Journal of Gerontology: BIOLOGICAL SCIENCES
2003, Vol. 58A, No. 6, 495–507

Differential Patterns of Age-Related Mortality Increase in Middle Age and Old Age

Shiro Horiuchi,[1] Caleb E. Finch,[2] France Meslé,[3] and Jacques Vallin[3]

[1]Laboratory of Populations, Rockefeller University, New York.
[2]Ethel Percy Andrus Gerontology Center, and Department of Biological Sciences, University of Southern California, Los Angeles.
[3]National Institute of Demographic Studies, Paris, France.

It is often assumed that aging is a uniform process throughout adulthood because of the approximately linear increase of logarithmic mortality. We explored this assumption by analyzing cause-specific mortality increases in France (1979–1994). Rising rapidly at ages 30–54 years (''middle age'') are death rates from malignant neoplasms at various sites, acute myocardial infarction, hypertensive disease, and liver cirrhosis. Steeply increasing at 65–89 years (''old age'') are death rates from certain infectious diseases, particularly of the respiratory system; certain types of accidents; nonalcoholic mental disorders (probably due mainly to Alzheimer's disease and senile dementia); heart failure; cerebrovascular disease; and some ''vague'' categories. The processes at work may be fundamentally different in these two life history stages, such that the mortality rise in middle age reflects specific chronic diseases that develop prematurely in some high-risk individuals, whereas the mortality increase in old age is dominated by senescent processes that eventually raise the vulnerability of almost all individuals to multiple pathologies.

MORTALITY increases notably with advancing age in adult humans. The steep rise of age-specific death rate emerges in most human populations in the fourth decade of life (in the 30s) and progresses throughout most of the remaining years. The elimination of such causes as accidents, homicide, suicide, and infectious and parasitic diseases extrapolates the start of the steep rise to the age of sexual maturity (1–4). This age-related increase in mortality is often considered a clear indication of senescent processes that proceed throughout the human life span. The logarithmic mortality curve appears fairly straight throughout most adult ages (Figure 1), with a monotonic appearance during most of adult life that could imply a stable and uniform process of progressive senescence. Although the exponential mortality increase tends to slow down at old ages in humans and many other species (5,6), usually the deceleration in humans is modest under the age of 100 years (7), as illustrated in Figure 1 by the slight concavity of mortality curves in the 80s and 90s.

Underlying the progressive mortality increase with age, however, are substantial age-associated changes in the cause of death (COD) structure. As illustrated with the data from France, 1979–1994, in Figure 2, the proportional distribution of deaths by cause changes considerably with advancing age. Mortality due to neoplasms shows this feature strikingly. The proportion increases markedly in the 30s, 40s, and 50s, reaching nearly 45% around age 60. Subsequently, it decreases at older ages to less than 15% from ages 85–89 and further to about 5% among centenarians. However, the proportion of deaths due to cardiovascular diseases continues to rise with age and is more than 40% in the 80s and 90s. Deaths due to respiratory diseases and ''unspecified causes'' become increasingly prevalent at the oldest ages.

Two types of statistical mechanisms could produce these age-associated shifts in COD. First, if death rates from some CODs rise with age faster than others (8–10), the proportion of deaths due to those CODs increases with age. This could also occur even if the rate of age-related mortality increase for each COD remains relatively constant over age. (For example, suppose the death rate from a certain disease increases continuously at the constant rate of 15% per year of age. Because this pace is faster than those of most other cause-specific death rates, the proportion of all deaths that are attributed to this disease will continue to rise with age, even though the rate of increase of mortality from the disease remains constant with age.) Second, the COD structure should vary with age if the rate of mortality increase for each COD changes with age, and the direction and extent of the change differ among CODs. It is well established that the rate of mortality rise varies markedly with age for some diseases (8–10). Breast cancer is a notable example. This phenomenon seems consistent with observed age variations in rates of some physiological changes (11–15).

The age variations in the COD structure suggest that, although the total mortality increases consistently over a wide range of adult age, physiological, pathological, and demographic processes underlying the monotonic appearance may differ considerably among life history stages, such as middle age (later reproductive age) and old age (post-reproductive age). According to evolutionary theories of aging, senescence and reproduction are considered to be

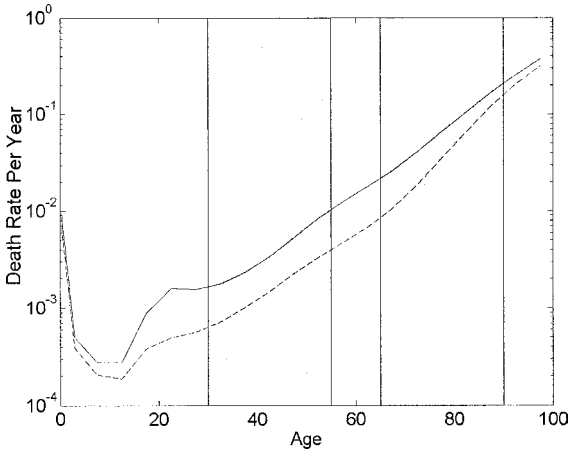

Figure 1. Age pattern of total mortality, France, 1979–1994 combined. The solid line indicates males and the dashed line indicates females. Shaded areas indicate the two age groups, 30–54 years and 65–89 years.

fundamentally linked to each other because the force of natural selection declines with age (16–20). Therefore, the bulk of reproductive effort is accomplished by young adults, with diminishing reproductive contribution at middle ages. At later postreproductive ages, natural selection is predicted to have little effect on the genetic determinants of senescent processes. Thus, the age-related decline in the force of natural selection seems to predict progressive adverse changes in organisms that raise mortality to high levels during the postreproductive phase of life.

If we assume that the mortality increase during the reproductive period and the mortality increase in the postreproductive period are the continuation of the same trend, deaths from chronic diseases in middle age can be considered simply as the results of senescent processes that are prematurely developed or actualized. Because the mortality increase in middle age is gradual and continuous as in old age, chronic processes such as progression of degenerative diseases and increasing vulnerability to infection are likely to be involved. However, chronic processes leading to the early deaths may be initiated or accelerated by factors that are not strongly associated with general senescent processes. They include excessive or unusual exposure to certain environmental risk factors (e.g., cigarette smoking and heavy alcohol consumption); different and more rare genetic risk factors than those that express detrimental effects at postreproductive ages; damages left by certain harmful episodes and conditions (e.g., infections and malnutrition) at young ages and before birth; and noninheritable chance variations during development (39).

Therefore, the decedents at middle ages may be considered primarily a small and special segment of the

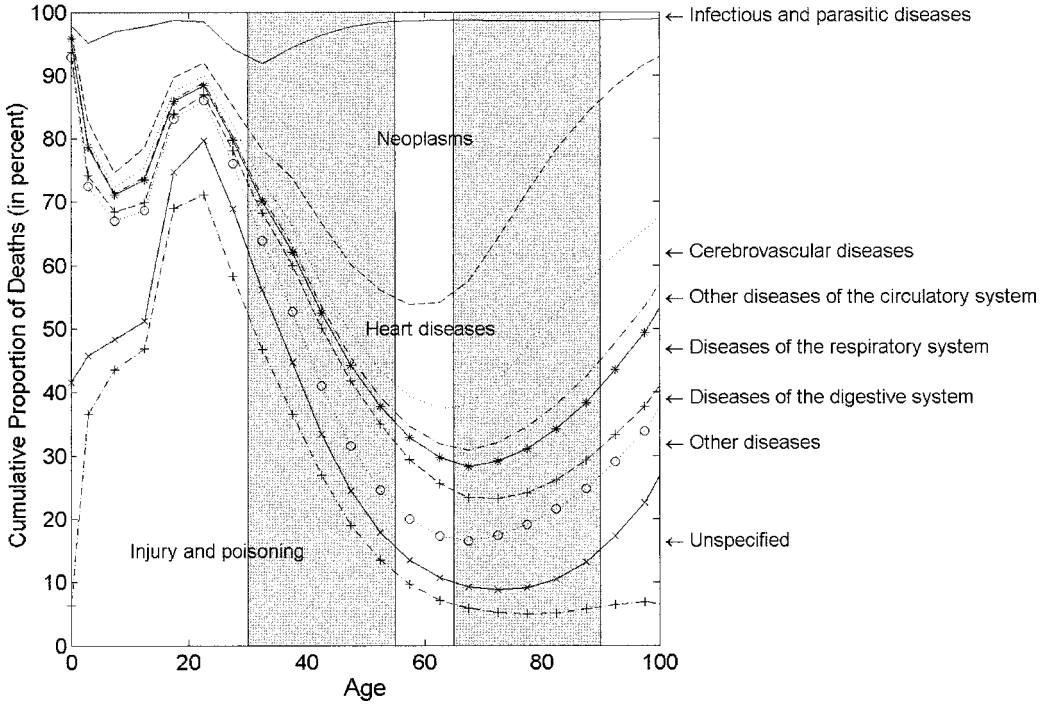

Figure 2. Age pattern of the cause-of-death structure, both sexes, France, 1979–1994 combined. Shaded areas indicate the two age groups, 30–54 years and 65–89 years. Each cause of death (COD) category does not correspond to a curve, but the area between the two adjacent curves. Namely, the proportion of deaths at the given age that are attributable to the COD category is indicated by the vertical distance between two adjoining curves. For example, the proportion of deaths from heart diseases is represented by the distance between the dashed line and dotted line. The dashed line shows the proportion of all deaths at the given age from causes *other than* infectious and parasitic diseases and neoplasms. At age 60, the dashed line indicates 54%. The dotted line shows the proportion of all deaths from causes *other than* infectious and parasitic diseases, neoplasms, and heart diseases. At age 60, the dotted line indicates 38%. Thus, the difference (i.e., the vertical distance) between the two curves is the proportion attributable to heart diseases, which is 16% (54%–38%) at age 60. (In this example, age 60 is chosen for simplicity, but actually the proportions are not given for single-year ages but for 5-year age intervals, and points placed at the middle of the intervals are linked by curves.)

population with high-risk profiles in terms of these factors. This notion is consistent with the relatively low proportion of all adult deaths that occur at ''middle ages'' in modern human populations. For example, among all decedents aged 15 years or older in France between 1979 and 1994, only 10% was at ages 30–54 years, whereas 67% was at ages 65–89 years.

Thus, we propose the hypothesis that CODs that exhibit a fast mortality increase in middle age and CODs that exhibit a fast mortality increase in old age should be substantially and systematically different, reflecting the differential characteristics of underlying chronic processes. To explore this hypothesis, we compute the rate of age-related rise in cause-specific mortality for middle age and old age separately, and compare the rate of mortality increase among different CODs and between the two age groups.

Method

Two 25-year age groups, 30–54 years and 65–89 years, were selected for ''middle age'' and ''old age,'' respectively. To measure the age-related increase in cause-specific mortality, we fit the Gompertz model to death rates by sex, age, and cause separately for the two age ranges. Because cause-specific mortality data are usually classified by 5-year age intervals, the death rate in the age intervals $[x, x+5)$ due to cause i is estimated by

$$\ln {}_5\hat{M}_{x,i} = \alpha_i + \beta_i(x + 2.5) \qquad (1)$$

for each sex and for each of the two age ranges. The slope parameter β_i is *the rate of relative mortality increase with age* (RMI).

Variations in RMIs are examined in two different ways: within-age-group comparison and between-age-group comparison. First, CODs that exhibit relatively high RMIs in comparison with other CODs are identified for each of the two age groups. It is expected that the set of CODs that have relatively high RMIs should be substantially and systematically different between middle age and old age. Second, the RMI is compared between middle age and old age for each of the COD categories. The p value for the RMI difference between the two age groups is calculated as a test of significance. It is expected (a) that a number of major CODs have considerably higher RMIs in one of the two age groups than in the other, and (b) that CODs with markedly higher RMIs in middle age than in old age and CODs with markedly higher RMIs in old age than in middle age should be systematically different. Thus, we investigate differential COD profiles of mortality increase in middle age and old age by combining the within-age-group and between-age-group comparisons.

An alternative to this approach is the life table aging rate analysis, which is useful for examining curvatures of mortality trajectories in detail (6,10). The life table aging rate at age x due to cause i is usually calculated by

$$\hat{k}_i(x) = \ln({}_5M_{x,i} / \ln {}_5M_{x-5,i}). \qquad (2)$$

However, the life table aging rate is not used in this study, because we analyze mortality by relatively (though not fully) *detailed* COD categories. For the confidence interval of the cause-specific life table aging rate to be reasonably small, a very large number of deaths from the cause are required for each of the two adjacent age intervals. This requirement is usually met for broad COD categories, but not necessarily for detailed COD categories.

The Gompertz equation is fitted to data by the weighted least-squares (WLS) linear regression: the values of α_i and β_i are determined so as to minimize

$$\sum_x {}_5D_{x,i}(\ln {}_5M_{x,i} - \ln {}_5\hat{M}_{x,i})^2, \qquad (3)$$

where ${}_5D_{x,i}$ is the number of deaths due to cause i in the age intervals $[x, x+5)$. The variance of $\ln {}_5M_{x,i}$ is well approximated by $1/{}_5D_{x,i}$ (21). The ordinary least-squares (OLS) regression is inappropriate for this analysis because the variance of $\ln {}_5M_{x,i}$ varies substantially with x. The statistical significance of the RMI difference between the two age groups is tested by the standard method for testing the difference between two OLS regression slopes (22), corrected for WLS regression.

For some CODs, it was impossible to calculate RMIs for both of the age ranges using the above-described method. For example, the number of deaths due to ''hyperplasia of prostate'' was zero in some 5-year age intervals between 30 and 54 years, thereby making the left side of Equation 1 to be negative infinity. This COD category, nevertheless, was used as it was without being combined with some other categories, partly because the number of deaths due to this cause in the age group of 65–89 years was sufficiently large enough to produce a reasonably narrow confidence interval for the RMI, and partly because the estimated RMI for 65–89 years was very high and considered noteworthy. Therefore, for some CODs, we show the RMI for one age range only.

The selection of two age groups, 30–54 years and 65–89 years, is based on age patterns of total (all causes combined) mortality in industrialized countries during the latter half of the twentieth century. Although the logarithmic mortality curve appears straight in adult age (Figure 1), the life table aging rate analysis, which captures age variations of mortality more sensitively than the semilogarithmic plotting, has revealed that the rate of mortality increase varies systematically with age (6,23). Typically, the relative rise remains fairly constant (i.e., Gompertzian) in the 30s and 40s, begins to accelerate further from around age 55 to the late 70s, and decelerate thereafter.

The present analysis does not include the two age groups 55–64 years and 90 years and older, in which deviations from the Gompertz equation are most pronounced because of notable accelerations and decelerations, respectively, of the logarithmic mortality increase. The exclusion of ages 55–64 years, separating 30–54 years and 65–89 years, is also based on the expectation that if middle age and old age are two different mortality regimes, their differences should emerge clearly by excluding the transition phase between the two.

Age patterns of mortality can be investigated cross-sectionally (period analysis) or longitudinally (cohort analysis). In this study, period patterns (1979–1994) are

analyzed. Period analysis and cohort analysis have relative advantages and disadvantages. Cohort data, which follow the same group of individuals over time, are strongly preferred for investigating effects of individual characteristics on age-related changes in mortality risk.

Cohort data on human mortality, however, have a special limitation. In modern societies, the environment changes considerably during the lifetime of a cohort. Thus, variations of cohort mortality over a long period of time reflect not only age-related changes of the cohort but also substantial changes of the environment (including medical technology and the standard of living). This problem is negligible for cohorts of short-lived animals in well-controlled laboratories, but could produce substantial biases if a human cohort is followed for several decades in a rapidly changing environment. Period data (cross-sectional data on all age groups in a certain period) can help to circumvent a limitation of cohort mortality data.

Furthermore, in most countries, COD data are tabulated by 5-year age intervals but not by year of birth. This makes it difficult to follow cause-specific mortality trajectories of cohorts.

Mortality data from France are used in this analysis. To minimize effects of *International Classification of Diseases* (ICD) changes, only the data in the ninth revision (ICD9) period, which started in 1979 in France, are analyzed. French data were selected mainly for three reasons. First, reported ages of older persons in some population segments of industrialized countries, including the United States, are not very accurate (24). Reported ages of older persons in France, however, are considered accurate (25). Second, a large population size is needed for analyzing cause-specific mortality trajectories, because the number of deaths could be very small when deaths are classified by sex, age, and cause. France is the second or third most populous country in Europe (after Germany and just passing the United Kingdom). Thirdly, patterns and historical trends of cause-specific mortality in France have been investigated thoroughly (26,27), which helps to interpret results of this study.

We note the caveat that the mortality and morbidity patterns in France may not be typical of other modern populations. As widely known as the ''French paradox,'' mortality and morbidity from ischemic heart diseases in France are low, relative to the levels of saturated fat consumption and serum cholesterol (28,29). However, previous demographic studies have shown that age trajectories of adult mortality in France are not particularly unique except for some cohort variations (23,30).

The analysis was started with 175 COD categories, and repeated with a gradually decreasing number of COD categories, which was finally reduced to 83 (Table 1). To obtain statistically reliable results, CODs that had small numbers of deaths and were neighboring within the ICD9 scheme were grouped together. However, caution was exercised to avoid combining CODs that have considerably different RMI values.

CODs are listed in Tables 1–4 in the order of ICD9. Some category names, particularly those including the word ''other,'' differ slightly between Tables 1 and 2 (comprehensive lists) and Tables 3 and 4 (selective lists) because of the different contexts. Data on COD should be used with caution. Because most death certificates are filled out without (or before) autopsy, reported CODs may not be fully accurate. In addition, coding practices may differ among countries and change over time. However, these errors and inconsistencies in the original 4-digit coding are expected to be reduced when those thousands of codes are grouped together (to 83 categories, in this study). Another problem is that a death could occur in the presence of multiple diseases. The physician is supposed to list these diseases and select the one that ''initiated the train of events leading directly to death'' (31) as the underlying cause of death. Interpretation of this definition, however, could be ambiguous in some cases.

Several COD names need additional remarks. The broad category of ''infectious and parasitic diseases'' in ICD includes highly contagious infectious diseases that are relatively prevalent in economically underdeveloped countries (cholera, diphtheria, measles, etc.) but excludes some major infections of heart, lung, kidney, and other organs, which are classified as diseases of the respective physiological systems. For example, viral pneumonia and bacterial pneumonia are not included in ''infectious and parasitic diseases'' but in ''diseases of the respiratory system.''

ICD9 includes Alzheimer's disease (code 331.0) and vascular dementia (as ''arteriosclerotic dementia'' of code 290.4), but their diagnoses in death certificates during the ICD9 period cannot be considered accurate because histopathologic assessment was not generally available. Probably deaths due to Alzheimer's disease or vascular dementia were attributed to a number of different 4-digit ICD codes. In Table 1, most of those codes are likely to be included in ''other mental disorders,'' ''other diseases of nervous systems and sensory organs,'' ''cerebrovascular disease'' (for some cases of vascular dementia), ''senility without mention of psychosis'' (if dementia is not reported), or ''other ill-defined conditions and symptoms.''

''Hypertensive disease'' in ICD may be considered a category for residual hypertension-related diseases. It includes hypertensive renal diseases and hypertensive heart failure but excludes some major diseases such as hypertension-related ischemic heart diseases, hypertensive cerebrovascular diseases, and pulmonary hypertension. ''Diseases of arteries, arterioles, and capillaries'' are essentially another category for residuals, excluding major atherosclerotic diseases of the heart, brain, lung, and kidney. Detailed information on exact correspondence between the COD categories used in this study and the 4-digit ICD9 codes can be obtained from the first author (S.H.) upon request.

Results

Table 1 shows the proportions of all deaths due to specific causes by sex for age ranges 30–54 years and 65–89 years, thus providing background information on the COD structure of the study population. Table 2 presents numerical results of the data analysis: estimated cause-specific RMIs for each age range, sex, and COD. Important findings in Table 2 are selected and summarized in Tables 3 and 4.

CODs are listed in those four tables in the order of ICD9 code.

Note that the main focus of this study is on age differentials in *cause-specific mortality rises* (Tables 2–4) rather than age differentials in *prevalence of CODs* (Table 1). For example, the 8th line of the ''neoplasms'' section of Table 2 shows that the death rate due to malignant neoplasm of the larynx is estimated to rise with age in males aged 30–54 years at the exponential rate of 0.1806 (corresponding to the geometric rate of 19.79%) per year of age. The rate is 0.0058 in ages 65–89 years, thus the difference between the two age groups is –0.1749. The difference is statistically significant and large enough to include malignant neoplasm of the larynx in Table 3, which lists CODs that exhibit fast mortality increase in middle age.

For some CODs, Tables 1 and 2 may appear inconsistent. Even though their RMIs in Table 2 decline from middle to old age, Table 1 shows that their proportions increase from middle to old age. For example, the RMI for ''chronic bronchitis and emphysema'' in males decreases from 0.1635 for ages 30–54 years to 0.1374 for ages 65–89 years, but its proportion of all-male deaths increases from 0.28% for ages 30–54 years to 1.75% for ages 65–89 years. This is possible because, if the RMI for a COD remains consistently higher than the RMI for total mortality throughout a certain age range, the proportion of deaths due to the COD keeps increasing in the age range, whether the RMI rises or declines.

Tables 3 and 4 show selected CODs that have particularly high RMIs at middle ages and old ages, respectively. As described earlier, RMIs can be compared among different CODs within the same age group, and for the same COD between the two age groups. These two different modes of comparison correspond, respectively, to the columns labeled WAG (within-age-group comparison) and BAG (between-age-group comparison) in Tables 3 and 4. Thus, for each of the 4 sex–age categories (2 sexes $\times$ 2 age groups), CODs that meet either one of the following two conditions are selected: (a) the RMI for the COD is higher than the RMI for all causes in the same age group by 0.03 or more; (b) the RMI for the COD in the age group is higher than the RMI for the same COD in the other age group by 0.05 or more. A difference of 0.03 in the RMI is substantial in that the ratio of two cause-specific death rates would double in 23 years (of age) if the difference continues.

These two arbitrary criteria are used because, in this study, the conventional tests of statistical significance are not very useful for identifying important CODs. For example, Table 2 shows 154 RMI differences between middle age and old age males and females, and 83% of the differences are statistically significant ($p < .01$). Because of the large number of deaths, which were recorded in the entirety of France during the 16-year period, a small observed difference that is usually considered insignificant from a substantive viewpoint could pass the conventional test of statistical significance. Recall that the statistical significance indicates that the difference in the population is unlikely to be *exactly* zero, but the difference may still be close to zero if the sample size is large.

Tables 3 and 4 reveal that the COD profile of mortality increase is strikingly different between middle age and old age. Out of 83 CODs in Table 2, 35 CODs and 32 CODs were selected for Tables 3 and 4, respectively, with only 6 overlapping CODs. Thus, according to the two criteria for mortality increase, the majority (70%) of CODs can be unambiguously split into the middle-age type and old-age type, roughly 50–50.

CODs that have high RMIs at middle ages (Table 3) include malignant neoplasms at various sites, acute myocardial infarction, ischemic heart diseases other than acute myocardial infarction, chronic rheumatic heart disease, hypertensive disease, chronic liver disease (both alcoholic and nonalcoholic), alcohol-related mental disorder, and multiple sclerosis. It should be noted that two major disease groups, malignant neoplasms and ischemic heart diseases, exhibit markedly rapid mortality increase in middle age.

It also seems important to notice that the list suggests strong involvement of some risk factors such as heavy drinking (alcoholic psychosis, alcohol dependence syndrome, and chronic alcoholic liver disease), disease history (acute rheumatic fever for chronic rheumatic heart disease and hepatitis B and C for nonalcoholic liver cirrhosis), and genetic factors (multiple sclerosis and subtypes of some malignant neoplasms). In addition, Table 2 shows that RMI differences between middle ages and old ages are generally greater for malignant neoplasms of respiratory organs than for most other malignant neoplasms, particularly among males, which may suggest stronger effects of smoking or environmental aerosols on the RMI in middle age than in old age.

The COD profile of mortality increase changes notably from middle age to old age. The increase of mortality from malignant neoplasms slows down considerably. As for cardiovascular diseases, the rise of mortality from ischemic heart diseases decelerates, but that from ''other heart diseases'' (mainly heart failure) and cerebrovascular disease accelerates.

In the list of CODs with high RMIs at old ages (Table 4), the following 6 points seem noteworthy.

1. The list includes several diseases that are always or usually caused by infection: acute respiratory infections, influenza, pneumonia, ''osteomyelitis, periostitis, and other infections involving bone,'' intestinal infectious diseases, and viral diseases (ICD9 codes 045–079).
2. The list also includes CODs that are related to a frail musculoskeletal system (including muscles of internal organs) and/or inappropriate neural control, such as accidental falls, accidental inhalation/ingestion of foreign bodies, accidents caused by fire and flames, and intestinal obstruction (without mention of hernia).
3. Rapidly becoming prevalent are two ''vague'' COD categories, ''senility without mention of psychosis'' and ''other ill-defined conditions and symptoms.''
4. The COD list for old age (Table 4) appears pathologically more diverse than that for middle age (Table 3), including diseases of the genitourinary, integumentary, and musculoskeletal systems. Although Table 4 has slightly fewer COD categories than Table 3, about one half of the CODs in Table 3 are malignant neoplasms.

Table 1. Proportion of Deaths From Selected Causes, for 2 Age Groups, 30–54 Years and 65–89 Years, by Sex: France, 1979–1994 Combined

	Males		Females	
Causes of Death	30–54 y	65–89 y	30–54 y	65–89 y
All causes	100.00	100.00	100.00	100.00
Infectious and parasitic diseases	3.80	1.36	2.15	1.40
Intestinal infectious diseases	0.04	0.07	0.05	0.11
Tuberculosis	0.32	0.27	0.23	0.18
Other bacterial diseases	0.29	0.53	0.38	0.59
Viral diseases	2.86	0.10	1.16	0.10
Other infectious and parasitic diseases	0.29	0.39	0.33	0.42
Neoplasms	30.03	29.66	40.64	20.78
Malignant neoplasm of lip, oral cavity, and pharynx	3.95	1.08	0.80	0.19
Malignant neoplasm of esophagus	2.33	1.27	0.39	0.24
Malignant neoplasm of stomach	1.02	1.80	0.99	1.37
Malignant neoplasm of small intestine, including duodenum	0.05	0.05	0.06	0.05
Malignant neoplasm of colon	0.98	2.29	2.00	2.35
Malignant neoplasm of rectum, rectosigmoid junction, and anus	0.49	1.01	0.81	0.80
Malignant neoplasm of other digestive organs	2.39	3.50	2.32	3.00
Malignant neoplasm of larynx	1.98	0.82	0.22	0.05
Malignant neoplasm of trachea, bronchus, and lung	7.16	5.84	2.08	0.96
Malignant neoplasm of other respiratory organs	1.55	0.65	0.45	0.18
Malignant neoplasm of bone, and connective and other soft tissue	0.43	0.20	0.51	0.16
Malignant neoplasm of skin	0.43	0.19	0.80	0.21
Malignant neoplasm of breast	0.05	0.05	12.83	3.00
Malignant neoplasm of cervix uteri	0.00	0.00	1.70	0.22
Malignant neoplasm of uterus, placenta, and body of uterus	0.00	0.00	1.87	0.96
Malignant neoplasm of ovary and other female genital organs	0.00	0.00	3.17	1.23
Malignant neoplasm of prostate	0.19	4.10	0.00	0.00
Malignant neoplasm of testis, penis, and other male genital organs	0.21	0.05	0.00	0.00
Malignant neoplasm of bladder, kidney, and other urinary organs	1.00	1.92	0.80	0.88
Malignant neoplasm of other and unspecified sites	3.03	2.36	4.38	2.43
Leukemia	0.90	0.88	1.64	0.78
Malignant neoplasm of other lymphoid and histiocytic tissue	1.09	0.89	1.49	0.96
Other neoplasms	0.80	0.70	1.33	0.74
Endocrine, nutritional, and metabolic diseases, and immunity disorders	1.08	2.07	1.28	3.39
Diabetes mellitus	0.55	1.17	0.64	1.90
Other endocrine, metabolic, nutritional, and immunity disorders	0.53	0.91	0.65	1.48
Diseases of the blood and blood-forming organs	0.21	0.47	0.37	0.53
Anemias	0.07	0.27	0.16	0.33
Other diseases of the blood and blood-forming organs	0.13	0.19	0.21	0.19
Mental disorders	3.07	1.61	2.06	2.46
Alcoholic psychoses	0.33	0.05	0.09	0.01
Alcohol dependence syndrome	2.34	0.38	1.44	0.11
Other mental disorders	0.41	1.19	0.53	2.34
Diseases of the nervous system and sense organs	1.70	2.01	2.37	2.30
Meningitis	0.10	0.04	0.10	0.05
Multiple sclerosis	0.14	0.02	0.52	0.05
Epilepsy	0.66	0.09	0.54	0.09
Other diseases of the nervous systems and sensory organs	0.80	1.85	1.21	2.12
Diseases of the circulatory system	16.36	37.19	11.89	43.63
Chronic rheumatic heart disease	0.15	0.13	0.44	0.32
Hypertensive disease	0.34	0.91	0.41	1.56
Acute myocardial infarction	6.15	8.08	1.83	7.38
Other ischemic heart diseases	1.06	3.45	0.35	3.19
Other heart diseases	3.97	10.31	3.43	13.39
Cerebrovascular disease	3.41	10.61	4.41	14.43
Diseases of arteries, arterioles, and capillaries	0.91	3.24	0.54	2.67
Phlebitis, thrombophlebitis, venous embolism, and thrombosis	0.12	0.21	0.22	0.38
Other diseases of the circulatory system	0.24	0.24	0.26	0.31
Diseases of the respiratory system	2.46	8.36	2.45	6.26
Acute respiratory infections	0.04	0.17	0.04	0.19
Influenza	0.06	0.19	0.07	0.29

Table 1. Proportion of Deaths From Selected Causes, for 2 Age Groups, 30–54 Years and 65–89 Years, by Sex: France, 1979–1994 Combined (*Continued*)

	Males		Females	
Causes of Death	30–54 y	65–89 y	30–54 y	65–89 y
Pneumonia	0.74	2.31	0.57	2.25
Chronic bronchitis and emphysema	0.28	1.75	0.15	0.87
Asthma	0.34	0.31	0.72	0.42
Bronchiectasis and other chronic obstructive pulmonary disease	0.37	1.90	0.36	0.88
Pneumoconiosis and other lung disease due to external agents	0.14	0.51	0.08	0.17
Other diseases of respiratory system	0.50	1.23	0.46	1.18
Diseases of the digestive system	8.69	5.27	10.16	5.03
Peptic ulcer of stomach and duodenum	0.30	0.48	0.16	0.43
Hernia of abdominal cavity	0.04	0.20	0.08	0.24
Noninfective enteritis and colitis	0.18	0.52	0.21	0.75
Intestinal obstruction without mention of hernia	0.13	0.46	0.21	0.80
Chronic alcoholic liver disease	4.19	0.96	5.27	0.32
Other liver cirrhosis	2.20	0.91	2.65	0.42
Other diseases of liver and biliary tract	0.55	0.62	0.78	0.81
Other diseases of the digestive system	1.10	1.13	0.81	1.27
Diseases of the genitourinary system	0.37	1.89	0.67	1.58
Nephritis, nephrotic syndrome, and nephrosis	0.29	1.18	0.40	1.12
Other diseases of the urinary system	0.06	0.34	0.13	0.41
Hyperplasia of prostate	0.00	0.25	0.00	0.00
Other diseases of genital organs	0.01	0.12	0.14	0.05
Complications of pregnancy, childbirth, and the puerperium	0.00	0.00	0.34	0.00
Diseases of skin and subcutaneous tissue	0.05	0.26	0.08	0.56
Diseases of the musculoskeletal system and connective tissue	0.15	0.34	0.39	0.72
Osteomyelitis, periostitis, and other infections involving bone	0.01	0.01	0.01	0.01
Other diseases of the musculoskeletal system and connective tissue	0.14	0.32	0.39	0.71
Congenital anomalies	0.24	0.03	0.49	0.04
Symptoms, signs, and ill-defined conditions	6.41	4.40	5.15	5.74
Senility without mention of psychosis	0.00	0.84	0.00	1.78
Other ill-defined conditions and symptoms	6.41	3.57	5.15	3.96
Injury and poisoning	25.38	5.08	19.52	5.56
Transport accidents	6.90	0.66	5.14	0.47
Accidental falls	1.25	1.39	0.75	2.86
Accidents caused by fire and flames	0.32	0.07	0.29	0.08
Accidental inhalation/ingestion of foreign bodies	0.48	0.37	0.50	0.42
Suicide and self-inflicted injury	9.67	1.30	8.36	0.63
Homicide and injury purposely inflicted by other persons	0.54	0.02	0.63	0.02
Other injuries and poisoning	6.23	1.28	3.85	1.08

5. Some relatively common diseases and injuries that seldom cause deaths at younger adult ages emerge as serious threats at older ages. They include anemia, influenza, skin diseases, and accidental inhalation/ingestion.
6. Table 4 includes nonalcoholic mental disorders, into which many deaths with vascular dementia or Alzheimer disease might have been classified.

Six CODs appear in both Tables 3 and 4, for two different reasons. First, 4 CODs have opposite age patterns of RMIs for males and females, and were selected for males in Table 3 and for females in Table 4. These CODs are ''diseases of arteries, arterioles, and capillaries,'' ''chronic bronchitis and emphysema,'' ''pneumoconiosis and other lung disease due to external agents,'' and ''noninfective enteritis and colitis.'' The sex differences may be partly due to higher exposure of middle-age males to some environmental risk factors such as smoking (for chronic bronchitis and emphysema) and occupational hazards (for pneumoconiosis and other lung disease due to external agents).

Second, some CODs have fast age-related increases of mortality in both middle and old age. RMIs for ''chronic bronchitis and emphysema,'' ''hernia of abdominal cavity,'' and ''other diseases of genital organs'' were higher than the RMI for all causes by .03 or more at both middle ages and old ages, for both males or females. In addition, a number of CODs have consistently high rates of age-related mortality increase in both middle and old ages, even though their rates of increase do not remain constant over age. In general, rates of increase in mortality from renal–cardiovascular disease categories tend to be high throughout adult ages. This

Table 2. Rates of Age-Associated Relative Increase in Cause-Specific Mortality (RMIs) for 2 Age Groups, 30–54 Years and 65–89 Years, by Sex: France, 1979–1994 Combined (Exponential rate times 100, per year of age, with 95% confidence interval)

	Males			Females		
Causes of Death	30–54 y	65–89 y	Difference	30–54 y	65–89 y	Difference
All causes	8.21 ± 0.06	9.27 ± 0.03	1.06*	7.87 ± 0.10	12.25 ± 0.03	4.38*
Infectious and parasitic diseases						
Intestinal infectious diseases	7.54 ± 3.00	**12.60** ± 1.10	**5.05***	7.24 ± 4.23	14.28 ± 0.98	**7.05***
Tuberculosis	9.30 ± 1.15	8.86 ± 0.57	−0.44	7.37 ± 2.04	10.71 ± 0.72	3.34*
Other bacterial diseases	10.04 ± 1.22	11.03 ± 0.41	0.99	8.35 ± 1.58	12.22 ± 0.41	3.87*
Viral diseases	−3.90 ± 0.38	3.93 ± 0.90	**7.83***	−6.13 ± 0.91	5.84 ± 0.86	**11.97***
Other infectious and parasitic diseases	7.72 ± 1.15	10.26 ± 0.47	2.54*	7.23 ± 1.67	12.17 ± 0.47	4.94*
Neoplasms						
Malignant neoplasm of lip, oral cavity, and pharynx	**16.08** ± 0.46	−0.14 ± 0.30	**−16.22***	**13.57** ± 1.33	5.12 ± 0.63	**−8.45***
Malignant neoplasm of esophagus	**18.36** ± 0.64	1.58 ± 0.28	**−16.78***	**16.72** ± 2.23	7.06 ± 0.58	**−9.66***
Malignant neoplasm of stomach	**14.28** ± 0.76	7.21 ± 0.23	**−7.06***	10.64 ± 1.06	9.43 ± 0.26	−1.20
Malignant neoplasm of small intestine, including duodenum	10.97 ± 3.04	5.94 ± 1.38	**−5.03***	**12.15** ± 4.31	6.16 ± 1.31	**−5.99***
Malignant neoplasm of colon	**14.89** ± 0.76	7.34 ± 0.20	**−7.54***	**13.97** ± 0.82	8.48 ± 0.19	**−5.49***
Malignant neoplasm of rectum, rectosigmoid junction, and anus	**15.00** ± 1.08	6.91 ± 0.30	**−8.09***	**12.85** ± 1.23	7.82 ± 0.33	**−5.04***
Malignant neoplasm of other digestive organs	**15.67** ± 0.50	4.45 ± 0.16	**−11.22***	**14.34** ± 0.77	7.43 ± 0.17	**−6.91***
Malignant neoplasm of larynx	**18.06** ± 0.70	0.58 ± 0.35	**−17.49***	**14.74** ± 2.87	3.76 ± 1.24	**−10.98***
Malignant neoplasm of trachea, bronchus, and lung	**16.28** ± 0.32	1.92 ± 0.13	**−14.36***	**12.70** ± 0.80	3.43 ± 0.29	**−9.27***
Malignant neoplasm of other respiratory organs	**15.43** ± 0.68	0.98 ± 0.38	**−14.45***	**11.08** ± 1.60	5.39 ± 0.67	**−5.70***
Malignant neoplasm of bone, and connective and other soft tissue	8.02 ± 0.93	4.56 ± 0.66	−3.47*	5.41 ± 1.28	5.84 ± 0.71	0.43
Malignant neoplasm of skin	6.44 ± 0.96	7.40 ± 0.64	0.95	5.66 ± 1.06	8.06 ± 0.61	2.40*
Malignant neoplasm of breast	**12.28** ± 3.20	6.32 ± 1.34	**−5.96***	**11.28** ± 0.31	3.73 ± 0.16	**−7.55***
Malignant neoplasm of cervix uteri	NC	NC	NC	6.93 ± 0.78	1.66 ± 0.61	**−5.28***
Malignant neoplasm of uterus, placenta, and body of uterus	NC	NC	NC	**11.64** ± 0.80	4.45 ± 0.29	**−7.19***
Malignant neoplasm of ovary and other female genital organs	NC	NC	NC	**13.49** ± 0.66	3.74 ± 0.26	**−9.75***
Malignant neoplasm of prostate	**24.54** ± 2.32	11.67 ± 0.15	**−12.87***	NC	NC	NC
Malignant neoplasm of testis, penis, and other male genital organs	−0.87 ± 1.28	7.35 ± 1.25	**8.22***	NC	NC	NC
Malignant neoplasm of bladder, kidney, and other urinary organs	**17.70** ± 0.86	6.62 ± 0.21	**−11.08***	**13.21** ± 1.25	7.77 ± 0.31	**−5.44***
Malignant neoplasm of other and unspecified sites	**11.85** ± 0.40	4.81 ± 0.19	**−7.04***	10.10 ± 0.49	6.24 ± 0.18	−3.86*
Leukemia	5.35 ± 0.63	8.18 ± 0.32	2.83*	4.90 ± 0.71	7.71 ± 0.33	2.81*
Malignant neoplasm of other lymphoid and histiocytic tissue	7.07 ± 0.58	6.05 ± 0.32	−1.02*	6.98 ± 0.77	5.67 ± 0.30	−1.31*
Other neoplasms	8.75 ± 0.70	7.05 ± 0.35	−1.70*	7.74 ± 0.82	7.90 ± 0.34	0.15
Endocrine, nutritional, and metabolic diseases, and immunity disorders						
Diabetes mellitus	10.58 ± 0.90	9.13 ± 0.28	−1.46*	**11.39** ± 1.26	10.23 ± 0.22	−1.15
Other endocrine, metabolic, nutritional, and immunity disorders	9.21 ± 0.89	**14.68** ± 0.32	**5.48***	8.02 ± 1.22	**16.28** ± 0.27	**8.26***
Diseases of the blood and blood-forming organs						
Anemias	7.72 ± 2.18	**14.00** ± 0.58	**6.29***	4.92 ± 2.25	**15.31** ± 0.57	**10.40***
Other diseases of blood and blood-forming organs	9.45 ± 1.72	9.08 ± 0.67	−0.37	7.67 ± 2.08	9.33 ± 0.69	1.66
Mental disorders						
Alcoholic psychoses	8.29 ± 1.14	0.27 ± 1.51	**−8.03***	8.93 ± 3.63	4.25 ± 2.52	−4.68
Alcohol dependence syndrome	9.00 ± 0.44	−1.42 ± 0.54	**−10.42***	8.54 ± 0.87	−1.85 ± 0.91	**−10.39***
Other mental disorders	−0.67 ± 0.88	**17.26** ± 0.31	**17.93***	3.61 ± 1.23	**17.83** ± 0.24	**14.22***
Diseases of the nervous system and sense organs						
Meningitis	6.88 ± 1.96	5.19 ± 1.41	−1.70	7.45 ± 3.15	7.53 ± 1.39	0.08
Multiple sclerosis	7.77 ± 1.71	−4.07 ± 2.28	**−11.84***	9.03 ± 1.44	−4.11 ± 1.43	**−13.13***
Epilepsy	3.42 ± 0.76	5.39 ± 0.97	1.97*	1.81 ± 1.23	7.60 ± 0.98	**5.79***
Other diseases of the nervous systems and sensory organs	7.61 ± 0.67	10.01 ± 0.23	2.40*	7.62 ± 0.85	10.61 ± 0.21	2.99*
Diseases of the circulatory system						
Chronic rheumatic heart disease	8.99 ± 1.60	5.17 ± 0.83	−3.83*	10.02 ± 1.57	4.66 ± 0.53	**−5.36***
Hypertensive disease	**14.14** ± 1.25	10.76 ± 0.31	−3.38*	**14.59** ± 1.86	13.62 ± 0.26	−0.97
Acute myocardial infarction	**12.80** ± 0.30	7.13 ± 0.11	**−5.67***	**14.04** ± 0.86	10.69 ± 0.12	−3.35*
Other ischemic heart diseases	**15.75** ± 0.78	9.60 ± 0.16	**−6.15***	**16.33** ± 2.08	13.81 ± 0.19	−2.51*
Other heart diseases	10.63 ± 0.33	**12.95** ± 0.09	2.32*	9.15 ± 0.53	**15.93** ± 0.09	**6.78***
Cerebrovascular disease	10.99 ± 0.36	**12.47** ± 0.09	1.49*	9.71 ± 0.48	14.73 ± 0.09	**5.02***
Diseases of arteries, arterioles, and capillaries	**13.13** ± 0.75	11.32 ± 0.17	−1.81*	8.62 ± 1.29	**16.56** ± 0.21	**7.93***
Phlebitis, thrombophlebitis, venous embolism, and thrombosis	9.88 ± 1.90	10.14 ± 0.64	0.26	8.79 ± 2.12	12.05 ± 0.50	3.26*
Other diseases of the circulatory system	10.50 ± 1.36	10.40 ± 0.59	−0.10	7.63 ± 1.90	13.65 ± 0.57	**6.02***
Diseases of the respiratory system						
Acute respiratory infections	7.89 ± 3.12	**16.80** ± 0.77	**8.91***	6.37 ± 4.63	**19.83** ± 0.86	**13.47***
Influenza	7.41 ± 2.67	**15.72** ± 0.72	**8.31***	4.24 ± 3.50	**18.25** ± 0.65	**14.01***

Table 2. Rates of Age-Associated Relative Increase in Cause-Specific Mortality (RMIs) for 2 Age Groups, 30–54 Years and 65–89 Years, by Sex: France, 1979–1994 Combined (Exponential rate times 100, per year of age, with 95% confidence interval) (*Continued*)

	Males			Females		
Causes of Death	30–54 y	65–89 y	Difference	30–54 y	65–89 y	Difference
Pneumonia	8.94 ± 0.76	**16.03** ± 0.21	**7.09***	6.95 ± 1.24	**18.70** ± 0.24	**11.75***
Chronic bronchitis and emphysema	**16.35** ± 1.49	**13.74** ± 0.23	−2.61*	**11.89** ± 2.65	**16.93** ± 0.37	**5.05***
Asthma	7.72 ± 1.07	7.24 ± 0.53	−0.48	7.41 ± 1.11	8.23 ± 0.46	0.83
Bronchiectasis and other chronic obstructive pulmonary disease	**16.61** ± 1.29	10.37 ± 0.22	**−6.24***	**14.76** ± 1.95	11.04 ± 0.33	−3.71*
Pneumoconiosis and other lung disease due to external agents	**15.42** ± 1.85	7.21 ± 0.41	**−8.21***	5.59 ± 3.38	**15.66** ± 0.80	**10.08***
Other diseases of the respiratory system	10.29 ± 0.92	**13.17** ± 0.27	2.88*	6.91 ± 1.39	**15.87** ± 0.31	**8.96***
Diseases of the digestive system						
Peptic ulcer of stomach and duodenum	**12.28** ± 1.28	10.67 ± 0.42	−1.61*	**11.23** ± 2.66	13.87 ± 0.50	2.64
Hernia of abdominal cavity	**13.90** ± 3.55	**14.99** ± 0.70	1.09	**15.64** ± 4.94	14.35 ± 0.66	−1.29
Noninfective enteritis and colitis	**12.51** ± 1.61	11.06 ± 0.42	−1.45	7.88 ± 2.07	13.82 ± 0.38	**5.94***
Intestinal obstruction without mention of hernia	10.14 ± 1.81	**14.31** ± 0.46	4.17*	9.27 ± 2.22	**16.29** ± 0.39	**7.03***
Chronic alcoholic liver disease	**12.03** ± 0.36	−3.47 ± 0.36	**−15.51***	9.85 ± 0.47	−5.69 ± 0.60	**−15.55***
Other liver cirrhosis	**13.72** ± 0.51	−0.31 ± 0.35	**−14.04***	**11.61** ± 0.70	−0.42 ± 0.47	**−12.02***
Other diseases of liver and biliary tract	10.55 ± 0.91	8.76 ± 0.37	−1.79*	9.41 ± 1.14	11.33 ± 0.34	1.92*
Other diseases of the digestive system	8.17 ± 0.60	9.99 ± 0.28	1.83*	7.92 ± 1.08	12.58 ± 0.28	4.66*
Diseases of the genitourinary system						
Nephritis, nephrotic syndrome, and nephrosis	10.38 ± 1.21	**14.57** ± 0.29	4.19*	9.25 ± 1.56	14.53 ± 0.31	**5.27***
Other diseases of the urinary system	10.35 ± 2.64	**15.71** ± 0.55	**5.37***	10.66 ± 2.90	15.22 ± 0.53	4.56*
Hyperplasia of prostate	NC	**16.18** ± 0.66	NC	NC	NC	NC
Other diseases of genital organs	**13.17** ± 9.29	**14.30** ± 0.93	1.13	7.12 ± 2.74	10.35 ± 1.35	3.23
Complications of pregnancy and childbirth	NC	NC	NC	−14.22 ± 2.93	NC	NC
Diseases of skin and subcutaneous tissue	8.11 ± 2.75	**16.13** ± 0.64	**8.02***	8.85 ± 3.29	**18.56** ± 0.50	**9.71***
Diseases of the musculoskeletal system and connective tissue						
Osteomyelitis, periostitis, and other infections involving bone	5.78 ± 7.60	**13.06** ± 2.87	**7.28**	NC	14.41 ± 2.86	NC
Other disease of the musculoskeletal system and connective tissue	10.47 ± 1.73	10.73 ± 0.52	0.26	8.37 ± 1.50	10.86 ± 0.36	2.49*
Congenital anomalies						
Symptoms, signs, and ill-defined conditions						
Senility without mention of psychosis	NC	**24.00** ± 0.42	NC	NC	**25.61** ± 0.35	NC
Other ill-defined conditions and symptoms	4.47 ± 0.23	10.83 ± 0.15	**6.36***	3.50 ± 0.40	14.11 ± 0.16	**10.61***
Injury and poisoning						
Transport accidents	−0.40 ± 0.22	3.78 ± 0.37	4.17*	0.89 ± 0.40	3.26 ± 0.43	2.37*
Accidental falls	5.53 ± 0.54	**15.87** ± 0.26	**10.33***	7.39 ± 1.12	**19.69** ± 0.22	**12.30***
Accidents caused by fire and flames	2.77 ± 1.04	7.90 ± 1.10	**5.12***	2.28 ± 1.70	10.71 ± 1.09	**8.43***
Accidental inhalation/ingestion of foreign bodies	5.25 ± 0.89	12.15 ± 0.49	**6.90***	6.48 ± 1.35	13.48 ± 0.48	**7.00***
Suicide and self-inflicted injury	1.14 ± 0.19	5.65 ± 0.26	4.51*	2.68 ± 0.32	1.42 ± 0.37	−1.26*
Homicide and injury purposely inflicted by other persons	−0.61 ± 0.84	2.34 ± 2.09	2.95*	−0.86 ± 1.23	3.74 ± 1.91	4.60*
Other injuries and poisoning	2.50 ± 0.24	6.01 ± 0.26	3.51*	3.18 ± 0.47	8.77 ± 0.28	**5.60***

Notes: NC = not calculated. RMIs that are greater than that of all causes combined by 3.0 or more are indicated in **bold**; and RMI differences (old age RMI minus middle age RMI) that are greater than 5.0 or smaller than −5.0 are shown in **bold.**

*Middle age RMI and old age RMI are significantly different ($p < .01$).

suggests that caution should be exercised not to overemphasize the differences between middle age and old age and overlook their commonalities.

Figure 3 displays some typical age trajectories of mortality for selected CODs that have higher RMIs at middle ages than old ages (3A) and CODs that have the opposite patterns (3B). The mortality curves tend to be concave in (A) and convex in (B), particularly around age 60.

Discussion

This analysis shows striking differences in the rates of changes for particular causes of death during middle age and old age. These two broad age groups are characterized by different profiles of mortality increase with advancing age.

The mortality rise in middle age (30–54 years) is dominated by major degenerative diseases such as malignant neoplasms, atherosclerosis, hypertension, cirrhosis, ulcer, and diabetes. These diseases tend to progress over several decades, with mortality risks that affect a subgroup of middle-aged individuals. In some cases, familial trends are associated with common genetic risk factors, such as apoE4 (apolipoprotein E4), a common allele that has a significant but modest association with increased cholesterol and with the risk of cardiovascular disease, particularly in middle age (32,33). Overall, the incidence of dominant genes for specific causes of mortality at middle ages and later is emerging as less common, whereas environmental factors are increasingly recognized (34). These perspectives do not rule out rare genes that promote longevity in diverse

Table 3. Causes of Death That Exhibit Fast Mortality Increase in Middle Age: France, 1979–1994 Combined

	Males		Females	
	WAG	BAG	WAG	BAG
Neoplasms				
Malignant neoplasm of lip, oral cavity, and pharynx	+	+	+	+
Malignant neoplasm of esophagus	+	+	+	+
Malignant neoplasm of stomach	+	+		
Malignant neoplasm of small intestine, including duodenum	+	+	+	+
Malignant neoplasm of colon	+	+	+	+
Malignant neoplasm of rectum, rectosigmoid junction, and anus	+	+	+	+
Malignant neoplasm of other digestive organs	+	+	+	+
Malignant neoplasm of larynx	+	+	+	+
Malignant neoplasm of trachea, bronchus, and lung	+	+	+	+
Malignant neoplasm of other respiratory organs	+	+	+	+
Malignant neoplasm of breast	+	+	+	+
Malignant neoplasm of cervix uteri				+
Malignant neoplasm of uterus, placenta, and body of uterus			+	+
Malignant neoplasm of ovary and other female genital organs			+	+
Malignant neoplasm of prostate	+	+		
Malignant neoplasm of bladder, kidney, and other urinary organs	+	+	+	+
Malignant neoplasm of other and unspecified sites[a]	+	+		
Endocrine, nutritional, and metabolic diseases, and immunity disorders				
Diabetes mellitus			+	
Mental disorders, and diseases of the nervous system and sense organs				
Alcoholic psychoses		+		
Alcohol dependence syndrome		+		+
Multiple sclerosis		+		+
Diseases of the circulatory system				
Chronic rheumatic heart disease				+
Hypertensive disease[b]	+		+	
Acute myocardial infarction	+	+	+	
Other ischemic heart diseases	+	+	+	
Diseases of arteries, arterioles, and capillaries[c]	+			
Diseases of the respiratory system				
Chronic bronchitis and emphysema[c]	+		+	
Bronchiectasis and other chronic obstructive pulmonary disease	+	+	+	
Pneumoconiosis and other lung disease due to external agents[c]	+	+		
Diseases of the digestive and genitourinary systems				
Peptic ulcer of stomach and duodenum	+		+	
Hernia of abdominal cavity[c]	+		+	
Noninfective enteritis and colitis[c]	+			
Chronic alcoholic liver disease	+	+		+
Other liver cirrhosis	+	+	+	+
Diseases of genital organs (excluding hyperplasia of prostate)[c]	+			

Notes: A plus sign for WAG indicates a notably faster mortality increase by within-age-group (WAG) comparison, i.e., RMI (relative mortality increase) for the cause in middle age is greater than RMI for all causes in middle age by 0.03 or more. A plus sign for BAG indicates a notably faster mortality increase by between-age-group (BAG) comparison, i.e., RMI for the cause in middle age is greater than RMI for the same cause in old age by 0.05 or more.

[a]Excluding all of the 19 specific sites of malignant neoplasm in Table 1.

[b]Excluding hypertension-related ischemic heart disease and cerebrovascular disease, and pulmonary hypertension.

[c]Appearing in both Tables 3 and 4.

environments, such as may be found in some families (35,36).

Other individuals may be at high risk from environmental exposure such as cigarette smoking, heavy alcohol consumption, high-fat and high-calorie diet, and occupational hazard. Another set of risk factors arises from low birth weight syndromes, which increase the risk of adult onset diabetes (type II), heart disease, and hypertension. Low birth weight with accelerated childhood growth, which occurs in many populations even in the absence of clinically defined maternal malnutrition, has not been associated with common genetic risk factors (37,38). Childhood infections can also cause adult mortality before old age, e.g., streptococcus infections are associated with a high incidence of focal myocardial damage (Ref. 19: pp. 492–493).

Another category of high risk may be acquired through random cellular events during development, e.g., events that lead to variations in vascular branching patterns, so that occlusions or aneurysms can have very different effects

Table 4. Causes of Death That Exhibit Fast Mortality Increase in Old Age: France, 1979–1994 Combined

	Males		Females	
	WAG	BAG	WAG	BAG
Infectious and parasitic diseases				
Intestinal infectious diseases	+	+		+
Viral diseases		+		+
Neoplasms				
Malignant neoplasm of testis, penis, and other male genital organs		+		
Endocrine, nutritional, and metabolic diseases, and immunity disorders				
Endocrine, metabolic, nutritional, and immunity disorders (excluding diabetes mellitus)	+	+	+	+
Diseases of the blood and blood-forming organs				
Anemias	+	+	+	+
Mental disorders, and diseases of the nervous system and sense organs				
Mental disorders (excluding alcoholic psychoses and alcohol dependence syndrome)	+	+	+	+
Epilepsy				+
Diseases of the circulatory system				
Other heart diseases[a]	+		+	+
Cerebrovascular disease	+			+
Diseases of arteries, arterioles, and capillaries[b]			+	+
Other diseases of the circulatory system[c]				+
Diseases of the respiratory system				
Acute respiratory infections	+	+	+	+
Influenza	+	+	+	+
Pneumonia	+	+	+	+
Chronic bronchitis and emphysema[b]	+		+	+
Pneumoconiosis and other lung disease due to external agents[b]			+	+
Other diseases of the respiratory system[d]	+		+	+
Diseases of the digestive and genitourinary systems				
Hernia of abdominal cavity[b]	+			
Noninfective enteritis and colitis[b]				+
Intestinal obstruction without mention of hernia	+		+	+
Nephritis, nephrotic syndrome, and nephrosis	+			+
Other diseases of the urinary system	+	+		
Hyperplasia of prostate	+			
Other diseases of genital organs[b]	+			
Other diseases				
Diseases of skin and subcutaneous tissue	+	+	+	+
Osteomyelitis, periostitis, and other infections involving bone	+	+		
Senility without mention of psychosis	+		+	
Other ill-defined conditions and symptoms		+		+
Injury and poisoning				
Accidental falls	+	+	+	+
Accidents caused by fire and flames		+		+
Accidental inhalation/ingestion of foreign bodies		+		+
Other injuries and poisoning[e]				+

Notes: A plus sign for WAG indicates a notably faster mortality increase by within-age-group (WAG) comparison, i.e., RMI (relative mortality increase) for the cause in old age is greater than RMI for all causes in old age by 0.03 or more. A plus sign for BAG indicates a notably faster mortality increase by between-age-group (BAG) comparison, i.e., RMI for the cause in old age is greater than RMI for the same cause in middle age by 0.05 or more.

[a]Excluding chronic rheumatic heart disease, hypertensive heart disease, and ischemic heart disease.

[b]Appearing in both Tables 3 and 4.

[c]Excluding heart disease, hypertensive disease, cerebrovascular disease, diseases of arteries, arterioles, and capillaries, phlebitis, thrombophlebitis, and venous embolism and thrombosis.

[d]Excluding acute respiratory infections, influenza, pneumonia, chronic bronchitis, emphysema, asthma, bronchiectasis, and other chronic obstructive pulmonary disease, pneumoconiosis, and other lung disease due to external agents.

[e]Excluding transport accidents, accidental falls, accidents caused by fire and flames, accidental inhalation/ingestion of foreign bodies, suicide and self-inflicted injury, homicide, and injury purposely inflicted by other persons.

on brain region functions (Ref. 39: p. 52). There are also indications of developmental variations in vascular thickness, which can influence the outcome of atherogenesis (Ref. 19: p. 341). The age at menopause may also be subject to nonheritable variations in the numbers of ovarian oocytes, e.g., identical twins may experience menopause up to 12 years apart (Ref. 39: pp. 22 and 23; Refs. 40 and 41). Variations in age at menopause can influence risk of osteoporotic fractures and atherogenesis.

The age-related rise in total mortality at old ages appears strongly associated with the gradual and progressive declines of various physiological functions. The deterioration may be attributable to long-term accumulation of small damages and/or debilitation by previous diseases. The aging immune and pulmonary systems increase the vulnerability to certain other infectious diseases. The frail musculoskeletal system and declining functions of neural control mechanisms and sensory organs raise the risk of certain types of accidents. Chronic cardiovascular diseases such as atherosclerosis and hypertension debilitate the heart, eventually leading to death from heart failure. Due to the declining ability to maintain homeostasis, physiological stresses that were not serious at younger ages become life threatening at old ages. Because of the simultaneous deterioration of multiple physiological systems, an increasing number of deaths occur in the presence of multiple diseases or without explicit manifestation of any specific diseases, making it more likely for physicians to use vague categories in the death certificates. The vulnerability to multiple pathologies is also reflected in the diversity of CODs at old ages. These physiological declines probably occur in most (if not all) individuals, though there may be substantial individual differences in the pace of decline. As discussed above, individual risk profiles may be subject to different types of random experiences during development, which cause minor deficits early in life to which are added random further insults, e.g., turbulent flow favors atherogenesis (42,43).

In summary, the mortality rise in middle age seems primarily attributable to specific chronic diseases that develop prematurely in high-risk individuals, whereas the mortality increase in old age seems dominated by senescent processes that eventually raise the general vulnerability of almost all individuals to multiple pathologies. The high-risk individuals at middle ages may have experienced unusually high exposure to some environmental hazards, have relatively uncommon genes that express adverse effects, or have specific disease histories or congenital defects. The difference can be considered to correspond, to some extent, to the conventional division of ''disease versus normal aging'' (44).

The idea that a few fundamentally different types of mortality force underlie observed variations of death rates is not new and has a long history (1). There are a number of versions of mortality partition, but they generally distinguish extrinsic mortality, which is either caused or initiated by something that originates *outside* the body, and intrinsic mortality, which is either caused or initiated by processes that originate *within* the body (1). This distinction between extrinsic and intrinsic mortality may not appear to be closely

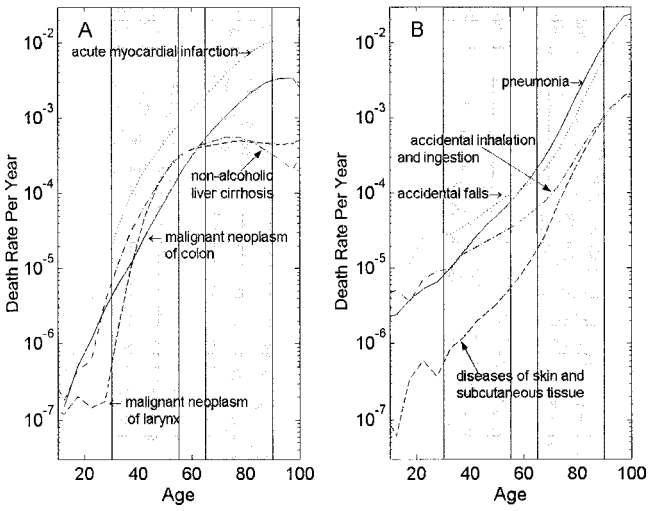

Figure 3. Age patterns of mortality for selected causes of death, French males, 1979–1994 combined. Shaded areas indicate the two age groups, 30–54 years and 65–89 years. **A**, Cause of death (CODs) with faster mortality increase at middle ages than at old ages: malignant neoplasm of colon (solid line); malignant neoplasm of larynx (dashed line); acute myocardial infarction (dotted line); other (i.e., nonalcoholic) liver cirrhosis (dashed–dotted line). **B**, CODs with faster mortality increase at old ages than at middle ages: pneumonia (solid); diseases of skin and subcutaneous tissue (dashed); accidental falls (dotted); accidental inhalation/ingestion of foreign bodies (dashed–dotted).

related to the differences in the COD profile of mortality rise between middle age and old age. Most CODs listed in Tables 3 and 4 are usually considered intrinsic (45), which is not surprising because gradual increases of cause-specific mortality in adult age are likely associated with chronic processes.

However, extrinsic and intrinsic factors may interact in causing a death, and extrinsic factors seem more strongly involved in chronic diseases that exhibit fast mortality increase in middle age than those in old age, even though the chronic diseases may be considered primarily intrinsic. Death rates from various malignant neoplasms, alcohol-related mental disorders, acute myocardial infarction, and chronic liver diseases rise faster in middle age than in old age. These diseases are generally considered relatively strongly associated with behavioral factors (e.g., smoking, alcohol consumption, diet, and exercise) and occupational hazards.

The relationships between the extrinsic-versus-intrinsic dichotomy and the RMI differences between middle age and old age, however, do not seem very simple. Relatively uncommon genetic risk factors, which are intrinsic, may be involved in some of the deaths from certain CODs that exhibit faster mortality increase in middle age than in old age. They include multiple sclerosis, diabetes mellitus, and several types of malignant neoplasms. Death rates for some types of accidents and infectious diseases rise more steeply in old age than in middle age, suggesting that the vulnerability to those extrinsic risks is greatly raised by intrinsic chronic processes.

Conclusion

This exploratory study indicates that relationships between senescent processes and the age-associated mortality increase are not so simple and straightforward as previously thought. The straight appearance of logarithmic mortality curves is widely considered as an indication of senescent processes that continue throughout most adult ages. However, our analysis of COD patterns suggest that physiological, pathological, and demographic processes underlying the consistent rise in total mortality may be substantially different between middle age and old age.

Acknowledgment

This research was supported by grants K02-AG00778 and R01-AG14698 to Dr. Shiro Horiuchi from the National Institute on Aging (NIA) and grants to Dr. Caleb Finch from the NIA, the Alzheimer Association, and the John Douglas French Alzheimer's Foundation.

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

References

1. Carnes BA, Olshansky SJ. A biologically motivated partitioning of mortality. *Exp Gerontol.* 1997;32:615–631.
2. Finch CE, Pike MC, Witten M. Slow mortality rate accelerations during aging in some animals approximate that of humans. *Science.* 1990;249: 902–905.
3. Jones HB. A special consideration of the aging process, disease, and life expectancy. *Adv Biol Med Physics.* 1956;4:281–337.
4. Luder HU. Onset of human aging estimated from hazard functions associated with various causes of death. *Mech Ageing Dev.* 1993;67: 247–259.
5. Vaupel JW, Carey JR, Christensen K, et al. Biodemographic trajectories of longevity. *Science.* 1998;280:855–860.
6. Horiuchi S, Wilmoth JR. Deceleration in the age pattern of mortality at older ages. *Demography.* 1998;35:391–412.
7. Horiuchi S. Interspecies differences in the life span distribution: humans versus invertebrates. In: Carey J, Tuljapurkar S, eds. *Life Span: Evolutionary, Ecological, and Demographic Perspectives. Popul Dev Rev.* (Supplement to Vol. 29). In press.
8. Simms HS. Logarithmic increase in mortality as a manifestation of aging. *J Gerontol.* 1946;1:13–26.
9. Kohn RR. Human aging and disease. *J Chron Dis.* 1963;16:5–21.
10. Horiuchi S, Wilmoth JR. Age patterns of the life-table aging rate for major causes of death in Japan, 1951–1990. *J Gerontol Biol Sci.* 1997; 52A:B67–B77.
11. Halbreich U, Lumley LA, Palter S, Manning C, Gengo F, Joe SH. Possible acceleration of age effects on cognition following menopause. *J Psych Res.* 1995;29:153–163.
12. Oliver CN, Levine RL, Stadtman ER. A role of mixed-function oxidation reactions in the accumulation of altered enzyme forms during aging. *J Am Geriatr Soc.* 1987;35:947–956.
13. Wikby A, Johansson B, Ferguson F, Olsson J. Age-related changes in immune parameters in a very old population of Swedish people: a longitudinal study. *Exp Gerontol.* 1994;29:531–541.
14. Wesson LG Jr. Renal hemodynamics in physiological states. In: Wesson LG Jr, ed. *Physiology of Human Kidney*, New York: Grune and Strattob; 1969:98–100.
15. Xu X, Laird N, Dockery DW, Schouten JP, Rijcken B, Weiss ST. Age, period, and cohort effects on pulmonary function in a 24-year longitudinal study. *Am J Epidemiol.* 1995;141:554–566.
16. Medawar PB. *Unsolved Problems of Biology.* London: H. K. Lewis; 1962.
17. Williams GC. Pleiotropy, natural selection and the evolution of senescence. *Evolution.* 1957;11:398–411.
18. Kirkwood TBL, Rose MR. Evolution of senescence: late survival sacrificed for reproduction. *Philos. Tran. R. Soc. Lond. [Biol.]* 1991; 332:15–24.
19. Finch, CE. *Longevity, Senescence, and the Genome.* Chicago: The University of Chicago Press; 1990.
20. Rose, MR. *Evolutionary Biology of Aging.* New York: Oxford University Press; 1991.
21. Brillinger DR. The natural variability of vital rates and associated statistics. *Biometrics.* 1986;42:693–734.
22. Brownlee, KA. *Statistical Theory and Methodology in Science and Engineering. 2nd Ed.* New York: John Wiley & Sons; 1965.
23. Horiuchi S, Coale AJ. Age patterns of mortality for older women: an analysis using age-specific rate of mortality change with age. *Math Popul Stud.* 1990;2:245–267.
24. Preston SH, Elo IT, Rosenwaike I, Hill M. African-American mortality at older ages: results of a matching study. *Demography.* 1996;33: 193–209.
25. Kannisto V. *Development of Oldest-Old Mortality, 1950–1990: Evidence From 28 Developed Countries.* Odense, Denmark: Odense University Press; 1994.
26. Vallin J, Meslé F. *Les Causes de Décès en France de 1925 a 1978.* Paris: Institut National d'Études Démographiques Presses Universitaires de France; 1988.
27. Meslé F, Vallin J. Reconstructing long-term series of causes of death: the case of France. *Hist Methods.* 1996;29:72–87.
28. Richard JL. Les facteurs de risque coronarien. Le paradoxe francais. *Arch Mal Coeur Vaiss.* 1987;80:17–21.
29. Law M, Wald N. Why heart disease mortality is low in France: the time lag explanation. *BMJ.* 1999;318:1471–1480.
30. Caselli G, Vallin J, Vaupel J, Yashin A. Age-specific mortality trends in France and Italy since 1900: Period and cohort effects. *Eur J Popul.* 1987;3:33–60.
31. World Health Organization. *International Classification of Diseases, 1975 Revision.* Geneva: World Health Organization; 1977.
32. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol.* 2002;155:487–495.
33. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet.* 2000;1:507–537.
34. Willett WC. Balancing life-style and genomics research for disease prevention. *Science.* 2002;296:695–698.
35. Puca AA, Daly MJ, Brewster SJ, et al. A genome-wide scan for linkage to human exceptional longevity identifies a locus on chromosome 4. *Proc Natl Acad Sci U S A.* 2001;9810505–9810508.
36. Finch CE, Ruvkun G. The genetics of aging. *Annu Rev Genomics Hum Genet.* 2001;2:435–462.
37. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull.* 2001;60:5–20.
38. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia.* 2002;45: 342–348.
39. Finch CE, Kirkwood, TBL. *Chance, Development, and Aging.* Oxford: Oxford University Press; 2000.
40. Do KA, Broom BM, Kuhnert P, et al. Genetic analysis of the age at menopause by using estimating equations and Bayesian random effects models. *Stat Med.* 2000;19:1217–1235.
41. Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause. *J Clin Endocrinol Metab.* 1998;83:1875–1880.
42. Gimbrone MA Jr, Topper JN, Nagel T, Anderson KR, Garcia-Cardena G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. *Ann N Y Acad Sci.* 2000;902:230–239.
43. Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med.* 1988;112:1018–1031.
44. Johnson, HA, ed. *Relations Between Normal Aging and Disease.* New York: Raven Press; 1985.
45. Carnes BA, Olshansky SJ, Grahn D. Continuing the search for a fundamental law of mortality. *Popul Dev Rev.* 1996;22:231–264.

Received February 21, 2003
Accepted February 28, 2003
Decision Editor: James R. Smith, PhD