(pEMC11s) alone, or in combination with 300 ng each of input plasmids. After 24 hours, cells were switched to differentiation medium (DM) for 48 hours and whole-cell extracts were subsequently prepared.

24. For immunofluorescence microscopy, cells were fixed directly in the culture wells for 30 min at room temperature with 4% paraformaldehyde diluted in phosphate-buffered saline (PBS). The cells were washed three times with PBS and then permeabilized for 5 min with 0.1% Triton X-100 and sodium citrate and blocked for 30 min in horse serum diluted 1:100 in PBS. After washes with PBS, cells were incubated for 60 min at room temperature with an antibody to anti-skeletal MHC (1:250, Sigma) diluted in 3% bovine serum albumin and PBS. After washes, cells were incubated for 30 min with a rhodamine-conjugated antibody to mouse immunoglobulin G (1:100 Oregon Red, Molecular Probes) diluted in 10% goat serum and PBS. Cells were kept in PBS to be photographed on a Olympus 1X70 fluorescence microscope.

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Increase of Maximum Life-Span in Sweden, 1861–1999

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A fundamental question in aging research is whether humans and other species possess an immutable life-span limit. We examined the maximum age at death in Sweden, which rose from about 101 years during the 1860s to about 108 years during the 1990s. The pace of increase was 0.44 years per decade before 1969 but accelerated to 1.11 years per decade after that date. More than 70 percent of the rise in the maximum age at death from 1861 to 1999 is attributable to reductions in death rates above age 70. The rest are due to increased numbers of survivors to old age (both larger birth cohorts and increased survivorship from infancy to age 70). The more rapid rise in the maximum age since 1969 is due to the faster pace of old-age mortality decline during recent decades.

The world record of human life-span seems to be moving upward over time, as suggested by the death in 1997 of Jeanne Calment at the documented age of 122.45 years (*1*). However, such events are a poor measure of the trend in achieved human life-span, which can be studied more effectively using data for well-defined populations. National demographic statistics suggest that the maximum age at death has been rising steadily in industrialized countries for more than 100 years (*2*).

Two important questions arise from this observation. First, has this upward trend been steady over time, or has it changed pace in recent years? Perhaps the increase has accelerated due to an intensification of efforts to promote the health of the elderly and to prevent or even cure ailments such as coronary heart disease, stroke, and cancer. Or perhaps the trend has decelerated because maximum ages now observed for humans are approaching a (hypothetical) biological limit. Second, what accounts for the increase in the maximum age at death? There are two competing explanations. One is that it is due merely to the larger size of contemporary populations, which increases the probability that at least one individual will survive to an extreme old age. Another possibility is that the increase reflects improvements in an individual's probability of survival, especially at older ages.

We have investigated these questions using Swedish national demographic data from 1861 to 1999, which are the longest available series of reliable information on the upper limits of achieved human life-span. Recorded maximum ages at death for men and women in Sweden centered around 101 years during the 1860s and around 108 years during the 1990s (Fig. 1). A statistical analysis indicates that the increase in the maximum age at death accelerated markedly around 1969, rising at a rate of 0.44 years per decade from 1861 to 1969 and 1.11 years per decade from 1969 to 1999. In both time periods, the maximum age at death was on average about 1.7 years lower for men than for women, although time trends for both sexes are similar (*3*).

Apparent trends in the maximum age at death can be distorted by changes in data quality. Inaccurately reported ages of very old persons and decedents have been common in official statistics for many countries (*2*, *4*). An improvement in data quality (i.e., fewer exaggerated reports of extreme old age) may lead to a decrease over time in the maximum reported age at death. Thus, a typical pattern is that the maximum age may decline for several years as data quality improves and then begin to increase. Only the latter increase, not the earlier decrease, reflects a true trend. Mortality data since 1861 in Sweden show none of the typical signs of age misreporting that are common elsewhere (*2*). Mortality histories for the countries of Western Europe and North America are largely similar to the Swedish experience, but no other country's data offer the possibility for reliable trend analysis in extreme old age over such a long period. For this reason, only Swedish data are used here, although the results should apply broadly to the populations of other highly industrialized countries.

We analyzed the effect of changes in demographic factors (birth counts and age-specific mortality rates) on the trend of the maximum age at death with the use of a model that treats the observed maximum age as a random variable with a theoretical probability distribution. This distribution is determined both by the underlying distribution of ages at death for individuals and by the initial size of a birth cohort (*5*). For this analysis, data on the maximum age at death were reorganized by year of birth (cohort) rather than by year of death (period) (Fig. 2). These two trends are similar and contain many of the same data points. However, some points appear in one series but not the other, because a death that qualifies as the oldest for a birth cohort may or may not be the oldest in the year of death, and vice versa.

Our analysis of the cohort trend in the maximum age at death relies on a reconstruction of Swedish mortality by year of birth back to 1751. The life tables and the methodology used to produce them are available on our Web site (*6*). Although there may be some question about the quality of period life tables from late 18th-century Sweden (especially at older ages), life tables for cohorts born in this era are more reliable because the quality of the statistical system improved over their lifetime. By the time such cohorts attained age 100 or 110, where problems of data quality are most severe, the Swedish statistical system was extremely accurate (*7*).

In order to determine probability distributions of the maximum age at death, a sequence of age-specific death rates for each cohort is needed. Death rates below age 80 were computed directly from national mortality statistics, reorganized in a cohort format (*8*). Death rates above age 80 were estimated by fitting a logistic function to observed death rates and then extrapolating this function to very high ages (*9*). It was neces-

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sary to assume that the age trajectory of the death rate at very old ages for each cohort follows a mathematical model for two reasons (i) because observed death rates at very old ages are highly erratic due to the small number of deaths and (ii) because death rates at ages above the observed oldest age at death cannot be calculated directly (*10*). Various mathematical models of mortality patterns have been used in previous studies; among them, logistic functions have been shown to fit observed age trajectories of mortality at the oldest ages extremely well (*11*).

Using birth counts, observed death rates below age 80, and estimated death rates above age 80, we calculated the probability distribution of the maximum age at death for each cohort (*12*). The *p*th percentiles of these distributions were then computed, with *p* equal to 10, 25, 50, 75, and 90 (*13*). We compared these percentiles to the actual maximum age at death for Swedish cohorts born from 1756 to 1884. Our statistical model yields predictions of the maximum age at death that track both the gradual increase over time and the shift of trend for cohorts born during the 1860s (corresponding to the shift in the period trend around 1969) (Fig. 3).

For this analysis, the trend in the 50th percentile, or median, of these distributions was taken to represent the underlying trend of the maximum age at death. Each median is a function of 121 factors: a birth count and age-specific cohort death rates from age 0 to 119. For each pair of adjacent cohorts, the change in the median from the older to the younger cohort was split into effects attributable to changes in these 121 factors (*14*). Then, the total effect of each factor (on the change in the median of the estimated distribution of the maximum age at death) was found by summing across all cohort pairs; effects due to changing death rates were aggregated by age group (Fig. 4).

These calculations demonstrate conclusively that the rise of the maximum age at death in Sweden from the 1860s to the 1990s (represented here by cohorts born from 1756 to 1884) was due primarily to reductions in death rates at older ages. Of the total increase, 72.5% is attributable to a decline in mortality above age 70, only about 12% to the increasing size of successive birth cohorts, and about 16% to mortality reductions below age 70. These results were almost identical when the analysis was done separately for men and women, so we only report findings for the total population.

The accelerated rise of the maximum age at death after 1969 is also tied to trends in death rates at older ages. It is known that the historic decline of old-age mortality (in Sweden and other highly industrialized countries) accelerated during the 1970s and 1980s (*15*). All other factors held constant, this change of trend should have pushed up the maximum age at death faster than before. This expectation is confirmed by our finding that, for cohorts reaching extinction after 1969, about 95% of the rise in the maximum age at death is attributable to the decline in death rates above age 70, compared to just over 60% for earlier cohorts (*16*).

It was known already that a reduction in old-age mortality has been the primary factor behind population aging and the "proliferation" of centenarians during recent decades in wealthy countries (*17*, *18*). Here, we have shown that mortality decline above age 70 has also been the main cause of a gradual increase in maximum achieved human life-span over more than a century. Only a minor part of this increase is due to the larger size of more recent cohorts (whether size is defined in terms of the number of children born each year or the number of persons who survive to old age) (*19*).

Our analysis refutes the common assertion that the human life-span is fixed and unchanging over time (*20*, *21*). Although the maximum has increased much more slowly than the average, the entire distribution of ages at death has been shifting upward for more than a century in

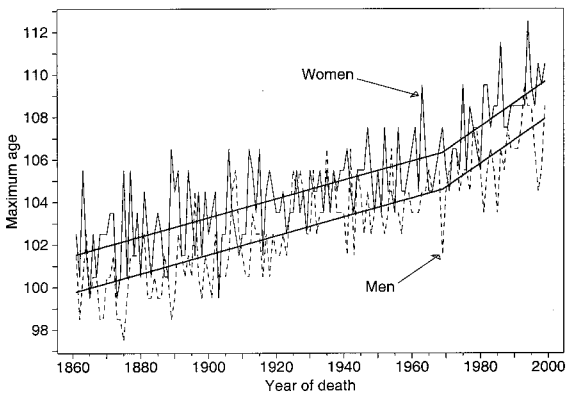

Fig. 1 (left). Annual maximum ages at death by sex, Sweden, 1861 to 1999, with trend lines. Trend lines follow a least-squares regression equation (*3*).

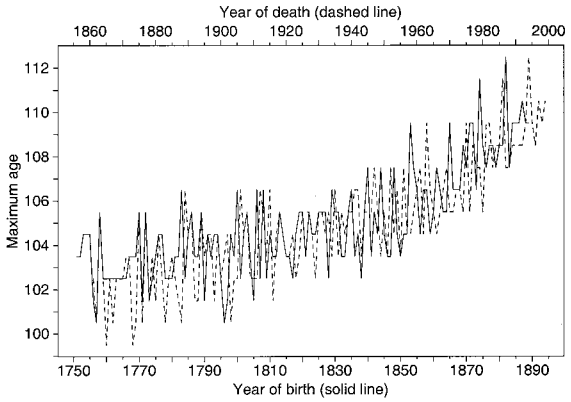

Fig. 2 (right). Annual maximum ages at death (sexes combined) in Sweden by year of death (1861 to 1999) and year of birth (1751 to 1889). The lag between the two series is 105 years (*32*).

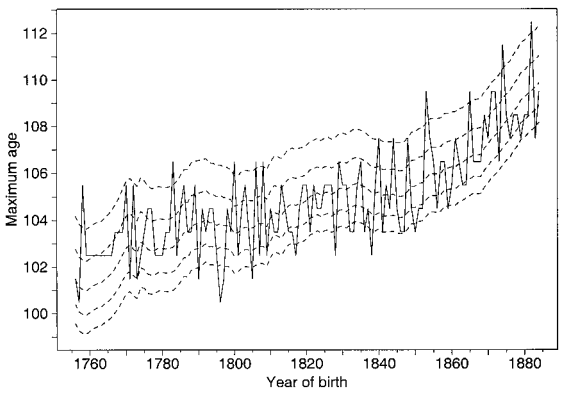

Fig. 3 (left). Annual maximum ages at death (sexes combined) of Swedish cohorts born 1756 to 1884 with percentiles of estimated probability distribution. Dotted lines correspond to the 10th, 25th, 50th, 75th, and 90th percentiles of the estimated distribution of the maximum age at death for each birth cohort (*13*).

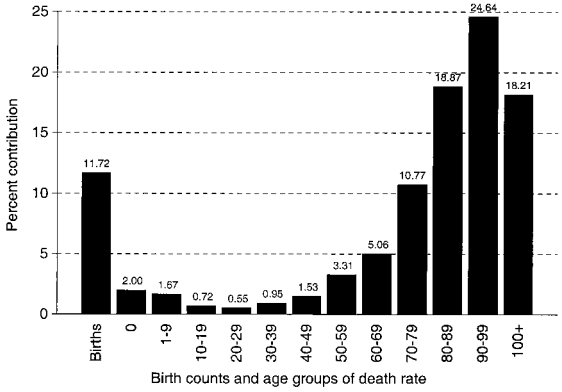

Fig. 4 (right). Percent contribution of changes in birth counts and age-specific death rates to the rise in the maximum age at death of Swedish cohorts born 1756 to 1884.

Sweden and, presumably, in other countries as well. Reductions in death rates at older ages, which have accelerated in recent decades, seem likely to continue (*22*, *23*) and may gradually extend the limits of achieved human longevity even further.

References and Notes

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3. The least-squares regression equation for the trend lines in Fig. 1 is as follows: age = 101.5369 + 0.0444 (year – 1861) + 0.0667 (year – 1969) $I_{year>1969}$ – 1.741 I_{male}, where age is the maximum age at death recorded for a calendar year (in A.D.), $I_{year>1969}$ is an indicator variable that equals one after 1969 and zero otherwise, and I_{male} equals one for males and zero for females. Thus, the slope of the trend lines is 0.0444 per annum before 1969 and 0.0444 + 0.0667 = 0.1111 afterwards. The year 1969 was chosen as the turning point for the slope because this choice maximizes goodness-of-fit (in R^2). This model provides a significantly better description of the data than a comparable one-slope model [$F(1,274) = 17.94$; $P < 0.0001$], whereas a four-slope model (different trends for men and women both before and after 1969) is only marginally better than the model shown here [$F(2,272) = 2.52$; $P = 0.0825$].
4. M. Hill, S. H. Preston, I. Rosenwaike, *Demography* **37**, 175 (2000).
5. The maximum age at death can be thought of as an extreme value of a statistical distribution (*24*, *25*). Suppose that $S(x)$ is the probability of survival from birth to age x for an individual chosen at random from a cohort of N births. The probability that the maximum age at death for this cohort lies above age x is given by $S^N(x) = 1 - [1 - S(x)]^N$. Accordingly, the maximum age at death is itself a random variable with a probability distribution, and this distribution is determined by N and the $S(x)$ function, or alternatively, by N and the probability distribution of ages at death, given by the function $f(x) = \frac{-dS(x)}{dx}$.
6. The Berkeley Mortality Database is available at http://demog.berkeley.edu/wilmoth/mortality.
7. The reporting of age at death in Swedish statistics is very accurate from 1861 onward, even at extremely high ages. Two factors account for an improvement in data quality around this time (*2*). First, the National Central Bureau of Statistics (also known today as Statistics Sweden) was founded in 1858. Second, the earlier national statistical system, though less rigorous, had been in place for over 100 years and provided a basis for verifying questionable claims of extreme old age. Since age misstatement was very rare after 1860, even at older ages, there was little opportunity for exaggerated reports of age at death among cohorts born in the 1750s and later.
8. The mortality experience of the cohort born in year t is described by a vector of age-specific death rates, $\mathbf{M_t} = (M_{0t}, M_{1t}, \ldots, M_{79t}, \hat{M}_{80t}, \ldots, \hat{M}_{119t})$, where M_{xt} is the observed age-specific death rate for cohort t between exact ages x and $x + 1$ (for $x = 0, 1, \ldots, 79$), and $\hat{M}_{xt}$ is a comparable value at higher ages (i.e., $x = 80, 81, \ldots, 119$) derived from a logistic model (*9*). Normally, the age-specific death rate for cohort t is $M_{xt} = D_{xt}/E_{xt}$, where D_{xt} and E_{xt} are corresponding death and exposure counts. However, for all calculations shown here, these values were smoothed over time by combining deaths and exposures for 11 cohorts centered on t. Thus, we define
$$M_{xt} = \sum_{u=t-5}^{t+5} D_{xu} \Big/ \sum_{u=t-5}^{t+5} E_{xu}$$
Likewise, pooled deaths and exposures over an 11-year window were used when estimating parameters of the logistic model for each cohort.
9. The logistic model can be written $\mu_t(x) = \frac{r \cdot C_t e^{\Theta_t x}}{1 + C_t e^{\Theta_t x}}$ where $\mu_t(x)$ is the force of mortality at exact age x for cohort t. Death rates for discrete age groups were approximated by taking the value of $\mu_t(x)$ at the midpoint of the interval [i.e., $\hat{M}_{xt} = \mu_t(x + 0.5)$ for $x = 80, 81, \ldots, 119$]. This model implies that death rates approach a fixed upper limit, denoted by r, as suggested both empirically and theoretically (*26*, *27*). The logistic model was fit to data for each cohort using observed death and exposure counts at ages 80 and above. Estimates of C_t and θ_t were obtained via the method of maximum likelihood. Following standard practice, we assumed that the number of cohort deaths between ages x and $x + 1$ (D_{xt}) follows a Poisson distribution with an intensity parameter $\lambda_{xt} = E_{xt} \cdot M_{xt}$ (*28*). The upper asymptote, r, was fixed at 1.25 because this value maximizes a global measure of goodness-of-fit (*29*). Although this assumption has no strong justification, it is convenient because cohort-specific estimates of r are highly unstable due to random fluctuations in death rates at older ages. Moreover, sensitivity analysis confirms that the results of interest here do not vary significantly with alternative choices of r.
10. It may seem strange to estimate death rates above the maximum age achieved by members of a cohort. However, according to our statistical model, observed ages at death are merely one realization of a random process that could have yielded other outcomes. At older ages where sample sizes are small, observed death rates (whether positive or zero) do not provide reliable estimates of the underlying probability distribution.
11. A. R. Thatcher, V. Kannisto, J. W. Vaupel, *The Force of Mortality at Ages 80 to 120* (Odense Univ. Press, Odense, Denmark, 1998).
12. Death rates for ages 80 and above were estimated according to the logistic formula (*9*) and combined with observed death rates from younger ages to obtain estimates of survival probabilities, $S_t(x)$, across the age range. Discrete survival probabilities (from birth) are as follows
$$S_t(x) = \begin{cases} 1 & x = 0 \\ e^{-\sum_{a=0}^{x-1} M_{at}} & x = 1, 2, \ldots, 80 \\ S_t(80) \cdot e^{-\sum_{a=80}^{x-1} \hat{M}_{at}} & x = 81, 82, \ldots, 120 \end{cases}$$
Using these survival probabilities and the original cohort size, N_t, the survival probability of the longest-lived individual in each cohort was obtained using the formula, $S_t^N(x) = 1 - [1 - S_t(x)]^{N_t}$. A small correction was employed to account for migration into or out of the cohort: N_t in the above formula was replaced by $N_t^* = \frac{N_t(80)}{S_t(80)}$ where $N_t(80)$ is the observed number of survivors in cohort t at age 80. Thus, N_t^* is the number of births that would have produced the observed number of survivors at age 80 in the absence of migration. International migration after age 80 is assumed to be negligible.
13. The pth percentile of the distribution of the maximum age at death is x such that $S_t^N(x) = 1 - \frac{p}{100}$.
14. The trend in the median (of the estimated distribution of the maximum age at death) was decomposed using an adaptation of a method originally applied to percentiles of the distribution of ages at deaths (*30*, *31*).
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16. The maximum age at death occurring in 1969 corresponds to an individual born around 1864, assuming a lag of 105 years as in Fig. 2 (*32*). Therefore, the same decomposition was performed separately for two groups of cohorts, 1756 to 1864 and 1864 to 1884.
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19. Similarly, variation in world record life-spans across species of mammals and birds depends much more on the rate of mortality increase with age (and thus the level of old-age mortality) than on the size of the populations that have been studied (*33*).
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29. Let $Y = 100[1 - S^N(X)]$, where X is a random variable representing the maximum age at death for any birth cohort and $S^N(x)$ is the survival function of the maximum age at death for the same cohort. Thus, Y expresses the cohort maximum age at death as a percentile of its underlying probability distribution. If the model is well specified, observed percentiles should be uniformly distributed between zero and 100. We fit the model using a range of plausible values for r (0.80, 0.85, ..., 1.40) and selected $r = 1.25$ because it yielded percentiles demonstrating the least evidence of non-uniformity according to three separate tests (chi-square, Kolmogorov-Smirnov, and Neyman). In any event, the decomposition is not highly sensitive to the choice of r. For example, with $r = 1$ instead of $r = 1.25$, the individual contributions shown in Fig. 4 change by no more than one percentage point.
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32. The lag of 105 years in Fig. 2 was chosen because the mean of the maximum age at death for cohorts born from 1756 to 1884 was 104.54.
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34. We thank K. Wachter for comments on an earlier version, C. Hart for programming assistance, and P. Vachon for data preparation. Supported by the National Institute on Aging (R01-AG11552, K02-AG00778, and R01-AG14698).

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