Infection, inflammation, height, and longevity

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Using historical data from cohorts born before the 20th century in four northern European countries, we show that increasing longevity and declining mortality in the elderly occurred among the same birth cohorts that experienced a reduction in mortality at younger ages. Concurrently, these cohorts also experienced increasing adult height. We hypothesize that both the decline in old-age mortality and the increase in height were promoted by the reduced burden of infections and inflammation. Thus, early growth and cardiovascular diseases of old age may share infectious and inflammatory causes rooted in the external environment.

aging | vascular disease | mortality | historical cohorts

Fig. 1. Model linking infectious exposure at earlier ages and external environment to inflammation, height, organ damage, morbidity, and mortality at older ages. Barker (10) and Fogel (11) emphasize dietary influences on growth/development as a central mechanism.

Life expectancy has doubled during the last 250 years from preindustrial norms of 35–40 years (1, 2). Although all ages have benefited, the increases among the elderly began many decades after the increases at younger ages (3). We have hypothesized that the historical increase in life expectancy at the older ages was due in part to life-long reduction in exposure to chronic inflammation (4). It is well known that the survivors of birth cohorts with lowered early age mortality due to infections experienced lower mortality throughout adult life (5–8), a relationship we have characterized as the "cohort morbidity phenotype" (4). Others have proposed that mortality at young and old age is linked by improvements in nutrition and a reduction in organ damage due to infections (9,10). We add the reduction in lifelong exposure to inflammation to these explanations and develop in more detail the physiological mechanisms linking lifetime exposure to infections and late life health outcomes. We also consider inflammation as a possible link between childhood mortality and adult height (11).

We argue that the demographic and economic revolutions beginning >200 years ago were accompanied by a physiological revolution, which occurred long before the benefits of modern medicine. The historical reduction in inflammation was an internal manifestation of the physiological revolution, which was also indexed by the historical increases in height. We propose a general model in which the reduction in lifelong levels of infections and inflammation reduced and delayed the atherosclerotic process and mortality due to heart disease and allowed increased height (Fig. 1). This heuristic model emphasizes the pathway from decreases in infection through reductions in inflammation but recognizes that other potential links include improvements in diet and nutrition and reductions in direct organ damage. Thus, our model considers a broader set of pathophysiological mechanisms linking health across the life course than presented heretofore.

Extensive debate over the causes of the historical mortality decline has not resolved the relative roles of improved public health, vaccines, income, and nutrition (1, 12). However, all of these factors would have reduced exposure to, resistance to, or consequences of infections. The role we hypothesize for inflammation considers the importance of heart disease as a historical cause of old-age mortality. Only recently have causes of death at old ages been reliably recorded; however, under reasonable interpretations of 19th century terminology, historical cause-of-death data indicate substantial cardiovascular mortality. In the earliest cause-of-death records for England and Sweden, the recorded cardiovascular deaths were comparable to infectious
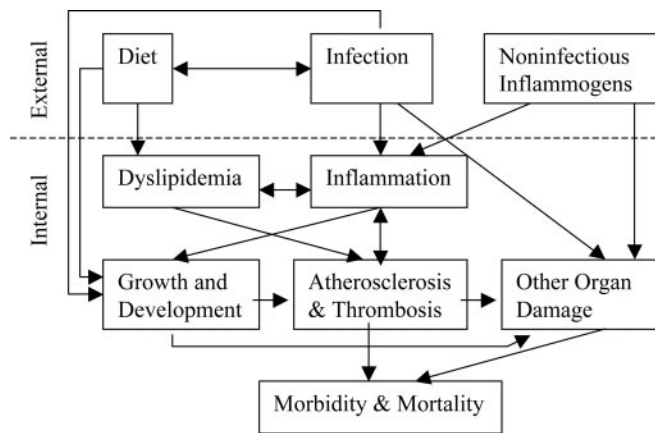
conditions as a cause of mortality at old age; however, at this time approximately half of mortality in old age was ascribed to unknown causes (13, 14). Where cause of death recording is not complete, Preston concludes deaths from unknown causes at older ages are most likely to be cardiovascular (14). When life expectancy increases from 40 to 70 years, reductions in cardiovascular disease are as important in total mortality decline as the combination of tuberculosis and all other infectious and parasitic conditions (14). Furthermore, Fogel showed that cardiovascular disease was twice as prevalent among older Army veterans born before 1845 vs. veterans born in the early 20th century (10).

The early mortality or medical records do not give any specific evidence for the prominence of atherosclerosis, which is the main cause of contemporary heart attacks and strokes. However, a significant literature indicates that atherosclerosis was an ancient human condition and was common before the 20th century. For instance, autopsies of Egyptian mummies found atherosclerotic plaques in a majority of this sample (16/24) (15, 16). As early as 1858, Virchow concluded that "an inflammation of the arterial coat was the starting point of the so-called atheromatous degeneration" (17).

In highly infectious environments, children are exposed to high inflammation levels, which promote the process of atherogenesis even without exposure to high-fat diets. Infections and inflammatory responses (18, 19) are recognized risk factors in atherogenesis, a lifelong process that begins *in utero* (20). In Norway, infant mortality rates, a proxy for exposure to infections among survivors, correlated strongly with arteriosclerotic deaths 40–69 years later for cohorts born from 1896–1925 (21). Con-
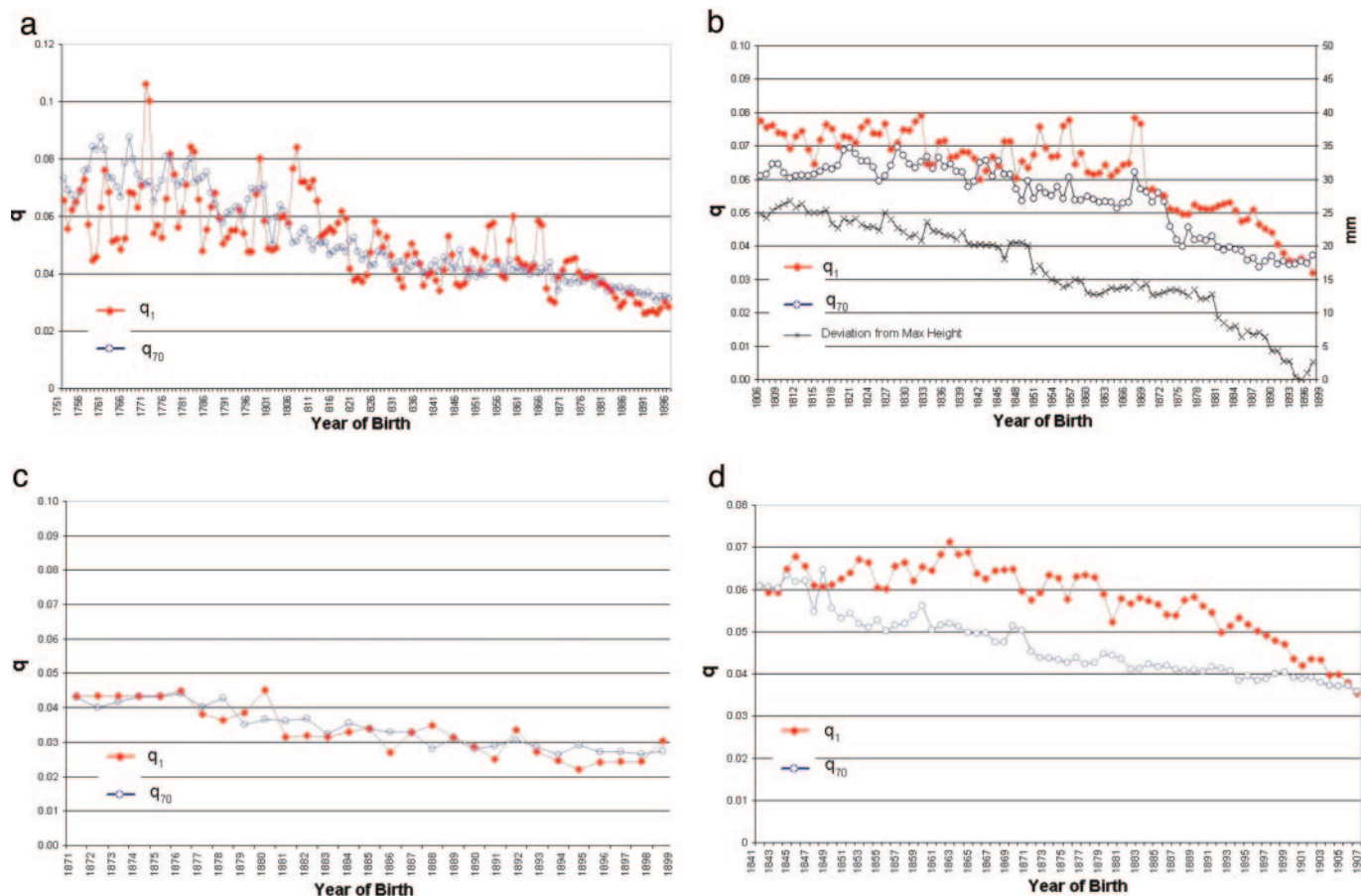

Fig. 2. Mortality of birth cohorts at ages 1 and 70 in Sweden (1751–1899) (*a*), France (1806–1899) (*b*), Switzerland (1871–1899) (*c*), and England (1841–1899) (*d*) with deviation from maximum cohort height at age 20–21 up to 1899 (measured in millimeters on right axis).

temporary populations with high mortality from infectious conditions have elevated circulating levels of "acute phase" inflammatory proteins, e.g., blood levels of C-reactive protein (CRP), IL-6, and fibrinogen. Elevations at even moderate levels are risk factors for heart attack and stroke (22). These inflammatory markers are typically elevated during infections, e.g., diarrhea, HIV, malaria, tuberculosis and other parasites, and periodontal disease (4, 23–25).

To further explore the cohort morbidity hypothesis (4), we examine statistical associations between early and later mortality for cohorts born up to 1900 in Sweden, England, France, and Switzerland. We hypothesize that historical trends in mortality at younger and older ages will be similar within cohorts. We also compare trends in childhood and middle-age mortality within cohorts. We expect these trends to be less similar to childhood mortality because people in middle age do not die from the chronic diseases developed through exposure to inflammation.

We focus exclusively on cohorts born before the 20th century, when levels of infection were high, but before smoking, a major inflammatory stimulus, became popular. Most importantly, these cohorts entered adulthood before general childhood immunizations and before antibiotics. The inflammatory mechanisms that we describe can only work when mortality from infection is high; once childhood infection is low, it can no longer be a factor in explaining old-age trends. In addition, by limiting our analysis to this period, all of the old-age mortality we examine takes place by 1973. Dramatic declines in old-age mortality occurring in many countries after ≈1970 may be better explained by medical and lifestyle factors.

Evidence of Cohort Mortality Links at Young and Old Ages

Cohort and period mortality data are available from varying dates: Sweden since 1751, France since 1806, England since 1841, and Switzerland since 1876. Mortality data are from the Human Mortality Database (www.mortality.org/Public/main.html) supplemented by data for France (27). Inclusion in this database is limited to countries where death registration and census data are virtually complete; to facilitate comparisons across time and place, similar techniques are used in constructing the data series. Because even the best historical data are liable to underregistration and age uncertainties, particularly at the youngest and oldest ages, much of our analysis is limited to those under 75 years of age. We examine childhood mortality at all ages, because infant mortality is usually the last age to achieve complete registration.

At the initial dates for our analyses, cohort life expectancy at birth was low: 34 years in Sweden, 38 years in France, 42 years in England, and 45 years in Switzerland. For the 1899 cohort, life expectancy had increased to 55 years in Sweden, 56 years in Switzerland, 53 years in England, and 50 years in France. These low life expectancies imply that all of these cohorts were exposed to highly prevalent infections.

Mortality at ages 1 and 70 of successive cohorts by year of birth up to 1899 show the strong link within cohorts of childhood and old-age mortality in the four countries (Fig. 2). The level of mortality and the pace of the decline varied across countries for various reasons, including different exposure to disease and different rates of urbanization and economic development that influenced both nutrition and the spread of public health

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reforms (1, 28, 29). England and France had higher mortality than Sweden and Switzerland for cohorts born in the later 19th century. In Sweden, mortality declines at ages 1 and 70 were clearly underway in cohorts born throughout the century. Such declines began later in France and England; declines in infant mortality were also somewhat delayed in France and England, relative to Sweden (28, 29) (Fig. 3, which is published as supporting information on the PNAS web site). In Switzerland, the decline was underway for cohorts born after 1875, when data become available.

The similarity of cohort mortality change at the two ages within each country is evident in Fig. 2. The trend in cohort mortality at age 70 (q_{70}) is strikingly like the historical trend in mortality at age 1 (q_1), which occurred 69 years earlier. For Sweden and Switzerland, the plots are superimposable; England and France show very similar trends, although q_1 is slightly higher than q_{70}. This graphical presentation suggests that the early and late age mortality for a cohort are mechanistically linked.

To further test our hypothesis that reduced levels of inflammation will delay aging processes relevant to mortality, we use a regression models approach to examine the similarity in temporal change between q_{70-74} and mortality in four stages of childhood: infancy, q_0; early childhood, q_{1-4}; later childhood, q_{5-9}; and adolescence, q_{10-14}. Mortality before age 15 provides a good index of the infectious exposure during development.

Most of the temporal variance in old-age mortality for a cohort is related to variance, in mortality before age 15: R^2, 87% in Sweden, 94% in France, 96% in Switzerland, and 96% in England (Table 1). The amount of variance explained in cohort old-age mortality by child mortality is similar across countries and potentially different disease environments. This similarity in temporal change in mortality at the young and old ages within cohorts supports a strong developmental relationship between childhood infection and old-age mortality.

We also compare the contemporary ("period") relationships between childhood and old-age mortality to assay the link between the contemporary vs. the developmental environment represented by the cohort formulation. The right side of Table 1 (Contemporary) shows the relationship between annual mortality rates of old-age mortality and childhood mortality in the same year. The proportion of variance explained, R^2, for periods are consistently lower than those for cohort relationships. Thus, the annual change in contemporary old-age mortality is not as well predicted by childhood mortality in the same year as is the cohort old-age mortality. In some age groups, the trends in childhood mortality are negatively related to contemporary trends in old-age mortality, indicating temporal change in opposite directions.

To further test our hypothesis, we examine relationships of the trend in "early adult" mortality (q_{30-34}) to childhood mortality (Table 3, which is published as supporting information on the PNAS web site). At this adult age, most mortality is not caused by the chronic diseases of old age, but primarily by infections, accidents, violence, and, in women, childbirth. Because of this cause-of-death structure, age 30–34 precedes the sharp life cycle acceleration of mortality reflecting the rate of senescence characterized by the Gompertz slope (4, 30). We would not expect as strong a relationship between cohort mortality trends between childhood and early adult ages as that observed for the older ages; rather, cohort mortality change in early adults should be more closely linked to contemporary change in child conditions.

As expected, the links between cohort trends in childhood mortality and early adult mortality are weaker than the links for old-age mortality. In Sweden and Switzerland, the R^2 is $\approx 70\%$ for the equations linking childhood and early-adult mortality, whereas in France the R^2 is only 7%. In addition, the contemporary change in young mortality and early adult mortality in the

Table 1. Regression of old-age mortality (q_{70-74}) on childhood mortality (q_0, q_{1-4}, q_{5-9}, and q_{10-14}) for cohorts born up to 1899, and regression of contemporary old-age mortality on childhood mortality for years up to 1899

Models	Cohort		Contemporary	
Sweden (1751–1899)	b	SE	b	SE
Intercept	−0.02	(0.01)*	0.10	(0.01)***
$q_{(0-1)}$	0.53	(0.08)***	0.72	(0.08)***
$q_{(1-4)}$	0.45	(0.08)***	0.39	(0.18)
$q_{(5-9)}$	0.78	(0.14)***	−2.33	(0.37)***
$q_{(10-14)}$	1.08	(0.26)***	5.27	(0.63)***
N = 149	$R^2 = 0.87$		$R^2 = 0.68$	
France (1806–1899)				
Intercept	0.04	(0.01)*	0.21	(0.02)***
$q_{(0-1)}$	0.04	(0.11)	0.52	(0.16)**
$q_{(1-4)}$	0.90	(0.14)***	−0.32	(0.30)
$q_{(5-9)}$	0.65	(0.25)*	−0.71	(0.46)***
$q_{(10-14)}$	4.05	(0.60)***	3.95	(1.11)**
N = 94	$R^2 = 0.94$		$R^2 = 0.33$	
Switzerland (1876–1899)				
Intercept	0.09	(0.00)***	0.25	(0.02)***
$q_{(0-1)}$	0.34	(0.08)**	0.40	(0.30)
$q_{(1-4)}$	0.17	(0.19)	−0.46	(1.01)
$q_{(5-9)}$	1.00	(0.40)*	0.73	(3.29)
$q_{(10-14)}$	2.43	(0.94)*	4.65	(4.56)
N = 24	$R^2 = 0.96$		$R^2 = 0.63$	
England (1841–1899)				
Intercept	0.19	(0.02)***	0.26	(0.04)***
$q_{(0-1)}$	−0.31	(0.14)*	0.24	(0.29)
$q_{(1-4)}$	0.02	(0.13)	0.40	(0.34)
$q_{(5-9)}$	1.72	(0.58)*	−1.53	(1.13)
$q_{(10-14)}$	3.14	(0.95)*	1.44	(1.65)
N = 58	$R^2 = 0.96$		$R^2 = 0.07$	

b, unstandardized regression coefficient; R^2, proportion of variance explained. *, $P < 0.05$; **, $P < 0.001$; ***, $P < 0.0001$. Sweden, England, and Switzerland (www.mortality.org/Public/main.html); France (27).

same calendar year is stronger than the cohort link (Table 3). The contemporary link between childhood and early-adult morality is also stronger than the contemporary link between childhood and old-age mortality (compare contemporary R^2, Tables 1 and 3). This closer relationship to contemporary mortality is expected, given the greater similarity of causes of mortality at young and middle age. The coefficients representing the effects of individual age groups vary in sign, which may reflect differences in timing of change in early adult mortality and that of children. We also examined the relationships between early adult and old-age mortality for the four countries, which are not as strongly related as childhood and old-age mortality.

Height is also linked to infections and the inflammatory response (Fig. 1). Inflammatory (host defense) responses to chronic infections, although adapted for survival, are also metabolically demanding. If infections occur during development, substantial energy is reallocated at the expense of growth, as required by the body for immune defense reactions and for repair (25, 31). In adults, the fever associated with severe infections increases resting metabolic rates by 25–100% (32, 33). Moreover, fever during respiratory and diarrheal diseases is usually accompanied by anorexia, which can reduce food intake by nearly 20% (34, 35). Although less is known about the energetics of host defense in children, the effects of chronic infections in growth stunting are consistent with the adult energy reallocation. In contemporary populations, ample evidence shows that childhood diarrhea, dysentery, HIV, and respiratory

Table 2. Regression of cohort height on cohort childhood mortality

Models	b	SE
France (1806–1899)[†]		
Intercept	1680.21	(2.74)***
$q_{(0–1)}$	−4.83	(17.42)
$q_{(1–4)}$	−63.82	(22.97)*
$q_{(5–9)}$	−318.40	(41.08)***
$q_{(10–14)}$	−307.65	(95.31)*
$N = 94$	$R^2 = 0.93$	
Sweden (1820–1895, every 5th year)[‡]		
Intercept	17,987	(1.21)***
$q_{(0–1)}$	−47.43	(9.17)**
$q_{(1–4)}$	−17.60	(12.18)
$q_{(5–9)}$	−4.10	(22.32)
$q_{(10–14)}$	−88.73	(58.08)
$N = 16$	$R^2 = 0.88$	
England (1841–1899)[§]		
Intercept	167.33	(36.55)***
$q_{(0–1)}$	46.79	(1.38)
$q_{(1–4)}$	−63.50	(24.71)*
$q_{(5–9)}$	93.40	(117.95)
$q_{(10–14)}$	−151.10	(214.47)
$N = 31$	$R^2 = 0.34$	

*, $P < 0.05$; **, $P < 0.001$; ***, $P < 0.0001$.
[†]Height age 20–21 in millimeters (42).
[‡]Height age 21 in centimeters (43).
[§]Height age 21 in centimeters (12).

infections have double-pronged impact by raising levels of inflammation and by reducing growth (36–38). Thus, even if food is not limiting, a reduction in the burden of infections will allow increased height and weight.

IL-6 and other cytokines elevated during inflammation can also impinge on growth. In a transgenic mouse model, where effects can be isolated from external pathogens, chronic IL-6 overexpression caused skeletal muscle atrophy (39). Cortisol, which is elevated during chronic infections and the inflammatory response, can cause growth stunting by impairing protein synthesis (40); cortisol elevation is common during malnutrition and is intensified by diarrhea (41).

The link between trends in height and mortality in childhood and at older ages is best examined for France by using annual height estimates for 1806–1899 (42). The other countries have limited data: Swedish height data are available for 5-year cohorts from 1820 to 1895 (43); England has comparable data for 31 years (1841–1887) (12); for Switzerland, the few years of data do not permit analysis. The data represent military recruits at ≈21 years of age; although a selected subpopulation, their trends in height are widely used to estimate historical population trends (10, 12).

The cohort height showed a strong similarity to the mortality trends at ages 1 and 70 in France (Fig. 2b). Thus, taller cohorts experienced lower early- and old-age mortality. This association of height and mortality holds for Sweden (Fig. 4, which is published as supporting information on the PNAS web site) but does not for England. The regression of height on cohort childhood mortality in France shows a strong inverse association ($R^2 = 93\%$, Table 2), equaling that for childhood mortality and old-age mortality ($R^2 = 94\%$, Table 1.) When height is added to the equation in Table 1, linking early- and late-age mortality, height is no longer significantly related to old-age mortality (Table 4, which is published as supporting information on the PNAS web site). This result strongly implies that childhood mortality is a proxy for the main cause of the relationship between height and old-age mortality and that height is an intermediate variable. Sweden showed similarly strong relationships between cohort height and childhood mortality ($R^2 = 88\%$) despite the more limited data for height, and as in France, adding height to the equation in Table 1 did not increase the explanatory power of the regression.

Discussion

This analysis shows two generalizable cohort effects, between early and later mortality and between early mortality and adult height. In four northwestern European countries from different periods of time from 1751 through 1899, the mortality decline among older persons occurred in the same cohorts that had experienced mortality decline as children. Strong inverse associations were also found between adult height and child and old-age mortality for cohorts. We interpret high childhood mortality as a direct index of the high environmental exposure to infections and inflammation by the survivors in the cohort.

These observations extend prior to findings of links between early-life infection and late-life health and mortality. In selected rural parishes of 17th century Sweden, high early infectious mortality was followed by high late-life mortality among survivors (6); Union Army veterans in the United States also showed links between early infections and late-life health (7). In the current Health and Retirement sample in the United States, survivors of childhood infection have worse health as adults (44). Thus, we propose that one mechanism linking childhood infections to old-age mortality is the higher lifetime burden of inflammation. This extension of prior models recognizes the potential roles of improved nutrition and the reduction in direct organ damage from infections. Fogel (10) has argued that a "techno-physiological revolution" increased energy available for growth and improved resistance to infection through improved food production and higher incomes enabling better living conditions. However, the increases in height did not always follow increases in income and nutrition; moreover, height decreased during some periods of improving income in early industrial cities (10, 12). We argue that a decrease in infections and ensuing inflammation had the potential to increase height independently of improved food intake.

Influential work by Barker and colleagues (9) has emphasized maternal malnutrition and retarded fetal growth as the main link between childhood conditions and adult morbidity. Organ insufficiency resulting from reduced fetal growth is one mechanism linking early- and late-life mortality. Moreover, infections can cause direct organ damage (13, 45), as in the classic example of heart valve damage from *Streptococcus* infections. Before antibiotics, survivors of rheumatic fever often had endocarditis with damage to heart valves that affected their subsequent mortality (46). Other microbial and parasitic infections can directly damage the lungs, kidneys, and other vital organs. In children, acute infections cause vascular endothelial damage that may persist for at least a year (47). Indirect cascades can arise through enteric infections, which impair intestinal transport of nutrients, e.g., children with diarrhea may suffer mucosal injury, which prevents recovery (48). In a rat model, cardiac muscle synthesis was impaired during sterile chronic diarrhea (49), which could be a factor in the association of infant diarrhea with later cardiovascular disease (50). Thus, the historical reduction of exposure to infections, by directly reducing organ damage, should also decrease subsequent mortality at older ages.

Our model (Fig. 1) posits that reduced infections at young ages delayed the development of atherosclerotic and thrombotic conditions by reducing the lifetime inflammatory burden. Although serum and tissues from before the 20th century are not available, to directly assess inflammation, there is substantial supporting data from contemporary infectious diseases. In countries with high endemic parasitism, up to 52% of children had serum CRP at ≥6 mg/liter (24, 25, 51–53), which is manyfold

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greater than the value for children from the United States. Adults with HIV, tuberculosis, malaria, and periodontal disease also experience elevations of CRP and IL-6 that exceed the risk levels for heart attack and stroke (4, 18, 19). Elevated serum CRP has also related to past exposure to specific common pathogens (54–56).

Because acute-phase inflammatory responses are essential for fighting infections, high levels of circulating CRP and other inflammatory markers are functional when infection is high. However, chronic infection may lead to chronically elevated levels of inflammation (57). Chronic exposure to even moderate levels of inflammatory factors appears to promote atherosclerosis and cardiovascular disease (4, 18).

The causal paths by which inflammation is associated with cardiovascular disease are not resolved, despite extensive discussion. Many researchers have come to recognize that the elevations of blood CRP and other inflammatory markers can be both outcomes and causes of the underlying pathophysiology (58). In a rat model of stroke, elevated CRP increased infarct size (59). Moreover, exogenous CRP promotes endothelial dysfunction by inducing receptors for oxidized low-density lipoprotein (LDL) (60) and by CRP binding to LDL, which directly enhance LDL uptake by vascular cells (61). Low HDL levels and oxidized LDL, both of which are atherogenic, may be consequent to chronic infections. During infections, HDL is remodeled by acute-phase proteins, which decreases its ability to protect LDL from oxidation (62–64). Low levels of HDL cholesterol relative to the United States are found in countries with high infectious loads (65, 66).

Contemporary cardiovascular conditions, including heart attack and stroke, result from blood flow blockage by thromboses formed on or captured by atheromas. Ruptured aneurysms also cause sudden death but contribute less mortality than thromboses. Aneurysms are also associated with inflammatory processes (67) and share risk factors with atherosclerotic disease, e.g., CRP elevations (68). In contemporary populations, heart disease is associated with a fatty diet and high lipid levels, including LDL cholesterol. However, heart attacks can occur without dyslipidemias. In the Framingham study, 1/3 of heart attacks occurred despite initially normal cholesterol levels (69). In serum from the original Framingham cohort, high CRP predicted stroke, after adjustment for total and HDL cholesterol

(70); these CRP elevations may be due to infections, smoking, or air pollution. Other evidence comes from the efficacy of certain drugs with antiinflammatory activities in reducing the risk of heart attack and stroke; besides aspirin, statins also have antiinflammatory activities (4, 71).

The model outlined in Fig. 1 also includes important links between maternal infections and inflammation to fetal and infant inflammation and growth. Maternal infections, including influenza, malaria, and tuberculosis, were common in Europe and the United States into the mid-20th century (1). Babies of mothers with infections can have elevated inflammatory markers and retarded uterine growth (26). Suboptimal adult female health may transgenerationally transmit the imprints of infections and inflammation as well as malnutrition while increasing the risk of smaller babies with lowered resistance to environmental pathogens. This additional path (Fig. 1) is not developed in the Barker hypothesis and is consistent with observations that improved infant mortality lags a generation behind the decline in adult mortality (5).

By emphasizing the early-life infectious effects on old-age mortality from vascular disease, we do not claim that this is an exclusive mechanism in all historical decline of old-age mortality. Direct damage to vital organs by infections was clearly important in these earlier times. Nor can we fully resolve cohort and period effects. Clearly in recent decades, many medical developments have further reduced old-age mortality. Nonetheless, we show that the cohort pattern of mortality decline occurred in four countries and over long periods that predated modern medical innovations in treating the causes of old-age mortality. Cohort mechanisms linking young- and old-age health conditions help to explain the relatively similar timing of the declines in old-age mortality observed throughout Europe. In many countries where mortality among children has declined markedly only in the last half century, a reduction in lifetime inflammation provides further momentum to reduce old-age mortality for some years ahead.

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