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Childhood adversity and cell-mediated immunity in young adulthood: Does type and timing matter?

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ABSTRACT

Childhood adversity can have powerful effects on health over the life course. Persistent changes in cell-mediated immune function may be one pathway linking adverse childhood experiences with later disease risk. However, limited research has examined childhood adversity in relation to cell-mediated immune function, and in particular, immune response to latent viruses in adulthood. The present study investigated the association of two types of childhood adversity, socioeconomic disadvantage during adolescence and abuse prior to age 18, with Epstein–Barr Virus (EBV) antibody titers in a large nationally representative sample of young adults aged 24–32 years. Data were drawn from the National Longitudinal Study on Adolescent Health, Wave 4 (n = 13,162). We examined the associations of three indicators of adolescent SES (parental education, household income, and occupational status) and frequency and timing of physical and sexual abuse with EBV antibodies, controlling for age, sex, race/ethnicity, and presence of a smoker in the household during adolescence. Lower parental occupational status and some categories of lower education were associated with elevated EBV antibodies ($p < .05$), and individuals who reported sexual abuse that occurred more than 10 times had elevated EBV antibodies relative to individuals who were not sexually abused ($p = 0.03$). Among individuals exposed to physical abuse, those who were first abused at age 3–5 years had heightened EBV antibodies relative to those first abused during adolescence ($p = 0.004$). This study extends prior research linking early adversity and immune function, and provides initial evidence that childhood adversity has a persistent influence on immune responses to latent infection in adulthood.

Adverse experiences in childhood, such as poverty and maltreatment, are associated with poor health over the life course (Shonkoff, 2011; Shonkoff et al., 2009). Research on the mechanisms that link adverse experiences in childhood to poor health outcomes is critical to identifying targets for intervention (Miller et al., 2011; Taylor, 2010; Taylor et al., 2011). Animal models and human correlational studies suggest cell-mediated immune function as a potential pathway by which early adverse experiences impact adult health (Danese and McEwen, 2012). Socioeconomic disadvantage (Dowd et al., 2009, 2010, 2012), maltreatment and neglect (Shirtcliff et al., 2009), and stressful life events (Caserta et al., 2008; Wyman et al., 2007) in childhood are associated with altered cell-mediated immune functioning during childhood, including immune responses to latent viruses. Childhood adversity is also associated with adult health conditions that indicate dysregulated immune function, including gastrointestinal disorders (Wegman and Stetler, 2009), rheumatoid arthritis (Dube et al., 2009; Von Korff et al., 2009), and heightened pro-inflammatory biomarkers (Danese et al., 2007). Persistent changes in cell-mediated immune function could be one pathway linking adverse childhood experiences to health conditions later in life; however, limited research has examined whether different types of childhood adversity differentially impact cell-mediated immune function and whether this effect is apparent in young adulthood. Furthermore, almost nothing is known about whether there are specific developmental periods during childhood when exposure to adversity may have particularly pronounced effects on long-term immune function relative to other periods of development. It is important to characterize changes in immune function in relation to various types and/or timing of childhood adversity in order to clarify the mechanisms that engender disease vulnerability in adulthood. In the present study, we investigated the association between two types of childhood adversity, socioeconomic disadvantage and abuse (with consideration of both frequency

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and timing), on cell-mediated immunity in young adulthood, as indicated by elevated Epstein–Barr Virus (EBV) antibody titers.

Cell-mediated immune functioning has an important role in defending against autoimmune diseases, destroying intracellular bacteria and tumor cells, eliminating viral infections, and other immune reactions (Deepe, 1990; Marshall, 2011). It is estimated that 80–90% of Americans are infected with EBV by age 40, and it asymptomatically remains in the body for life (Glaser et al., 1991; Jones and Straus, 1987). Adequate cell-mediated immune function is required to maintain EBV in a latent state. Immunosuppression can cause EBV to reactivate and release antigens of the virus, which produces an antibody response (Glaser et al., 1991). Therefore, higher levels of EBV antibodies provide an indirect measure of one aspect of cell-mediated immune function, because elevated EBV antibodies reflect a failure of cellular immune processes to impede reactivation of the latent virus (Glaser et al., 1991; Segerstrom and Miller, 2004). Evidence suggests that psychosocially-induced immunological alterations can have implications for infectious illnesses, wound healing, progression of human immunodeficiency virus and cancers, and other diseases of aging (Godbout and Glaser, 2006; Kiecolt-Glaser and Glaser, 1995).

EBV antibody titers are recognized as one of the strongest immune-related correlates of psychosocial stress (Herbert and Cohen, 1993b; McDade and Hayward, 2009; McDade et al., 2000). In adult samples, increased EBV antibody titers have been associated with a wide variety of stressors, including caregiving for family members with Alzheimer's disease (Kiecolt-Glaser et al., 1987b), poor quality marriages (Kiecolt-Glaser et al., 1987a), marital separation or divorce (Kiecolt-Glaser et al., 1987a), medical school exams (Glaser et al., 1985a, 1986), perceived stress (Borders et al., 2010), loneliness (Glaser et al., 1985b), and discrimination (McClure et al., 2010). However, the majority of prior studies of stress in relation to EBV antibodies focus on concurrent acute and chronic stressors or laboratory challenges, rather than experiences from early life (Segerstrom and Miller, 2004). In a meta-analysis of over 300 empirical articles describing the relationship between psychological stress and immune system function in humans, Segerstrom and Miller (2004) identified only nine studies examining the persistent effect of stressors that occurred years in advance of immune assessment (referred to as "distant stressors" with combat exposure the most common stressor assessed); none of these studies considered adversities in early life.

Several previous studies have examined childhood adversities in relation to indicators of cell-mediated immune response to latent viruses in children and adolescents (Caserta et al., 2008; Dowd et al., 2012; McDade et al., 2000; Shirtcliff et al., 2009; Wyman et al., 2007). Using data on U.S. children ages 6–16 drawn from the National Health and Nutrition Examination Survey, Dowd and colleagues (Dowd et al., 2012) found that family poverty was associated with heightened antibody response to cytomegalovirus (CMV). In another study, (Shirtcliff et al. (2009) found elevated levels of antibodies to herpes simplex virus-1 (HSV-1) among adolescents who experienced early adversity due to institutionalization or physical abuse relative to healthy control participants. This study provides some evidence for an enduring influence of early experiences on immune functioning, because the observed differences were present many years after the institutionalized children were adopted into improved child-rearing settings. Because data linking childhood adversities to markers of immune control in adulthood are lacking, the extent to which childhood adversity has an enduring influence on cell-mediated immune functioning is unknown.

Within prior research on childhood adversity and immune biomarkers, it is common for studies to examine only one form of adversity (e.g., maltreatment or socioeconomic status) (Slopen et al., 2011). Although consideration of a single exposure can provide valuable information, studies that examine multiple types of stressors are able to distinguish whether certain types of stressors (e.g., acute, chronic) are more strongly associated with changes in immune functioning, which has implications for prevention. Related, research is needed is needed to extend knowledge about how timing of childhood adversity affects later physiological consequences. Studies that have examined timing of childhood adversity in relation to other physical (Bosch et al., 2012; Flaherty et al., 2009; Jun et al., 2011; Tottenham and Sheridan, 2010; Wilkin et al., 2012; Ziol-Guest et al., 2009) and mental (Fisher et al., 2010; Kaplow and Widom, 2007; Keiley et al., 2001; Kotch et al., 2008; Thompson et al., 2012; Thornberry et al., 2001; Wilkin et al., 2012) health outcomes suggest that timing matters – however, across existing studies, there are no consistent patterns to suggest that earlier or later exposure is more detrimental. Earlier exposure to adversity may have larger health consequences relative to later exposure, because physiological plasticity may be greater during early development (Gluckman et al., 2007). Alternatively, younger children may be buffered from experiences that would result in distress among older children because of their limited cognitive skills (Kaplow and Widom, 2007; Keiley et al., 2001), resulting in more detrimental effects of stressors experienced later in childhood.

Using data from the National Longitudinal Study on Adolescent Health (Add Health), the present study examined adverse childhood and adolescent experiences in relation to cell-mediated immune function in young adulthood. Specifically, we examined the associations between three indicators of SES during adolescence as well as physical and sexual abuse prior to age 18 with EBV antibodies. Among respondents who were abused, we also examined if the timing and frequency of abuse was associated with immune control in young adulthood. We hypothesized that lower SES in adolescence and exposure to abuse prior to age 18 would be associated with elevated EBV antibodies in young adulthood, and that more frequent and earlier experiences of abuse would be associated with poorer immune control relative to later experiences of abuse. Finally, in light of research suggesting that cigarette smoking (Anda et al., 1999; Lee et al., 2012) or depression (Dunn et al., 2012; Herbert and Cohen, 1993a) may be pathways linking childhood adversity to compromised immune-related processes, we examined current smoking and depressive symptoms as potential mechanisms for observed associations.

1. Methods

1.1. Sample

Data for this study were drawn from Add Health, an ongoing nationally-representative school-based study of adolescents in grades 7 through 12 that began in 1994 and has followed respondents into young adulthood (Udry et al., 1997). Add Health was designed to examine predictors of health-related behaviors, and particularly the role of social context. To date, there have been four follow-up surveys. Details about Add Health have been described in other publications (Harris et al., 2003; Resnick et al., 1997; Udry et al., 1997), and can be found at http://www.cpc.unc.edu/projects/addhealth/design. The present study utilized data from Waves 1 and 4.

At Wave 1, a multi-stage sampling design was used to enroll students into the study. A systematic random sample of 80 high schools was selected from the 26,666 U.S. high schools that had at least an 11th grade and at least 30 students in the school. These 80 schools were selected proportional to enrollment size. Schools were stratified by region, urbanicity, school type, and percentage of White students prior to sampling. For each of these selected high

schools, the largest feeder school was also invited to participate. Overall, 79% of contacted schools agreed to participate, which resulted in a total of 134 schools. Almost all participating schools (96%) hosted a confidential in-school survey (September 1994–April 1995) that was completed by 90,118 of 119,233 eligible students (75.6%). Students enrolled in the selected high schools were eligible to be a part of the main in-home sample. From April 1995 to December 1995, 20,745 students completed in-home interviews (79.5%). Wave 4 data were collected in 2008–2009, which included in-home follow-up interviews with 15,701 in-home Wave 1 respondents (80.25% of eligible sample members, e.g., not deceased, and residing in the United States); 14,800 of these participants were assigned a grand sample weight to contribute to the nationally representative estimates. At Wave 4, participants ranged in age from 24 to 32 years. Survey data were collected using a 90-min computer-assisted interview. Immediately after the survey, interviewers collected biological specimens, including blood spots.

Of the 14,800 Add Health participants in the national sampling frame, 13,244 respondents had a valid assessment of EBV antibodies, while 1,566 (10.61%) did not. Add Health participants with and without measures of EBV antibodies were similar in age, parental education, household income during adolescence, parental occupation, and exposure to abuse ($p > .05$); however, they differed by sex and race, whereby males and African Americans were disproportionately less likely to have a measure of EBV antibodies. In order to be included in our analysis we required that respondents had a valid assessment of EBV antibodies and at one least valid response to questions about childhood physical or sexual abuse. Accordingly, a total of 13,162 respondents comprised the analytic sample for this study. At Wave 1, written parental/guardian consent and adolescent assent were obtained, and written consent was obtained from Wave 4 respondents.

1.2. Measures

1.2.1. Cell-mediated immune function

At Wave 4, blood spot samples were collected for laboratory analysis of EBV antibody levels (au/mL). Following a standard protocol, trained and certified interviewers used a finger prick to collect capillary whole blood spots on standardized filter paper using sterile disposable lancets (see Whitsel et al. for details (Whitsel et al., 2012)). Blood spots were dried, shipped to the University of Washington, Department of Laboratory Medicine, frozen until processing, and then analyzed for EBV antibodies using an adaptation of a previously published assay protocol (McDade et al., 2000). Previous validation studies indicate a high correlation between serum and blood spot samples of EBV antibody titers (McDade et al., 2000). Because of the positively skewed distribution of EBV antibodies, we transformed this measure to a log-scale for analyses.

1.2.2. Socioeconomic status in adolescence

Household socioeconomic status (SES) during adolescence was reported at Wave 1, when respondents were ages 12–20. We examined three indicators of SES: highest level of parent education, total household income, and highest parental occupational status. Parents reported their highest educational attainment (less than high school; business, trade, or vocational high school; completed high school or received GED; business, trade, or vocational school post-high school; less than college; college graduate; professional training beyond college; missing response). If parent responses were missing ($n = 1799$, 13.7%), we used adolescent reports instead. Parents also reported pre-tax total income for everyone in the household, including income from welfare benefits, dividends, and other sources (≤$20,000; $20,001–$40,000; $40,001–$60,000; >$60,001; missing response). Adolescents reported the main occupations of their mothers and fathers. From their responses, we created four categories: professional/manager; technical/office worker/sales; service industry, construction, transportation, or military; missing response.

1.2.3. Childhood abuse

At Wave 4, respondents were asked to retrospectively report on experiences of physical and sexual abuse. To assess physical abuse, respondents were asked: *Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or down stairs?* To assess sexual abuse, respondents were asked: *How often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?* Respondents also reported the frequency that either of these abuses occurred. Response options included: 1 time, 2, 3–5, 6–10 times, or more than 10 times. From these responses, we created two four-category variables: never, 1–2, 3–10 times, and more than 10 times. If a respondent endorsed either physical or sexual abuse, they were asked to report their age that the time that each event first occurred. We created a six-category variable to reflect age at first abuse, consistent with prior research and stages of child development (Andersen et al., 2008). Categories included: infancy (0–2 years), preschool (3–5 years), latency (6–8 years), pre-pubertal (9–10 years), pubertal (11–13 years), and adolescence (14–17 years).

1.2.4. Potential pathways

We examined current smoking and depressive symptoms as potential mechanisms for observed associations. Current smoking was defined as a 3-category variable: *regular* (daily smoking for the past 30 days), *intermittent (*smoking on 1–29 out of the past 30 days), and *none* (Lloyd-Richardson et al., 2002). Depressive symptoms were assessed using a 9-item version of the Center for Epidemiological Studies of Depression Scale (CES-D) (Radloff, 1977).

1.2.5. Control covariates

Informed by previous research (Borders et al., 2010; McClure et al., 2010; McDade, 2005), we included a number of potential confounders of the associations between SES and abuse with EBV, including sex, age (continuous, years), race/ethnicity (White; Black; Asian; Hispanic; Native American, multi-racial, and other), and smoker present in the household during adolescence (yes, no, missing).

1.3. Statistical analysis

Linear regression models were used to examine the associations of adolescent SES and physical and sexual abuse prior to age 18 with EBV antibodies. We examined and present associations for SES indicators first, in order to identify significant SES covariates to use in analyses focusing on physical and sexual abuse. We used a sequential model building approach, starting first with a baseline model that included sex, age, race/ethnicity, and presence of a smoker in the household during adolescence. To examine indicators of SES in adolescence in relation to EBV antibodies, we included each indicator of SES in the baseline model individually, and then significant SES indicators together.

We examined the associations between any exposure to physical or sexual abuse, as well as frequency of exposure, in relation to EBV antibodies in models adjusted for age, sex, race/ethnicity, smoker in household during adolescence, parental education, and parent occupation status. We included significant SES covariates in these models, because physical abuse and sexual abuse were more commonly reported among individuals from lower SES

households, consistent with other research (Green et al., 2010). In analyses to examine if developmental timing of first exposure to physical or sexual abuse had an impact on EBV antibodies in young adulthood, we estimated two models; the first compared individuals exposed in all age categories to individuals never exposed to abuse, and the second was an exposed only analysis, comparing individuals exposed to abuse at different ages (adolescence was used as the reference). Analyses restricted to individuals who reported abuse allowed us to directly test if abuse earlier in childhood was more strongly associated with EBV antibodies relative to abuse during adolescence. As a final step, we examined current smoking and depressive symptoms as potential pathways linking adversity to EBV by evaluating models that included these variables. We did not include these covariates in our main analytic models, because they are hypothesized to lie on the causal pathway.

In preliminary models, we tested for potential interactions by sex using interaction terms, given that some studies have found that stressors are more strongly associated with elevated EBV antibody levels among females compared to males (Kiecolt-Glaser et al., 1993; McDade et al., 2000; Panter-Brick et al., 2008). Interaction terms did not provide evidence for significant differences by sex, so we present results for the full sample combined. All analyses were performed in SAS Version 9.2., and account for the complex sample design. Post-stratification weights were applied to adjust for the sampling design and non-response and to generate population-level estimates of associations (Biemer and Aragon-Logan, 2011). Statistical significance was established at $p < .05$.

2. Results

Table 1 provides a description of the sample. The mean age of respondents was 29 years (standard error [SE] = 0.12). Females comprised half of the sample. Approximately 66% of the respondents were non-Hispanic White, 14% were African American, 11% were Hispanic, 3% were Asian, and 6% were coded as "other race" which included multi-racial individuals, Native Americans, and other groups with low representation in the sample. The sample was heterogeneous with regard to SES during adolescence. For example, 12.5% of respondents did not have a parent that completed high school, and 13% of respondents had a parent with education beyond a college degree. Approximately 19% lived in households with annual incomes less than $20,000, and 16% lived in households with annual incomes greater than $60,000. Similarly, there was heterogeneity in parental occupational status across the sample, with 32% of the respondents having a parent in a managerial or professional occupation.

Approximately 18% of the sample reported physical abuse prior to 18 years of age; 8% reported that it occurred 1–2 times, 5% reported that it occurred 3–10 times, and 5% of respondents reported that it occurred more than 10 times. Sexual abuse prior to age 18 was reported by just over 5% of respondents: 3% of respondents reported that it occurred 1–2 times, 2% reported that it occurred 3–10 times, and 1% reported that it occurred more than 10 times.

Table 2 presents the distributions of age at first abuse exposure among individuals who reported physical or sexual abuse. Among individuals exposed to physical abuse, there was heterogeneity in the timing of first exposure: 14% during the preschool period, 19% during the latency period, 11% in the pre-pubertal period, 22% during the pubertal period, and 34% during adolescence. Among individuals exposed to sexual abuse, 28% during the preschool period, 26% during the latency period, 16% in the pre-pubertal period, 16% during the pubertal period, and 13% during adolescence.

Table 3 presents a series of linear regression models to investigate the association between three indicators of adolescent SES on EBV antibody levels in young adulthood. The baseline model (Model 1) shows that EBV antibodies are significantly higher among females compared to males, among non-Hispanic Black, Hispanic,

Table 1
Sample characteristics ($N = 13162$).

	N[a]	Percent or mean (SE)
EBV antibody titers (mean, au/mL)	13162	151.00 (1.47)
Age (mean)	13162	28.95 (0.12)
Sex (%)		
Male	5996	49.47 (0.67)
Female	7166	50.53 (0.67)
Race (%)		
Black	2538	14.23 (1.90)
Asian	733	2.87 (0.70)
Hispanic	1902	11.03 (1.60)
Multi-racial, native Am., other	866	5.59 (0.48)
White	7123	66.28 (2.83)
Parent education, Wave 1 (%)		
Parent did not attend or unsure	234	1.97 (0.21)
Less than high school	1642	12.15 (1.10)
High school/GED/Voc. High school	3355	27.42 (1.09)
Some voc. or tech. post-secondary	1162	9.85 (0.63)
Some college	2566	18.96 (0.64)
College	2373	16.83 (0.70)
More than college	1830	12.81 (1.27)
Family income, Wave 1 (%)		
Missing	3128	21.60 (0.93)
<$20,000	2358	18.94 (1.27)
$20,001–$40,000	3134	24.57 (0.82)
$40,001–$60,000	2407	18.50 (0.77)
>$60,001	2135	16.38 (1.17)
Parent occupation, Wave 1 (%)		
Missing	1074	8.36 (0.65)
Service/construction/military	4522	35.22 (1.20)
Technical/sales/office worker	3197	24.90 (0.72)
Professional/manager	4369	31.52 (1.40)
Smoker in home, Wave 1 (%)		
Missing	1788	12.03 (0.74)
Yes	5157	42.29 (1.15)
No	6217	45.68 (1.08)
Physical abuse[b]		
1–2 times	1139	8.34 (0.38)
3–10 times	693	5.11 (0.28)
>10 times	626	4.64 (0.29)
None	10651	81.90 (0.65)
Sexual abuse[b]		
1–2 times	337	2.65 (0.21)
3–10 times	202	1.56 (0.14)
>10 times	157	1.03 (0.21)
None	12429	94.76 (0.31)

[a] *Note:* table presents un-weighted frequencies (N) and weighted means and percents.
[b] Sample totals are slightly smaller for physical and sexual abuse due to missing responses for 53 and 37 respondents, respectively.

Table 2
Frequencies of self-reported age at first abuse exposure among individuals reporting abuse.[a]

	Physical abuse ($N = 2280$)		Sexual abuse ($N = 670$)	
	N	Percent (SE)	N	Percent (SE)
Infancy (0–2)	66	3.51 (0.58)	41	5.91 (1.19)
Preschool (3–5)	324	14.17 (1.00)	169	28.28 (2.25)
Latency (6–8)	422	19.07 (1.05)	166	26.21 (2.57)
Pre-pubertal (9–10)	272	11.41 (0.90)	94	16.19 (2.05)
Pubertal (11–13)	453	21.70 (1.20)	113	16.49 (1.94)
Adolescent (14–17)	743	33.64 (1.31)	87	12.83 (1.59)

SE = standard error.
[a] *Note:* table presents un-weighted frequencies (N) and weighted percents; 178 respondents who reported physical abuse and 26 respondents who reported sexual abuse did not provide an age for first occurrence, and therefore are excluded.

and "other race" individuals compared to Whites, and among individuals with a smoker residing in the household during adolescence (p-values < .05). In Models 2, 3 and 4, we examined the association between highest parental education, annual household income, and highest parental occupation and EBV antibodies, controlling for the covariates in Model 1.

Parental education was associated with EBV antibodies (Model 2). Compared to individuals with a parent who completed more than a college degree, having parents with less than a high school degree was only marginally associated with elevated EBV antibodies ($p = 0.051$), while having parents with a high school degree, or some college were associated with elevated EBV antibodies (p-values < .05). Household income during adolescence was not significantly associated with EBV antibodies (Model 3). Model 4 shows that respondents whose parents had lower status occupations had elevated EBV antibodies compared to respondents whose parents had managerial or professional occupations (p-values < .05). When parental education and occupation were included together, the coefficients were attenuated, as expected; however some indicators for highest parental education and occupation remained significant. Notably, the coefficients for age, sex, and race/ethnicity remain consistent after adjustment for all indicators of SES during adolescence.

Table 4 presents associations between physical and sexual abuse and EBV antibodies in models adjusted for age, sex, race/ethnicity, smoker in household during adolescence, and parental education and occupational status. The variables for exposure to any physical abuse or any sexual abuse by age 18 were not associated with elevated EBV antibodies (Model 1a and 1b), and physical abuse, regardless of frequency, was not associated with EBV antibodies (Model 2a, p-values > .05). Sexual abuse occurring more than 10 times was associated with elevated EBV antibodies ($\beta = 0.13$, $p = 0.03$), but sexual abuse that occurred less frequently was not (Model 2b). In analyses to examine potential sensitive periods related to timing of first abuse, physical abuse that began during the preschool years had a significantly greater association with EBV antibodies relative to individuals that were never exposed to abuse (Model 3a: $\beta = 0.17$, $p = 0.04$) or physical abuse that began during adolescence (Model 4a: $\beta = 0.15$, $p = .004$). We did not observe any pronounced associations based on timing of first onset of sexual abuse, in models that compared sexual abuse by developmental period to individuals who were never sexually abused (Model 3b), or respondents who were first sexually abused during adolescence (Model 4b).

As final step, we examined depressive symptoms and current smoking status as potential mechanisms for the significant associations that were observed. Our results were unchanged in models that adjusted for smoking or depressive symptoms (not presented).

3. Discussion

The present study examined associations between SES in adolescence and childhood physical and sexual abuse on Epstein–Barr Virus (EBV) antibody titers, a measure of cell-mediated immunity.

Table 3
Regression coefficients for the relationship between adolescent socioeconomic context and log EBV antibody titers (au/mL) in young adulthood ($N = 13162$)[a].

	β (Standard error) Model 1	Model 2	Model 3	Model 4
Sex				
Female	**0.15 (0.02)*****	**0.15 (0.02)*****	**0.15 (0.02)*****	**0.15 (0.02)*****
Male	–	–	–	–
Age	**0.01 (0.01)****	**0.02 (0.00)****	**0.02 (0.00)****	**0.02 (0.00)****
Race				
Black	**0.20 (0.03)*****	**0.20 (0.03)*****	**0.20 (0.03)*****	**0.20 (0.02)*****
Asian	−0.01 (0.04)	−0.01 (0.04)	−0.01 (0.04)	−0.02 (0.04)
Hispanic	**0.09 (0.03)****	**0.08 (0.03)***	**0.08 (0.03)****	**0.08 (0.03)***
Multi-racial, Native American, other	**0.09 (0.03)****	**0.09 (0.03)****	**0.09 (0.03)****	**0.09 (0.03)****
White	–	–	–	–
Smoker in home, Wave 1				
Missing	0.04 (0.03)	0.04 (0.03)	0.07 (0.04)∼	0.03 (0.03)
Yes	**0.05 (0.02)****	**0.04 (0.02)**∼	**0.05 (0.02)***	**0.04 (0.02)***
No	–	–	–	–
Parent education				
Parent did not attend or uncertain		0.00 (0.06)		
Less than high school		0.07 (0.03)∼		
High school/GED/Vocational high school		**0.10 (0.03)****		
Some voc. or tech. post-sec.		0.07 (0.04)∼		
Some college		**0.09 (0.03)****		
College		0.05 (0.03)		
>College degree		–		
Family income, Wave 1				
Missing			0.00 (0.03)	
<$20,000			0.04 (0.03)	
$20,001–$40,000			0.05 (0.03)∼	
$40,001–$60,000			0.01 (0.03)	
>$60,000			–	
Parent occupation, Wave 1				
Missing				0.05 (0.03)∼
Service/construction/military				**0.07 (0.02)****
Technical/sales/office worker				**0.05 (0.02)***
Professional/manager				–
R^2	0.03	0.03	0.03	0.03

$^{***}p < .0001$, $^{**}p < .01$, $^{*}p < .05$, $\sim p < .10$.

[a] All models are weighted and take into account complex sample design. Beta-coefficients are based on linear regression models predicting log-transformed EBV antibody titers.

Table 4
Regression coefficients for the relationship between frequency of abuse and timing of 1st onset of abuse and log EBV antibody titers (au/mL) in young adulthood[a,b,c].

	Physical abuse				Sexual abuse			
	β (Standard error)				β (Standard error)			
	Model 1a	Model 2a	Model 3a	Model 4a	Model 1b	Model 2b	Model 3b	Model 4b
	N = 13,109	*N* = 13,109	*N* = 12,931	*N* = 2,280	*N* = 13,125	*N* = 13,125	*N* = 13,099	*N* = 670
Any abuse	0.03 (0.02)				0.00 (0.03)			
Frequency								
1–2 times		0.05 (0.03)				−0.06 (0.05)		
3–10 times		−0.01 (0.03)				0.03 (0.05)		
>10 times		0.04 (0.04)				**0.13 (0.06)***		
None		–				–		
Timing of 1st abuse								
Infancy (0–2 years)			−0.19 (0.11)∼				0.02 (0.13)	
Preschool (3–5 years)			**0.17 (0.04)****				0.02 (0.07)	
Latency (6–8 years)			−0.01 (0.04)				−0.02 (0.06)	
Pre-pubertal (9–10 years)			0.00 (0.05)				0.01 (0.08)	
Pubertal (11–13 years)			0.04 (0.04)				0.03 (0.08)	
Adolescent (14–17 years)			0.03 (0.04)				−0.10 (0.08)	
Never abused			–				–	
Timing of 1st abuse among exposed								
Infancy (0–2 years)				−0.20 (0.12)∼				0.13 (0.17)
Preschool (3–5 years)				**0.15 (0.05)****				0.10 (0.11)
Latency (6–8 years)				−0.03 (0.06)				0.09 (0.12)
Pre-pubertal (9–10 years)				−0.02 (0.06)				0.10 (0.11)
Pubertal (11–13 years)				0.02 (0.06)				0.12 (0.12)
Adolescent (14–17 years)				–				–
R^2	0.03	0.03	0.03	0.04	0.03	0.03	0.03	0.04

$^{***}p < .0001$, $^{**}p < .01$, $^{*}p < .05$, $\sim p < .10$

[a] Beta-coefficients are based on linear regression models predicting log-transformed EBV antibody titers. All models are weighted, take into account complex sample design, and are adjusted for age, race, smoker in household at Wave 1, parental education, and parent occupation status at Wave 1.

[b] Sample sizes vary slightly across models due to missing data on reports of physical and sexual abuse, and age at first onset of abuse. The sample sizes decrease in Model 3 because 178 respondents who reported physical abuse and 26 respondents who reported sexual abuse did not provide an age at first occurrence. In Model 4, the sample sizes reflect only individuals who reported abuse and provided an age at first occurrence.

[c] R^2 values reflect the full model (i.e., coefficients presented in the table, and covariates listed in Footnote 1).

Our results were partially consistent with our hypotheses, revealing that some aspects of childhood adversity may influence adult immune response to latent infection, with associations that varied based on type, timing, and frequency of adversity. Specifically, we found significant associations between some categories of lower parental education, low parental occupational status, and sexual abuse that occurred more than 10 times with elevated EBV antibodies in a nationally representative sample of young adults in the United States. We also found that among individuals exposed to physical abuse, those who were first abused during early childhood (ages 3–5) had significantly heightened EBV antibodies relative to individuals who were first exposed in adolescence. This study offers important new insight into the physiological mechanisms that link early adversity to later health status and suggests that adverse experiences in childhood and adolescence may have a persistent influence on immune control, which may be a pathway through which childhood adversity affects later health outcomes. This study extends prior research linking early adversity and immune function (Miller et al., 2011; Taylor, 2010; Taylor et al., 2011), because to our knowledge it is the first to examine several types of childhood adversity in relation to cell-mediated immune function in adulthood in detailed and careful way, and to document that experiences in childhood or adolescence have a persisting influence on immune responses to latent infection in adulthood.

Our finding that low parental education and occupational status during adolescence is related to elevated EBV antibodies in young adulthood is consistent with some previous research reporting associations between childhood SES and heightened inflammatory markers in adulthood such as C-reactive protein and fibrinogen (Pollitt et al., 2007). It is also consistent with cross-sectional associations between SES and immune responses to latent infections in children (Dowd et al., 2012) and adults (Dowd and Aiello, 2009; Dowd et al., 2008; Stowe et al., 2010). For example, in a study of older Latino adults ages 60–100 years in Sacramento, CA, Dowd and colleagues found that individuals with lower education had elevated CMV and HSV-1 antibodies relative to individuals with the highest level of education (Dowd et al., 2008). Others have reported that adults with less than a high school education had higher HSV-1 antibodies relative to those with a high school education or more; notably, this study did not find a similar pattern for EBV antibody titers (Stowe et al., 2010). These observed relationships are also consistent with a growing body of research documenting SES gradients in relation to other indicators of immune function in youth samples, including elevated pro-inflammatory markers (Dowd et al., 2010; Miller and Chen, 2007; Murasko, 2008), and prevalence of common chronic infections (Dowd et al., 2009). It is unclear why household income was not associated with elevated EBV antibodies in the present study. It is possible that household income during adolescence had an effect that was not sustained into young adulthood. Because different aspects of SES assess distinct aspects of social position and social status (Krieger et al., 1997), it may be that parent education and occupation capture aspects of social class that have a more persistent influence on immune regulation than family income. Alternatively, household income may have been reported less accurately than the other indicators of SES we considered.

Our hypothesis that experiences of physical or sexual abuse would be associated with elevated EBV antibodies in young adulthood was only partially supported. Our global measures of exposure to any physical abuse or any sexual abuse were not associated with elevated EBV antibodies, suggesting that for the majority of individuals exposed to physical or sexual abuse, there was no detectable association with immune responses to latent

EBV in young adulthood. From this study, we are unable to determine whether there was a short-term effect of adversity on EBV antibodies (e.g., an effect that was not sustained into young adulthood) or if there was never a detectable effect of adversity on EBV antibodies. Although this finding was surprising in light of research that has documented associations between child abuse and pro-inflammatory markers in adults (Danese et al., 2007), it is consistent with results from a meta-analysis (Segerstrom and Miller, 2004) that did not find reliable alterations in immune control. However, the meta-analysis focused specifically on natural killer cell cytotoxicity, the only outcome examined often enough to be considered, among individuals who reported traumatic experiences in the distant past. It may be the case that childhood traumatic experiences must be chronic and severe in order to have an impact on immune response to latent viruses that is sustained into adulthood, which may explain why we only observed elevated EBV antibodies among individuals who experienced sexual abuse more than 10 times. The lack of association between physical abuse and EBV antibodies contrasts with a study showing elevated HSV-1 antibodies among adolescents with a history of physical abuse (Shirtcliff et al., 2009). The discrepancy between our findings may be due to the older age of our sample (i.e., more time has passed since experiences of abuse) or differences in assessment of abuse. In the Shirtcliff and colleagues study (2009), physical abuse was identified based on substantiated Child Protective Service reports or parent self-report of physically abusing their children, whereas we focused on self-reports of abuse.

Our results provide partial support for our hypothesis that earlier first experiences of abuse would be associated with poorer immune control relative to later experiences of abuse, as a timing effect was observed only for physical abuse. Specifically, we found that among young adults who reported any physical abuse, individuals who were first abused between the ages of three and five had elevated EBV antibodies compared to individuals who were first abused as adolescents. Although the importance of developmental timing of exposure has not been examined previously in relation to immune functioning, our finding contributes to a growing body of research that has considered timing of adverse experiences in relation to other physical and mental health outcomes. Our findings of a sensitive period for the effects of physical abuse during the preschool years is consistent with some research which shows that earlier exposures present greater risk for poor physical (Ziol-Guest et al., 2009) and mental (Keiley et al., 2001; Kotch et al., 2008) health outcomes compared to later exposure. However, it contrasts with some other studies (Flaherty et al., 2009; Thornberry et al., 2001), which find the opposite. For example, one study found adversity during the second six years of life had a more pronounced effect on physical health at 12 years, relative to adversities in the first six years of life (Flaherty et al., 2009). Additional research, with more in-depth information about severity and chronicity of abuse, is needed to understand why we observed an early sensitive period for the impact of physical abuse but not sexual abuse on immune function. Further research is also needed to identify potential mechanisms that may connect childhood adversity to elevated EBV antibodies in young adulthood. In the present study, neither depressive symptoms nor current smoking explained the associations we observed. It will be valuable to examine other potential physiological or psychosocial mechanisms, such as current SES or supportive relationships. For example, Fagundes and colleagues found that social support interacted with SES to predict EBV antibody titers in a sample of breast cancer patients (Fagundes et al., 2012). Notably, in the study by (Fagundes et al. (2012), depression also did not function as a mediator. Finally, the proportion of the variance explained by our models (R^2 values) did not change with the addition of the abuse measures, and our models explained only 3–4% of the variance in EBV antibodies; this indicates a need to examine other social and biological factors for understanding the population distribution of EBV antibodies.

Future studies are needed to examine how changes in cell-mediated immune function in response to childhood adversity may be connected to adult health outcomes. The health consequences of changes in antibody titers to latent herpes viruses such as EBV have not been determined for healthy populations, and a concrete risk-threshold does not exist (Dowd and Aiello, 2009; Herbert and Cohen, 1993b). Although it is currently unknown whether subclinical stressor-induced immune alterations have substantial implications for long-term health, several recent studies provide strong evidence that herpes virus antibodies can enhance production of pro-inflammatory cytokines, including IL-6, tumor necrosis factor-α, and IL-1β (Glaser et al., 2006; Roberts et al., 2010), and are associated with mortality (Roberts et al., 2010).

The results from this study should be considered in the context of several limitations. First, our measures of parental occupation, and for some respondents (13.7%), parental educational attainment, relied on adolescent-report. These assessments likely involved some degree of measurement error; if errors in reporting were random, this would result in misclassification and therefore underestimation of true associations (Rothman et al., 2008). Second, we were unable to use a measure of poverty-to-income ratio, due to a large amount of missing data for number of people in household at Wave 1. For the subset of respondents with valid information on household income and number of respondents, we calculated a poverty-to-income ratio and examined whether this measure was associated with EBV antibodies. Similar to the unadjusted household income variable, poverty-to-income ratio during adolescence was not associated with EBV antibodies in young adulthood in this sample. Third, we utilized retrospective reports of abuse, which has been shown to result in false-negatives (i.e., under-reporting) (Della Femina et al., 1990; Hardt and Rutter, 2004; Williams, 1995). Furthermore, there could be measurement error in reports of age at first abuse, particularly for abuse during the earliest years of life. A recent study compared prospective and retrospective reports of maltreatment in relation to psychopathology and found even stronger results for prospective report versus retrospective self-reported abuse (Scott et al., 2012); thus, if error in reporting is present, we expect that our findings are biased toward the null. Of note, Add Health attempted to reduce recall bias by using an audio computer-aided self-interview technique for obtaining answers to these sensitive questions. Fourth, questions on abuse did not collect information about duration; therefore, while it was possible to discern the age that the abuse began and the frequency of exposure, we were not able to account for how long it persisted (e.g., if the abuse was limited to the early childhood years, or if continued throughout adolescence), which may have implications for immune functioning.

In conclusion, using a large nationally-representative sample of young adults in the U.S., this study provided novel evidence that lower SES and sexual abuse occurring more than 10 times prior to age 18 are associated with elevated EBV antibodies, a marker of cell-mediated immune functioning, in young adulthood. We also observed that ages 3–5 might be a sensitive period during development when physical abuse has a particularly pronounced effect on later immune functioning relative to later developmental periods. Future research is needed to examine specific social and environmental mechanisms that may explain these associations, and the implications of elevated EBV antibodies for other subclinical and clinical health outcomes. In addition, studies with repeated assessments of both social experiences and immune functioning across developmental stages are needed to clarify the short- and long-term implications of early adversity on the immune system, and potential sensitive periods for immune system development. Knowledge about the physiological mechanisms that link adverse

experiences in childhood and adolescence to adult health will aid in the development of biologically-informed interventions targeting children or adolescents experiencing childhood adversity to protect long-term health.

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