Early origins of health disparities: infectious burden and socioeconomic status in U.S. children.

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Abstract:

Socioeconomic status is consistently associated with adult and child health. Recent work in biodemography suggests that life-time exposure to infection and inflammation may be an important determinant of later-life morbidity and mortality, and that height is one useful marker of this exposure. Early exposure to infections during critical periods can predispose individuals to chronic disease, in part through the reallocation of energy away from growth needed for immune and inflammatory responses. Recent work has found that markers of inflammation vary by socioeconomic status in adults, but little is known about the sources of these differences in inflammation. This paper uses novel biomarker data from the Third National Health and Nutrition Examination Survey (NHANES III) to test whether the burden of common chronic infections such as Helicobacter Pylori (H Pylori) and Cytomegalovirus (CMV) is related to socioeconomic status in U.S. children ages 6 and older, and whether these chronic infections contribute to health outcomes including height for age. We find significant associations between family income, parental education, and race/ethnicity and several individual infections as well as our overall burden of infection index. Burden of infection is found to be significantly associated with height-for-age net of race/ethnicity, family income, and parental education.

BACKGROUND

Socioeconomic status is consistently associated with adult and child health. Recent work has suggested that gradients in child health by family income begin early in life, and may get steeper with age(1, 2). Pathways such as health behaviors and access to medical care have thus far not explained much of these relationships(1, 3). Recent work in biodemography has suggested that a reduction in life-time exposure to infection and inflammation may be have been an important determinant of cohort declines in later-life morbidity and mortality. Crimmins and Finch argue that cohorts with lower infectious disease mortality in childhood can be characterized by a "cohort morbidity phenotype" that links their early life experience to later life cohort mortality patterns. They also suggest that these cohort differences in chronic inflammation are reflected in differences in adult height as a result of the high metabolic demands of the inflammatory response(4). Adult height, in turn, has been of interest to economists due to its consistent relationship with wages, performance on cognitive tests, and longevity(5, 6).

Early exposure to infections during critical periods is thought to predispose individuals to chronic disease, in part through the reallocation of energy away from growth needed for immune and inflammatory responses(7). In this way, responses to early environments may model immune system and growth trade-offs for the remainder of the life course(7). *In utero* exposure to the 1918 flu pandemic has been found to increase the risk of health outcomes including cancer, hypertension, and heart disease, as well as lower educational attainment and income(8, 9). These results illustrate the potential for early life

events to influence human capital accumulation as well as health, reinforcing health inequalities across the life course.

Markers of inflammation were recently found to vary by socioeconomic status in U.S. adults(10-12). Seroprevalence rates of several persistent infections have also been found to differ among adults by race/ethnicity and socioeconomic status in the U.S.(13, 14). Given the substantial differences in mortality rates by socioeconomic groups in the U.S.(15, 16), we ask whether differences in early infectious exposures that vary by factors such as socioeconomic status and race/ethnicity contribute to a "morbidity phenotype" gradient within cohorts. This "morbidity phenotype" gradient, caused by differential exposure and/or susceptibility to infectious disease early in life, can potentially contribute to health inequalities in two ways, both through direct links to later life health and through effects on cognitive functioning and human capital accumulation. While relationships between socioeconomic status, inflammation, and infections are beginning to be explored in adults, little is known about whether disparities in infections and inflammation exist at young ages in the U.S.

In addition to the idea that lifelong burden of infection and inflammation may help explain cohort changes in life expectancy over the least century(17), there is growing evidence linking specific chronic infections to chronic disease outcomes in contemporaneous populations. For example, herpesviruses such as cytomegalovirus (CMV) and herpes simplex virus type 1 (HSV-1) have been linked to inflammatory processes, cardiovascular disease, frailty, cognitive outcomes, and Alzheimer's disease (18-22). Much earlier in the lifecourse, recent work has suggested a link between fetal exposure to herpesviruses and preterm birth(23). Exposure to CMV and HSV-1 is very

common in early life (24), with average seroprevalence in the U.S. close to 50% in the 20-29 age group, rising to 89% by ages 70-79(24). Although infection with CMV and HSV-1 often passes undiagnosed because of their asymptomatic properties, these viruses remain latent in the host for life, with risk of reactivation due to stress and aging (25). While most people will get infected with these viruses by the time they reach older ages, it is possible that individuals infected earlier in life will face a greater pro-inflammatory toll over their life course due to the need for sustained immune vigilance over these viruses.

Helicobacter pylori (*H. pylori*) is another prevalent pathogen that can lie dormant in the body for decades until the bacteria-host equilibrium is disturbed. Besides its well-known role in peptic ulcer disease, *H pylori* is the major risk factor for gastric cancer. *H pylori* has also has been implicated in the development of stroke and ischemic heart disease, through suggested pathways including chronic inflammation, lipid alterations, and endothelial dysfunction(26). Hepatitis B virus (HBV), known for its role in chronic liver disease, has been hypothesized to contribute to artherogenic diseases via systemic effects on immune response and colonization of vascular tissues, though the evidence for its association with stroke and myocardial infarction is mixed(11, 12). Hepatitis A, though commonly thought to be eliminated from the body after acute infection, may also persist in the host or establish a chronic, subclinical inflammatory condition. Seropositivity to hepatitis A was found to be associated with both coronary artery disease (CAD) and elevated C-reactive protein (CRP) levels in U.S. adults, after controlling for age, race, sex, smoking, diabetes, cholesterol, hypertension, other infections, and occupational status(27).

Beyond the impact of individual infections, there is developing evidence that the presence of multiple chronic infections may contribute to disease through an overall

downregulation of immune function and a systemic pro-inflammatory environment (28-31). These persistent infections provide a unique opportunity to examine a specific immunological pathway through which socioeconomic status may affect health outcomes.

This paper seeks to bring together these different lines of research with novel biomarker data to test whether the burden of common chronic infections including Helicobacter Pylori (H Pylori), Cytomegalovirus (CMV), herpes simplex virus-1, Hepatitis A Virus (HAV) and Hepatitis B Virus (HBV) is related to socioeconomic status in U.S. children ages 6 and older, and whether this infectious burden contributes to health outcomes including height for age in U.S. children.

DATA

The analyses are based on data from the National Health and Nutrition Examination Survey (NHANES III), collected in two phases from 1988 to 1994. NHANES III contains a cross-sectional representative sample of the U.S. civilian non-institutionalized population, with an oversample of Mexican Americans and non-Hispanic Blacks. Data were collected in household face-to-face interviews and medical examinations, which included the collection of blood and urine for laboratory tests. Details of the sampling design and protocol are available from National Center for Health Statistics(32). There are 6936 children age 6-17 in the interview sample.

MEASURES

Sociodemographics: Childhood socioeconomic status is measured as the years of education of the household reference person and annual family income. Family income is coded as the

midpoint of each of the 26 reported categories (using $65,000 for the incomes above $50,000), adjusted for inflation between the two NHANES III phases using the Consumer Price Index. Income was then log-transformed due to the skewness of the distribution. Race/ethnicity is categorized in four categories (non-Hispanic White, Non-Hispanic Black, Mexican-American, and Other).

Individual Infections: We use available seropositive status for *H.pylori*, CMV, HSV-1 HBV, and HAV, coded as 1=seropositive, 0=seronegative). *H. pylori* serologic testing was done using a commercial IgG ELISA (Wampole Laboratories, Cranbury NJ)(33). *H Pylori* testing was conducted on samples from Phase I only. CMV specific IgG seropositivity was measured with an ELISA (Quest International Inc., Miami FL)(34). Solid-phase enzymatic immunodot assays were used to detect antibody seropositivity to HSV-1(33). HSV-1 serostatus was obtained only for respondents ages 12 and older. Hepatitis B serostatus was determined by core antigen enzyme-linked immunoassay (CORAB, Abbott Laboratories)(32) Testing for HAV serostatus was determined using a commercially available enzyme immunoassay (HAVAB-EIA, Abbott Laboratories, Abbott Park, Illinois)(35).

Burden of infection: Serostatus to *H. pylori*, CMV, HAV, and HBV are used to construct several burden of infection indices. Due to sample limitations (*H. pylori* was tested only in samples from phase I of the survey), we create two different burden of infection indices:

Burden1= CMV, HAV, HBV & *Hpylori,* n=2075 (0= 0 infections, 1= 1 infection, 2= 2 infections, 3= 3-4 infections)

Burden2=CMV, HAV, & HBV, n=4501 (0=0 infections, 1= 1 infection, 2=2-3 infections)

As HSV-1 was tested only in respondents 12 and older, this would further limit our sample and thus it is excluded from our burden of infection ordered logit models, though included in the structural equation models that can take into account missingness.

Outcomes: Height is measured as the sex- and age-specific z-score, based on the 2000 CDC growth charts. General health status is assessed by the parent based on traditional 5-point scale (excellent, very good, good, fair, or poor). While a large literature has documented relationships between self-rated health and health outcomes such as mortality in adults(36), less is known about the meaning of this measure in children, reported by parents. Nonetheless, this measure has been the focus of much of the literature on income gradients in children's health(1, 2, 37), and alternative summary measures of children's health are difficult to obtain. We dichotomize health status into 0=excellent or very good health, and 1= good, fair, or poor health. Chronic respiratory conditions are measured by asking whether a doctor ever said the child has asthma or chronic bronchitis.

METHODS

Logit models are used to estimate the association between race/ethnicity, education, and income and seropositivity to individual infections, as well as the association between infections and dichotomous poor/fair health and respiratory illness measures. Ordered logit models are used to estimate the association between SES and categorical burden of infection. Linear regression models are used to estimate the association between individual infections and height z-scores. We compare both traditional regression models and structural equation models (SEM) for our analyses. The advantages of SEM over standard regression analyses relate to its handling of measurement and missing data. In

the SEM models, burden of infection is conceptualized as a latent variable measured with a number of indicators. We use confirmatory factor models to first allow the covariance structure of the data to capture the burden of infection variable better than the more crude count index measure. The second major advantage to SEM concerns the practical constraints of the NHANES III data, where some infections have been measured in different subsets of the sample (for instance, H.pylori was assessed only during phase I (1988-1991)). With regression methods, we would have to exclude any cases missing H pylori. SEM allows us to use all observations by calculating the covariance matrix from all available data points. Our full model is shown in Figure 1. First we build the measurement models for health and infectious burden. Second, we study the 'bivariate' patterns of the three factors (SES, infectious burden, and height).

RESULTS.

Descriptive Statistics for the NHANES III sample are shown in Table 1. Among U.S. children aged 6-17, seroprevalence of CMV was 38.5%, H Pylori 26.6%, Hepatitis A 9.9%, and Hepatitis B 1.8%. Among children ages 12-17, seroprevalence of HSV-1 was 41.8%.

Table 2 reports associations between sociodemographic characteristics and each infection based on individual logit models for seropostivity of each infection. Table 2 also shows similar results for ordered logit models predicting the odds of different levels of infection burden in the last three columns. These models are all simultaneously adjusted for race/ethnicity, education of the household reference person, and family income. The odds of being infected with H Pylori, CMV, HSV-1, and Hepatitis B are significantly

higher for non-Hispanic black compared to non-Hispanic White children, with no increased likelihood seen for Hepatitis A. For Mexican-American children, there are increased odds of infection with H Pylori, CMV, HSV-1, and Hepatitis A compared to non-Hispanic white children. In addition to race/ethnicity, education of the household reference person is significantly associated with the likelihood of infection for all pathogens. Net of education and race/ethnicity, increased family income is associated with lower odds of infection for CMV, HSV-1, and Hepatitis B. The coefficients for the association between family income and H Pylori and Hepatitis B are of similar magnitude to the other infections but the standard errors are less precise due to the smaller sample size tested for H Pylori and the small number of cases of Hepatitis B. The results for burden of infection are similar to those of the individual infections. Non-Hispanic Blacks have greater odds of seropositivity to more infections as measured by Burden2, and Mexican-Americans have greater odds of seropositivity to more infections compared to non-Hispanic whites for both definitions of burden of infection. Parental education and family income are significantly related to the total number of infections after adjustment for race/ethnicity.

Table 3 shows results from logit models of how the individual infections are associated with the likelihood of reporting poor/fair health and asthma/respiratory problems. Linear regression is used to predict height for age z-scores. The first column for each outcome reports unadjusted relationships, the second column reflects results adjusted for age, sex, race, education and income. We see that while CMV, H pylori, and Hepatitis A are associated with greater odds of reporting poor/fair health in crude models, only Hepatitis A remains a significant predictor of poor/fair health after adjusted for

race/ethnicity, income, and education. While the coefficients on all infections are positive in both unadjusted and adjusted models, no infection significantly predicts greater odds of reporting asthma or chronic respiratory symptoms. Looking at height-for-age z-scores, the coefficients on all infections, both unadjusted and adjusted, are negative, suggesting a decrease in height for age with the presence of infection. CMV, HSV-1, and Hepatitis A significantly predict lower height-for-age in unadjusted models, with only Hepatitis A remaining significant after adjustment for race/ethnicity, income, and education.

Turning to the burden of multiple infections, we see evidence that the presence of multiple infections does contribute to the likelihood of reporting poor or fair health and to a reduction in height-for-age, with weaker results seen for reporting of asthma/chronic respiratory problems. After adjusting for age, sex, race/ethnicity, family income, and education of the household head, having two or three rather than 0 infections is associated with 91% higher odds of reporting poor/fair health (Burden 1). Looking again at Burden 1, having 2-3 rather than 0 infections is associated with 126% higher odds of reporting asthma/chronic respiratory problems after adjusting for age, sex, race/ethnicity, family income, and education. Looking at height-for-age, we see that having one infection compared to none is associated with a .143 standard deviation reduction in height-for-age, while having 2 or 3 infections compared to none is associated with a reduction in height-for-age of .552 standard deviations. These results are significant and remain robust to the inclusion of controls for race/ethnicity, family income, and education of the household head. Results for the alternative burden variable (Burden2) that includes *H Pylori* are also shown in Table 4a. Results for poor/fair health are significant only in unadjusted models, there are no significant results for asthma/chronic respiratory problems, while the results

for height-for-age are significant and similar in magnitude to the first burden of infection variable.

Table 5 shows the correlations between each individual infection. The correlations suggest a moderate positive association among most infections, with HBV having the weakest relationship to other infections. Overall, these results suggest some degree of clustering of individual infections that might contribute to the concept of a latent burden of infection variable. (Description of results of SEM models to be added here).

DISCUSSION:

To our knowledge, this is the first paper to examine the relationship between the burden of chronic infections, socioeconomic status, and health outcomes in U.S. children. The paper finds that family income and parental education are significantly associated with the likelihood of infection with several persistent infections in U.S. children aged 6-17, as well as the overall burden of multiple infections. In turn, there is evidence that the burden of multiple infections is associated with shorter height-for-age and an increased likelihood of reporting poor or fair health. This suggests that even in the context of relatively contemporary cohorts (aged 6-17 in 1988-1994) of U.S. children, infectious environments encountered early in life may be contributing to growth and future health outcomes. Moreover, the prevalence of individual infections and co-infection differs significantly by family income, parental education, and race/ethnicity, suggesting one pathway through which social factors might get embodied at an early age and contribute to later life health disparities.

This work seeks to bring together several disparate literatures to shed light on the early origins of health disparities in the United States. First, recent work has suggested that life-long chronic inflammation as a result of early infectious environments might contribute to cohort differences in mortality. This work has focused on differential infectious environments over time or across countries with different levels of development. We extend this work to look for potential sources of differences in inflammatory burden within cohorts, specifically differences by race/ethnicity and family income and education. One strength of this work is the use of individual data measuring exposure to infections, as opposed to previous work looking at infant mortality rates as a proxy for early life infectious exposures. While we acknowledge that our particular infections are also imperfect proxies for the overall pathogen and inflammatory burden, we have used multiple methods including structural equation models to confirm the validity of a latent infectious burden construct.

Epidemiological research has also recently highlighted the potential role of persistent infections in the development of inflammation-related diseases of aging. This paper examines for the first time socioeconomic differences in U.S. children in several pathogens that have been specifically implicated in chronic disease. This work lays the foundation for exploration of a novel proximate biological pathway through which socioeconomic status may be related to health outcomes.

Future work should examine the sources of differential rates of seropositivity among U.S. children. With current NHANES III data, it is impossible to distinguish whether different rates are a result of increased *exposure*, increased *susceptibility,* or both. While H Pylori, Hep A and Hep B all have some hygiene and sanitiation related etiologies,

CMV and HSV-1 are extremely prevalent and spread through very casual contact similar to other common viruses such as colds. It is therefore less obvious why rates of these viruses would differ by social factors in the U.S. It is possible that in groups with historically higher rates of infection who predominantly live and work together, higher levels would persist over time due to the mathematics of transmission dynamics. Environmental factors associated with socioeconomic status such as household crowding, use of public transportation, or the number of children in the household, could contribute directly to exposure risk. Suppressed immune function as a result of stress, poor nutrition, smoking, or other environmental exposures could increase susceptibility to infections given equal levels of exposure. Low social status as well as indicators of pyschosocial stress have been linked to increased risk of respiratory infections in humans and other primates in experimental studies (38-41). Much less is known about the links between social status, stress, and susceptibility to infections in the broader U.S. population. Low social class was associated with lower secretory immunoglobulin (sIgA), cited as a first line of defense against infection, in a large community sample in Scotland (42). Taken together, these studies suggest that psychological stress associated with low SES could down-regulate various aspects of the cellular immune response, increasing susceptibility to infection. These ties are speculative at this time with respect to the current findings, and future work should aim build evidence regarding the sources of such early disparities in infections.

NHANES III biological specimen testing also pre-dated high sensitivity C-reactive Protein testing, and therefore we were unable to directly test the links between SES, infections, and inflammation in U.S. children. As new data become available, we are eager to directly test whether differences in chronic infections contribute to differences in

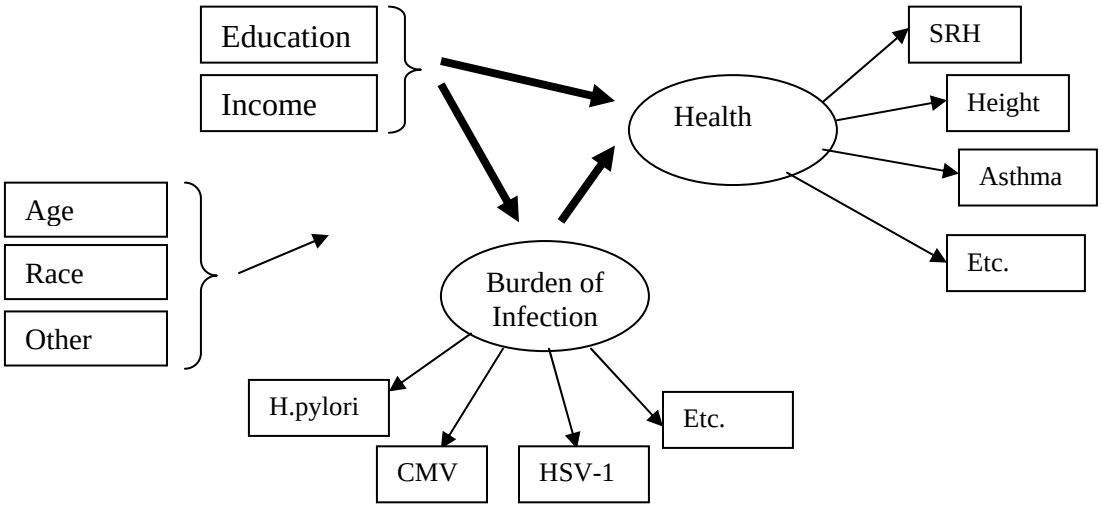
inflammatory burden amongst U.S. children, and whether these differences might help explain differences in chronic disease later in life.

With regards to height-for-age, our results suggest that the relationship between infectious environments and height may not be a historical relic or exist only in developing countries. The relationship between early environments and height has often been expressed in terms of net nutrition, to which infections detract. One might think that infections would take less of a toll on height in countries or cohorts where undernutrition is less of a concern. We thus found it more surprising that infections and height are linked in U.S. children in 1988-1994, though we did not examine food intake directly. It is possible that these relationships reflect not a direct link between infections and height in the children measured, but perhaps a relationship between the overall health of the mother and the height of the child. The mother herself may have been affected by early infectious environments, and these infections may also be more likely to be passed on to the child without directly affecting his height. The relationship between infectious burden and height-for-age was robust to inclusion of both mother's and father's height. We also tested whether the child's infectious burden predicted the mother's height, which would have suggested a more intergenerational story, but these results were not significant (not shown).

In sum, a high lifetime burden of chronic infections may lead to overall heightened inflammation and earlier development of chronic disease and mortality. The social distribution of these infections and their combined burden is thus an important topic for research on health disparities. This paper suggests that disparities in infectious burden

may begin early in life in the U.S, and these infections may also manifest themselves in children's growth and development early in life.

Figure 1. Conceptual model:



References.

1. Case, A., D. Lubotsky, and C. Paxson, *Economic Status and Health in Childhood: The Origins of the Gradient.* American Economic Review, 2002. **92**(5): p. 1308-1334.
2. Currie, J. and M. Stabile, *Socioeconomic Status and Child Health: Why Is the Relationship Stronger for Older Children?* American Economic Review, 2003. **93**(5): p. 1813-1823.
3. Dowd, J.B., *Early childhood origins of the income/health gradient: The role of maternal health behaviors.* Social Science & Medicine, 2007. **65**(6): p. 1202-1213.
4. Crimmins, E.M. and C.E. Finch, *Infection, inflammation, height, and longevity.* PNAS, 2006. **103**(2): p. 498-503.
5. Deaton, A., *From the Cover: Economics of Health and Mortality Special Feature: Height, health, and development.* Proceedings of the National Academy of Sciences, 2007. **104**(33): p. 13232-13237.
6. Case, A., and Christina Paxson, *Stature and Status: Height, Ability and Labor Market Outcomes* National Bureau of Economic Research Working Paper #12466, 2006.
7. McDade, T.W., *Life history, maintenance, and the early origins of immune function.* American Journal of Human Biology, 2005. **17**(1): p. 81-94.
8. Almond, D. and B. Mazumder, *The 1918 influenza pandemic and subsequent health outcomes: An analysis of SIPP data.* American Economic Review, 2005. **95**(2): p. 258-262.
9. Almond, D., *Is the 1918 Influenza Pandemic Over? Longâ€ Term Effects of In Utero Influenza Exposure in the Postâ€ 1940 U.S. Population.* Journal of Political Economy, 2006. **114**(4): p. 672-712.
10. Loucks, E.B., L.M. Sullivan, L.J. Hayes, et al., *Association of Educational Level with Inflammatory Markers in the Framingham Offspring Study.* Am. J. Epidemiol., 2006. **163**(7): p. 622-628.
11. Alley, D.E., T.E. Seeman, J.K. Kim, et al., *Socioeconomic status and C-reactive protein levels in the US population: NHANES IV.* Brain Behavior and Immunity, 2006. **20**(5): p. 498-504.
12. Ranjit, N., A.V. Diez-Roux, S. Shea, et al., *Socioeconomic Position, Race/Ethnicity, and Inflammation in the Multi-Ethnic Study of Atherosclerosis.* Circulation, 2007. **116**(21): p. 2383-2390.
13. Dowd, J.B., A.E. Aiello, and D.E. Alley, *Socioeconomic Gradients in Cytomegalovirus Seropositivity in the U.S.: NHANES III.* Epidemiology and Infection, 2008.
14. McQuillan, G.M., D. Kruszon-Moran, B.J. Kottiri, et al., *Racial and Ethnic Differences in the Seroprevalence of 6 Infectious Diseases in the United States: Data From NHANES III, 1988-1994.* Am J Public Health, 2004. **94**(11): p. 1952-1958.

15. Meara, E.R., S. Richards, and D.M. Cutler, *The Gap Gets Bigger: Changes In Mortality And Life Expectancy, By Education, 1981-2000.* Health Aff, 2008. **27**(2): p. 350-360.
16. Lantz, P.M., J.S. House, J.M. Lepkowski, et al., *Socioeconomic Factors, Health Behaviors, and Mortality: Results From a Nationally Representative Prospective Study of US Adults.* JAMA, 1998. **279**(21): p. 1703-1708.
17. Finch, C.E. and E.M. Crimmins, *Inflammatory Exposure and Historical Changes in Human Life-Spans.* Science, 2004. **305**(5691): p. 1736-1739.
18. Liu, R., M. Moroi, M. Yamamoto, et al., *Presence and severity of chlamydia pneumoniae and cytomegalovirus infection in coronary plaques are associated with acute coronary syndromes.* International Heart Journal, 2006. **47**(4): p. 511-519.
19. Sorlie, P.D., F.J. Nieto, E. Adam, et al., *A Prospective Study of Cytomegalovirus, Herpes Simplex Virus 1, and Coronary Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study.* Arch Intern Med, 2000. **160**(13): p. 2027-2032.
20. Itzhaki, R.F., M.A. Wozniak, D.M. Appelt, et al., *Infiltration of the brain by pathogens causes Alzheimer's disease.* Neurobiology of Aging, 2004. **25**(5): p. 619-627.
21. Aiello, A.E., M.N. Haan, L. Blythe, et al., *The Influence of Latent Viral Infection on Rate of Cognitive Decline over 4 Years.* Journal of the American Geriatrics Society, 2006. **54**(7): p. 1046-1054.
22. Schmaltz, H.N., L.P. Fried, Q.L. Xue, et al., *Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women.* J Am Geriatr Soc, 2005. **53**(5): p. 747-54.
23. Gibson, C.S., P.N. Goldwater, A.H. MacLennan, et al., *Fetal exposure to herpesviruses may be associated with pregnancy-induced hypertensive disorders and preterm birth in a Caucasian population*.* BJOG: An International Journal of Obstetrics and Gynaecology, 2008. **115**(4): p. 492-500.
24. Staras, S.A.S., S.C. Dollard, K.W. Radford, et al., *Seroprevalence of Cytomegalovirus Infection in the United States, 1988-1994.* Clin Infect Dis, 2006. **43**(9): p. 1143-1151.
25. Koch, S., R. Solana, O.D. Rosa, et al., *Human cytomegalovirus infection and T cell immunosenescence: A mini review.* Mechanisms of Ageing and Development, 2006. **127**(6): p. 538-543.
26. Manolakis, A., A.N. Kapsoritakis, and S.P. Potamianos, *A review of the postulated mechanisms concerning the association of Helicobacter pylori with ischemic heart disease.* Helicobacter, 2007. **12**(4): p. 287-297.
27. Zhu, J., A. Quyyumi, J. Norman, et al., *The Possible Role of Hepatitis A Virus in the Pathogenesis of Atherosclerosis.* The Journal of Infectious Diseases, 2000. **182**(6): p. 1583-1587.
28. Elkind, M.S.V. and J.W. Cole, *Do common infections cause stroke?* Seminars in Neurology, 2006. **26**(1): p. 88-99.

29. Espinola-Klein, C., H.J. Rupprecht, S. Blankenberg, et al., *Impact of Infectious Burden on Extent and Long-Term Prognosis of Atherosclerosis.* Circulation, 2002. **105**(1): p. 15-21.
30. Zhu, J., A.A. Quyyumi, J.E. Norman, et al., *Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels.* Am J Cardiol, 2000. **85**(2): p. 140-6.
31. Fernandez-Real, J.-M., A. Lopez-Bermejo, J. Vendrell, et al., *Burden of Infection and Insulin Resistance in Healthy Middle-Aged Men.* Diabetes Care, 2006. **29**(5): p. 1058-1064.
32. Gunter, E., B. Lewis, and S. Koncikowski, *Laboratory Procedures Used for the Third National Health and Nutrition Examination Surveys (NHANES III), 1988-1994, National Center for Health Statistics, Hyattsville, MD.* 1996.
33. *NHANES III Second Laboratory Data File Documentation, Series 11, No. 2A.* 1998 [cited 2007 October 30]; Available from: http://www.cdc.gov/nchs/nhanes/nhanes3/lab2-acc.pdf.
34. *Antibody to Cytomegalovirus IgG and IgM. NCHS NHANES III Documentation, Codebook and Frequencies page.* 2006 [cited 2007 October 30]; Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes3/depp.pdf.
35. Bell, B.P., D. Kruszon-Moran, C.N. Shapiro, et al., *Hepatitis A virus infection in the United States: Serologic results from the Third National Health and Nutrition Examination Survey.* Vaccine, 2005. **23**(50): p. 5798-5806.
36. Idler, E.L., L.B. Russell, and D. Davis, *Survival, Functional Limitations, and Self-rated Health in the NHANES I Epidemiologic Follow-up Study, 1992.* Am. J. Epidemiol., 2000. **152**(9): p. 874-883.
37. Currie, A., M.A. Shields, and S.W. Price, *The child health/family income gradient: Evidence from England.* Journal of Health Economics, 2006. **In Press, Corrected Proof**.
38. Cohen, S., S. Line, S.B. Manuck, et al., *Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates.* Psychosom Med, 1997. **59**(3): p. 213-221.
39. Cohen, S., *Social Status and Susceptibility to Respiratory Infections.* Ann NY Acad Sci, 1999. **896**(1): p. 246-253.
40. Cohen, S., W.J. Doyle, R.B. Turner, et al., *Childhood Socioeconomic Status and Host Resistance to Infectious Illness in Adulthood.* Psychosom Med, 2004. **66**(4): p. 553-558.
41. Cohen, S., *The Pittsburgh common cold studies: Psychosocial predictors of susceptibility to respiratory infectious illness.* International Journal of Behavioral Medicine, 2005. **12**(3): p. 123-131.
42. Evans, P., G. Der, G. Ford, et al., *Social Class, Sex, and Age Differences in Mucosal Immunity in a Large Community Sample.* Brain, Behavior, and Immunity, 2000. **14**(1): p. 41-48.

Table 1. Descriptive statistics, NHANES III children age 6-17.

	Mean or proportion	Standard error
Age	10.84	(.09)
Household size	4.65	(.06)
Income (infl.-adjusted dollars)	$37,073.7	(1210.7)
Education of head (years)	12.49	(.13)
Female	48.8%	(.01)
Race		
NH white	66.0%	(.03)
NH black	15.5%	(.02)
Mexican American	8.8%	(.02)
Other	9.6%	(.02)
Infections – proportion seropositive		
CMV	38.5%	(.02)
H. pylori	26.6%	(.01)
HSV-1	41.8%	(.02)
Hep. A	9.9%	(.01)
Hep. B	1.8%	(.00)
Burden1 (CMV, HAV., HBV)		
0	55.9%	(.02)
1	38.0%	(.02)
2-3	6.1%	(.01)
Burden2 (H. pyl, CMV, HAV, HBV)		
0	45.7%	(.02)
1	36.2%	(.01)
2	14.0%	(.01)
3-4	4.0%	
Health outcomes		
Fair/poor health	4.6%	(.00)
Good/fair/poor health	25.3%	(.02)
Asthma & bronchitis	13.6%	(.01)
Height (age-specific z-scores)	.17	(.03)

Note: adjusted for sampling design.

TABLE 2. The effect of demographics and socioeconomic status on each infection.

	H.pylori	CMV	HSV	Hep.A	Hep. B	Burden 2	Burden 1
Age	0.085***	0.034**	0.020	0.025	0.059	0.047**	0.031*
	(0.021)	(0.014)	(0.065)	(0.042)	(0.073)	(0.022)	(0.016)
Female	-0.167	0.254*	0.021	0.106	-0.229	-0.031	0.237*
	(0.143)	(0.132)	(0.155)	(0.207)	(0.316)	(0.117)	(0.135)
Black	0.844***	0.264**	0.464***	-0.353	0.861*	0.459**	0.140
	(0.182)	(0.132)	(0.172)	(0.293)	(0.508)	(0.193)	(0.134)
Mexican	0.342*	0.780***	0.667***	1.296***	-0.953	0.900***	1.112***
	(0.173)	(0.140)	(0.205)	(0.223)	(0.758)	(0.245)	(0.170)
Other	0.571**	0.934***	0.848**	1.215***	2.716***	1.518***	1.339***
	(0.262)	(0.345)	(0.356)	(0.342)	(0.585)	(0.393)	(0.378)
Education	-0.089***	-0.053***	-0.125***	-0.079**	-0.162**	-0.106***	-0.073***
	(0.027)	(0.019)	(0.039)	(0.040)	(0.070)	(0.020)	(0.019)
Income (log)	-0.129	-0.153**	-0.284***	-0.206**	0.227	-0.223**	-0.159**
	(0.103)	(0.069)	(0.100)	(0.087)	(0.263)	(0.099)	(0.065)
N							

*** p<0.01, ** p<0.05, * p<0.1

Shown are coefficients and standard errors.

Note: results for single infections are from logistic models, results for infection burden from ordered logistic models. The estimation adjusts for sampling design.

TABLE 3. The effect on health outcomes of single infections, gross and net effects.

	Poor/fair health		Asthma/Chronic Respiratory		Height Z-scores	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
H. pylori	0.755***	0.386	0.109	0.205	-0.130	-0.0985
	(0.229)	(0.256)	(0.330)	(0.368)	(0.0833)	(0.0836)
CMV	0.641***	0.180	0.193	0.199	-0.126**	-0.0671
	(0.207)	(0.207)	(0.177)	(0.209)	(0.0481)	(0.0503)
HSV-1	0.430	-0.231	0.218	0.284	-0.165*	-0.0295
	(0.328)	(0.305)	(0.221)	(0.234)	(0.0990)	(0.109)
HAV	1.121***	0.476*	0.336	0.440	-0.448***	-0.340***
	(0.258)	(0.252)	(0.245)	(0.286)	(0.0910)	(0.101)
HBV	0.110	-0.321	0.605	0.638	-0.371	-0.302
	(0.680)	(0.788)	(0.480)	(0.413)	(0.270)	(0.276)

*** p<0.01, ** p<0.05, * p<0.1

Shown are coefficients and standard errors.

Note: Each coefficient shown in the table is a results from a separate regression model. Results for poor/fair health and asthma were estimated using logistic regression. Results for height were estimated using OLS. Model 1 adjusts for age and gender. Model 2 adjusts for age, sex, race, family income and education of the household head.

TABLE 4a. The effect on health outcomes of infection burden (burden2).

	Poor/fair health		Asthma		Height	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Age	-0.0487	-0.0401	0.0443	0.0532	0.0262**	0.0256**
	(0.0394)	(0.0426)	(0.0298)	(0.0341)	(0.0120)	(0.0118)
Female	0.0494	0.00723	-0.277	-0.335	-0.0785	-0.0569
	(0.198)	(0.215)	(0.197)	(0.211)	(0.0600)	(0.0592)
Black		0.932**		0.263		0.318***
		(0.383)		(0.263)		(0.0791)
Mexican		1.878***		-0.488		-0.216***
		(0.355)		(0.419)		(0.0734)
Other		0.679		-0.482		-0.519***
		(0.724)		(0.628)		(0.0885)
Education		-0.0933***		0.0176		0.0136
		(0.0317)		(0.0368)		(0.0125)
Income (log)		-0.228		0.245**		-0.000832
		(0.143)		(0.116)		(0.0393)
Burden2, ref.=0						
1	0.272	-0.124	-0.00846	0.116	-0.144**	-0.145**

	(0.308)	(0.331)	(0.257)	(0.295)	(0.0691)	(0.0721)
2	0.622	-0.267	0.192	0.453	-0.368***	-0.262**
	(0.377)	(0.380)	(0.339)	(0.425)	(0.113)	(0.123)
3-4	1.680***	0.297	0.567	1.054	-0.701***	-0.378**
	(0.429)	(0.535)	(0.830)	(0.961)	(0.210)	(0.182)

*** p<0.01, ** p<0.05, * p<0.1
Shown are coefficients and standard errors.
Note: The results in each column and for each of the two burdens were estimated in separate models. Results for poor/fair health and asthma were estimated using logistic regression. Results for height were estimated using OLS. Model 1 adjusts for age and gender. Model 2 adjusts for age, sex, race, family income and education of the household head.

TABLE 4b. The effect on health outcomes of infection burden (burden1).

	Poor/fair health		Asthma		Height	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Age	0.0611*	0.0774**	0.00249	0.00719	0.00698	0.00852
	(0.0362)	(0.0386)	(0.0226)	(0.0232)	(0.00850)	(0.00900)
Female	0.278*	0.309*	-0.245	-0.298*	-0.115*	-0.111*
	(0.164)	(0.182)	(0.170)	(0.172)	(0.0584)	(0.0599)
Black		0.659***		-0.142		0.173***
		(0.235)		(0.164)		(0.0591)
Mexican		1.113***		-0.554**		-0.217***

		(0.239)		(0.278)		(0.0722)
Other		0.337		-0.0969		-0.166
		(0.552)		(0.531)		(0.107)
Education		-0.0979***		0.0294		0.0126
		(0.0250)		(0.0297)		(0.0103)
Income (log)		-0.383***		-0.134		0.0176
		(0.0939)		(0.0838)		(0.0319)
Burden1, ref.=0						
1	0.472**	0.140	0.198	0.198	-0.139**	-0.110*
	(0.201)	(0.224)	(0.176)	(0.200)	(0.0546)	(0.0582)
2-3	1.607***	0.648**	0.569*	0.815*	-0.544***	-0.386***
	(0.299)	(0.308)	(0.336)	(0.435)	(0.104)	(0.121)

TABLE 5. Correlations among individual infections

	H. pylori	CMV	HSV-1	HAV	HBV
H. pylori	1				
CMV	.24***	1			
HSV-1	.38***	.36***	1		
HAV	.27***	.32***	.29***	1	
HBV	.05	.09	.30***	.18**	1

*** p<0.01, ** p<0.05, * p<0.1
Note: not adjusted for sampling design.