Inflammatory Exposure and Historical Changes in Human Life-Spans
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Science **305**, 1736 (2004);
DOI: 10.1126/science.1092556

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

ity between pre- and postnatal environments is increasing. In some developing societies, the postnatal food-energy environment has dramatically changed even within a generation, but fetal growth is still markedly constrained; this may explain the rapid increase in the incidence of T2D seen in such populations (*25*).

The experimental and prospective clinical studies add weight to the epidemiological data and suggest that early development does have significant echoes in disease risk throughout life. There is a growing awareness of the potential for epigenetic change to play a role in disease generation. A key issue is the relative importance of early-life events in informing interventional strategies during human development versus those instituted in adult life. If appetite, food choice, and exercise propensity are partially induced during early development as in experimental animals (*30*, *65*), then postnatal life-style interventions may be less effective than hoped. It seems that increasing awareness of the need to promote the health and nutrition of females of reproductive age is one important element for the prevention of chronic disease in future generations across the globe.

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66. M.A.H. is supported by the British Heart Foundation. We thank C. Pinal for her assistance on the manuscript.

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Most explanations of the increase in life expectancy at older ages over history emphasize the importance of medical and public health factors of a particular historical period. We propose that the reduction in lifetime exposure to infectious diseases and other sources of inflammation—a cohort mechanism—has also made an important contribution to the historical decline in old-age mortality. Analysis of birth cohorts across the life-span since 1751 in Sweden reveals strong associations between early-age mortality and subsequent mortality in the same cohorts. We propose that a "cohort morbidity phenotype" represents inflammatory processes that persist from early age into adult life.

A long-term decline in mortality, beginning before 1800 in some countries in Northern Europe, has resulted in a 50% increase in adult life expectancy (*1*, *2*). Childhood mortality has decreased by 90%, and this has been attributed mainly to a decreased incidence of infectious disease (*2*–*4*). After 1850, older-age mortality declined, with greater improvement in recent decades (*1*, *5*). Most explanations of the long-term decline in mortality have focused on improvements in sanitation, nutrition, income, and medicine. We develop the specific hypothesis that decreased inflammation during early life has led directly to a decrease in morbidity and mortality resulting from chronic conditions in old age.

Our argument is supported by recent research linking an individual's exposure to past infection to levels of chronic inflammation and to increased risk of heart attack, stroke, and cancer. For example, the risk of heart attack and stroke is correlated with serum levels of inflammatory (acute phase) proteins such as C-reactive protein (CRP) (*6*–*8*). Within individuals, CRP levels are

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also correlated to the number of seropositivities to common pathogens, indicating a history of infections (*7*, *8*). Furthermore, drugs with anti-inflammatory activities [nonsteroidal anti-inflammatory drugs (NSAIDs), statins] reduce the risk of vascular events and possibly Alzheimer's disease (*9*, *10*), implying links between the levels of inflammation and major chronic conditions important in old age.

Links Between Health in Early Life and in Later Life

Much evidence links early-life infections with later morbidity, including cardiovascular and respiratory disease, cancer, and diabetes. Some infections directly cause organ damage; the classic example is rheumatic heart disease, which increases adult morbidity from heart valve damage incurred from childhood streptococcal infections (*11*). The presence of early-life infections has also been associated with late-life chronic disease and mortality, as shown in many examples from early to recent times. In rural 18th-century Sweden, greater exposure to infections during infancy was associated with higher old-age mortality (*12*). Among U.S. Civil War veterans, infectious disease in early adulthood was associated with heart and respiratory problems after age 50 (*13*). Moreover, respiratory infections in early life were associated with later lung impairments (*12*, *14*). Adult cardiovascular disease has also been associated with cohort levels of infant diarrhea and enteritis (*15*). Among Americans currently in their 50s, those who experienced major childhood illness are 15% more likely to report having cardiovascular conditions and twice as likely to have cancer or chronic lung conditions (*16*). Finally, declining infection during the 20th century has been estimated to explain 11 to 24% of the reduction in late-life morbidity and mortality (*13*).

These associations between early and later morbidity and mortality imply cohort-specific effects on adult mortality trends, especially in old age when vascular conditions and cancer dominate mortality. Cohort effects could arise from the common epidemiological environments that members of a particular birth cohort experience in their younger lives. Thus, changes in the epidemiological environment that occur within a given historical period would affect surviving members of cohorts for the rest of their lives. Enduring effects of early environment, even if conditions improved at later periods, could be designated as a "cohort morbidity phenotype."

As early as 1934, Kermack *et al*. (*17*) noticed that as mortality at younger ages improved in successive cohorts in England and Sweden, the adult survivors in those cohorts also had lower mortality. From this they hypothesized that maternal health and child environment were major determinants of health at later ages, or that the mortality characteristics of a cohort persisted throughout its life-span. In 1956, Jones (*11*) developed further links between cohort mortality at younger and older ages in Swedish 18th- and 19th-century populations by examining mortality rates over the life-span. Although infant mortality was not then available for cohorts born before 1895, Jones concluded that birth cohorts had parallel mortality curves across the adult ages and that mortality curves across the life-span were displaced to lower values in more recent cohorts. He hypothesized that "the physiological age of each new generation is remaining more youthful at the same chronological age" (*11*). This is an important observation, because most biologists and demographers examining mortality change over time at older ages have concentrated on adult mortality.

With the longer data series now available for Sweden, we have updated Jones' observations, graphing age-specific mortality rates for five birth cohorts from 1751 to 1940 (Fig. 1A). The age-specific mortality across the life-span shows progressive downshifts in age-specific mortality for later-born cohorts. Mortality at any given age across the life-span is lower in successive cohorts. Thus, cohorts with lower young-age mortality also have lower mortality at any given age in later life, consistent with Jones' hypothesis.

The cohort analysis also reveals that the major declines in mortality have had little effect on the basic rate of mortality acceleration during aging, as shown for cohorts by parallel linear slopes of mortality on semi-logarithmic plots (Fig. 1A). Data from most human populations show regular relationships of mortality at one adult age to mortality at the preceding age and subsequent ages, in which mortality accelerates more or less smoothly during adult life up to the oldest ages, with a characteristic "Gompertz slope" (*18*). The present cohort data show that major improvements in human environments, which lowered overall mortality by as much as 90%, have not altered the characteristic mortality acceleration during aging. Even transient adversity may shift the line upward, without change in slope (*18*). These progressive reductions in mortality are more resolved when plotted as cohorts rather than as conventional plots of period age-specific mortality over time (Fig. 1B). The similarity of mortality slopes at the older ages observed in the cohort plots is not found in period age-specific mortality curves, which tend to converge at older ages.

Using the Swedish data for individual ages during childhood and old age for persons born in each year from 1751 to 1927, we can further develop two points presaged by Kermack *et al*. (*17*) and Jones (*11*): (i) that the historical mortality decline among the old and young begins in the same cohort, and (ii) that infant mortality has a stronger relationship to later-life mortality than does mortality in subsequent childhood years. Examination of annual trends in childhood and old-age mortality for cohorts born from 1751 to 1927 indicates that declines in mortality after age 70 tend to lag about 70 years behind those for infants (*19*). When we relate childhood mortality to later-age mortality for Swedish birth cohorts born in the 177-year period from 1751 to 1927, we find strong relationships between rates of childhood mortality and mortality for cohort survivors in old age. Most variance in the 177-year series of old-age mortality for cohorts was explained by mortality before age 10. Moreover, the annualized effect of each childhood year on old-age mortality is three times as great for infant mortality than for mortality in subsequent childhood years. This confirms the greater effect of infant versus childhood mortality on old-age mortality observed in a small, rural Swedish region (*12*).

Adult Disease, Infection, and Inflammation

We hypothesize that chronic inflammatory mechanisms drive much of the influence of early-life infections on later morbidity and mortality. As noted above, in contemporary populations, serological indicators of infection and inflammatory indicators are related to vascular disease and many other morbidities of aging. Markers of inflammation include elevations of blood CRP as well as interleukin-6, tumor necrosis factor–α, and fibrinogen (components of the acute phase inflammatory response). Such inflammatory responses can be induced by invading pathogens, as well as by trauma or internal tissue injury. Infections may be local agents in vascular disease, whereas asymptomatic arterial lesions (which are ubiquitous at early ages) appear to progress through inflammatory processes (*20*). Atheromas contain macrophages and other cells that secrete inflammatory proteins, which, if chronically elevated, may be in themselves pathogenic rather than simply indicators of risk. CRP, for example, can activate the complement system and increase low-density lipoprotein uptake by macrophages (*6*). Thus, adaptive responses to short-term infections or injury can become maladaptive in the long term—a double-edged sword that evolutionary biologists refer to as antagonistic pleiotropy.

In the past, substantial proportions of populations in countries that now have low mortality suffered conditions that chronically elevate inflammatory markers. Among populations that still have relatively high mortality, these conditions remain highly prevalent. For

instance, many people living in relatively high-mortality conditions contract chronic tuberculosis, diarrheas, and parasite-borne diseases such as malaria that persistently elevate blood CRP, as observed in tuberculosis (*21*) and infections of *Escherichia coli* and *Helicobacter pylori* (*22*). These associations of CRP with infections suggest that the historical decline in infections would have lowered exposure to CRP and other inflammatory proteins. *H. pylori* is an instructive example. This common bacterium is the major cause of peptic ulcers but is also associated with coronary disease (*23*). *H. pylori* infections are usually acquired in childhood and persist throughout life. In the past, many if not most individuals in what are now low-mortality countries carried *H. pylori*, but because of improved public health and hygiene, infections have declined. For example, *H. pylori* infections decreased by a factor of 6 in birth cohorts of the Bristol *Helicobacter* Project (*24*). Periodontal disease, another source of chronic inflammation, was highly prevalent but has now declined with the introduction of dental hygiene in countries with currently low mortality. Periodontal disease has been associated with chronically high levels of CRP and possibly heart disease (*24*). These and other examples suggest that public health and medical interventions have led to a lower level of diverse infections, which in turn has resulted in reduced inflammation throughout life in modern populations. Thus, the factors that reduce mortality within specific historical periods have also resulted in reductions in lifetime levels of inflammation and old-age mortality within cohorts.

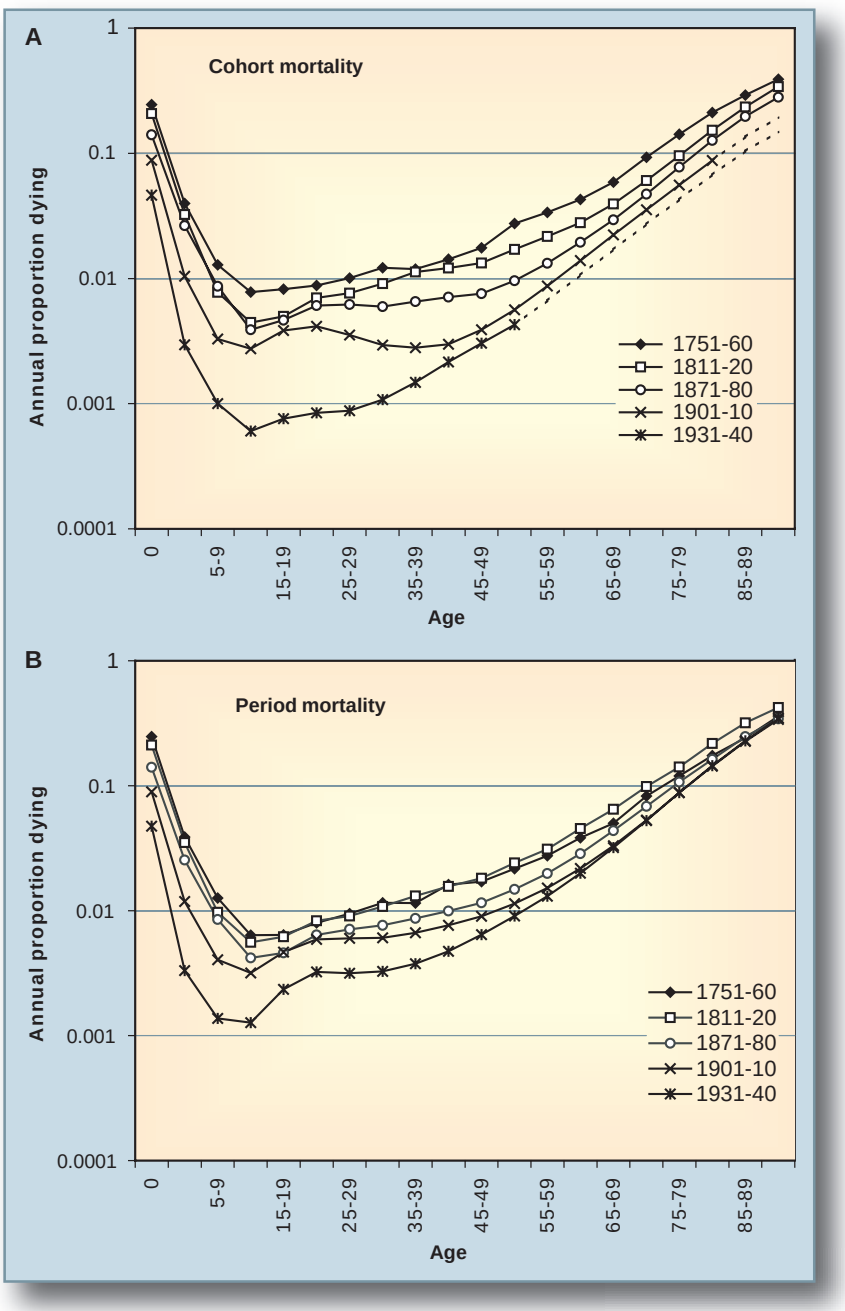

Fig. 1. Age-specific mortality over the life-span, Sweden, 1751 to 1940 (semi-logarithmic plots). Data source: Berkeley Mortality Database. (**A**) Cohort mortality for persons born in the specified years. (**B**) Period mortality occurring in the specified years. Mortality is estimated for the later years of the last birth cohort, assuming that mortality at adjacent age groups has the same relationship as that in the prior cohort, and is represented by a dotted line.

The Role of Nutrition?

Malnutrition at early ages, including in utero, is also hypothesized to influence later-life morbidity and mortality (*2*, *25*). The "fetal origins" hypothesis of Barker *et al*. (*26*) associates low birth weight with maternal malnutrition, leading to higher morbidity at later ages from cardiovascular disease, hypertension, and type 2 diabetes. Attenuated fetal growth is thought to impair organ and vascular development and to alter metabolic set points. Not all evidence supports an exclusive role of malnutrition in the fetal-origins hypothesis. For example, maternal infections from diseases such as tuberculosis, which was common until well into the 20th century, also impair fetal growth (*2*, *4*, *12*). Moreover, the famine in rural Finland from 1866 to 1868 tripled death rates at 0 to 9 years but did not alter the survivors' life-spans (*27*).

We would argue that the inflammatory-infection and nutrition hypotheses are not competing but complementary in linking two mechanisms of morbidity in early and later life: Even well-fed babies are vulnerable to rampant infections, and infections alone can cause malnutrition and later deficiencies. Childhood diarrheas, for example, impair cardiac muscle synthesis (*28*), which could underlie associations of infant diarrhea with later cardiovascular disease (*16*). Slowed infant growth in the Barker hypothesis (*26*) could thus be consequent to infections that cause inflammatory responses as well as impair nutrient absorption. Using historical Swedish cohorts to test both hypotheses, Bengtsson and Lindstrom (*12*) concluded that the level of infection among infants had a stronger influence than food availability on later-life mortality and life expectancy, and they implicated respiratory mechanisms. In addition, we suggest that the systemic inflammatory processes recognized in modern populations are important as risk factors in vascular disease.

Early-life infection may also explain effects of the season of birth on longevity.

Among birth cohorts of the 19th and early 20th centuries from Northern Europe, those born in the spring eventually lived 3 to 6 months longer than autumn births, with corresponding differences in some later-life diseases (*26*). Although seasonal variations in nutrition were emphasized, we would also suggest a role of inflammation.

Conclusions

Long-term declines in mortality for cohorts born in Sweden from the middle of the 18th century into the 20th reveal important links between mortality in old age and in early life. Cohort levels of mortality during childhood are related to cohort mortality in old age, which implies an imprint of early exposures on the cohort morbidity phenotype. Thus, improved public health conditions and medical interventions have both immediate and long-term benefits: a reduction in current mortality combined with the enduring effects of an improved early environment. Our argument implies that mortality in later-born cohorts should be lower over the entire lifespan. Although infection and inflammation are particularly elevated in childhood when infections are very prevalent, chronic infections and lifelong inflammation should characterize all ages in populations with high infectious mortality.

Improved childhood health and survival along with reduced chronic infections and inflammation are attributed to improved public health, medical advances, and an improved standard of living. The links between young- and old-age mortality help to explain the widespread recent declines in old-age mortality and to anticipate further declines in populations where declines of early-age mortality have more recently appeared. The rapid decline in old-age mortality in developed countries that began in the latter part of the 20th century took researchers by surprise. Because few medical breakthroughs occurred before the onset of the decreased mortality from heart disease and stroke in the 1960s, this decline is generally attributed to lifestyle change and medical advances (*29*). According to our hypothesis, these improvements in part originated as cohort effects from reduced early morbidity.

The stability of cohort mortality slopes (Gompertz slope), despite the remarkable variability of overall mortality (Fig. 1A) (*18*), implies that future increases in life expectancy from reduced inflammatory causes may be relatively small, particularly in populations that have had low levels of childhood infection for many decades and now may be approaching a lower limit. These findings from many fields suggest that inflammatory processes that influence the outcomes of aging can be kindled or quenched by exposure to extrinsic infections, inflammatory stimuli, and nutrition. A new theory of human health in life history could emerge from a fuller accounting of inflammatory exposures from gestation to old age.

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30. We thank A. Hagedorn and R. Vejella for data analysis and graphics, and B. Henderson, V. Longo, B. Teter, and A. Watts for helpful comments. Supported by National Institute on Aging (NIA) grants AG13499, AG05142, and AG14751 and the Alzheimer's Association (C.E.F.) and by NIA grant AG17265 (E.C.). C.E.F. is co-founder, stockholder, and member of the science advisory board of Acumen Pharmaceuticals Inc., which is developing treatments for Alzheimer's disease.