

Aging and Inflammation in Two Epidemiological Worlds

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Abstract

Humans evolved in a world with high levels of infection resulting in high mortality across the lifespan and few survivors to advanced ages. Under such conditions, a strong acute-phase inflammatory response was required for survival; however, inflammatory responses can also promote chronic diseases of aging. We hypothesize that global historical increases in lifespan at older ages are partly explained by reduced lifetime exposure to infection and subsequent inflammation. To begin a test of this hypothesis, we compare C-reactive protein (CRP) levels in two populations with different epidemiological environments: the Tsimane of Bolivia and persons in the U.S. High CRP is significantly more prevalent among the Tsimane up through middle age; by age 40, the Tsimane have spent as many years with high CRP as Americans at age 55. Further test of the links between infection, inflammation, and chronic diseases of aging among the Tsimane, requires collection of age-specific indicators of atherosclerosis and cardiac function.

Introduction

Explanations of increases in life expectancy at the older ages often focus on the role of relatively recent medical advances and behavioral changes. The historical reduction of infections is recognized as a major factor in the decline of early age mortality in the past two centuries: We and others have noted that cohorts who experienced lower mortality when young also experienced reduced mortality among survivors in old age.¹⁻⁴ It is further hypothesized that population levels of inflammation have decreased over time in parallel with the reduction in mortality from infectious diseases.^{1,2} A reduction in the prevalence and duration of time spent with infectious conditions should lower the levels of life time inflammation. Because chronically elevated blood levels of inflammatory cells and proteins are independent factors in the atherosclerotic process, reductions in lifetime levels of inflammation should slow deterioration in the cardiovascular system with aging, as well as delaying the onset of chronic cardiovascular diseases of old age.⁵⁻⁹ Cohort reductions in inflammation should result in increased ages of mortality, heart attack, stroke, and cognitive loss.^{8,9} The hypothesis that lifetime inflammation has decreased in modern populations and that aging processes are consequently delayed relative to historical populations can not be directly tested because of the lack of tissue samples from these earlier eras. As an approach to testing the inflammation-aging hypothesis in modern populations, we compare C-reactive protein (CRP) levels in two populations with different epidemiological environments: the Tsimane of the Bolivian Amazon versus samples from the U.S.

Method

Lacking statistically valid blood or tissue samples from historical populations, we sought a contemporary population which had limited exposure to modern medicine with a high level of mortality that would provide a useful calibration for understanding past populations and modern epidemiologic transitions. The Tsimane are indigenous foragers in the Bolivian Amazon with limited access to modern medicine, low life expectancy, and high mortality from infection. We examined C-reactive protein (CRP), a serum marker of inflammation, across the age range in this population for comparison with age-specific CRP and mortality levels in the U.S. These two populations represent extremes in contemporary levels of infectious mortality, exposure to inflammation, and life expectancy.

In July 2002, Kaplan and Gurven initiated long-term research on Tsimane life history. Data were collected on demographic, economic, social and health characteristics of over 2,200 Tsimane living in 17 study villages.⁹ These forager-horticulturalists live in about sixty small villages of extended family clusters located in a forested lowland tropical area. Despite their exposure to Jesuit missionaries in the late 17th century, the Tsimane were never successfully settled in missions and are relatively unacculturated. Their isolation will not last much longer because of increasing access to market towns, especially as supplies of forest game and fish diminish with increased encroachment by loggers and colonists. The life history data provide the basis for estimating life expectancy over the past 15 years in this population

Inflammation is indicated in both countries by levels of serum CRP. Elevation of CRP is an acute phase response to infection that mediates bacterial clearance and is widely used to indicate systemic inflammation. However, chronic exposure to even moderately high CRP is associated with increased risk of cardiovascular events and other disabilities of aging in long-

lived populations.^{9,11} We examine age-specific prevalence of high C-reactive protein (CRP) and estimate the number of years spent with high CRP for survivors up to specified ages.

For the Tsimane CRP was assayed in whole blood collected by venipuncture, during medical examinations in four villages from 607 people over the age of 4 during the summers of 2004 and 2005. Whole blood was hand-centrifuged on site at ambient temperature and then frozen and stored in liquid nitrogen pending transport to the U.S. for assay. Assays were done using the Immulite 2000, high-sensitivity CRP assay, a solid-phase, chemiluminescent immunometric assay with a mean replicate coefficient of variation of 5.6% (Immulite 2000, Diagnostics Products Corporation). Values from this assay were then standardized to the assay used for the United States. An indication of reliability is that the percentages with high serum CRP among the Tsimane reported using this assay resemble those reported for Tsimane children from assays of dried blood spots after using the conversion formula.¹²

The U.S. data on CRP are from the National Health and Examination Study (NHANES 1999-2002), a nationally representative sample of noninstitutionalized persons collected from 1999 through 2002. Values of serum CRP were determined from samples analyzed by high-sensitivity latex-enhanced nephelometry on a BNII Nephelometer (Dade Behring).¹³ The assay used monoclonal anti-CRP antibodies and a calibrator that was traceable to the WHO Reference Material. The mean replicate coefficient of variation for the assay is 6.4%.¹³

This analysis defined CRP >3.0 mg/L as the cutoff for high CRP, which indicates high cardiovascular risk.¹⁴ Because we are interested in lifetime exposure to high inflammation, we use the age-specific prevalence of high CRP to estimate the years lived with high CRP by specified ages for both the Tsimane and U.S. The calculation assumes that the prevalence of high CRP observed in an age interval represents the proportion of life lived with high CRP for

those who survive through the interval. We also assume that the prevalence of high CRP below the age of measurement (4 years for the Tsimane and 2 years for the U.S.) is equal to that in the 5-9 age range.

Results

A Tsimane life table was constructed by Gurven from recent interviews representing the period from 1950-1989 (29,464 person-years of life).¹⁰ Recent life expectancy, 42.8 years, is very close to that in 19th century Western Europe, e.g. Sweden in 1843 (42.6 years) (Figure 1). Demographic analysis of historical and contemporary lifetables shows the remarkable similarity of the cause of death structure for populations with similar levels of mortality, despite some regional variations.¹⁵ The similarity of the levels and the age-specific pattern of age-specific mortality for the Tsimane and Sweden suggests that both the Tsimane and those living in Northern Europe 150 years ago suffered from high levels of infectious mortality and morbidity.¹⁶ Medical examinations of 2,800 Tsimane in 2004 and 2005 also documented the high levels of endemic parasitism and infection. More than two-thirds (69%) were infected with at least one species of intestinal parasite at the time of the exam, while more than 60 percent had symptoms of either a gastrointestinal or respiratory illness. On the other hand, there is almost no obesity among the Tsimane. In contrast to the Tsimane, the current U.S. life expectancy is almost twice as high (77.2 years) with infections responsible for only a small percentage of deaths.

Figure 1 about here

The age-specific proportions with serum CRP >3.0 mg/ml differ strikingly between the U.S. and Tsimane (Figure 2). The Tsimane have significantly higher age-specific proportions with high serum CRP up to age 45-54 than in the U.S. The proportion with high CRP among young Tsimane adults exceeds U.S. values for ages 65 and over. These remarkable elevations of CRP can be attributed to endemic infections in the Tsimane, as documented above. Few U.S. children have high CRP at any time relative to the Tsimane because childhood infections are less prevalent in the U.S. Nonetheless, in both samples, the percentage with high CRP rises after childhood. Factors associated with chronically high CRP in low mortality countries include obesity, smoking, and the onset of cardiovascular conditions and other chronic degenerative diseases of aging.^{17,18} At the older ages, the Tsimane and U.S. populations have similar serum CRP.

Figure 2 about here

Lifetime exposure to high levels of CRP is implicated in the development of atherosclerosis. Longer exposure to high inflammation early in life results in the Tsimane having lived more years with high inflammation by the time they reach adulthood. Years lived with high inflammation estimated from the prevalence is shown in Figure 2. By age 15, the average Tsimane has lived 6.1 years with high CRP, whereas the average time in U.S. is only 1.5 years. By age 40, the Tsimane have spent as more years with high CRP as have Americans at age 55. Over their entire life history up to age 70, the Tsimane spend more years and a greater proportion of life with high CRP than in the U.S.

Figure 3 about here

Conclusion

The Tsimane population gives a unique opportunity to evaluate the role of CRP in an epidemiologic setting with current mortality as high as that in 19th century Europe. This evidence shows that persons in a high-mortality, highly infectious environment have higher CRP in the first four decades of life than those in a low-mortality, low-infection environment. Based on the association of CRP elevations with future cardiovascular events in populations with lower mortality and infections, we hypothesize that premature cardiovascular disease is a factor in the higher adult mortality of Tsimane. Studies of young persons in the U.S. have linked high CRP to vascular deterioration beginning in childhood.^{19,20} In the U.S. and other generally healthy populations, individual exposure to common infections has been associated with both CRP levels and with risk of cardiovascular events.⁶ Thus, the greater exposure of Tsimane to inflammation could promote earlier vascular disease and other dysfunctions of aging. Conversely, the reductions in inflammatory exposure in countries like the U.S. may have been a significant factor in delaying aging and mortality.

It is not straightforward to compare levels of CRP among the Tsimane to those in other populations. Most reports on CRP in populations come from those with low mortality and of European extraction; most do not show an age pattern of change in CRP but report on one age group or do not differentiate by age. However, growing evidence suggests that CRP levels vary widely around the world. Tsimane children have higher levels of CRP than children in Kenya and Samoa which would be consistent with relative levels of infection.¹² Tsimane adults also have higher CRP than those in the indigenous North Asian Yakut population, a group with

relatively high, but recently decreasing, life expectancy due to rapid social change in the area that was once the Soviet Union.²¹ In fact, CRP levels among the Yakut are almost as low as in Japan which has much lower levels of CRP than those in the U.S., U.K., and Germany (Snodgrass et al. 2007, Yamada et al. 2001).^{21,22} On the other hand, the Tsimane adults 45 and older have a median CRP level (3.0 mg/L) close to that of adult American Indian population (3.2 mg/L) with low levels of infection, but high levels of diabetes and other cardiovascular risk factors.²³

In populations with low levels of infection and mortality, high inflammation has been strongly implicated in the pathophysiology of arterial degeneration and immunosenescence, as well as in a wide variety of chronic diseases including diabetes,²⁴ metabolic syndrome,²⁵ congestive heart failure,²⁶ Alzheimers,^{27,28} and disability.²⁹ There are obviously additional paths to those we emphasize here linking life circumstances to inflammation and disease. These links between inflammation and most major health problems support the hypothesis that inflammation is a common mechanism of many degenerative conditions linked to aging.^{27,30,31}

Further testing of our hypothesis requires new information on the role of arterial disease in adult mortality among the Tsimane. We must also test competing hypotheses about mortality from immune dysfunctions caused by high levels of lifetime infection and inflammation. CRP, for example, can impair the differentiation of antigen-presenting monocytes (dendritic cells).³² While the Tsimane are rapidly gaining access to medicine and immunizations, we may be able to glean critical insights about the nature of mortality in a highly infectious environment that will more fully explain the doubling of life expectancy during the last 200 years and the potential for further increases in many parts of the world. In addition this would provide evidence of

antagonistic pleiotropy, i.e. a process that enhances survival and reproductive success in the young, but with delayed adverse consequences at older ages.⁶

Acknowledgements

This work was supported by NIH grants R01AG024119, R01 AG13499, P30AG17265, NSF Grant BCS-0136274, the Ellison Foundation, and the Ruth Ziegler Fund.

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Figure 1: Probability of dying among Tsimane (1950-89), Sweden (1843), and U.S. (2001)

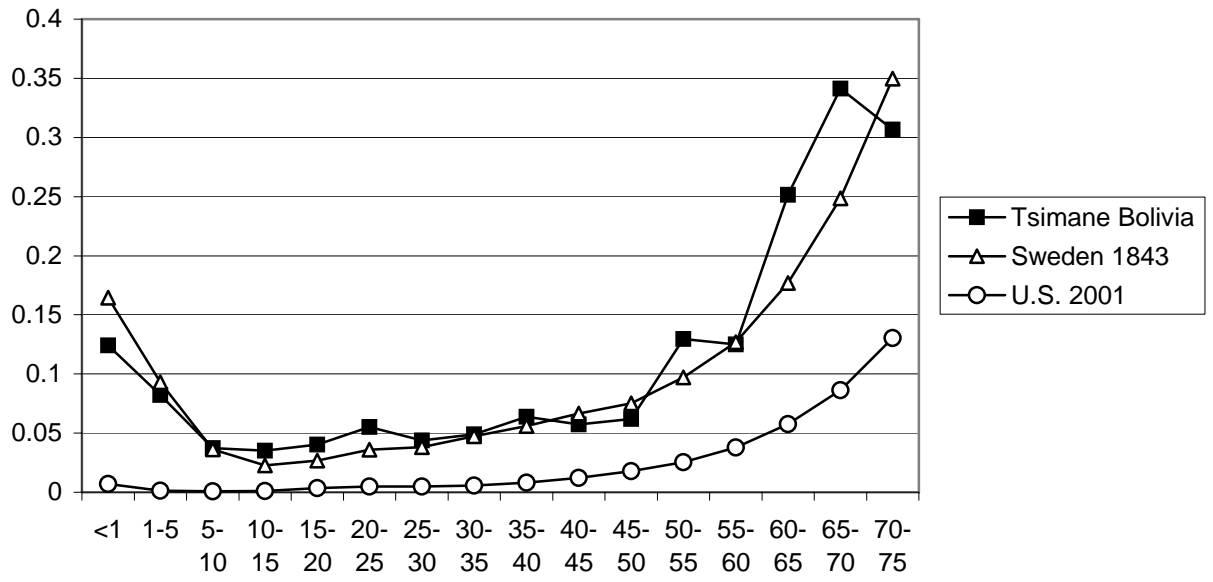


Figure 2: Prevalence of High Risk CRP (>3mg/L) in Bolivia and the U.S.

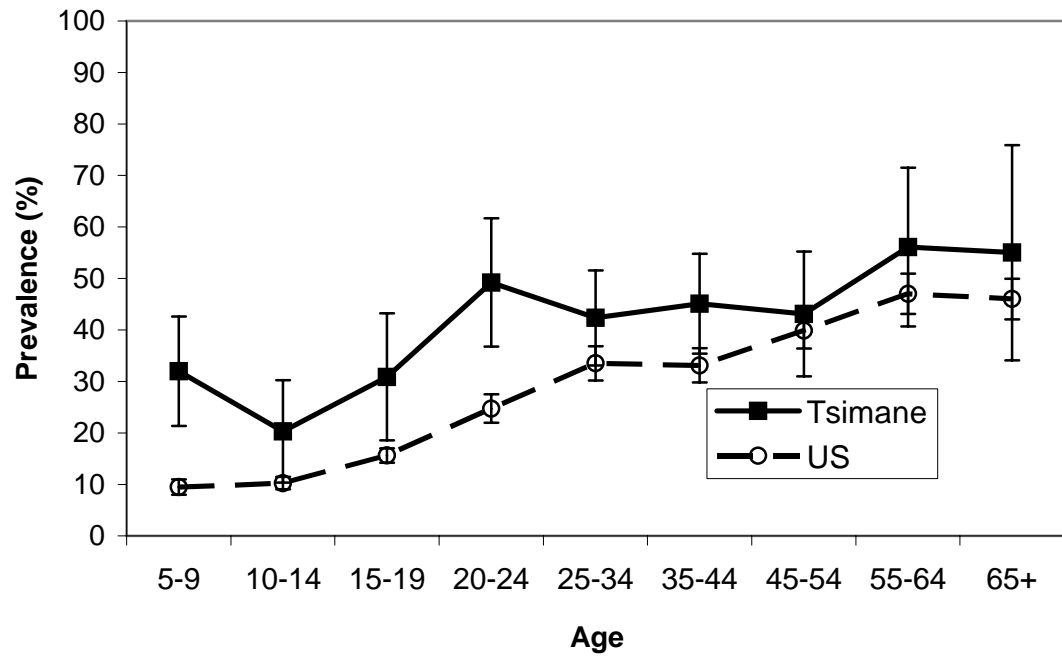
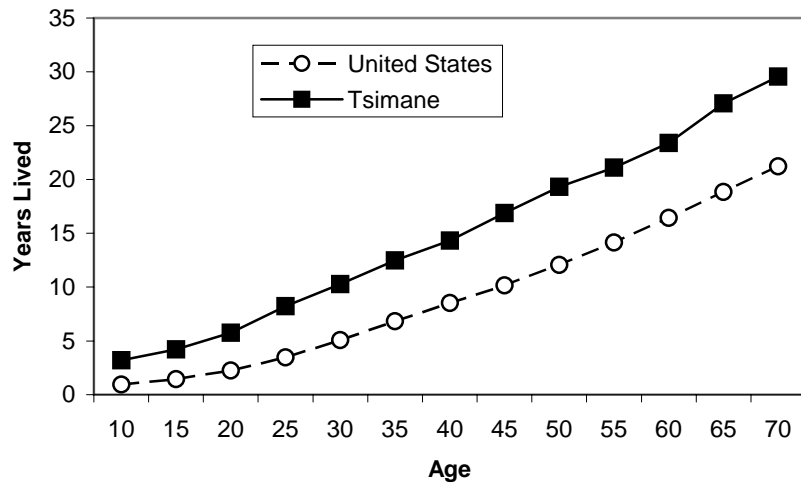


Figure 3: Years lived with High CRP for those who survive to specified age



Supplementary material

Table 1: Years lived with high CRP for those who survive to specified age; Proportion of life lived with high CRP up to specified age

Age	Tsimane		United States	
	Yrs.with High CRP	Proportion of Life Lived with High CRP	Yrs.with High CRP	Proportion of Life Lived with High CRP
10	3.6	.36	1.0	.10
15	6.1	.41	1.5	.10
25	10.3	.41	3.5	.14
35	15.0	.43	6.8	.19
55	24.5	.45	14.1	.26
65	30.1	.46	18.8	.29