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Early origins of health disparities: Burden of infection, health, and socioeconomic status in U.S. children

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ABSTRACT

Recent work in biodemography has suggested that lifetime exposure to infection and inflammation may be an important determinant of later-life morbidity and mortality. Early exposure to infections during critical periods can predispose individuals to chronic disease, in part through the reallocation of energy away from development needed for immune and inflammatory responses. Furthermore, markers of inflammation are known to vary by socioeconomic status in adults and may contribute to overall socioeconomic health inequalities, but little is known about how the sources of this inflammation differ over the life course. This paper uses novel biomarker data from the Third National Health and Nutrition Examination Survey (NHANES III) to test the association of the burden of common chronic infections (*Helicobacter pylori* (*H. pylori*), cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), hepatitis A and hepatitis B) with height-for-age and asthma/chronic respiratory conditions in U.S. children ages 6 and older, and the association of these chronic infections to children's socioeconomic status. A higher burden of infection is found to be associated with lower height-for-age as well as an increased likelihood of asthma net of race/ethnicity, family income, and parental education. Children with lower family income, lower parental education, and non-white race/ethnicity have a higher likelihood of infection with several individual pathogens as well as the overall burden of infection. Differential exposure and/or susceptibility to infections may be one mechanism through which early social factors get embodied and shape later-life health outcomes.

Background

Recent work in biodemography has suggested that reductions in lifetime exposure to infection and inflammation may 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 (Crimmins & Finch, 2006; Finch & Crimmins, 2004). More broadly, life-course epidemiology has drawn attention to the potential long-term impacts of early-life exposures for the development of chronic disease (Ben-Shlomo & Kuh, 2002). Social scientists are also increasingly drawing links between early-life conditions and later-life outcomes (Case, Fertig, & Paxson, 2005; Hayward & Gorman, 2004; Heckman, 2006), however, the precise biological pathways linking early-life conditions to later-life outcomes are not well understood.

Early exposure to infections during critical periods is thought to predispose individuals to chronic disease, in part through the reallocation of energy away from development needed for immune and inflammatory responses (McDade, 2005). Early environments may model immune and inflammatory responses for the remainder of the life course. It is well known that socioeconomic status (SES) is consistently associated with adult health outcomes. Childhood socioeconomic status may shape early-life exposures such as chronic infections, with potentially important implications for later chronic disease. Infections may have a direct impact not only on adult health, but also on future socioeconomic outcomes. For example, *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 (Almond, 2006; Almond & Mazumder, 2005). These results illustrate the potential for early-life infections to influence human capital accumulation as well as health, reinforcing health inequalities across the life course.

In contemporary cohorts, markers of inflammatory proteins such as C-reactive protein (CRP) have been found to vary by socioeconomic status in U.S. adults (Alley et al., 2006; Loucks et al.,

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2006; Ranjit et al., 2007). The sources of these differences in adult inflammation are less clear, but differences in pathogen burden are one possibility (Zhu, Quyyumi, Norman, Csako, et al., 2000). Infections elicit an inflammatory response from the innate immune system upon entry into the body, and chronic infections may elicit a persistent inflammatory response (Eskandari & Sternberg, 2002; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Segerstrom & Miller, 2004).

Seroprevalence rates of several persistent infections have been found to differ among adults by race/ethnicity and socioeconomic status in the U.S. (Dowd, Aiello, & Alley, 2008; McQuillan et al., 2004; Zajacova, Dowd, & Aiello, in press). If differences by socioeconomic status or race/ethnicity exist in the early acquisition of lifelong chronic infections, this might contribute to later-life health inequalities in two ways; through direct links to later-life health and/or through effects on cognitive functioning and human capital accumulation. Currently, little is known about whether differences in chronic infections exist during the critical early ages in U.S. children.

Infections and chronic disease

In addition to the idea that the lifelong burden of infection may help explain cohort changes in life expectancy over the last century (Finch & Crimmins, 2004), there is growing epidemiological 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 (Aiello et al., 2006; Itzhaki, Wozniak, Appelt, & Balin, 2004; Liu et al., 2006; Schmaltz et al., 2005; Sorlie et al., 2000). Focusing earlier in the life course, recent work has suggested a link between fetal exposure to herpesviruses and preterm birth (Gibson et al., 2008). Exposure to CMV and HSV-1 is very common in early life (Staras et al., 2006), with average seroprevalence in the U.S. close to 50% in the 20–29 age group, rising to 89% by ages 70–79 (Staras et al., 2006). 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 (Koch, Solana, Rosa, & Pawelec, 2006). Most people will be infected with these viruses by the time they reach older ages, but it is possible that individuals infected earlier in life will face a greater pro-inflammatory toll over their life course.

In addition to herpesviruses, several other pathogens have been linked to the development of chronic disease. *Helicobacter pylori* (*H. pylori*) 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 been implicated in the development of stroke and ischemic heart disease through suggested pathways including chronic inflammation, lipid alterations, and endothelial dysfunction (Manolakis, Kapsoritakis, & Potamianos, 2007). *H. pylori* has also been explicitly implicated in growth impairment in children (Mohammad, Hussein, Coward, & Jackson, 2008; Prentice & Darboe, 2008). 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 (Ishizaka et al., 2002; Rong et al., 2007; Sung, Song, Choi, Ebrahim, & Davey Smith, 2007). Hepatitis A (HAV), 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 (Zhu, Quyyumi, Norman, Costello, et al., 2000). 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 (Elkind & Cole, 2006; Espinola-Klein et al., 2002; Fernandez-Real et al., 2006; Zhu, Quyyumi, Norman, Csako, et al., 2000).

Infections and health outcomes in children

Height

Although much prior research has focused on links between infections and adult chronic health outcomes, the health costs of early infections may manifest themselves earlier in the life course. One potential marker of the costs of infection is differences in growth, which has rarely been explored in children in developed countries. Crimmins and Finch suggest that cohort differences in infectious burden are reflected in differences in adult height as a result of the high metabolic demands of the inflammatory response (Crimmins & Finch, 2006). Pro-inflammatory cytokines such as TNF-alpha and Interleukin-6 released in response to infection may directly affect the process of bone remodeling required for long bone growth, and direct viral infection of osteoclasts and osteoblasts has also been detected (Stephensen, 1999). Other mechanisms through which chronic infections are thought to affect growth include lower food intake, impaired nutrient absorption and direct nutrient loss (Stephensen, 1999). Height may also be a useful marker of broader health capital. Adult height has been of interest to economists due to its consistent relationship with wages, performance on cognitive tests, and longevity (Case & Paxson, 2006; Deaton, 2007).

Asthma

Asthma causes considerable morbidity in U.S. children and is the third leading cause of hospitalization in persons 18 or under in the United States (Eder, Ege, & von Mutius, 2006). Debate around the secular trend in increased asthma and other allergic diseases has focused on the "hygiene hypothesis," the idea that modern under-exposure to infectious agents may lead to immature and pro-allergic immune responses (Liu, 2007; Strachan, 1989). On the other hand, asthma is an inflammatory airway condition that may be exacerbated by infection-induced production of pro-inflammatory cytokines such as IL-6, which have been found to contribute to the structural remodeling of the airway wall in chronic asthma (Rodel et al., 2000). The expected association of infectious burden with reported asthma in U.S. children is thus not clear a priori.

This paper seeks to bring together these different lines of research with novel biomarker data to test (1) whether the burden of common chronic infections including *H. pylori*, cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), hepatitis A virus (HAV) and hepatitis B virus (HBV) is related to socioeconomic status in U.S. children ages 6–16, and (2) whether this infectious burden is associated with height-for-age or reported asthma/chronic respiratory conditions in U.S. children.

Data

The analyses are based on data from the National Health and Nutrition Examination Survey (NHANES III), collected between 1988 and 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