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Limits to Human Life Expectancy: Evidence, Prospects, and Implications

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ESTIMATES OF LIMITS TO HUMAN LIFE SPAN—the “biologically” maximum length of life—and of population life expectancy are made by demographers, biologists, and actuaries. Despite the significance of a life expectancy limit for private and public pension programs, the Social Security Trust Fund in the United States (Preston, 1991) and comparable funds in other aging, industrial societies, and for private and public acute and long-term health insurance, there is little consensus on the value at which the limit is set.

Perspectives on the issue can be roughly divided into three groups. The “traditionalists” suggest that the limit is not significantly greater than current life expectancy, namely about 85 years (Olshansky, Carnes, and Cassel, 1990; Fries, 1990). The limit is viewed as due to biological senescence, which is not affected by changing the mortality of specific causes. A “visionary” perspective suggests that, while life expectancy limits are due to senescence, advances in biomedical research will raise those limits in the future (in some 25 to 50 years). Since senescence itself is thereby modified, life expectancies of 100 to 125 years (Strehler, 1975) or more (150 to 200 years, Rosenberg et al., 1973; Walford, 1983) might be achievable. It is suggested that altering senescence has implications for age-dependent diseases (Strehler, 1975: Figure 2). An “empiricist” perspective contends that we are not currently near a life expectancy limit, because mortality is declining and progress is being made in the treatment and management of the chronic diseases and disabilities that dominate mortality at later ages. It is observed that, if recent mortality declines of about 2 percent per year continued, life expectancies

of 95 to 100 years could be achieved by the year 2080 (Ahlburg and Vaupel, 1990; Guralnik, Yanagishita, and Schneider, 1988; Schneider and Guralnik, 1990; Guralnik and Schneider, 1987: 134). This perspective suggests that senescence is multidimensional, with each dimension associated with chronic disease. Hence, progress in treating or preventing such disease (e.g., atherosclerosis, Alzheimer's disease, osteoporosis) represents progress in altering senescence. To evaluate these perspectives, we review the definition of a "limit" and assess data and methodologies for its evaluation.

One issue is the use of "endpoint of life," or mortality, data. Investigators who extrapolate mortality trends or manipulate "endpoints" in competing-risk calculations (Chiang, 1968) use only the distribution of ages at death, population counts by age, and causes of death. Interdependence between competing diseases and senescence is not mathematically identifiable from endpoint data alone (Tsiatis, 1975; Peterson, 1976).

There is overwhelming evidence that health processes and mortality at advanced ages are affected by health-related behavior, physical activity, nutrition, and socioeconomic conditions. Though the importance of such factors is accepted, they are often not incorporated in models—an inconsistency between the state of scientific knowledge and model specification.

A second issue is conceptual. It has been suggested that intrinsic biological processes limiting life span (i.e., senescence) will be empirically manifest in a human survival curve that becomes increasingly "square" or "rectangular." In other words, the probability of survival remains very high until advanced age, at which point senescence dominates mortality and the probability of survival drops to near zero in a short age range. The problem here is that if individual differences in the biological endowment for life span exist, the curve will not be perfectly square. Once this is accepted, then additional parameters describing the biologically allowed variation of ages at death must be estimated. These additional parameters are not uniquely identifiable from mortality data. Thus, for every model with rectangularization that fits a set of mortality data, a model without rectangularization can be constructed that fits equally well in the presence of unmeasured fixed, or time-varying, risk factors (Manton and Tolley, 1991).

Identifiability is especially difficult to demonstrate with time-varying risk factors. Strehler and Mildvan (1960) and Sacher and Trucco (1962) presented multidimensional models of senescence and mortality. In empirical studies of human populations, they reduced their models to Gompertz functions¹ (Strehler, 1975). The Gompertz function was rationalized by assuming that mortality at advanced ages is dominated by one dimension, associated with the risk of death, that represents a single physiological function which simultaneously weights all variables and all magnitudes of displacement from physiologically optimal operating ranges (Sacher and Trucco, 1962: 1005). Other theorists (Economos, 1982; Rosenberg et al., 1973) prefer

alternative forms of age dependence for mortality such as introduced by Weibull (1939). Rectangularization cannot be empirically proven using either the Gompertz or Weibull models, because alternative models without rectangularization can easily be made to fit data equally well if unobserved risk factors are present (Manton and Tolley, 1991).

Representing mortality by a single age-dependent dimension assumes that a single senescent process dominates at advanced age. Biologists often assume that limits to life expectancy are genetically determined, species-specific processes (Hayflick, 1965; Strehler, 1975). Though genetic factors influence length of life, they operate in complex internal and external environments that both mitigate and exacerbate their consequences. Each organ system may have multiple genetically determined parameters controlling how long a system functions (Strehler, 1975; Shock et al., 1984). Moreover, genetically determined rates of functional loss can be accelerated (e.g., effects of smoking on pulmonary function) or slowed (e.g., effects of restriction of fat intake on atherosclerosis) by changes in behavior. In vitro studies of tissue from human donors aged 30 to 80 showed a loss of replicative potential of cells with age too slow (Martin, Sprague, and Epstein, 1970) to be consistent with the estimates of limits in Table 1. Hence, it is unlikely that life expectancy is determined by a unidimensional process of "senescence." We must know (a) how organ systems interact, each differentially losing functionality with age, and (b) how environmental factors compensate for, or aggravate, genetically determined changes in organ systems.

We consider these issues in steps. First, we examine "traditionalist" and "visionary" estimates of limits to life expectancy and the methods and data used to make them. Second, we examine long-lived populations. Their survival defines a lower bound to a theoretical limit—that is, a theoretical limit must be higher than observed life expectancy. Third, we use a model to estimate life expectancy limits from data on multiple time-varying risk factors and functioning.

Estimates of human life expectancy limits

Table 1 presents estimates from: (a) independent cause elimination of exogenous causes of death (lines 1–4); (b) a cross-country "composite" of the "best" observed mortality rates (line 5); (c) models of "rectangularization" (lines 6–8); and (d) Gompertz and Weibull models of aging kinetics (lines 9–10). Life expectancies in Japan are presented for comparison. While life expectancy in Japan is high, Japanese are subject to a number of health hazards (e.g., high consumption of salt and pickled foods; inadequate animal protein intake in rural areas; high alcohol consumption; stress; smoking; Araki and Murata, 1986; Reed, 1990; Kuller and Reisler, 1971). Five of the

TABLE 1 Estimates of limits to human life expectancy and observed life expectancy in selected low-mortality populations

	Year	Both sexes	Males	Females
Cause elimination		Theoretical limits		
Bourgeois-Pichat	1952	77.3*	76.3*	78.2*
Bourgeois-Pichat	1978	77.1*	73.8*	80.3*
Nihon University	1982	80.3	79.8	80.7*
Olshansky et al.	1990	85.0	82.0	88.0
International composite				
Siegel	1980	76.6*	73.8*	79.4*
Models of rectangularization				
Benjamin and Haycocks	1970	77.7*	74.8*	80.6*
Ryder	1975	84.0	82.4	85.6
Fries	1980	85.6	85.6	85.6
Models of aging kinetics				
Strehler	1975			
Cause elimination		85–90		
Gompertzian kinetics		100–125		
Rosenberg et al.	1973			
Cause elimination		98.8		
Weibull kinetics		100–198		
		Observed life expectancy		
Japan	1990 ^a	78.9	76.0	82.4
Okinawa prefecture	1987 ^b	80.0	77.2	82.7
Shimane prefecture	1987 ^b	79.4	75.5	83.3

* Estimated limit now surpassed by life expectancy observed in Japanese national or prefecture population.

^a Data from Retirement Commission, with infant mortality adjusted.

^b Estimates made from Japanese vital statistics publications.

ten estimates of limits for females, and four of ten for males, have already been surpassed by the Japanese.

All of the analyses represented in Table 1 imply the decomposition of the distribution of ages at death into a subdistribution due to "exogenous" causes, which can be eliminated, and a subdistribution due to "endogenous" causes, which are age determined and cannot be eliminated without intervening in senescence. Estimates of the subdistributions are not mathematically identifiable from mortality data (Tsiatis, 1975; Peterson, 1976) without strong, and sometimes implausible, assumptions (e.g., positing that diseases operate independently and that certain diseases represent irreducible forces of senescence) or without detailed information on changes in health before death.

Cause-elimination models

The estimates in lines 1–4 in Table 1 were made using techniques (Chiang, 1968) in which “exogenous” causes of death are eliminated by assuming they are independent of endogenous causes. Nothing in the methodology empirically identifies causes as exogenous or endogenous (Olshansky, Carnes, and Cassel, 1990: 637). Such calculations are useful in estimating the effects on life expectancy of “rare” and acute causes of death. As Chiang (1968) makes clear (p. 244), the independent competing-risk model describes death as an instantaneous event so that two causes of death by definition cannot exist simultaneously, that is, dependence is assumed “impossible.” Such a model may approximate reality for death from external causes (e.g., automobile accidents) or acute infectious disease (e.g., influenza, typhoid, diphtheria). For chronic diseases with long and complex natural histories, however, the approximation is not appropriate. Aggregating causes of deaths will not represent (a) risk-factor and disease dependency that has operated over time to affect deaths from a cause outside the grouping, or (b) joint occurrences of diseases at death in multiple-cause-of-death data—for example, diabetes and heart disease contribute to more deaths than are reported in mortality data limited to underlying causes of death (Manton and Stallard, 1984; Park, Yokoyama, and Tokuyama, 1991).

To estimate dependency among causes of death requires more information than is found in mortality data. For example, two causes may depend on the same risk factor (e.g., smoking). In a risk-factor model, dependency may be small at early ages because only a small proportion of persons with elevated risks will have died (e.g., by age 40 only a small proportion of smokers have died; for other “risk” factors, say a genetic disorder such as muscular dystrophy, the loss of at-risk persons may be high at age 25). At advanced ages (e.g., 80+), however, dependency due to smoking is significant because, by that age, the risk-factor distribution is significantly altered by selection (i.e., few heavy smokers are left alive). Cause-elimination estimates of life expectancy assuming independence of causes are higher than cause-elimination estimates assuming dependence (based on pre-death health data) if medical intervention is directed solely at preventing death while leaving risk factors unchanged. The reverse is true if the intervention alters risk factors and is begun early. For instance, intervening in smoking at a young age may eliminate a significant proportion of the force of mortality of multiple lethal diseases (e.g., lung cancer, heart disease, stroke, chronic pulmonary disease) and disability from multiple conditions (e.g., osteoporosis, osteoarthritis, peripheral circulatory diseases; Benowitz, 1988).

The lack of information on risk factors and on disease and senescence in independent competing-risk models can produce apparent contradictions.

TABLE 2 Expected percent of deaths and expected mean time to death, in years, for six causes, at birth and at age 85, by sex: US white population, 1968 and 1987

Cause of death	Males					Females				
	Percent of deaths		Mean time to death			Percent of deaths		Mean time to death		
	1968	1987	1968	1987	Increase 1968-87	1968	1987	1968	1987	Increase 1968-87
	At birth									
All causes	100.0	100.0	67.9	72.4	4.5	100.0	100.0	75.4	79.2	3.8
Cancer	14.6	20.6	68.5	71.8	3.3	13.9	17.7	69.3	72.0	2.7
Diabetes	1.5	1.4	69.8	72.7	2.9	2.4	1.9	74.3	77.3	3.0
Cardiovascular disease	42.4	38.0	71.7	75.8	4.1	42.0	40.0	79.7	83.3	3.6
Stroke	9.6	5.9	76.2	79.1	2.9	15.2	9.7	80.8	83.9	3.1
Influenza and pneumonia	3.7	3.7	70.5	81.4	10.9	4.1	4.2	77.8	86.2	8.4
Chronic obstructive lung disease	2.7	4.8	70.6	76.4	5.8	0.7	3.0	70.5	76.4	5.9
	At age 85									
All causes	12.9	21.5	4.7	5.4	0.7	30.0	31.1	5.6	6.9	1.3
Cancer	1.0	2.6	3.8	4.5	0.7	1.7	3.1	4.5	5.4	0.9
Diabetes	0.2	0.2	3.9	4.5	0.6	0.4	0.6	4.2	5.6	1.4
Cardiovascular disease	6.0	9.4	4.7	5.6	0.9	14.5	79.8	5.7	7.1	1.4
Stroke	2.1	1.9	4.6	5.4	0.8	5.8	5.1	5.4	6.7	1.3
Influenza and pneumonia	0.8	1.6	5.3	6.3	1.0	1.8	2.7	6.4	7.8	1.4
Chronic obstructive lung disease	0.2	0.9	3.8	4.5	0.7	0.8	0.8	4.9	5.5	0.6

SOURCE: Tabulations of national underlying-cause-of-death files.

In Table 2 we present, for six causes, US data on the proportion of deaths and mean time to death (at birth and age 85) in 1968 and 1987. The mean age at death increased between 1968 and 1987 for all six causes regardless of whether the proportion of deaths caused by a disease increased or decreased. For example, between 1968 and 1987 the life table mean age at death from cancer increased by 3.3 years for males and 2.7 years for females.

In Table 3 we show the effect on life expectancy (at birth and age 85) of separately eliminating each of the six causes of death. For males, eliminating all cancer deaths increases life expectancy at birth by 1.9 years in 1968 and 2.8 years in 1987. Corresponding figures for females are 2.3 and 3.0 years. The effect of eliminating cancer would increase if circulatory disease risk continues to decline.

The cause-elimination model requires classifying mortality into exogenous causes to be eliminated and endogenous causes that cannot be elim-

TABLE 3 Effect on life expectancy, in years, at birth and at age 85, of separately eliminating six causes of death, by sex: US white population, 1968 and 1987

Cause of death	Males		Females	
	1968	1987	1968	1987
At birth				
Cancer	1.9	2.8	2.3	3.0
Diabetes	0.2	0.2	0.3	0.2
Cardiovascular disease	6.4	5.5	5.5	5.6
Stroke	0.9	0.5	1.5	0.9
Influenza and pneumonia	0.5	0.3	0.5	0.4
Chronic obstructive lung disease	0.3	0.3	0.1	0.4
At age 85				
Cancer	0.3	0.6	0.3	0.4
Diabetes	0.0	0.1	0.1	0.1
Cardiovascular disease	3.1	3.4	3.6	4.8
Stroke	0.7	0.4	1.0	0.7
Influenza and pneumonia	0.3	0.4	0.3	0.4
Chronic obstructive lung disease	0.1	0.2	0.0	0.1

SOURCE: Tabulations of national underlying-cause-of-death files.

inated. The theoretical limit to life expectancy is obtained by eliminating all exogenous causes. For a counter-example, if each of the six causes in Table 3 were *individually* eliminated (a conservative approach ignoring the non-linearity in cause-elimination calculations), the sum of the effects suggests a “theoretical” limit to life expectancy at birth for females in 1968 of 85.6 years (a 10.2-year gain over the level shown in Table 2) and in 1987 of 89.7 years (a 10.5-year gain). However, none of the causes was “eliminated.” Collectively, the six causes account for 78.3 percent of deaths in 1968 and 76.5 percent in 1987. Thus, the 3.8-year gain in life expectancy between 1968 and 1987 is attributable to a delay in the age at death due to these and other causes. If the same rate of delay (0.2 years per calendar year) continued, then female life expectancy at birth would reach 85 years in 2016. With a 10–11-year effect attributable to elimination of the six causes, the theoretical limit to life expectancy in 2016 would be 95–96 years.

The preceding discussion suggests the need to take account of factors not described in competing-risk models to estimate meaningful life expectancy limits. First, life expectancy increases need not be due to cause elimination. Despite a 4.5-year increase in life expectancy for males, and 3.8 years for females, the proportion of deaths due to cancer and cardiovascular disease (CVD) increased for males (from 57.0 percent to 58.6 percent) and

females (from 55.9 percent to 57.7 percent) between 1968 and 1987. Thus, the onset of diseases can be delayed without reducing their cause-elimination effect.

Second, a decrease in mortality at young ages may raise risks at later ages. For CVD, a cause with declining early mortality risks, the proportion of deaths occurring past age 85 has increased. Thus, a person could have a heart attack at age 50, be saved from it, and die at 75 of a second heart attack. Alternatively, a person could survive several heart attacks, incur cardiac damage, and manifest congestive heart failure at age 85—an advanced stage of the same disease process. The independent cause-elimination life table does not permit death from an “eliminated” disease at a later age, that is, a cause is assumed eliminated forever. This is unrealistic. A person with one heart attack has a higher probability of dying of a second (or later) heart attack than the general population (Tolley and Manton, 1985; Hartunian, Smart, and Thompson, 1981). This possibility is acknowledged in “cause-delay” models (Manton, Patrick, and Stallard, 1980). Of course, ancillary data are required to estimate a delay for each cause.

Third, though more information on mortality is now available (e.g., data on multiple-cause mortality from 1968 to 1988, a time period adequate to identify associated-cause occurrences of chronic disease and to estimate “patterns of failure” cause-elimination models for cohorts), investigators still use cross-sectional, underlying-cause data (Olshansky, Carnes, and Cassel, 1990).

Fourth, in cause-elimination calculations, the increase in life expectancy is a nonlinear function of the proportion of deaths eliminated. Thus, gains in life expectancy do not decompose into additive components (Tsai, Lee, and Hardy, 1978; Strehler, 1975). The competing-risk model is useful in examining the effect of eliminating individual causes of death (if these are not too large a proportion of total mortality) but not for determining a life expectancy limit, because, as more causes are eliminated, life expectancy increases nonlinearly *without* limit (Strehler, 1975).

Finally, changes in US mortality between 1968 and 1987—the example used here—were partly due to the alteration of risk factors, which delays the onset and retards the progression of chronic disease. Data from the National Health and Nutritional Examination Surveys from 1960 to 1980 show declines in cigarette smoking, levels of cholesterol, and rates of hypertension in the age group 65 to 74 (NCHS, 1988: 96, 100, 101). Risk-factor reduction is not represented in the competing-risk model. The fact that the cause-elimination effect, the mean age at death from a disease, and the proportion of deaths due to a disease all increase with time can be explained by using data on physiological “failure” processes underlying related and interacting diseases. Diabetics have a lower cell replication potential (Mooradian, 1988) and die at earlier ages from a number of diseases (Balkau

et al., 1991), while immune dysfunction underlies other diseases (Gerkins et al., 1974).

Construction of international composites

An alternative approach (exemplified by line 5 of Table 1) is to examine age-, sex-, and cause-specific mortality rates for developed countries, selecting the lowest rate to form a “best” composite profile. Since the rates are abstracted, on a cause-, age-, and sex-specific basis from multiple independent populations, disease dependencies are not represented. For example, despite relatively high levels of dietary fat in France, CVD mortality is low—possibly due to high levels of alcohol consumption. These low CVD risks may be associated with high cirrhosis mortality rates. Selecting the lower CVD mortality rate does not represent this dependency. Similarly in Japan, CVD risk is low, while stroke risk is high (Reed, 1990).

Rectangularization: The relation of the mean and variance of the age at death

The estimates in lines 6, 7, and 8 in Table 1 were obtained by extrapolating life expectancy (the mean age at death) to the point at which the variance of the distribution of ages at death reached an irreducible minimum (Fries, 1980). This implies “rectangularization” of the life table survival curve, as preventable deaths are eliminated until only deaths due to “senescence” remain. This approach raises conceptual and methodological issues.

Simms (1942) defined senescence as the physiological distance to death (e.g., the ability of mice at different ages to survive certain amounts of blood loss). This definition has continued to be used, with senescence defined by “loss” of organ capacity (e.g., loss of renal or pulmonary function; Shock et al., 1984), which is thought to decrease an organism’s “vitality” or ability to maintain “homeostasis,” or avoid death. However, senescence is, most generally, the universal decline in the physiological state of organisms of a given advanced “age,” with the increased risk of death being a consequence of senescence—in other words, risk of death is an indirect measure of senescence. Using the risk of death to measure senescence becomes problematic as advances in biomedical science alter the relation of physiological parameters to death, that is, the “approximation” becomes less valid. The ability to extend life in the face of age-related functional decrements requires developing new duration-based measures of health (WHO, 1984) and more precisely defining senescence. For example, it was suggested that “active” life expectancy, the amount of time for which specific levels of physical performance are maintained, be measured. Thus, it is increasingly important that senescence be measured directly as the “state” of an individual’s phys-

iology and not by the distance to death. We provide such a “state” definition later in our risk-factor dynamics model. These new definitions require more information than is available in mortality data.

One approach to estimating the limit is by extrapolating life expectancy changes at different ages to a point of convergence (Fries, 1980). The point of convergence is affected by the ages for which life expectancy changes are extrapolated and the time period of the extrapolation. For example, if life expectancy changes at ages 65 and 85 for the period 1900 to 1978 are linearly extrapolated, they converge at 95.3 years. If the extrapolation is based on changes from 1968 to 1978, an estimate of 96.8 years is obtained. As another example, mortality rates for the population aged 85 and above were relatively stable from 1980 to 1988 while the mean age of the population aged 85 and above increased—suggesting that mortality rates at specific ages above 85 declined. From 1988 to June 1991 mortality rates for the population above age 85 declined by 8.5 percent, from 157.2 to 143.8 per 1,000 (NCHS, 1991). For US white females, the group with the highest life expectancy and presumably the group closest to the limit, the decline from 1988 to 1991 was 8.3 percent—to 135.7 per 1,000. Thus, extrapolation using data from 1980 to 1988 would show little change; starting in 1988, large declines would be manifest—in an age category that is itself becoming progressively older.

A second strategy is to analyze changes in the relation of the mean age at death to the variance of age at death either past certain ages or for certain proportions of deaths. This approach shows no tendency toward rectangularization of the US survival curve between 1962 and 1979 (Myers and Manton, 1984a,b). Rothenberg, Lentzner, and Parker (1991) found no evidence of rectangularization from 1962 to 1984. The age to which one in 100,000 persons is expected to live (“life endurancy”) increased by three years for males (109 to 112) and four years for females (110 to 114) between 1960 and 1980 in US life tables (SSA and Faber, 1982). Thus, recent US experience provides no evidence of convergence to a life expectancy limit at current levels.

There is a problem in assessing “rectangularization” regardless of the procedure used: namely, if genetic heterogeneity in ages at death exists, the “ultimate” survival curve is not “square” (i.e., all deaths do not occur at precisely the same age). If senescent (irreducible) variability in ages at death exists, tests of the hypothesis of “curve squaring” will be confounded because the amount of variability in ages at death due to genetic factors is not identifiable from mortality data. This problem is similar to determining which causes are “endogenous” in cause elimination—again, a determination that cannot be made using mortality data. Even if death is due to a genetically controlled process (e.g., pre-menopausal breast cancer), the exact age at death is altered by environment, treatment, behavior (e.g., age at first pregnancy; MacMahon, Cole, and Brown, 1973), and the organism’s vitality.

Without information identifying genetic determinants and time-varying risk factors, the hypothesis of curve squaring is not testable (Manton and Tolley, 1991).

Aging kinetics

To represent the “visionary” perspective, we present two final estimates in Table 1. Both investigators estimated life expectancy limits by cause elimination and by assuming that body temperature and rate of energy expenditure decreased over time. Cause-elimination estimates are higher than those in line 4. Rosenberg et al. (1973) eliminated “vascular lesions, cancer and heart diseases,” and Strehler (1975) eliminated “circulatory and neoplastic diseases.” In calculating the limit if senescence were changed, Strehler assumed a 25 percent reduction in the Gompertz aging rate. Rosenberg et al. assumed that declines in body temperature altered the coefficients in a Weibull model of mortality. Again, only mortality data were used to estimate limits for either the cause-elimination or aging kinetics models, and thus they suffer from the same lack of identifiability as the other methods.

Survival in study populations with highly favorable mortality conditions

To produce meaningful estimates of life expectancy limits requires more information than is found in mortality data. One way to increase information is to examine life expectancy in populations living in conditions favorable for survival. These are populations that, in addition to having access to good medical care and living in favorable environments, have “healthy lifestyles.” By “healthy lifestyles” we mean (a) avoidance of risk factors (e.g., no smoking; light or no drinking), (b) nutritional control (maintaining moderate body weight relative to height; reducing the proportion of calories from fat; preserving micro-nutrient intake; enhancing intake of anti-oxidants such as betacarotene and Vitamin E), and (c) exercise (to maintain cardiovascular fitness and to keep metabolic parameters, such as glucose metabolism, in order). “New” elderly cohorts will have less exposure to infectious diseases because of improved immunization (e.g., polio, hepatitis B, influenza vaccines), will have better nutrition at earlier ages, and will seek health care as soon as health problems arise. For example, persons with high cholesterol due to genetic causes may identify the problem earlier and seek medical treatment—a course that offers better survival chances than waiting for a disease event. Thus, information on health status before death can be increased by selecting populations with specific health and behavioral characteristics. Our selection of populations was not based on genetic endowment for longevity but on healthy life practices, prospectively determined. Such

populations, though practicing healthier lifestyles than the general US population, still manifest behavioral heterogeneity.

In examining life expectancy limits, we also need to consider the logic of statistical inference. As stated earlier, the theoretical limit must be higher than any life expectancy observed in a free-living population. The upper confidence bound of a life expectancy estimate for a study population indicates the probability of a theoretical limit x years higher—there is a 2.5 percent chance of the limit being two standard deviations higher than the observed life expectancy. Thus, inference about a limit is one-sided since the observed (realized) population value eliminates consideration of all lower values.

A number of studies have produced estimates of life expectancies that exceed the “traditionalist” estimates shown in Table 1. We describe ten studies of seven independent populations.

(1) Enstrom (1989) studied 5,231 male high priests in the Church of Jesus Christ of Latter-Day Saints (“Mormons”)² and 4,613 wives aged 25–99 years. He assessed lifestyle characteristics in 1979 and followed mortality to 1988.

(2) Enstrom (1989) selected a subgroup from the Alameda County, California study population whose health practices are similar to those of Mormon high priests; he followed 1,036 males and 1,254 females from 1974 to 1988.

(3) Kaplan et al. (1987) examined 18-year survival of the total Alameda County study ($N = 6,584$). They used regression to adjust standardized mortality ratios for risk factors.

(4) Enstrom (1989) examined the mortality (1980–87) of all Mormon high priests living in California (~21,000) between 1980 and 1987 and compared it with that of the 1979 cohort (1).

(5) We analyzed data from an insured group (representing 100,000 person-years of experience) of mostly Mormons followed to 1988 or until death or change in insurance coverage ended observation. Persons as old as 105 were observed. This population strictly adhered to Mormon practices, most being church employees, and lived in the United States and Canada.

(6) Snowdon (1988) studied 35,000 Seventh Day Adventists followed from 1960 to 1980, examining the effect on life expectancy of the length of time spent in the church.

(7) Blair et al. (1989) studied the effects of physical activity on 10,224 males and 3,120 females followed for eight years in Dallas (110,482 person-years). They made detailed measurements of fitness and risk factors.

(8) Lew and Garfinkel (1984, 1987) studied 1,000,000 persons in an American Cancer Society (ACS) study and a subgroup who were aged 65 + in July 1962 or who reached 65 by 30 June 1972 ($N = 466,277$). To supplement experience at advanced ages, they followed men born before

1888 and women born before 1886 to 30 June 1979. A special review was made of 106 men and 354 women reporting ages over 100. The oldest man was 109, the oldest woman 114. The population was middle class (36 percent were college educated) and followed good health practices.

(9) Paffenbarger et al. (1986) studied 16,936 Harvard alumni from classes of 1916 to 1950 to examine the effect of physical fitness on a highly educated population. The group was questioned on physical activity, health practices, and other factors in 1962 and 1968; 1,413 deaths were recorded for ages 35 to 80 (213,716 person-years) between 1962 and 1978.

(10) Lindsted, Tonstad, and Kuzma (1991) examined a subset of 9,484 male Seventh Day Adventists responding to a questionnaire in 1960 for whom exact birth dates were known. They studied the effects of physical activity on mortality over 26 years and used regression to control for race, smoking, education, illness, body mass index, marital status, and nutrition.

The quality of age reporting in cross-sectional census data is an issue above ages 65 to 70 (Coale and Kisker, 1990). Most of the studies were epidemiological projects funded by the US National Institutes of Health, whose age-reporting, mortality follow-up, and health assessment methodologies satisfied scientific peer review. Methods are discussed in published documents for most studies. The fifth group is an insured population whose insurance records were analyzed.

Enstrom and Kanim (1983) reviewed the characteristics of these and other long-lived study and survey populations and found them to be nationally representative. Enstrom reported that nonsmoking members of health-conscious religious groups from a number of studies had standardized mortality ratios similar to those of the Mormon high priests (Enstrom, 1989: Table 7). Enstrom (1989) cross-validated the results of studies and used the population of 21,000 Mormon high priests in California to test for bias in the 1979 high priest cohort. We used both high priest studies to evaluate the experience of the Mormon insured population. Replication in independent populations (using differing methodologies) increases confidence in results. Additionally, in long-term studies most exposure at later ages is for people whose age was less than 70 at the start of the study. Thus, age reporting at advanced ages is more reliable in long-term closed-cohort studies (since follow-up time is exactly known) than in census data. Also in these studies, cross-referencing of source documents (e.g., Division of Motor Vehicle records, death and birth certificates, baseline self-reports, church and health records, insurance and employment files) is frequently part of the study design, and is used to maximize completeness of death registration and to validate ages and dates of health events. In the Mormon insurance study, the lower the age reported, the lower the premium charged—in other words, there is a financial incentive to understate age. Once contact is lost, a person is censored (i.e., he no longer contributes experience to survival).

The study populations are sizable and the period of follow-up is lengthy. They represent a large number of person-years of exposure to mortality in a variety of environments. Though following “healthy” practices, the populations are free-living and did not necessarily practice healthy lifestyles their entire lives (for instance, 25 percent of Mormon high priests were former smokers). The Seventh Day Adventists were often adult converts, with the length of time from conversion being positively correlated with mortality reduction. Groups with long follow-up (e.g., the ACS study; the 26-year study of Seventh Day Adventists) had significant exposure before CVD mortality began to decline in the United States in the late 1960s, a situation that may bias estimates downward.

The religious populations smoked and drank little, and practiced “good” nutrition. Nutrition and lifestyle were, however, not physiologically optimal. Only devout Seventh Day Adventists restricted protein and fat intake. Mormons have few restrictions regarding meat or sugar intake. Nonetheless, these and other study populations show large reductions in mortality risks. For example, of 306 Catholic Sisters living in an institution followed from 1936 to 1988, those who were highly educated had a median survival of 89.4 years (Snowdon, Ostwald, and Kane, 1989). A study of physicians ($N = 4342$) who were Seventh Day Adventists (graduates of Loma Linda University) had mortality 44 percent lower than that of the US white male population (Ullmann et al., 1991). Thus, the ten studies described above are not unique in showing much-reduced mortality. There is also little in Mormon, Catholic, and Seventh Day Adventist tenets specifically concerning physical fitness. Physical activity affects a number of physiological parameters (e.g., vital capacity, serum cholesterol, blood pressure, glucose tolerance) and causes of death (including cancer and CVD; Paffenbarger et al., 1986; Fiatarone et al., 1990; Blair et al., 1989). Studies of physical activity suggest that its effect on mortality increases with age and is partly independent of known risk factors (Ekelund et al., 1988). Thus, physical activity may affect risk factors not regularly measured—for instance, leukocyte counts (affecting blood pressure; Friedman, Selby, and Quesenberry, 1990), plasma fibrinogen (affecting clotting and thrombosis; Lee et al., 1990; Vane, Anggard, and Botting, 1990), serotonin (affecting smooth muscle contraction in arteries; Golino et al., 1991; McFadden et al., 1991).

Tolley and Manton (1991) review the use of published data to make actuarial calculations. One problem in comparing mortalities is that populations have different age distributions. Since mortality depends strongly on age, a high rate in one population may simply reflect an older population structure. Consequently, mortality rates are often standardized before being compared, meaning that effects due to differences in age distributions are removed. Comparisons are conducted using standardized mortality ratios (SMRs)—a statistic that can be constructed for the entire age span or a subset of ages. The SMR is the average ratio of the mortality rate in a population

relative to the hypothetical mortality rate that would have occurred had the age-specific mortality rates of a second (the standard) population applied. An SMR of 1.0 indicates equal mortality in two populations.

The SMR for ages y through z is,

$$\text{SMR}_{y,z} = \frac{\sum_{x=y}^z D_x}{\sum_{x=y}^z E_x \cdot q_x} \quad (1)$$

where D_x is the number of deaths between ages x and $x+1$, and E_x is the number of persons exposed at age x . Thus, the SMR is the ratio of observed to expected deaths where expected deaths are generated from the q_x (probability of death between ages x and $x+1$) from a baseline life table. The SMR-adjusted probability of death, q_x^* , is $q_x^* = 1 - (1 - q_x)^{\text{SMR}_{y,z}}$ for $y \leq x \leq z$. Age-specific life expectancies, e_x^* , for the study population are obtained using q_x^* in place of q_x in life table calculations. When the age distribution is truncated, $\text{SMR}_{y,z}$ is assumed constant for all higher ages at the level calculated for the highest age domain (y, z) in the truncated age distribution. The values of q_x were derived from sex-specific US life tables for 1986 (Spencer, 1989).

Population heterogeneity and mortality selection were handled in several ways in the studies. Mortality selection effects were small in the ACS study (Lew and Garfinkel, 1984) because of the reduced heterogeneity of health characteristics. Several of the studies (e.g., Kaplan et al., 1987) statistically controlled for known risk-factor heterogeneity in calculating SMRs. Furthermore, the SMRs represent selection to the highest age observed—in other words, they represent the average risk relative to that experienced by the US population for each age in the study population. The effects of age selection are manifest in the number of deaths by age in the subpopulations used to calculate each age-specific mortality rate for the SMRs.

The SMRs for the study populations, displayed in Table 4, show low mortality over most of the life span. At ages 25–99 for males, SMRs range between .16 and .51 for six studies, that is, at or below the level necessary to achieve a life expectancy of 85 years (Olshansky, Carnes, and Cassel, 1990). The lowest SMRs imply life expectancies of approximately 100 years. In some studies, SMRs for females are as low as for males, or lower (e.g., .22; Blair et al., 1989), even though female mortality in the standard population (US 1986) is lower.

SMRs for Harvard alumni performing 2,000 kcal of physical activity per week are about half the mortality rates of the US white male population in 1980. For those with physical activity up to 3,500 kcal/week, the SMRs (not shown) were lower.

One has to make an assumption about the SMR applicable in the highest, open-ended age category. Fortunately, assumptions about the SMR at ages beyond those observed in the studies only modestly affect life ex-

TABLE 4 Standardized mortality ratios (mortality rates expressed as the fraction of the corresponding age- and sex-specific mortality rates in the US life table for 1986) in selected studies of populations with healthy lifestyles

Study population ^a	Males			Females		
	25-99	25-64	65-99	25-99	25-64	65-99
Mormon insured population (1980-88)	.35	.19	.48	.46	.23	.55
Mormon high priests with healthy practices (1980-88)	.33	.22	.43	.52	.47	.59
Alameda County population with healthy lifestyles (1965-82)	.22	—	—	.48	—	—
Blair et al. (1978-86; age-adjusted)	.29	—	—	.22	—	—
Alameda County 18-year follow-up (1969-87; regression-adjusted for risk factors and age)	.16	—	—	—	—	—
Seventh Day Adventists (1960-80; age-adjusted; 12 or more years in religion)	.51	—	—	—	—	—
Males						
Harvard alumni (1962-78; physically active)	.79	.65	.53	.51		
Males						
American Cancer Society (1960-72)	.50	.38	.46	.57	.72	
Females						
American Cancer Society (1960-72)	.70	.59	.65	.78		

^a For further description of study populations and for sources of data, see text.

pectancy estimates at birth and at ages 30 and 65, because proportionately little person-year exposure occurred above ages 100 or 105. To confirm this, we calculated life expectancy in three ways. We calculated SMRs for ages 25–99 and then (when possible) for ages 25–64 and 65–99 to allow SMRs to change over age. Third, we eliminated all experience over age 100. The three sets of calculations had little effect on life expectancy estimates at birth. Furthermore, since we are estimating a theoretical “upper” bound to life expectancy, underestimating an SMR is a more serious error (since a single empirical counter-observation invalidates a theoretical limit) than a modest overestimate (since the “bound” is necessarily above any observed life expectancy).

Evidence from risk-intervention studies suggests that SMRs can decrease at later ages. In studies of physical activity, SMRs decreased with age (Blair et al., 1989; Ekelund et al., 1988; Paffenbarger et al., 1986) or with time elapsed since healthy practices started. In these cases risk heterogeneity may not be constant, as is assumed in “frailty” models of mortality. Instead, the intervention may change the risk-factor distribution so as to become more favorable with time. We examine the effect of “time-varying” covariates (and time-varying heterogeneity and mortality selection) in our risk-factor model.

Table 5 presents life table estimates (e_x , l_x , and, average lifespans, \bar{x}_x) calculated from the SMRs in Table 4, along with corresponding estimates for selected low-mortality national or regional populations. Comparisons within the table and with Table 1 are instructive. Compared to the US 1986 life table (bottom line of Table 5), the Mormon insured population has the smallest advantage at age 30: 12.9 years for males ($\bar{x}_{30} = 86.7$) and 8.9 years for females ($\bar{x}_{30} = 88.9$).

The most longevous group is the Alameda County population with 18 years of follow-up, among whom (using SMRs adjusted for risk factors) males on average survive to 98.0 years—24.2 years longer than the US male population at large. Analogous calculations for females show that the greatest advantage—18.6 years—is exhibited by the Blair et al. population ($\bar{x}_{30} = 98.6$ years). Thus, there are natural populations whose life expectancy exceeds by a substantial amount all estimates in Table 1 except those by Strehler and by Rosenberg et al. The estimates in Table 5 are not based on a cause-elimination model but on statistical analyses of mortality in populations living in favorable environmental, health care, and lifestyle conditions.

A multivariate model of chronic disease risk factors

Our calculations for populations with good health practices used more information by stratifying on risk factors and health practices for long periods

TABLE 5 Estimates of life expectancy in years (e_x) and proportions surviving (l_x) at various ages for select populations

Study population ^a	Males					Females								
	e_0	e_{30}	l_{30}	e_{65}	l_{65}	e_{85}	l_{85}	e_0	e_{30}	l_{30}	e_{65}	l_{65}	e_{85}	l_{85}
Mormon high priests (1980-88)	(86.5)	57.5 (87.5)	.987	25.5 (90.5)	.903	12.7 (97.7)	.591	(86.5)	57.3 (87.3)	.989	24.9 (89.9)	.915	11.0 (96.0)	.618
Mormon high priests with healthy practices (1980-88)	(88.9)	59.7 (89.7)	.989	27.4 (92.4)	.917	14.1 (99.1)	.640	(89.5)	60.2 (90.2)	.991	27.4 (92.4)	.932	12.8 (97.8)	.684
Alameda County population with healthy lifestyles (1965-82)	(92.4)	63.1 (93.1)	.991	30.4 (95.4)	.934	16.4 (101.4)	.704	(87.5)	58.3 (88.3)	.990	25.7 (90.7)	.921	11.6 (96.6)	.641
Mormon insured population (1980-88)	(85.7)	56.7 (86.7)	.986	24.8 (89.8)	.897	12.2 (97.2)	.572	(88.1)	58.9 (88.9)	.999	26.3 (91.3)	.925	12.0 (97.0)	.656
Japan (1988)	(75.8)	32.9* (77.9)	.960*	16.2 (81.2)	.821	—	—	(81.9)	38.3* (83.3)	.977*	20.2 (85.2)	.910	6.0 (91.0)	.457
Blair et al. (1978-86; age-adjusted)	(88.4)	59.2 (89.2)	.989	27.0 (92.0)	.914	13.8 (98.8)	.630	(98.1)	68.6 (98.6)	.995	35.0 (100.0)	.963	19.0 (104.0)	.816
Alameda County 18-year follow-up (1969-87; regression-adjusted for risk factors and age)	(97.4)	68.0 (98.0)	.994	34.8 (99.8)	.952	20.0 (105.0)	.775	—	—	—	—	—	—	—
Seventh Day Adventists (1960-80; age-adjusted; 12 or more years in religion)	(80.5)	51.9 (81.9)	.980	20.8 (85.8)	.854	9.0 (94.0)	.443	—	—	—	—	—	—	—
Okinawa (1987)	(77.2)	49.1 (79.1)	.971	18.9 (84.9)	.815	8.1 (93.1)	.352	(82.7)	53.5 (83.3)	.988	21.1 (86.1)	.910	7.7 (92.7)	.523
Shimane (1987)	(75.5)	49.9 (79.9)	.979	16.5 (81.5)	.809	4.6 (89.6)	.304	(83.3)	54.3 (84.3)	.986	21.7 (84.3)	.911	6.7 (91.7)	.576
United States (1986)	(71.5)	43.8 (73.8)	.962	14.8 (79.8)	.734	5.8 (90.8)	.203	(78.5)	50.0 (80.0)	.978	19.0 (84.0)	.843	7.2 (92.2)	.396
								Females						
								Males						
American Cancer Society population (1960-72; good health; nonsmokers) (Lew and Garfinkel, 1987)		45 (80.0)		17.8 (82.8)		10.8 (85.8)			49.2 (84.2)		21.3 (86.3)		13.3 (88.3)	
Change (in years) in US life expectancy 1973-83		2.5		1.4		0.8			2.2		1.4		1.3	

NOTE: Values in parentheses represent the average life span (mean age at death): $\bar{x}_0 = x + e_x$.
^a For further description of study populations and for sources of data, see text and Table 1. * Values are for age 45.

before death (up to 26 years). We further increased information by modeling time-varying risk factors. This differs from the approach of Tsevat et al. (1991), who translated longitudinal risk-factor data into a cross-sectional simulation model. They assumed risk factors to be independent and did not model them above age 85. Thus, that effort is not comparable to the model we present below.

We model the relation of mortality and time-varying covariates as two interrelated processes (Woodbury and Manton, 1977). The first describes how a vector of N risk factors changes, f_{ix} , for individual i between age x and $x+1$. The dependence of f_{ix+1} on f_{ix} is described by regression.³ The second, $\mu_x(f_{ix})$, describes mortality for individual i at age x as a Gompertz function of age and a quadratic function of the f_{ix} .⁴ The Gompertz function is consistent with exponentially-increasing human mortality between ages 30 and 90 observed in a wide range of mortality data (Wetterstrand, 1981). The Gompertz parameter θ is the annual percentage increase in mortality per year of age—with values of 7 to 10 percent commonly reported. The scale parameter of the Gompertz is replaced by a quadratic function of f_{ix} to generalize the Gompertz function to $\mu_x(f_{ix})$. If f_{ix} does not change over age, then $\mu_x(f_{ix})$ is a Gompertz function indexed by θ . If f_{ix} is unchanged over age for a population of individuals with different risk levels indexed by i , then $\mu_x(f_{ix})$ defines a family of Gompertz functions, each indexed by i and θ . Most generally, if f_{ix} changes according to the covariate process, the age trajectory of $\mu_x(f_{ix})$ is more general than the Gompertz. If the covariate process changes f_{ix} so the quadratic function increases with age, then the trajectory of $\mu_x(f_{ix})$ (and mortality) increases faster than a Gompertz function indexed by θ . This requires that the effect of time-varying covariates in the risk-factor process be compensated for by reductions in θ . If all influential time-varying covariates are included in f_{ix} , θ would be zero; that is, the age increase in $\mu_x(f_{ix})$ is explained by time-varying covariates.

The two-component process clarifies difficulties in mathematically identifying “senescence” and “rectangularization.” If no covariates, f_{ix} , are measured, then $\mu_x(f_{ix})$ is a Gompertz function with, for adult mortality, a θ of 7 to 10 percent. When f_{ix} is measured, the age variation in the Gompertz may be explained by risk-factor change. If the risk factors predict increases in age at mortality, θ declines, that is, “aging” is described by changes in measured covariates. Thus, by measuring its parameters, any process may be translated from the “residual” senescence term (θ) to the observed process f_{ix} . In the competing-risk model, this is equivalent to discovering that “endogenous” causes are preventable or treatable due to increases in knowledge, and must therefore be reclassified as “exogenous” and be “eliminated.” The “cause” itself is not changed, only the level of knowledge about it and its control. Endogeneity (and senescence) is not a disease characteristic, but rather reflects knowledge of how to control diseases.

Reclassification of processes from endogenous to exogenous is occurring with increasing frequency owing to rapid increases in scientific knowledge. For example, senile dementia is now described by several conditions, such as Alzheimer's disease, micro-infarct dementia, or clinical depression; physical frailty is, in part, described by osteoporosis; atherosclerosis is a reversible disease process in persons with both manifest (Brown et al., 1990; Ornish et al., 1990) and latent (Pekkanen et al., 1990) disease. In the period 1965–85 rheumatic diseases became increasingly better defined, which led to improved management and survival for a number of them—often using existing pharmacological agents (e.g., cancer chemotherapy drugs such as methotrexate) in new areas of application (Fries, 1989). Even if “senescent” factors are genetically determined, knowledge of their consequences may lead to interventions counteracting those effects, for instance, the use of cholesterol-lowering drugs in cases of familial hypercholesterolemia (Kane et al., 1990).

Thus, as scientific knowledge improves, “residual” heterogeneity represented by θ is “assigned” to time-varying covariates. This is the identifiability problem for rectangularization models using only endpoint-of-life data. In other words, a test of the Gompertz function using only mortality data is confounded by the effects of unobserved fixed, or time-varying, covariates. Current biomedical research focusing on specific physiological processes will produce interventions that decrease disability and increase active life expectancy (Fries, 1989; Schneider and Guralnik, 1987). Senescence is a multidimensional process that appears “immutable” for those dimensions which are currently not well described, particularly because it is more difficult to reverse physiological damage, once it occurs, than it is to preserve function starting at younger ages.

The two-component process describes cohort survival (Manton, Singer, and Woodbury, 1991). Changes in survival and in the age trajectory of risk factors are determined by the interaction of mortality and multivariate risk-factor processes over time.⁵ To estimate the improvement in survival attributable to maintaining “good” risk-factor values over age, we modified parameters of the covariate process. We did not change the mortality function $\mu_x(f_{ix})$; rather, we simulated changes in “time-varying” risk factors on mortality assuming no interventions in “senescence” in terms of distance to death (θ). This generates a life expectancy “limit” based on modification of the age trajectory of risk factors (the currently “observed” components of “aging”). In this sense, the estimates are “conservative.” Evidence from at least one study (Hosking et al., 1989) suggests that treatment (surgery) improved survival over five years of follow-up at advanced ages (e.g., 90+).

There is increasing evidence identifying the health consequences of risk factors at advanced ages. Data suggest that risk-factor modification is possible in the elderly (Meyers et al., 1991). Reductions in smoking have a beneficial effect on mortality at advanced ages (e.g., 90–94) for both males and females

(Lew and Garfinkel, 1987: 119 and 121; Hermanson et al., 1988), including increases in life expectancy for persons over age 65 (LaCroix et al., 1991). Improvement in life expectancy due to physical fitness continued over nine years of observation in Ekelund et al. (1988) and was most pronounced at higher ages in Blair et al. (1989) and Paffenbarger et al. (1986). Lindsted, Tonstad, and Kuzma (1991) found an effect of physical activity (measured 26 years earlier) on total mortality to 96 years of age, even though the relation was statistically controlled for medical conditions and risk factors. The upper confidence bound of this estimate, 109 years, suggests a positive effect on survival of physical activity nearly to the limits of the human life span. Heavy alcohol consumption had adverse mortality effects for males and females up to age 85+ (Lew and Garfinkel, 1984). Applegate, Hughes, and VanderZwaag (1991) verified risk-factor effects on angiographically confirmed coronary disease in the elderly.

Models of aging where glucose causes protein cross-linkage and reduces cell-replication potential is one example of how physical activity may affect medical conditions (cancer as well as heart disease) and their age at manifestation (Paffenbarger et al., 1986; Blair et al., 1989). Cerami (1985) hypothesized that glucose metabolism affects fundamental (molecular) physiological dimensions of aging. Hence, physical activity may slow the glucose-related dimensions of aging and the development of multiple "age-dependent" diseases (Rowe, 1988; Helmrigh et al., 1991). The inverse situation (e.g., diabetics die of multiple conditions at earlier ages, reflecting "accelerated" aging) has been demonstrated in a number of studies (Jones, 1956; Balkau et al., 1991). We can also expect interaction between risk factors, such that a reduction of two (or more) risk factors has a synergistic effect. A study of 132 healthy obese (120 percent to 160 percent of ideal weight) elderly persons suggested that obesity and lack of physical activity contributed to loss of physiological function independent of age (Meyers et al., 1991). This may explain why disability predicts mortality well—for example, if physical activity is reduced, say due to osteoarthritis, multiple physiological systems are adversely affected and "aging" accelerates.

We estimated the risk-factor model from data on 5,209 males and females assessed biennially between 1950 and 1984 in the Framingham, Massachusetts Heart Study. The cohort, initially aged 29–62, was, by 1984, aged 63–96. We examined risk-factor levels, their changes, and their interaction with mortality. The 11 risk factors were diastolic and systolic blood pressure, smoking, vital capacity index (VCI), blood glucose, hematocrit value, body mass index (BMI), serum cholesterol, sex, pulse rate, and left ventricular hypertrophy (LVH; cardiac enlargement). These represent circulatory risk factors (e.g., serum cholesterol, blood pressure) and markers of aging (Manton, Stallard, and Dowd, 1991); some represent both. Elevated blood glucose is a chronic metabolic state influencing other pathological

changes (e.g., micro-vascular disease, kidney dysfunction, hypertension; Rowe, 1988). The alteration (cross-linking) of cellular protein by glucose is a determinant of biological senescence at a molecular level (Cerami, 1985). VCI, which indicates age-related loss of collagen integrity (Ashley et al., 1975), is a measure of the accumulated lung damage due to smoking. Pulse rate, BMI, VCI, and LVH are correlated with physical fitness (Blair et al., 1989; Meyers et al., 1991). Serum cholesterol is associated with age changes in metabolism so that (a) serum cholesterol is associated with circulatory disease risk to advanced ages and (b) low serum cholesterol and elevated high density lipoprotein (HDL; a subfraction of cholesterol) levels are markers for longevity (Kasim, 1987; Kreisberg and Kasim, 1987; Nikkila and Heikkinen, 1990; Glueck et al., 1976). For example, in one study, a life expectancy of 79.1 years was observed for males with hypobeta lipoproteinemia and 87.3 years for females (Glueck et al., 1976).

We calculated a limit to life expectancy using risk-factor levels and trajectories modified to reflect "optimal control," in which the variance of all risk factors is reduced to zero (i.e., no risk heterogeneity) and their means are held to "optimum" values (close to population values observed at age 30). Genetic variation is represented by the Gompertz function—that is, heterogeneity in the ages at death produced by senescence ($\theta = 8.05$ percent for males and 8.12 percent for females; Manton and Tolley, 1991).

In Table 6, which compares baseline and intervention projections, life expectancy increased by 25.6 years for males and 17.1 years for females. These life expectancies ($\bar{x}_{30} = 99.9$ years for males and $\bar{x}_{30} = 97.0$ years for females) are 21 to 24 years less than the highest achieved age confirmed for a human (McWhirter, 1984). Survival (i.e., l_x) at advanced ages drops rapidly with age because of the Gompertz function. The results for 34 years of follow-up are similar to those for the 20-year Framingham data (e.g., $\bar{x}_{30} = 99.2$ years for males), suggesting that age/risk-factor relations did not change at advanced ages (i.e., in the last 14 years of follow-up; Manton, Stallard, and Dowd, 1991). The loss of female life expectancy advantage over male life expectancy may be due to the long time past menopause (Manton and Woodbury, 1983): hormonal differentials protective against circulatory disease (e.g., estrogens keep total cholesterol low and HDL cholesterol high) decline at menopause (Hazzard, 1990; Manton and Woodbury, 1983), allowing circulatory damage to accumulate (Matthews et al., 1989). The higher prevalence of chronic conditions (e.g., hypertension, obesity, diabetes) among females in their 60s and 70s may manifest itself in mortality at higher ages as diseases progress and interact (Manton, 1990).

SMRs for males are .38 at age 45 and .23 at age 65, increasing to .25 at age 85 (reflecting nonlinearities in the age trajectory of risk factors). This is a smaller SMR reduction than in some studies of the effect of physical activity on mortality. SMR reduction is smaller for females. At age 65, mor-

TABLE 6 Estimates of baseline mortality and projected estimates of mortality assuming health interventions during the Framingham Heart Study: Life expectancy in years (e_x) and proportions surviving (l_x) at various ages

	Males						Females					
	e_{30}	l_{30}	e_{65}	l_{65}	e_{85}	l_{85}	e_{30}	l_{30}	e_{65}	l_{65}	e_{85}	l_{85}
Baseline mortality	44.3 (74.3)	1.0	15.0 (80.0)	.785	5.0 (90.0)	.220	49.9 (79.9)	1.0	18.8 (83.3)	.870	6.8 (91.8)	.390
Projected mortality with risk-factor intervention	69.9 (99.9)	1.0	36.3 (101.3)	.979	20.0 (105.0)	.840	69.0 (97.0)	1.0	39.0 (104.0)	.960	18.5 (103.5)	.830
	Males						Females					
	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$	$x = 30$
Projected q_x with intervention	.000	.0015	.006	.030	.000	.002	.000	.002	.0075	.038	.008	.08
US 1986 life table q_x	.002	.004	.026	.119	.001	.002	.001	.002	.014	.08	.008	.08
SMR $_x$	—	.38	.23	.25	—	1.0	—	1.0	.54	.47	—	.47
Standardized mortality ratio: SMR $_x$ (projected as ratio of US 1986)												

NOTE: Values in parentheses represent the average life span (mean age at death): $\bar{x}_x = x + e_x$.
 SOURCES: Framingham Heart Study data and Spencer (1989).

tality is 54 percent of the US 1986 female life table value; at age 85, it is 47 percent. Female reductions are also smaller than in some study populations (Blair et al., 1989). In the United States between 1940 and 1987, age-adjusted mortality rates declined by 56 percent for females and 42 percent for males (NCHS, 1990). Such declines from current US mortality levels would produce a life expectancy exceeding 85 years. Though such declines occurred in the past, there is no guarantee they can do so again. Nevertheless, pessimistic statements about reductions of adult mortality were made as it declined between 1940 and 1987 (NCHS, 1964: 42). It is worth noting that populations with healthy lifestyles have life expectancies as high as those calculated for the “optimal” control scenario. This suggests that life expectancy under the “optimal” control scenario may not be the theoretical upper limit, because altering multiple risk factors at younger ages affects correlated, but currently unmeasured, risk factors. If the Gompertz parameter were reduced by 10 percent to reflect this effect, the life expectancy limit for males would increase by 6.2 years—from 99.2 to 105.4 years.

The model can be used to assess the effects of health events more proximate to death, such as change in function. We applied the model to persons aged 65–115, using data from (a) the 1982 and 1984 US National Long Term Care Surveys (NLTCs) and (b) a sample of Medicare-eligible persons from four US counties for 1985 to 1989. In the NLTCs, we analyzed 27 functional measures (Manton, Stallard, and Woodbury, 1991) to identify six dimensions of functional status. Scores on the six dimensions were used in the dynamic model. The NLTCs are nationally representative, reflecting a large amount of exposure (about 80,000 person-years) and about 5,000 deaths in the four-year period 1982–86. These data describe age-related loss of physical and mental abilities necessary to perform life-supporting activities. This loss of function has a “negative” feedback on other physical parameters. The combined samples in the four counties in the second study contained 16,600 persons with age determined from Medicare records. In that study, 31 health and functioning measures were assessed in baseline and recurrent surveys (Manton et al., 1991). Our analysis generated six disability scores, which we used in the dynamic model.

The relative mortality risks of the most to the least impaired groups observed in the two elderly populations reached 20 to 1. The θ parameter in the NLTCs data decreased by 55.2 percent (to 3.64 percent) for females and 50.2 percent (to 4.01 percent) for males from the θ estimated from mortality data alone (8.12 and 8.05 percent). Thus, the disability scores explained much of the effect of age-related unobserved factors on mortality represented by the Gompertz function. In other words, if disability processes could be controlled, the “aging rate” (θ) could be reduced by more than half—compared to the 25 percent reduction assumed by Strehler (1975). Controlling risk factors for diseases that cause disability has a more direct

TABLE 7 Estimates of life expectancy at selected ages, in two longitudinally followed US populations for persons who remain fully functional

Age	National Long Term Care Survey		Medicare: Four counties	
	Males	Females	Males	Females
65	20.0 (85.0)	30.4 (95.4)	23.6 (88.6)	33.4 (98.4)
75	14.6 (89.6)	24.9 (99.9)	19.7 (94.7)	27.9 (102.9)
85	11.7 (96.7)	20.2 (105.2)	16.3 (101.3)	23.0 (108.0)
95	8.7 (103.7)	16.3 (111.3)	13.5 (108.5)	19.0 (114.0)

NOTE: Values in parentheses represent the average life span (mean age at death): $\bar{x}_x = x + e_x$.
 SOURCES: 1982 and 1984 NLTCs and Health Care Financing Administration (1991).

effect on health at advanced ages than controlling CVD risk factors. In the CVD risk-factor analysis θ did not change, indicating that effects were proportional to age. Disability is farther along in the causal chain from risk factors to death. The capacity to control disability was demonstrated in geriatric evaluation units (Rubenstein and Josephson, 1989). New evidence has come to light about controlling risk factors (e.g., increasing calcium intake and exercise to prevent osteoporosis) for diseases that cause functional decline. In Fiatarone et al. (1990) weight training benefited a frail, institutionalized population aged 86–96, with muscle strength increasing an average of 174 percent and some persons no longer needing wheelchairs. Fries (1989) discussed improvements in treatment of rheumatic diseases between 1965 and 1985, with some previously fatal conditions now being nearly curable (e.g., Wegener's granulomatosis). The ten-year survival rate from systemic lupus erythematosus increased from 60 to 95 percent. Thus, it is possible to influence disabling processes, once viewed as senescence, by prevention, treatment, and rehabilitation.

Table 7 presents life expectancy estimates for persons projected to remain functional at ages 65, 75, 85, and 95. These represent simulations in which functional status is not allowed to change and θ , the senescence parameter, is reduced.

In the four-county data, life expectancy for females aged 65 who remain functional is 33.4 years (i.e., $\bar{x}_{65} = 98.4$). Male life expectancy is 23.6 years ($\bar{x}_{65} = 88.6$). In the NLTCs, life expectancy for females remaining active is 30.4 years at age 65 ($\bar{x}_{65} = 95.4$). Male life expectancy is 20.0 years ($\bar{x}_{65} = 85.0$). In both populations life expectancy levels were consistent with the risk-factor model and with selected population estimates. Females have an

advantage of about ten years in life expectancy. Male life expectancy increased less with functional improvement than with control of CVD risk factors. This is reasonable since CVD risk factors were selected to be predictive of male mortality. The data on physical functioning are more informative about female mortality, suggesting that preserving physical activity has greater benefits for females (see Blair et al., 1989). Thus, currently unobserved female mortality risk factors may be more strongly associated with diseases that cause chronic impairment (e.g., osteoporosis, rheumatoid arthritis, Alzheimer's disease).

Conclusions

We assessed theoretical limits to life expectancy estimated from mortality data. We then examined estimates from studies using more information on health and functioning. One set of studies comprised longitudinally followed populations with good health practices. In several of these studies, heterogeneity was statistically controlled when estimating SMRs. A second set of studies examined time-varying covariates in a model of risk-factor and mortality interactions.

Results from all of the studies are summarized in Figures 1 and 2.

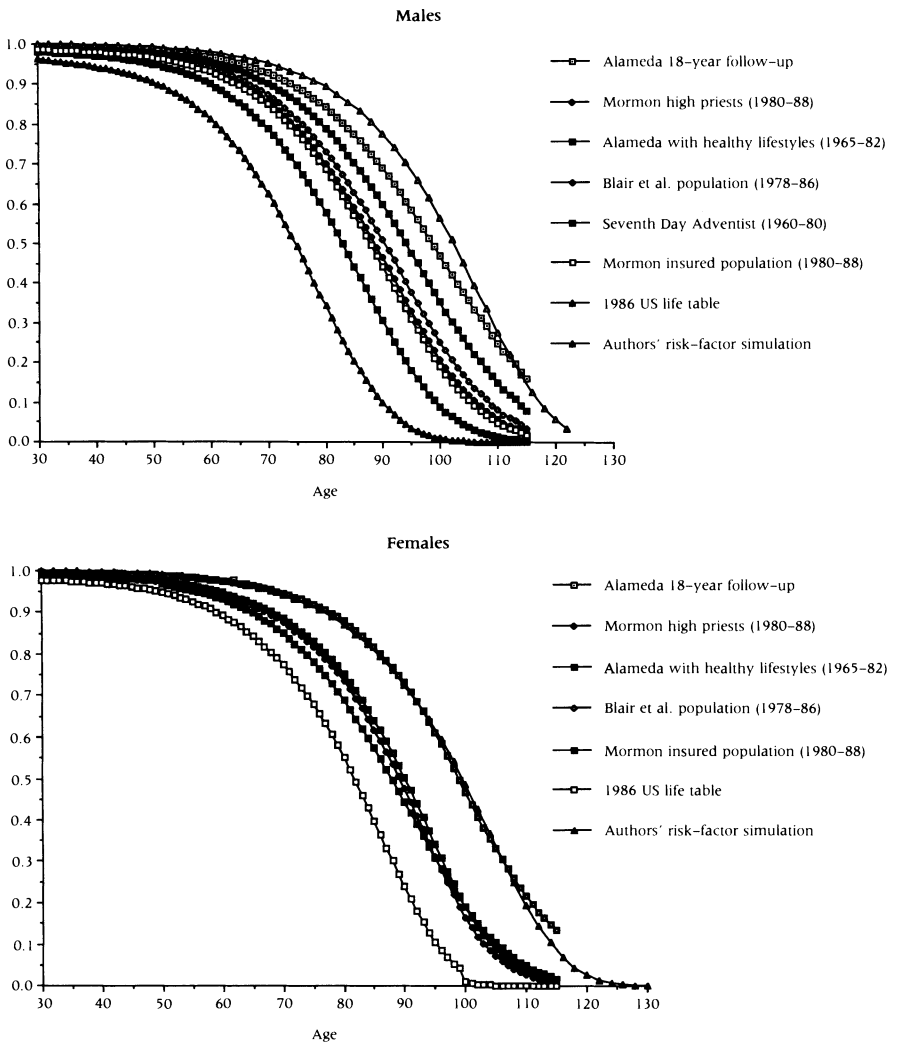
The range of male and female survival curves shown in Figure 1 falls between the model-based theoretical upper limit and the 1986 US life tables. For males the curves spread over the full range. For females the Blair et al. and the Alameda County healthy lifestyles curves are close to the theoretical curves, with the other populations falling within a narrow, intermediate band. None of the curves, even for populations with extreme life expectancy, are "rectangular," that is, all represent significant heterogeneity in age at death due to the Gompertz function. Most of the increase in life expectancy is due to increased survival above age 75, with few persons surviving to extreme ages (i.e., beyond 120 years).

Estimates from the risk-factor model assumed that, of three ways to change mortality—case-fatality reduction, risk-factor intervention, and slowing of the "aging" rate—a life expectancy of 95 to 100 years (with a standard deviation of about 10 years) might be achieved by "optimal" risk-factor interventions. This is consistent with life expectancy limits suggested for populations manifesting "good" health behavior over many years. Our estimates from the multivariate model of functional disability showed similarly high life expectancies. In the simulations of functional status, aging processes were allowed to change.

In Figure 2 we present male and female life expectancy in a bar chart. We see that the most long-lived of the special population groups have life expectancies equal to, or, for females, exceeding those from the risk-factor optimization model.

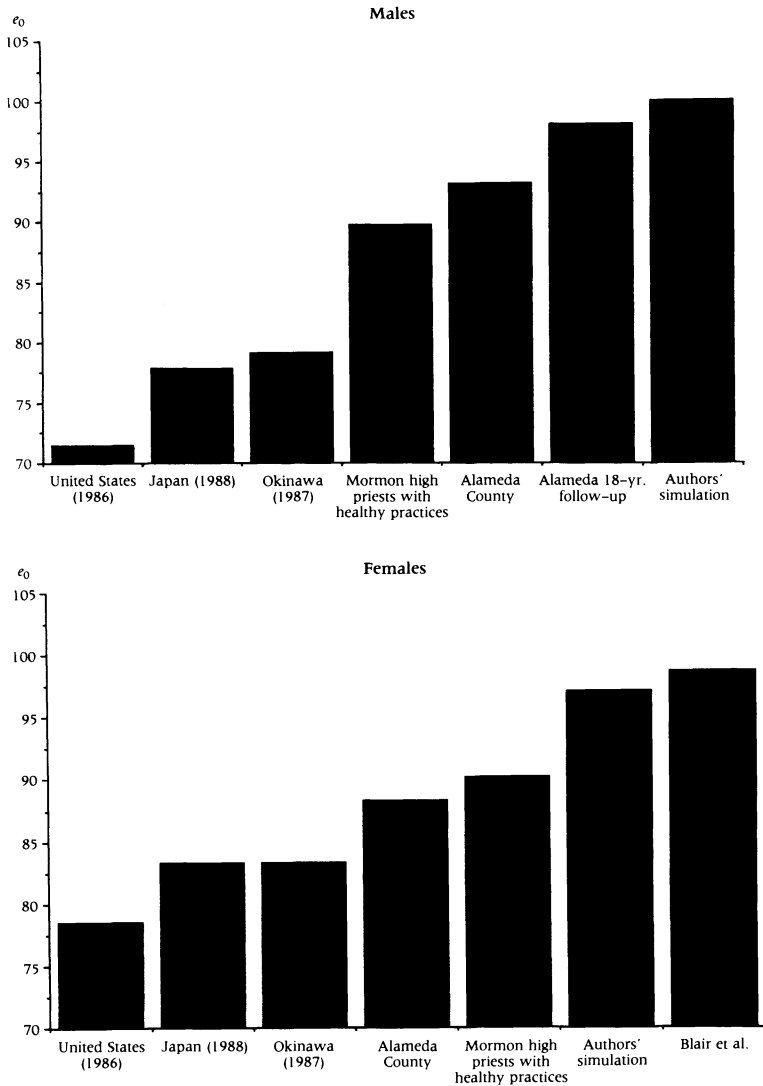
Future research could cause these “limits” to be surpassed by translating more dimensions of senescence into measurable processes in $\mu_x(f_{ix})$. Progress is occurring in identifying risk factors for functional disability. Promising treatments are being examined for osteoporosis. New anti-hypertensive medications also improve lipid profiles and blood glucose levels (Pollare, Lithell, and Berne, 1989). Effects of human growth factor on the age rate of protein

FIGURE 1 Survival curves beyond age 30 according to the US 1986 life table and as calculated for selected US study populations and as estimated from the authors’ risk-factor simulation model, by sex



SOURCES: See text.

FIGURE 2 Life expectancy (e_0 , in years) in two national populations and as calculated for selected US study populations and as estimated from the authors' risk-factor simulation model, by sex



SOURCES: See text.

synthesis have been shown in a clinical trial (Rudman et al., 1990). Exogenous estrogens and tamoxifen (a compound blocking breast tumor estrogen receptors) improve blood lipid profiles and help maintain bone density. Exogenous estrogens may increase female life expectancy by three years. Ta-

moxifen produces many of the effects of estrogen and reduces breast cancer risk. GCSF (Granulocyte Colony Stimulating Factor—approved by the US Food and Drug Administration to counter side effects of chemotherapy but also useful in stimulating the immune system), genetic engineering (e.g., retroviruses to upgrade insulin production), improved immunological control (e.g., use of monoclonal antibodies), the effect of exercise on metabolic parameters, and methods for reversing atherosclerosis (Ornish et al., 1990) are being investigated. Thus, life expectancy in the United States and other industrialized countries may be raised at advanced ages, not only by intervening in chronic disease processes, but also by developing interventions for aspects of senescence for which there are now scientifically meaningful labels (i.e., Alzheimer's disease, osteoporosis, etc.) and descriptions. If this continues, then higher life expectancies may be achieved. Thus, the special difficulty in controlling senescence may not be physiological "immutability" (e.g., lung cancer is a *non*-senescent process for which current treatment is not effective) but rather the need to identify and characterize the many dimensions now labeled as "senescence."

With reference to the United States, a life expectancy of 100 years has implications for the Social Security and Medicare Trust Funds, private pension systems, health insurance, and the health care system. Social Security Trust Fund requirements strongly depend on life expectancy. Per capita acute and long-term care needs rise with age. This anticipation of rising costs as a population ages assumes a pessimistic view of the implications of life expectancy increase. An optimistic view suggests that life expectancy increases will be associated with improvements in the health and functioning of the oldest-old population—in other words, that an equilibrium exists between life expectancy and the health and functioning of elderly populations. There are two pieces of evidence for this: (a) improvements in the risk-factor profile of the population aged 65 to 74 years from 1960 to 1980 ("age" is represented by risk-factor levels in the forecasting model), and (b) decreases in disability prevalence rates above age 65 from 1982 to 1989 (Manton, 1991). To take advantage of this equilibrium requires that social conventions and government policy be modified (Strehler, 1975) so that employment options and eligibility for retirement benefits are based less on fixed criteria of chronological age and more on the functional capacity of the individual.

Notes

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1 This function, due to Benjamin Gompertz (1825), represents the mortality rate at age x as $\mu(x) = Bc^x$. An equivalent form is $\mu(x) = \alpha \exp(\theta x)$, where α and θ are parameters, with $\alpha = B$ and $\theta = \ln c$.

2 The term ‘‘Mormon’’ refers to members of the Church of Jesus Christ of Latter-Day Saints. The office of high priest denotes strong commitment to the health and moral tenets of the Church.

3 The risk-factor model (Woodbury and Manton, 1977) is comprised of two processes. The first is a vector auto-regressive model of risk factors,

$$\underline{f}_{ix} = \underline{u}_x + \underline{R}_x \underline{f}_{i,x-1} + \underline{e}_{ix} \tag{2}$$

where \underline{f}_{ix} is a vector of N risk factors measured at age x for person i ; $\underline{f}_{i,x-1}$ is the vector a year earlier; \underline{u}_x is a vector of constants; \underline{R}_x is an $N \times N$ matrix of regression coefficients relating future and past risk-factor values; and \underline{e}_{ix} is a vector of residuals.

4 The second process describes mortality as a quadratic function of risk-factor values generated from equation (2) multiplied by a Gompertz function of age,

$$\mu(\underline{f}_{ix}; \text{age}_{it}) = [\underline{\mu}_0 + \underline{b}^T \underline{f}_{ix} + \frac{1}{2} \underline{f}_{ix}^T \underline{B} \underline{f}_{ix}] \cdot \exp(\theta \cdot \text{age}_{it}). \tag{3}$$

In (3) \underline{b} (a vector) and \underline{B} (a matrix) are linear and quadratic coefficients for \underline{f}_{ix} [determined by (2)] at the age at time t . The effect of each risk factor is multiplied by $\exp(\theta \cdot \text{age}_{it})$, representing the average age-specific effects of unobserved risk factors (Manton and Tolley, 1991). Thus, risk-factor effects are scaled by a Gompertz to reflect interaction with ‘‘senescence.’’

5 Life table functions are calculated from difference equations using parameter estimates from the mortality, $\mu_x(\underline{f}_{ix})$, and covariate process equations. The survival function, l_x , is

$$l_{x+1} = l_x |I + \underline{V}_x \underline{B}_x|^{-1/2} \exp\left\{ \frac{\underline{\mu}_x(\underline{v}_x) + \underline{\mu}_x(\underline{v}_x^*)}{2} - 2\underline{\mu}_x\left(\frac{\underline{v}_x + \underline{v}_x^*}{2}\right) \right\}. \tag{4}$$

In (4) \underline{v}_x and \underline{V}_x are means and variances of \underline{f}_{ix} . The matrix \underline{B}_x and the vector \underline{b}_x are from (3). Each term in \underline{B} is multiplied by a Gompertz to make it age dependent, e.g., $\underline{B}_x = \underline{B} \exp(\theta x)$. Parameters of the distribution of risk factors (\underline{v}_x and \underline{V}_x) are updated to reflect mortality selection. The mortality-adjusted mean, \underline{v}_x^* , is

$$\underline{v}_x^* = \underline{v}_x - \underline{V}_x^* (\underline{b}_x + \underline{B}_x \underline{v}_x). \tag{5}$$

The mortality-adjusted variance is

$$\underline{V}_x^* = (I + \underline{V}_x \underline{B})^{-1} \underline{V}_x. \tag{6}$$

We update \underline{v}_x^* and \underline{V}_x^* to reflect changes due to dynamics (2) over a one-year period, i.e.,

$$\underline{v}_{x+1} = \underline{u}_x + \underline{R}_x \underline{v}_x^* \tag{7}$$

and

$$\underline{V}_{x+1} = \underline{R}_x \underline{V}_x^* \underline{R}_x^T + \underline{\Sigma}_{x+1} \tag{8}$$

where \underline{R}_x is from (2) and $\underline{\Sigma}_x$ is diffusion, i.e., $E(\underline{e}_{ix} \underline{e}_{ix}^T)$, where $\underline{e}_{ix} = \hat{\underline{f}}_{ix} - \underline{f}_{i(x-1)}$, where $E(\cdot)$ is the expectation operator and superscript T is vector transposition.

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