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Do environments in infancy moderate the association between stress and inflammation in adulthood? Initial evidence from a birth cohort in the Philippines

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ABSTRACT

Chronic inflammation is a potentially important pathway through which psychosocial stressors increase risk for cardiovascular disease. However, prior research on stress and inflammation has been conducted almost exclusively in high income, industrialized populations with low levels of infectious disease. In this study we test the hypothesis that psychosocial stressors are associated with elevated concentrations of C-reactive protein (CRP) among young adults in the Philippines (n = 1622), who have grown up in an ecological and epidemiological setting that differs substantially from that of the US. In addition, we apply a developmental, ecological perspective to consider whether microbial and nutritional environments in infancy alter patterns of association between stressors and CRP. Data come from the Cebu Longitudinal Health and Nutrition Survey, a prospective cohort study that began collecting data in 1983–1984 when participants were *in utero*. A series of regression models indicate trends toward significant interactions between perceived stress and environmental factors in infancy, including exposure to animal feces, season of birth, and birth weight. Parental absence in childhood was a significant predictor of CRP in adulthood in interaction with exposure to animal feces in infancy. Positive associations between stressors and CRP were only evident for individuals with lower levels of microbial exposure in infancy, or lower birth weight. These results suggest that early environments influence the development of inflammatory phenotypes in ways that moderate sensitivity to psychosocial stressors in adulthood, and they underscore the value of a comparative, developmental approach to research on social environments, inflammation, and disease.

1. Introduction

Inflammation plays a central role in innate immune defenses against infectious disease (Kumar and Clermont, 2004), but recent research has focused on the role of chronic, low-grade inflammatory processes in the pathophysiology of a wide range of chronic degenerative diseases (Libby et al., 2002; Pearson et al., 2003). In particular, elevated concentrations of C-reactive protein (CRP) have been consistently associated with increased risk for cardiovascular disease (Ridker et al., 1998), type II diabetes (Pradhan et al., 2001), late-life disability (Kuo et al., 2006), and mortality (Harris et al., 1999; Jenny et al., 2007). A parallel line of research has demonstrated that psychosocial stressors are positively associated with inflammation (Lutgendorf et al., 1999; Maes et al., 1999; Owen et al., 2003; McDade et al., 2006; Miller et al., 2009a,b; Kiecolt-Glaser et al., 2010), pointing toward inflammation as a potentially important pathway through which psychosocial environments shape risk for cardiovascular disease, and other diseases of aging (Black, 2002; Steptoe et al., 2007).

Relatively few studies have pursued a developmental, life course approach to evaluating the long-term effects of early psychosocial stressors on inflammation, with a few notable exceptions. Maltreatment and social isolation in childhood have been associated with elevated CRP in young adults in New Zealand (Danese et al., 2007), while harsh family environments and socioeconomic adversity early in life predict elevated CRP and enhanced inflammatory responses to challenge in the US and Canada (Taylor et al., 2006; Miller et al., 2009a,b; Miller and Chen, 2010).

A limitation of current research on stress, inflammation, and disease is that it has focused almost exclusively on individuals living in affluent, industrialized settings where the epidemiologic environment is defined by low prevalence of infectious diseases and high prevalence of chronic degenerative diseases of aging. Yet three-fourths of the world's deaths from coronary heart disease now occur in lower and middle income nations (Gaziano et al., 2010).

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This fact alone should motivate more international research on the causes and consequences of variation in inflammation, particularly since evidence is accumulating for considerable differences in baseline CRP concentrations across international settings (Vikram et al., 2003; Albert et al., 2004; Araújo et al., 2004; Ye et al., 2007).

In addition, there is a particularly compelling scientific rationale for embracing a more comparative, ecological approach: The human immune system is characterized by considerable developmental plasticity and ecological sensitivity, and nutritional and microbial exposures in infancy are important determinants of variation in aspects of immunity within and across populations (Yazdanbakhsh et al., 2002; McDade, 2003, 2005; Blackwell et al., 2010). By historical standards, people living in contemporary environments like the US enjoy unprecedented access to calorie-dense foods, low demands for physical activity, and regimes of sanitation and hygiene that have reduced—by orders of magnitude—the frequency and diversity of microbial exposures and burdens of infectious disease (Barrett et al., 1998; Popkin and Gordon-Larsen, 2004; Rook et al., 2004). From the perspective of ecology and evolutionary biology, it is reasonable to ask whether research conducted exclusively among overnourished, "under-infected" populations can adequately capture the full range of variation that is necessary to understand the determinants of inflammatory phenotypes and their consequences for disease (McDade, 2003; Gurven et al., 2008).

The implications of this perspective for research on social environments, inflammation, and disease have yet to be explored. The first objective of this paper is to investigate whether psychosocial stressors (perceived stress in adulthood, adversity during childhood), predict elevated CRP among young adults in the Philippines. The Philippines is a lower-middle income nation that exemplifies current global trends toward increasing rates of overweight/obesity, cardiovascular diseases, and the metabolic syndrome as a result of recent economic, dietary, and lifestyle transitions (Tanchoco et al., 2003; Adair, 2004; Pedro et al., 2007). However, infectious diseases still account for significant burdens of morbidity and mortality, and respiratory infections rank beside ischemic heart disease as the top causes of mortality (WHO, 2006). Previously, we have shown that lower birth weight is associated with higher CRP in young adulthood in the Philippines, and that elevated levels of microbial exposure in infancy predict lower CRP (McDade et al., 2010). We have interpreted these findings in light of prior research pointing toward microbial exposures in infancy as normative ecological inputs that are important to guiding the development of the immune system. In the absence of such inputs, poorly regulated, or self-directed inflammatory activity may be more likely to occur.

The second objective of this paper is to build on this prior research and consider whether associations between psychosocial stressors and inflammation are moderated by early environmental exposures–exposures that influence inflammatory phenotypes in adulthood but that may be overlooked by studies conducted in affluent industrialized settings. Specifically, we hypothesize that psychosocial stressors will be positively associated with CRP for individuals born at lower birth weight, and for individuals with lower levels of microbial exposure in infancy. For individuals born at higher birth weights, and with higher levels of microbial exposure, we hypothesize that associations between stressors and CRP will be attenuated or absent.

2. Methods

2.1. Participants and data collection

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) is an ongoing cohort study in Metro Cebu, Philippines. Cebu is the second largest metropolitan area in the Philippines, and when the CLHNS began collecting data in 1983 Filipino families lived in a wide range of settlements, including rural towns and remote outlying areas, as well as dense urban areas with affluent neighborhoods and poorly constructed squatter camps (McDade and Adair, 2001; Adair et al., 2011). Approximately half the homes in the study had electricity, more than three quarters collected water from an open source, less than half used a flush toilet, and more than half had animals (e.g., dogs, chickens, goats, pigs) roaming under, around, or in the house. Since the CLHNS included households across the full range of socioeconomic conditions and settlement types in Cebu the sample includes substantial variation in environmental conditions.

The study began with the recruitment of 3327 pregnant women representative of the childbearing population in Cebu (Adair et al., 2011). A single stage cluster sampling procedure was used to randomly select 17 urban and 16 rural neighborhoods, and households were surveyed to locate all pregnant women. Home visits were made prior to birth, immediately following birth, and every 2 months for 2 years. Follow-up surveys were conducted in 1991–1992, 1994–1995, 1998–1999, and 2002, with the most recent comprehensive survey conducted in 2005 when the offspring were 20–22 years of age. Complete anthropometric, environmental, socio-demographic, psychosocial, and CRP data were available for 1651 participants. An additional 29 women pregnant at the time of the survey were not included in the analyses due to the effect of pregnancy on inflammation, yielding a final sample size of 1622. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

Participants provided information on household demographics, economic activities and resources, environmental quality, psychosocial factors, and health behaviors in face-to-face interviews conducted in their homes. Interviewers also provided assessments of household and neighborhood attributes. Standard procedures (Lohman et al., 1988) were implemented in the home to collect anthropometric measures of standing height (without footwear), weight (in light clothing), skinfold thicknesses, and waist circumference.

The original sample is representative of live singleton births to women in Cebu in 1983–1984, but a substantial number of participants have been lost to follow up, mainly due to migration out of the Metro Cebu area. We evaluated how the sample for this analysis differed from the original cohort as assessed when the study started in 1983. Compared to those with incomplete data, participants remaining in this study had higher mean birth weights (mean (SE) difference = 58.2 (15.9) grams, $p < 0.001$), they were more likely to come from families that owned their homes in 1983 (73.2% vs. 57.6%, $p < 0.001$), and that lived outside of urban communities (25.2% vs. 21.8%, $p < 0.05$). Participants did not differ with respect to household income or assets at baseline.

2.2. CRP analysis

Blood samples were collected in 2005 into EDTA-coated vacutainer tubes in the participants' homes in the morning after an overnight fast. Blood samples were kept in coolers on ice packs during transport for no more than 2 h and were then centrifuged at a central facility at the University of San Carlos to separate plasma prior to freezing at −70 °C. Samples were express shipped to Northwestern University on dry ice and stored frozen at −80 °C until analysis. CRP concentrations were determined using a high sensitivity immunoturbidimetric method (Synchron LX20, lower detection limit: 0.1 mg/L).

2.3. Measures of childhood adversity and perceived stress in adulthood

As a lower-middle income nation the overall level of material deprivation is higher in the Philippines than in the US and other