warner, H.R., eds. Gender, health and longevity: multidisciplinary perspectives. New York: Springer, 1990:25–37.

Received February 10, 1995
Accepted June 22, 1996

Appendix

Decomposition of Mortality Acceleration

The all-cause LAR can be expressed as a weighted average of cause-specific LARs:

$$k(x) = \frac{1}{\mu(x)}\frac{d\mu(x)}{dx} = \sum_i \frac{\mu_i(x)}{\mu(x)}\frac{1}{\mu_i(x)}\frac{d\mu_i(x)}{dx} = \sum_i d_i(x)k_i(x)\,, \tag{A.1}$$

where $\mu_i(x)$ and $k_i(x)$ are the force of mortality and LAR, respectively, for cause i, and $d_i(x)$ is the density function that represents the proportional distribution of deaths at exact age x among different causes: the sum of $d_i(x)$ over cause i is one. It should be noted with caution that $k_i(x)$ and $d_i(x)$ are not independent: if $k_i(x)$ is relatively high, then $d_i(x)$ tends to increase with age. With data classified by five-year age groups, the $d_i(x)$ function can be estimated by

$$\hat{d}_i(x) = \frac{\hat{\mu}_i(x)}{\sum_i \hat{\mu}_i(x)} \text{ where } \hat{\mu}_i(x) = \sqrt{M_i(x,5)M_i(x-5,5)}\,, \tag{A.2}$$

where $M_i(x,5)$ is the death rate due to cause i between ages x and $x+5.0$. This approximation seems sufficiently accurate, since the maximum proportional difference between $k(x)$ obtained directly by Eq. (2) and $k(x)$ constructed using Equations (A.1) and (A.2) for the 12 LARs (3 countries × 2 sexes × 2 ages) decomposed in this study was 0.6%.

The decomposition of $k(x)$ in Eq. (A.1) can be extended to decomposition of all-cause SDMA, defined in Eq. (3), such that:

$$g(x_1,x_2) = \sum_i c_{si}\,, \tag{A.3}$$

where $$c_{si}(x) = [d_{if}(x_2)k_{if}(x_2) - d_{if}(x_1)k_{if}(x_1)] - [d_{im}(x_2)k_{im}(x_2) - d_{im}(x_1)k_{im}(x_1)]\,.$$

Now d's and k's have an additional subscript, f (female) or m (male). c_{si} may be interpreted as the contribution of cause i to the sex difference in all-cause mortality acceleration.

Eq. (A.3) indicates that the sex difference in all-cause mortality acceleration is determined by both sex-and-age variations in the cause-specific LARs and sex-and-age variations in the distribution of deaths among causes, suggesting that a further decomposition by these factors may be possible. This can be done by applying the decomposition method by Kitagawa (1955) in two steps: first, to $k_{ij}(x_2)$–$k_{ij}(x_1)$ for each sex j ($j=f$ or m); next, to the sex difference in $k_{ij}(x_2)$–$k_{ij}(x_1)$. Then c_{si} is expressed as:

$$c_{si} = c_{ki} + c_{di} + c_{ri}\,, \tag{A.4}$$

where

$$\begin{aligned} c_{ki} &= \bar{d}_i\,\{[k_{if}(x_2) - k_{if}(x_1)] - [k_{im}(x_2) - k_{im}(x_1)]\} = \bar{d}_i\, g_i(x_1,x_2)\,, \\ \bar{d}_i &= [d_{if}(x_1) + d_{if}(x_2) + d_{im}(x_1) + d_{im}(x_2)]\,/\,4\,, \\ c_{di} &= \bar{k}_i\,\{[d_{if}(x_2) - d_{if}(x_1)] - [d_{im}(x_2) - d_{im}(x_1)]\}\,, \\ \bar{k}_i &= [k_{if}(x_1) + k_{if}(x_2) + k_{im}(x_1) + k_{im}(x_2)]\,/\,4\,, \end{aligned}$$

and

$$c_{ri} = \left[\frac{d_{if}(x_1) + d_{if}(x_2)}{2} - \frac{d_{im}(x_1) + d_{im}(x_2)}{2}\right]\left[\frac{k_{if}(x_2) + k_{im}(x_2)}{2} - \frac{k_{if}(x_1) + k_{im}(x_1)}{2}\right]$$

$$+ \left[\frac{k_{if}(x_1) + k_{if}(x_2)}{2} - \frac{k_{im}(x_1) + k_{im}(x_2)}{2}\right]\left[\frac{d_{if}(x_2) + d_{im}(x_2)}{2} - \frac{d_{if}(x_1) + d_{im}(x_1)}{2}\right].$$

$\bar{d}_i$ is the mean of d_i's and $\bar{k}_i$ is the mean of k_i's. c_{ki} may be interpreted as the effect of sex difference in the cause-specific mortality acceleration; c_{di} the effect of sex difference in the age-related change of the proportion of deaths that are attributed to the cause; and c_{ri} a residual term representing interactions between sex differences and age differences in k_{ij}'s and d_{ij}'s. Thus c_{si}, c_{ki}, c_{di}, and c_{ri} are called the total (TT) effect, mortality acceleration (MA) effect, death distribution effect, and residual (RS) effect, respectively. c_{ri} may be difficult to interpret.

The death distribution effect can be called the mortality increase (MI) effect, since it is derived mostly from sex differences in cause-specific mortality increase. The death distribution effect is the effect of the sex difference in the change of the proportion of death due to the cause, which would be identical to the sex difference in the cumulated relative increase of the cause-specific mortality, if the cumulated relative increases of mortality from all causes are the same for males and females. Since the sex difference in the average all-cause LAR between ages 55 and 75 is small compared with cause-specific LAR variations, the death distribution effect comes essentially from sex differences in the average cause-specific LAR level between 55 and 75.