Title: Neighborhoods and immune function in young adulthood

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Very Brief Background

A burgeoning field of research has found that chronic stress associated with adverse social and physical environments (e.g. poverty, violence) is associated with the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis system (Do et al., 2011; Karb et al., 2012). If prolonged or recurrent, imbalances in the HPA system can subsequently alter immune function and increase the risk for infectious disease, cancer and cardiovascular disease (Dhaber, 2012). However, few studies have explored the potential benefits of living in an immigrant or ethnic enclave on biological health despite prior research linking residence in an enclave to health outcomes associated with immune function. For example, one study found that Latino foreign born residents living in census tracts with a higher proportion of immigrants had lower rates of asthma and other respiratory problems (Cagney et al., 2007) while others found Mexican American women (second and later generations) living in a Latino enclave had lower rates of obesity compared to their peers in less segregated neighborhoods (Kershaw et al., 2013). Thus, the aims of this study are:

(1) To examine the effects of exposure to neighborhood Latino immigrant concentration during adolescence on young adults' cell-mediated immune function. Specifically, what are the effects of living in a Latino immigrant enclave during adolescence on immune function during young adulthood (net of current neighborhood)?

(2) To examine the moderating role of race/ethnicity and foreign birth on the relationship between neighborhood Latino immigrant concentration during adolescence and immune function in young adulthood. For example, is the potential effect of Latino immigrant concentration on cell-mediated immunity only significant for Latino or foreign born adolescents or is the effect significant for all adolescents living in the census tract?

(3) Age in years at wave 1 was also examined as a potential moderator to examine if the potential effect of Latino immigrant concentration on cell mediated immune function varied by adolescent development. Specifically, was the effect stronger or weaker depending on exposure occurring during early vs. later adolescence.

Methods

Study Design and Sample

Secondary data from the National Longitudinal Study of Adolescent Health (Add Health), waves 1 (1994-1995) and 4 (2007-2008) were utilized for this study. Add Health is a school-based, longitudinal study whose participants were in the 7th-12th grade at the first wave of data collection. To date, four waves of data have been collected from multiple sources and contexts providing a rich data source to examine the effects of the social environment on health and well-being during the transition from adolescence to adulthood (Harris et al, nd). The overall unweighted response rate for wave 4 was 80.3%; Add Health analyses found negligible non-response bias and that wave 4 participants were representative of those from wave1 (Brownstein et al, nd).

The sampling frame for this study consisted of those participants from the first and fourth waves of the Add Health study who were EBV seropositive (N=11,915). Participants missing data on model covariates were excluded from analysis (n=709 or 6%) for a final sample size of 11,206. We found no statistically significant differences in the levels of EBV antibody between young adults excluded from the sample for missing data and those included in the final analysis.

Measures

Dependent Variable

Cell-Mediated Immune Function

Latent herpes viruses, such as Epstein-Barr virus (EBV) are particularly useful biomeasures of immune function because after the initial infection the virus remains latent for life (Glaser et al., 1991; Stowe et al., 2010). Individuals with competent immune systems typically maintain a steady state of herpes virus antibodies kept in balance through the action of cytotoxic T-cells However, chronic stress decreases leukocyte production and functioning with the resulting immunosuppression enabling reactivation of the herpes virus and subsequent increases in antiviral antibodies (Stowe et al., 2010; Ford & Stowe, 2013).

Wave 4 of Add Health includes a measure of EBV antibodies enabling researchers to examine immune function as an outcome. Trained interviewers were used to collect capillary blood samples via a finger stick (Whitsel et al, 2012). The blood was collected on standardized filter paper, dried and shipped to the University of Washington, Department of Laboratory Medicine for analysis using an adapted version of a validated protocol (McDade et al., 2000). A commercial ELISA kit (DiaSorin, Stillwater, MN) was used to assay the blood spots for EBV viral capsid antigen (VCA) IgG antibodies; the sensitivity of the EBV assay was 9 AU/ml (plasma equivalent of 25), the within-assay coefficient of variation was 3.9%, and between-assay coefficient of variation was 10.2%. EBV concentrations (AU/ml) of a sample of dried blood spot and paired serum samples were strongly correlated (Whitesel et al, 2012).

Because the Add Health documentation does not identify the cut-off values for EBV seronegative individuals, the protocol developed by Dowd et al., (in press) was employed in which the bottom 10% of the EBV antibody levels were considered to be EBV negative (n=1323

with EBV VCA IgG antibodies < 49 AU/ml). Analyses found the EBV antibody level was positively skewed, thus the measure was log transformed for the final analyses.

Primary Independent Variables of Interest

Neighborhood Latino Immigrant Concentration, Waves 1 and 4

The neighborhood was defined as the census tract of residence; consistent with previous research. Wave 1 neighborhood measures were derived from the 1990 U.S. Census and provided to researchers in Add Health's contextual data set. Latino immigrant concentration was measured via the mean of 3 standardized items: proportion of Latino/Hispanic residents, proportion of linguistically isolated residents and proportion of foreign born residents (α=0.95). The wave 4 Latino immigrant concentration measure was identical to wave 1 except the data were derived from the 2009 American Community Survey 5-Year Estimates (α=0.93).

Individual Sociodemographic Factors

Individual sociodemographic factors were examined as potential moderators of the relationship between Latino immigrant concentration and cell mediated immune function (EBV antibody levels). *Race/ethnicity* and *foreign birth* (yes/no) were included as moderators to investigate the extent to which the potential effect of Latino immigrant concentration on cell-mediated immunity was only significant for Latino or foreign born adolescents or if the effect was significant for all adolescents living in the census tract. Adolescents were asked to select the racial category(ies) they identified with the most and in a separate question, if they were of Latino or Hispanic origin. Categories were created in which adolescents who reported they were of Latino or Hispanic origin were categorized as "Latino/Hispanic" regardless of their race; all other adolescents were categorized as non-Hispanic white, black/African American, Asian, multiracial and "other". *Age in years* at wave 1 was also examined as a potential moderator to

examine if the potential effect of Latino immigrant concentration on cell mediated immune function varied by adolescent development. Specifically, was the effect stronger or weaker depending on exposure occurring during early vs. later adolescence.

Potential Confounding Measures

The study incorporated an extensive set of measures based on prior research and theory that could potentially influence immune function as well as the effect of neighborhood Latino immigrant concentration on immune function. Neighborhood context measures at both waves included *Black residential concentration* measured as the proportion of Black residents in the census tract; *concentrated poverty* measured as the mean of 4 standardized items: proportion of households below poverty, proportion of households on public assistance, total unemployment rate and proportion of female-headed households with children; *residential instability* measured as the mean of 2 standardized items: proportion of households living in the census tract for 5 years or more and proportion of owner occupied homes; *population density* measured as the number of persons per km.

Individual-level measures at wave 1 included gender; parental economic hardship (received food stamps, housing assistance or AFDC in the past year; yes=1); lived in a two parent household at wave 1 (yes=1); and *parental education* (less than high school, high school degree/GED, some college vs college degree or more). Individual-level measures at wave 4 included two measures of *economic hardship* – (1) public assistance (on public assistance, welfare payments, or food stamps between waves 3 and 4) and (2) trouble paying bills in prior year (respondent/household had trouble paying rent/mortgage, trouble paying gas/electric/oil bills, no phone service due to inability to pay, or worried about running out of money for food); *college degree* (bachelor degree or higher); *body mass index* (BMI= weight (kg)/ height (m^2)

with BMI categories as underweight [16.5 to <18.5], normal weight [18.5 to <25], overweight [25 to <30] and obese [30 and higher]); *smoked in the prior 30 days*; *alcohol abuse* (continuous measure of DSM IV alcohol abuse symptoms, range 0-4); *depression* (CESD depression scale); count of common subclinical symptoms in the prior week (e.g. fever); count of common infectious or inflammatory diseases (e.g. influenza, rheumatoid arthritis); and if participant took anti-inflammatory medication within a certain time frame (e.g. corticosteroids, NSAIDS).

Analysis

Descriptive statistics were conducted using SAS survey procedures, version 9.2 (SAS Institute, Cary, NC) to examine sample characteristics. Multilevel modeling was employed using random intercepts multivariable linear regression models with HLM 6.08 software (Scientific Software International, Lincolnwood, IL). Four models were analyzed – the full model and three models examining the cross-level interactions between Latino immigrant concentration and age, race/ethnicity and foreign birth. Because Add Health does not provide survey weights for multilevel models analyzing neighborhoods, all multilevel analyses were conducted unweighted. However, school stratification variables were included in the multilevel analyses to adjust for the sampling design as directed by Add Health (personal communication, Kim Chantala, Add Health User's Conference, 2008). These variables included geographic area (Northeast, West, Midwest, and South – reference), school size, school urbanicity, school type (public or private) and ethnic mix (proportion of students who were non-Hispanic White). Sensitivity analyses were conducted using standard multivariable linear regression (all neighborhood measures disaggregated to the individual level), weighted (to account for attrition, oversampling) and adjusted for the complex survey design. Findings of both analytic strategies were consistent with one another, thus we

present the findings from the multilevel analyses due to our primary interest in the wave 1 neighborhood effects.

Results

Multilevel linear regression: Relationships between neighborhood Latino immigrant concentration and EBV antibody levels in young adulthood – National Survey of Adolescent Health (Add Health), Waves 1-4, N=11,206

	Model 1 b(SE)	**Model 2 b(SE)**	**Model 3 b(SE)**	**Model 4 b(SE)**
Level 1 Fixed Effects				
Wave 1 Sociodemographic Factors				
Age in years (w1)	0.005 (0.01)	0.006 (0.01)	0.005 (0.01)	0.005 (0.01)
Race and ethnicity				
Latino/Hispanic	0.048 (0.02)*	0.047 (0.02)*	0.049 (0.02)*	0.046 (0.02)*
Black	0.154 (0.02)***	0.154 (0.02)***	0.168 (0.02)***	0.154 (0.02)***
Asian	-0.013 (0.03)	-0.013 (0.03)	-0.019 (0.03)	-0.016 (0.03)
Multiracial	0.055 (0.03)	0.055 (0.03)	0.042 (0.03)	0.055 (0.03)
Other	0.058 (0.05)	0.058 (0.05)	0.047 (0.05)	0.057 (0.05)
White (reference)				
Foreign born	-0.017 (0.02)	-0.020 (0.02)	-0.014 (0.02)	-0.010 (0.03)
Level 2 Fixed Effects				
Wave 1 Neighborhood Context				
Latino immigrant concentration	-0.030 (0.01)**	-0.030 (0.01)**	-0.019 (0.03)	-0.030 (0.013)*
Latino immigrant concentration * age		0.004 (0.01)		
Latino immigrant concentration*Latino/Hispanic			-0.013 (0.03)	
Latino immigrant concentration*Black			0.0583 (0.04)	
Latino immigrant concentration*Asian			-0.0004 (0.05)	
Latino immigrant concentration*multiracial			-0.052 (0.67)	
Latino immigrant concentration*other			-0.142 (0.09)	
Latino immigrant concentration*foreign birth				-0.009 (0.01)
Black concentration	-0.014 (0.01)	-0.014 (0.01)	-0.010 (0.01)	-0.014 (0.01)
Concentrated poverty	0.008 (0.01)	0.008 (0.01)	0.007 (0.01)	0.008 (0.01)
Residential instability	0.006 (0.01)	0.006 (0.01)	0.006 (0.01)	0.006 (0.01)
Population density	0.005 (0.01)	0.004 (0.01)	0.004 (0.01)	0.004 (0.008)
Intercept	4.89 (0.04)***	4.89 (0.04)***	4.90 (0.04)***	4.89 (0.04)***
Random Effect				
Tau	0.00008	0.00008	0.00013	0.00004

Unweighted analysis adjusted for wave 1 and 4 potential confounding measures and stratification variables of geographic region, school urbanicity, school size, and ethnic mix.
***p<0.001, **p<0.01, *p<0.05

Brief Discussion and Next Steps

Our study is one of the first to find evidence that living in a Latino immigrant enclave during adolescence is associated with lower EBV antibody levels in young adulthood, adjusting for current neighborhood conditions and neighborhood- and individual-level confounding measures.

However, none of the potential moderators –age, race/ethnicity and foreign birth significantly affected the relationship between living in a Latino immigrant enclave during adolescence and young adult immune function. These findings suggest a lagged protective effect of living in a Latino immigrant enclave during adolescence on adult immune function and an effect that was significant regardless of age, race/ethnicity or foreign birth.

The next steps for this paper prior to presentation are to explore the extent to which there may be a cumulative protective effect of living in a Latino immigrant enclave on adult immune function taking into account the four waves of contextual data. A significant, but smaller negative association was found in our analysis between wave 4 Latino immigrant concentration and adult immune function, but the association was rendered non-significant when the wave 1 Latino immigrant concentration was included in the model. Thus, exploration of potential cumulative effects is warranted. In addition, we will explore mediating mechanisms through which living in a Latino immigrant enclave may influence immune function, including social support, social cohesion and healthy norms.

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