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Race/ethnic and socioeconomic differences in stress and immune function in The National Longitudinal Study of Adolescent Health

Jennifer B. Dowd [a, b, *], Tia Palermo [c], Laura Chyu [f], Emma Adam [d, f], Thomas W. McDade [e, f]

[a] CUNY School of Public Health, Hunter College, 2180 Third Avenue, New York, NY 10035, USA
[b] CUNY Institute for Demographic Research (CIDR), One Bernard Baruch Way, New York, NY 10010, USA
[c] Program in Public Health, Department of Preventive Medicine, Stony Brook University (SUNY), Health Sciences Center 3-071, Stony Brook, NY 11794, USA
[d] School of Education and Social Policy, Northwestern University, 2120 Campus Drive, Evanston, IL 60208, USA
[e] Department of Anthropology, Northwestern University, 1810 Hinman Avenue, Evanston, IL 60208, USA
[f] Cells to Society: The Center on Social Disparities and Health, Institute for Policy Research, Northwestern University, 2040 Sheridan Road, Evanston, IL 60208, USA

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ABSTRACT

Stress and immune function may be important mediators of the strong association between social factors and health over the life course, but previous studies have lacked the data to fully explore these links in a population-based sample. This study utilizes data from Waves I–IV of the U.S. National Longitudinal Study of Adolescent Health (Add Health) to test the associations of race/ethnicity and socioeconomic status (SES) with levels of perceived stress and exposure to stressful life events (SLE) among 11,050 adult respondents aged 24–32 in 2008–2009. We further tested whether race/ethnicity and SES were associated with Epstein–Barr Virus (EBV) specific IgG antibodies, an indirect marker of cell-mediated immune function. Finally, we tested whether measures of stress were associated with EBV IgG and whether there was evidence that they explain any associations between race/ethnicity, SES and EBV IgG. We found strong associations between lower SES and higher levels of perceived stress (OR 2.07, 95% CI 1.73–2.48 for < high school vs. college or above) and a high level of stressful life events (OR 7.47, 95% CI 5.59–9.98 for < high school vs. college or above). Blacks had higher odds of a high level of stressful life events compared to whites (OR 2.00, 95% CI 1.63–2.47), but not higher perceived stress (OR 1.11, 95% CI 0.96–1.28). Blacks also had significantly higher EBV levels compared to whites ($\beta = 0.136$, $p < 0.01$), *but lower SES was not associated with higher EBV IgG.* We found no evidence that stressful life events or perceived stress were associated with EBV IgG in this sample, and thus did not account for racial differences in EBV IgG. These results suggest consistent race/ethnic and SES differences in stressful life events, and confirm race/ethnic differences in markers of immune function that may have health implications across the life course.

1. Introduction

Stress is hypothesized to be an important determinant of multiple health outcomes as well as a potential mediator of the strong association between social factors and health over the life course (Seeman et al., 2010). Moreover, there is strong evidence that the immune system plays a mediating role in the association between psychosocial stress and health outcomes (Segerstrom and Miller, 2004). Thus far, the majority of population-based studies of stress and biological indicators have come from middle-aged and older populations (Glei et al., 2007; Seeman et al., 1997), with little data available on these interactions earlier in the life course. There is evidence that early environments can model immune system development through nutritional and infectious exposures as well as stress-related neuroendocrine pathways (Coe and Laudenslager, 2007; Fagundes et al., 2013; McDade, 2005).

One approach to investigating immune function in population-based studies is the IgG immune response to herpesviruses, such as Epstein–Barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV), or cytomegalovirus (CMV) (Glaser and Kiecolt-Glaser, 2005; McDade et al., 2000a,b). These viruses are distinctive because once infected, the host is not able to eliminate the virus. Adequate cell-mediated immune function is required to

* Corresponding author. CUNY School of Public Health, Hunter College, 2180 Third Avenue, New York, NY 10035, USA.
E-mail addresses: jdowd@hunter.cuny.edu, jennbeamdowd@gmail.com (J.B. Dowd), tia.palermo@stonybrookmedicine.edu (T. Palermo), laurachyu@gmail.com (L. Chyu), ek-adam@northwestern.edu (E. Adam), t-mcdade@northwestern.edu (T.W. McDade).

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maintain the virus in a dormant (i.e. non-replicating) state (Glaser et al., 1991). However, when immune control is weakened, the virus begins to replicate, which in turn stimulates memory B lymphocytes to increase output of virus-specific IgG antibody (Cacioppo et al., 2002). This results in the seemingly paradoxical observation that increased antibody levels ('titers') reflect poorer immune control (Glaser et al., 1991; Kuo et al., 2008). Thus higher EBV antibodies, one focus of this study, provide an indirect measure of one aspect of cell-mediated immune function (Glaser et al., 1991; Segerstrom and Miller, 2004).

The psychoneuroimmunological literature has found consistent associations between herpesvirus antibody titers and stress-related immune suppression (Glaser and Kiecolt-Glaser, 2005), although these findings are most often measured *via* short-term stressors in specialized populations. In particular, studies that have linked herpesvirus antibodies to stressors include academic stress in medical students and military cadets (Glaser et al., 1999; Sarid et al., 2002), caregiving for a family member with Alzheimer's disease (Glaser and Kiecolt-Glaser, 1997), involvement in a poor quality marriage (Herbert and Cohen, 1993), anticipation of space flight by astronauts (Mehta et al., 2000) and early childhood adversity including institutionalization and physical abuse (Shirtcliff et al., 2009). Elevated EBV antibodies specifically have been associated with chronic psychosocial stress in Samoan adolescents, discrimination-related stress in Latino immigrants in Oregon, and in U.S. adolescents in the Great Smoky Mountains exposed to life strain and traumatic events (McClure et al., 2010; McDade, Stallings, Angold, et al., 2000; McDade et al., 2000). Thus far, the majority of this research has come from small-scale, community-based samples that may not generalize to the broader U.S. population. Previous work using nationally representative data from the National Health and Nutritional Examination Survey (NHANES) cross-sectionally linked markers of socioeconomic status (SES) to elevated antibody titers of a related herpesvirus, cytomegalovirus (CMV) (Dowd and Aiello, 2009; Dowd et al., 2012). With the limited data on chronic or acute stressors available in NHANES, the connection between SES, stress, and impaired immune function was only speculative in these studies. The current study addresses this gap by examining the connections between social factors, stress, and immune function in young adults in a prospective survey.

Exposure to stressors is hypothesized to be patterned by the social environment (Baum et al., 1999), but little recent empirical evidence from the U.S. has explicitly examined this link. Lantz et al. found higher numbers of negative life events and higher ratings of marital, parental, and financial stress for those with less education and income among adults aged 24–64 years in the American's Changing Lives Study (Lantz et al., 2005), while Gryzwacz and colleagues found that adults aged 25–74 with lower levels of education reported *fewer* daily stressors in the National Study of Daily Experiences, but these stressors were more severe (Grzywacz et al., 2004). A small but growing literature suggests that SES may moderate associations between stress and health. Results from an adult German sample found that the association between CMV IgG and psychological stress was strongest in low SES individuals (Rector et al., 2014). Low SES has also been found to predict exaggerated stress reactivity of immune (Brydon et al., 2004) and HPA-axis activity (Gruenewald et al., 2006; Kunz-Ebrecht et al., 2004). The higher frequency or severity of stressors among disadvantaged individuals may deplete their "reserve capacity," leading to an erosion of the ability to cope with stress, which may manifest itself biologically (Gallo and Matthews, 1999). Individuals with the dual burden of socioeconomic disadvantage and race/ethnicity related stressors may be at even greater risk of limited access to psychosocial and material coping mechanisms (Myers, 2009). The idea of impaired coping is consistent with the biological conceptualization of allostatic load (Seeman et al., 2010).

The current study utilizes prospective data from Waves I–IV of the National Longitudinal Study of Adolescent Health (Add Health) to examine the associations between race/ethnicity and SES, stress, and EBV IgG levels. We hypothesized that black and lower SES respondents would report higher levels of perceived stress and a greater number of stressful life events. We also hypothesized that lower SES and black race/ethnicity would be associated with higher EBV IgG levels, and that these associations would be partially explained by higher levels of reported stress.

2. Data and methods

Data come from the National Longitudinal Study of Adolescent Health (Add Health), a longitudinal study of a nationally representative sample of adolescents begun in 1994–1995 and followed through 2008. Four waves of data are available, and the surveys collect data on social, economic, psychological and physical well-being with contextual data on the family, neighborhood, community, school, friendships, peer groups, and romantic relationships. Collection of biological data including EBV antibodies via dried blood spot was expanded in Wave IV to understand the social, behavioral, and biological linkages in health trajectories as the Add Health cohort ages through adulthood (Carolina Population Center). At the time of the Wave IV interview, respondents were between 24 and 32 years old, and included 80.3% of the eligible Wave I in-home sample respondents. Those lost to follow-up since Wave 1 were significantly more likely to be male, Hispanic or Asian, non-US born, and have a parent with less than a high school education. Trained and certified interviewers used a finger prick to obtain whole blood spots that were dried and shipped to the University of Washington Medical Center Immunology Lab, in Seattle WA for analysis. The blood spots were frozen until processing, and then analyzed for Epstein–Barr viral capsid antigen IgG using an adaptation of a previously validated ELISA protocol (McDade et al., 2000). Acceptability of the assay was determined by comparing the EBV optical density concentrations of the quality control samples with their established values. The sensitivity of the EBV assay was 9 AU/ml (arbitrary units per milliliter), the within-assay coefficient of variation was 3.9%, and the between-assay coefficient of variation was 10.2%. EBV concentrations of 162 dried blood spot and paired serum samples were strongly linearly associated (Pearson $r = 0.95$). Additional details of the protocol are available at: http://www.cpc.unc.edu/projects/addhealth/data/guides/add-health-wave-iv-documentation-measures-of-inflammation-and-immune-function (Whitsel et al., 2012). *IRB approved Add Health contracts for restricted data access are in place at both Northwestern University and Stony Brook University.*

2.1. Measures

Because associations between stress and herpesvirus antibody titers depend on having been previously infected, the primary outcome variable in this analysis was EBV IgG antibody titers for those respondents who are EBV seropositive. As Add Health has not yet provided guidance regarding seropositivity cut-offs despite the importance of excluding seronegatives for analysis (Dowd et al., 2013b; Slopen et al., 2013b), we estimated those seropositive as the top 90% of antibody levels for the survey-weighted population based on recent nationally representative estimates from NHANES (Dowd et al., 2013). Continuous EBV antibody levels were logarithmically transformed to normalize the distribution. Sensitivity analyses examining threshold effects for high EBV titers (top 10% and top 25%) as the outcome revealed similar substantive results and are available upon request.