Annals of Epidemiology 23 (2013) 275–280

Contents lists available at SciVerse ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

# Racial–ethnic differences in Epstein–Barr virus antibody titers among U.S. children and adolescents

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ARTICLE INFO

*Article history:*
Received 12 September 2012
Accepted 15 February 2013

*Keywords:*
Disparities
Epstein–Barr virus
EBV
Viral reactivation
Race
Ethnicity
Stress
Immunity
Immune function

ABSTRACT

*Purpose:* To examine racial–ethnic differences in Epstein–Barr virus (EBV) antibody levels among U.S. children and adolescents. Elevated titers among seropositive youth can indicate viral reactivation—an indirect measure of impaired cell-mediated immunity.
*Methods:* Data from the 2003–2010 National Health and Nutrition Examination Survey were analyzed using multivariable linear regression accounting for the complex survey design and potential confounders. The sample comprised 4663 black-African American, Mexican American, and white youth aged 6–17 years who were EBV seropositive.
*Results:* EBV antibody levels were significantly higher for black-African American youth compared with their white peers ($b = 0.343$, $P < .0001$). Gender-stratified models were consistent with the total sample except differences in EBV antibody levels were greater between black-African American and white males ($b = 0.525$, $P < .0001$) than between black-African American and white females ($b = 0.169$, $P = .0185$). Differences in EBV antibody levels between Mexican American and white youth were only marginally significant in the total and the gender-stratified samples.
*Conclusions:* Black–white differences in EBV antibody levels were found suggesting EBV reactivation and potential disparities in immune function among minority youth. Research on multilevel factors contributing to the disparities is needed, including potential health implications over the life course for minority youth.



## Introduction

Racial–ethnic disparities in infectious and chronic disease are prevalent within the United States and occur across the life course [1]. Researchers hypothesize that these disparities are explained in part by the minorities' increased exposure to chronic stressors and the consequent dysregulation of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system [2–8]. This line of inquiry is supported by a substantial body of experimental research on the deleterious effects of chronic psychosocial stress to immune function [9–11], but few investigations of potential racial–ethnic differences in these pathways have been conducted due to sample size limitations [12]. Nationally representative surveys have increasingly incorporated biomarkers into their design [13–15], including latent herpes virus antibodies that researchers can use to measure viral reactivation—an indirect measure of impaired cell-mediated immunity [9,12,16,17]. The larger diverse samples associated with these surveys increase the statistical power to detect subgroup differences and strengthen the generalizability of the findings. Herpes viruses are particularly useful biomarkers to measure immune function because after initial infection, the virus remains latent for life [9,16,17]. Individuals with competent immune systems typically maintain a steady state of herpes virus antibodies kept in balance through the action of cytotoxic T-cells [17]. However, chronic stress decreases leukocyte production and functioning with the resulting immunosuppression enabling reactivation of the herpes virus and subsequent increases in antiviral antibodies [17]. Chronic or repeated viral reactivation can lead to prolonged or recurrent inflammation and impairment of cellular immunity, which depending on the viral pathogen can increase host susceptibility to other infectious pathogens, cancer, or chronic disease (e.g., cardiovascular disease and autoimmune disorders) [10,16–18].

Population-based studies to date have primarily focused on racial–ethnic variation in the prevalence of latent herpes viruses, particularly herpes simplex virus 1 and 2 (HSV-1 and HSV-2) and cytomegalovirus (CMV). Evidence from these studies indicate black–African American and Mexican American children and adults are more likely to be seropositive for these infections compared

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http://dx.doi.org/10.1016/j.annepidem.2013.02.008

with their white peers, above and beyond socioeconomic differences between the racial–ethnic groups [19–23]. However, research on racial–ethnic differences in viral reactivation is more limited, and the findings have been mixed. For example, in a nationally representative sample of CMV-positive adults, black-African Americans were found to have higher CMV levels compared with whites, but no significant differences between Mexican Americans and whites were found [24]. In contrast, a community study found that both black-African American and Mexican American adults were more likely to experience HSV-1 reactivation compared with white adults, but no significant racial–ethnic differences were found in Epstein–Barr virus (EBV) reactivation [17]. Among children and adolescents, a nationally representative study found no significant racial–ethnic differences in the level of CMV antibodies among CMV-seropositive youth aged 6–16 years [25]. However, because CMV is less common among children and adolescents [25] than adults [24], examination of other latent herpes virus infections more prevalent earlier in the life course may be needed to enhance statistical power. EBV, for example, is one of the most common latent herpes viruses in children and adolescents with approximately 90% of the U.S. population experiencing primary infection before young adulthood [9,16,17]. Therefore, this study builds on the aforementioned research using a nationally representative sample of children and adolescents to examine racial–ethnic differences in the level of EBV antibodies among seropositive youth—an indicator of viral reactivation and impaired cellular immunity.

## Methods

### *Study design and sample*

This study used a cross-sectional survey design with secondary data from the continuous National Health and Nutrition Examination Survey (NHANES), 2003–2010 [13]. The continuous NHANES uses a multistage probability sampling design with oversamples of certain population groups to enable stable estimation of the subgroups in statistical analyses. Data were collected across the waves via (1) an in-home survey conducted by trained interviewers using Computer-Assisted Personal Interview technology and (2) a physical examination with laboratory testing conducted by a health care team via the NHANES mobile examination center (MEC) approximately 2 weeks after the in-home survey. Survey items were asked to a responsible adult for youth younger than 16 years of age, whereas youth aged 16 years and older were asked the survey items directly with the exception of household information (e.g., income). Blood was drawn by a certified phlebotomist via venipuncture at the MEC and surplus sera stored. Unweighted response rates for the survey and laboratory testing among respondents aged 6–19 years ranged from 81%–91% across the survey years [13].

The sample for this study included EBV-seropositive youth aged 6–17 years who self-identified (or caregiver-identified) as black-African American, Mexican American, or white for the purpose of examining racial–ethnic differences in EBV antibody levels. The racial–ethnic categories were discrete in that the black-African American and white youth denied Hispanic origin. Although NHANES conducted EBV antibody testing on participants up to 19 years of age [13], the present study limited the age range to 17 years as stressors associated with normative life events (e.g., moving away from parents) between the ages 18 and 19 years could confound the findings [26,27]. Participants missing data on the variables of interest were excluded from the study ($n = 426$ or 8.4%) for a total sample size of 4663 seropositive youth. Analysis of missing data found youth who were black-African American or Mexican American were more likely to be excluded. However, no significant differences were found in either the presence or the level of EBV antibody in those participants excluded from the study due to missing data and those included in the present analyses.

### *Measures*

#### *Dependent variables*

EBV antibody was the dependent variable of interest. EBV testing was conducted by NHANES on the stored surplus sera of children and adolescents using a commercial enzyme immunoassay (EIA) kit (Diamedix Corporation, Miami, FL) for EBV viral capsid antigen (VCA) immunoglobulin G antibodies. Qualitative and quantitative values were obtained via an EIA index. The commercial assay kit defined participants as EBV seronegative if their EIA index was less than 0.90, equivocal if their levels were between 0.90 and 1.099, or positive if their levels were equal to or greater than 1.10 [13,28]. Per NHANES, youth with equivocal responses ($n = 44$) were excluded from the analyses. The dependent variable, EBV antibody was a continuous outcome derived from the quantitative EIA index. NHANES provides a complete description of the laboratory methodology for the commercial EIA kit on their Web site [13], and according to the manufacturer, the sensitivity and specificity of the test were greater than 95% [28].

#### *Primary independent variables*

Race–ethnicity was the primary independent variable of interest. NHANES created the racial–ethnic categories based on parent–guardian or youth self-identification [13]. Participants were first asked if the focal child or adolescent was considered to be Hispanic or Latino, and if yes, what country his or her ancestors came from. A list of racial categories was then shown and the participant was asked what race(s) they considered the focal child or adolescent to be. For youth who were Hispanic or Latino (regardless of race), NHANES categorized them in the public use data set as Mexican American if their ancestors came from Mexico or as "other" Hispanic if their ancestors came for a country other than Mexico. Youth who were not considered to be Hispanic or Latino were then categorized as black-African American, white, or other [13]. Because of the ambiguity of the other race–ethnic category (composed of youth were considered to be mixed race, Asian, American Indian, Alaskan native, or Native Hawaiian) and the small sample size of youth who were categorized as other Hispanic, our study focused on those youth who were Mexican American, black-African American or white.

#### *Potential confounding variables*

Additional measures based on prior research and theory that could influence immune function and potentially confound the relationships between race–ethnicity and EBV were included in the analyses. For example, immune function varies during the transition from childhood to adolescence due to maturation and puberty [29], thus a continuous measure of age was examined. Gender also was included as hormonal fluctuations associated with puberty, particularly estrogen, can impair the immune response [29–31]. Consistent with prior research [25,32], an indicator for foreign birth was included to account for the possibility of differential exposure to EBV in the early life environment among immigrant youth. Low socioeconomic status was associated with CMV antibody levels among youth in prior research [25], thus two indicators of household socioeconomic status were examined—low education (highest level of education in household less than high school) and family poverty (ratio of family income to poverty $<100\%$). Because household crowding can increase exposure to and the transmission of infectious pathogens, a continuous measure of household size was