

The Effect of Perceived Stress on Epstein-Barr Virus Antibody Titers in Appalachian Ohio Women

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Keywords

Epstein-Barr virus · Stress, physiological · Appalachia region · Health behavior · Vaccination

Abstract

Objective: The Appalachian population suffers a disparate burden of chronic stress leading to high perceived stress. The study aim was to determine the association between perceived stress and Epstein-Barr virus (EBV) antibody titers, along with the impact of perceived social support, Appalachian self-identify, and health behaviors. **Methods:** Serum EBV VCA-IgG antibody titer levels from 169 female Appalachian residents (aged 18–26 years) were examined. Perceived stress, perceived social support, Appalachian self-identity, and health behaviors were assessed via self-administered questionnaires. **Results:** There were 169 of 185 women positive for EBV. Among these women, the median EBV antibody titer level was 404 U/mL (range 101–6,464), and the overall geometric mean was 563.2 (95% CI 486.6–651.9). For a 1-point increase in perceived stress, the EBV antibody titer increased by 1.92% (95% CI 0.04–3.76%). For every point increase in perceived social support, the EBV antibody titer decreased by 1.00% (95% CI 0.06–1.98%). Per-

ceived stress was significantly associated with sleep quality, BMI, and current smoking status, but not with binge-drinking, drug use, or Appalachian self-identity. No mediating effects of sleep quality, BMI, binge-drinking, current drug use, or >4 sexual partners were observed in the relationship between perceived stress and EBV titer level. **Conclusion:** Young Appalachian women reported high levels of perceived stress that were significantly associated with higher EBV titers. Higher perceived social support was associated with lower EBV titers. Health behaviors and Appalachian self-identity did not impact the relationship between perceived stress and EBV titers.

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Introduction

Appalachia is a region of the USA that includes all of West Virginia plus pieces of 12 states from New York to Mississippi. It has an area of around 205,000 square miles and >25 million people live in the region. Unique to this area, almost 42% of the region is defined as rural [1]. Appalachian populations have a particularly high health burden because of lower incomes and poorer educational

attainment when compared to the rest of the USA [1–3]. Appalachian populations generally have higher rates of smoking and obesity, along with higher rates of substance abuse and mental health problems such as depression and anxiety, than those living outside of the region [4, 5]. These stressors and disparity are not unique or different from other low-income segments of the US population. The unique aspect is the culture and setting of the Appalachian population; even though they comprise the majority in their living areas, they can still suffer from discrimination if they are perceived by others as Appalachian. The Appalachian community has a somewhat complex relationship with self-identity as it battles with being seen as “backward” and “hillbilly” but also being deeply religious and family-oriented (characteristics associated with strong social support). Therefore, individuals who identify as Appalachian may benefit from the buffering effects of enhanced social cohesion, mutual social support, and a stronger sense of community [6].

These stresses of the Appalachian environment could contribute to some of the observed disparity in health. Our interest is in the impact of these stressors on the immune response of young Appalachian women to vaccinations. Individuals with a lower socioeconomic status are infected with herpes viruses earlier in life than those individuals with a higher socioeconomic status [7]. Additionally, those with a lower socioeconomic status are more likely to be seropositive for multiple pathogens and show evidence of viral reactivation [7, 8]. Studies have shown that chronic stress suppresses cell-mediated immunity, while acute stress activates it [9]. Populations that are at an increased risk for chronic depression, stress, and discrimination may be at a higher risk for the reactivation of immunosuppression-related herpes virus. However, we hypothesize that Appalachian residents who self-identify as Appalachian may be protected from these stressors by their cultural congruence that leads to enhanced social cohesion, mutual social support, and a stronger sense of community, similar to the ethnic density effects seen in Hispanic populations [10].

Epstein-Barr virus (EBV) is a herpes virus that is most often associated with infectious mononucleosis [11]. By the age of 19 years, 82.9% of the world is infected with EBV, most without clinical evidence [11, 12]. EBV preferentially infects B lymphocytes, and can cause either a latent infection or an infectious virus by resting in memory B cells [13, 14]. Latent EBV infection can be later reactivated when induced by local trauma and systemic stress [15, 16]. EBV antibody titer levels can be a marker of poor immune function as studies have demonstrated

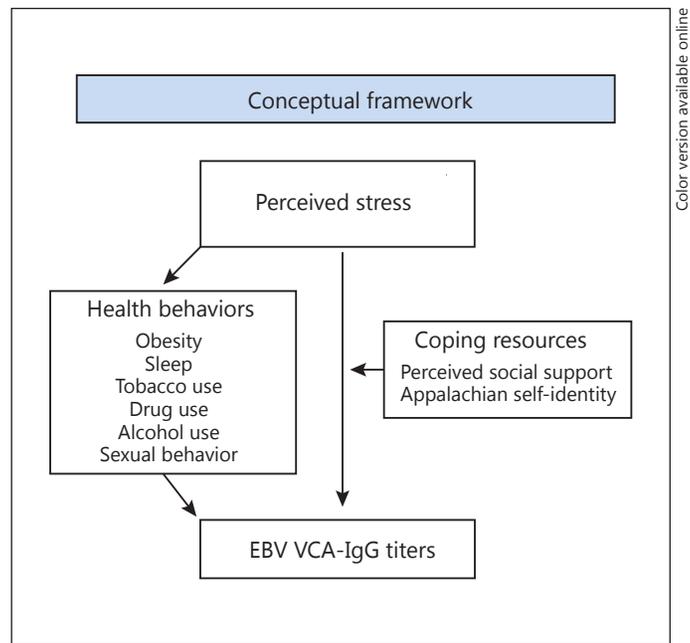


Fig. 1. Conceptual model.

that increased titers occur when the cellular immune system is compromised [17]. Immune dysregulation associated with psychological stress can downregulate both virus-specific antibody responses and responses to the antigens present in vaccines [17].

Due to the burden of stressors in the Appalachian region compared to in the rest of the USA, the Appalachian population may be particularly at risk for immune dysregulation that results in higher EBV titers. As shown in Figure 1, we hypothesized that higher perceived stress in Appalachian women would be associated with higher EBV titers. In addition, we anticipated that greater perceived social support and Appalachian self-identification may reduce the impact of perceived stress. Finally, higher perceived stress is associated with poor health behaviors including obesity, poor sleep, and tobacco, drug, and alcohol use. Thus, the potential mediating role of health behaviors in the expected association between perceived stress and EBV antibody titers was also examined.

Methods

Study Design

The National Institutes of Health Centers for Population Health and Health Disparities (NIH CPHHD) was established in collaboration between the Ohio State University Comprehensive

Cancer Center and the University of Michigan to focus on health in underserved areas, initially targeting Appalachian Ohio. Baseline data from the second Community Awareness, Resources, and Education (CARE II) study, an initiative of the CPHHD addressing the high cervical cancer incidence and mortality in Appalachia, was analyzed. CARE II included 4 projects. Data from project 3, a prospective cohort study that investigated the immune response to the HPV vaccination in young women, aged 18–26 years old, was used. This study looked at determining if serum HPV 6, 11, 16, and 18 antibody responses to Gardasil vaccine were altered by stress. Baseline blood and questionnaire data from participants enrolled in this study were utilized for analysis prior to vaccination. Participants were eligible to be included in our analyses if they were measured to have a positive EBV titer at baseline, as this study was specifically looking at factors associated with EBV reactivation. The Ohio State University Cancer Institutional Review Board approved the study (2010c114, approved 6/11/2012). All participants signed a written informed consent.

Psychosocial Measures

The 14-item Perceived Stress Scale (PSS) was used to assess perceived stress level. All 14 items are assessed on a 4-point scale, for a total possible score of 0–56. This instrument has been proven both reliable and valid [18].

The Multidimensional Scale of Perceived Social Support assesses the adequacy of support from family, friends, and significant others. There are 12 items, each scored from 1 to 7, for a possible total score of 12–84 [19]. Higher scores indicate more social support. This measure has good factorial validity, and good internal and test/retest reliability over a variety of populations [20].

Socioeconomic status was defined as total combined household income in the past year before taxation, including income from all wages, salaries, Social Security or retirement benefits, and help from relatives.

Appalachian self-identity was a self-reported response to the question “Do you consider yourself to be Appalachian?” The response options were “Yes,” “No,” and “I don’t know.” We have previously shown that Appalachian self-identity is associated with longer residence in a county, a greater religious association, both parents having been raised in an Appalachian county, living in a neighborhood with a name, having private health insurance, living in the southern region of Ohio, and living in a rural rather than an urban Appalachian county [21].

Health Characteristics/Behaviors

BMI was calculated from the participant’s height and weight, which were obtained during their baseline visit. Tobacco, drug, and alcohol use were all self-reported. Drug use was defined as any illicit drug use in the past 6 months including marijuana, stimulants, depressants, and inhalants.

The Pittsburg Sleep Quality Index (PSQI) was used to measure sleep quality. This self-report measure assesses sleep quality and disturbances over the past month and provides 7 component scores as well as a global score. Global scores range from 0 to 21 with scores of >5 indicating poor sleep quality. This scale has good validity and reliability in nonclinical settings [22, 23].

EBV Antibody Titers

Serum was assayed for EBV VCA-IgG antibody using Euroimmun EBV ELISA plates (Morris Plains, NJ, USA). EBV VCA-IgG

antibody titers were assessed according to the manufacturer’s instructions (except for the few modifications listed) [24]. For each ELISA plate, 3 controls, 1 positive sample, 1 negative sample, and 3 calibrators were run in duplicate. Samples were diluted 1:101 with a dilution buffer according to company protocol. Six serial 2-fold dilutions of each sample were assayed. The last dilution factor with a positive IgG value determined the IgG antibody titer. Calculated viral titers for each sample were plotted and samples were rerun if the end point did not fall within the linear range ($\pm 15\%$). A negative EBV value was one in which the dilution end point was zero.

Statistical Analyses

Summary statistics were used to describe demographic characteristics and EBV VCA-IgG antibody titer levels. These include the average and standard deviation for continuous covariates and the count and percentage for categorical covariates. Associations between each risk factor of interest and EBV VCA-IgG antibody titer level were estimated through linear regression models and were described by the estimated regression coefficient and associated 95% confidence interval (CI). Interaction tests between PSS level and potential modifiers, such as education, income level, and perceived social support, were used to evaluate if the effect of PSS level on EBV VCA-IgG titer level varied with each potential modifier. All analyses were conducted on the natural log-transformed EBV VCA-IgG antibody titer level. Multivariable regression models were developed after consideration of univariable estimates and our conceptual model. Mediation effects were assessed by the method of proportion of treatment effect explained, with bootstrap CIs for potential mediators that attenuated the effect of interest and were related to the predictor in question [25, 26]. All CIs were 2-sided and unadjusted for multiple comparisons. All analyses were performed in STATA v13 (StataCorp, College Station, TX, USA).

Results

Participant Characteristics

Of the 185 women recruited into the project, 16 (9%) were EBV-negative at the baseline assessment. These participants were not included per the exclusion criteria, resulting in 169 women being available for analysis. The median EBV antibody titer level was 404 U/mL (range 101–6,464), and the overall geometric mean was 563.2 (95% CI 486.6–651.9). Study participants’ demographic characteristics are presented in Table 1. Approximately 20% indicated current drug use (70% of these used marijuana only), and just over one-third (37%) indicated binge-drinking in the past month (defined as ≥ 5 drinks on one occasion). Clinically disturbed sleep (PSQI > 5) was common, affecting 53% of the sample. In this sample, 33.9% were from Muskingum County, 29.8% from Athens County, 7.7% from Hocking County, 7.1% from Ross County, 4.8% from Meigs County, and the remaining

Table 1. Characteristics of the participants

	EBV-positive (n = 169)
Age, years (mean ± SD)	22.9±2.4
Race	
White	144 (85.2)
Other	25 (14.8)
Household income	
<USD 15,000	38 (22.5)
USD 15,000–29,999	23 (13.6)
≥USD 30,000	57 (33.7)
Don't know/prefer to not answer	51 (30.2)
Self-identification as Appalachian	
No/don't know	99 (58.6)
Yes	70 (41.4)
Appalachian Scale (mean ± SD)	53.0±12.4
Marital status	
Married or living with a partner	54 (32.5)
Divorced/separated	7 (4.2)
Never been married	105 (63.3)
Education	
High school graduate or less	55 (32.5)
Some college or greater	114 (67.5)
BMI (median (range))	26.4 (15.4–53.0)
Normal or underweight (BMI <25)	82 (48.5)
Overweight or obese (BMI ≥25)	84 (49.7)
Tobacco use	
Never	112 (66.3)
Former	10 (5.9)
Current	47 (27.8)
Drug use	
None in the past 6 months	124 (73.4)
Used in the past 6 months	37 (21.9)
Prefer to not answer	8 (4.7)
Binge-drinking ^a	
No	103 (61.0)
Yes	63 (37.3)
More than 4 male sexual partners ^b	
No	49 (32.2)
Yes	103 (67.8)
PSQI score ^c	
Mean ± SD	6±3.5
Not clinically disturbed (≤5)	89 (52.7)
Clinically disturbed (>5)	80 (47.3)
MSPSS ^d	
Mean ± SD	68.7±14.7
Median (range)	71.5 (12–84)
PSS ^e	
Mean ± SD	23.6±7.8
Median (range)	23 (6–52)

Values are expressed as n (%), unless otherwise indicated. Groups may not add up to column totals due to missing data.

^a Consuming ≥5 drinks on one occasion in the past month. ^b Of a total of 152 women who had had at least 1 sexual partner. ^c Pittsburgh Sleep Quality Index. ^d Multidimensional Scale of Perceived Social Support. ^e Perceived Stress Scale.

16.7% from the surrounding counties. Overall, these locations are predominantly rural. Although residency in an Appalachian community was a requirement for participation, only 41% of the women considered themselves to be “Appalachian.”

Relationship between Perceived Stress and EBV VCA-IgG Titer Levels

The scores for the PSS are presented in Table 1. Perceived stress exhibited significant unadjusted relationships with EBV antibody titer levels. For every one point increase in perceived stress, the EBV antibody titer increased by 1.92% (95% CI 0.04–3.76%; Table 2). Age, marital status, educational attainment, and Appalachian self-identity were not significantly associated with perceived stress in the unadjusted analysis (Table 2). More affluent households (those with household incomes >USD 30,000 vs. <USD 15,000 per year) had lower levels of perceived stress (Table 2; *p* < 0.05). Perceived social support was negatively associated with perceived stress. For every point increase in perceived social support, the PSS decreased by 0.22 units (95% CI 0.15–0.30; Table 2). Greater perceived social support was significantly related to lower EBV antibody titers. For every point increase in perceived social support, the EBV antibody titer decreased by 1.00% (95% CI 0.06–1.98%). Appalachian self-identity did not impact the relationship between perceived stress and EBV titers. Perceived social support did not appear to modify the relationship between PSS and EBV antibody titers.

Potential Mediation of the Associations between Perceived Stress and Higher EBV Antibody Titers according to Health Behaviors

Perceived stress was significantly positively associated with sleep quality (1.15, 95% CI 0.86–1.44), BMI (0.20, 95% CI 0.05–0.35), and current tobacco smoking (3.76, 95% CI 1.17–6.35). Perceived stress was not significantly associated with current drug use (0.99, 95% CI –1.88 to 3.86) binge-drinking (–0.26, 95% CI –2.70 to 2.18) or >4 male sexual partners (1.24, 95% CI –1.40 to 3.89). Formal analysis of mediation revealed that the observed attenuation of the relationship between PSS and EBV titer level, when potential mediators were included in the models, were well within what would be expected due to chance. All bias-corrected CIs for the percentage decrease in the PSS coefficient due to mediation contained zero, indicating that no significant mediating effects of any candidate mediator were observed in the relationship between perceived stress and EBV titer level.

Table 2. Associations of demographic characteristics, perceived stress, and coping resources with EBV titer level (EBV transformed to the natural log scale)

Predictors	Unadjusted association with EBV titer, coefficient (95% CI)	Unadjusted association with PSS, coefficient (95% CI)
<i>Demographic factors</i>		
Age	0.05 (−0.01 to 0.11)	−0.42 (−0.91 to 0.07)
Marital status		
Married or living with partner	0.19 (−0.12 to 0.50)	0.37 (−2.18 to 2.91)
Never married or divorce or separated	reference	reference
Education		
High school graduate or less	0.25 (−0.07 to 0.56)	2.24 (−0.28 to 4.77)
Some college or greater	reference	reference
Household income level		
<USD 15,000	reference	reference
USD 15,000–30,000	0.31 (−0.18 to 0.79)	1.10 (−2.92 to 5.11)
>USD 30,000	−0.51 (−0.89 to −0.13)	−3.55 (−6.73 to −0.37)
Missing/don't know	−0.04 (−0.43 to 0.35)	−1.41 (−4.67 to 1.84)
<i>Behavioral health factors</i>		
PSQI ^a	0.01 (−0.03 to 0.05)	1.15 (0.86 to 1.44)
BMI	0.02 (0.003 to 0.04)	0.20 (0.05 to 0.35)
Current smoking (yes vs. no)	0.17 (−0.15 to 0.50)	3.76 (1.17 to 6.35)
Drug use (yes vs. no)	−0.16 (−0.51 to 0.19)	0.99 (−1.88 to 3.86)
Binge-drinking (yes vs. no)	0.06 (−0.24 to 0.37)	−0.26 (−2.70 to 2.18)
More than 4 male sexual partners (yes vs. no)	0.08 (−0.25 to 0.40)	1.24 (−1.40 to 3.89)
<i>Psychological distress</i>		
PSS ^b	0.02 (0.0004 to 0.04)	–
<i>Coping</i>		
MSPSS ^c	−0.01 (−0.02 to −0.001)	−0.22 (−0.30 to −0.15)
Self-identification as Appalachian		
No/don't know	reference	reference
Yes	0.08 (−0.22 to 0.37)	0.46 (−1.96 to 2.87)
Appalachian Scale	−0.004 (−0.02 to 0.01)	−0.13 (−0.23 to −0.04)

^a Pittsburg Sleep Quality Index. ^b Perceived Stress Scale. ^c Multidimensional Scale of Perceived Social Support.

Discussion

This study found that women residing in Appalachian regions of Ohio, aged 18–26 years, reported high levels of perceived stress. The reported perceived stress mean and range were comparable to women surviving a heart attack [27], and much higher than an Australian study on women's health and well-being [28]. Previous studies have reported associations between a variety of forms of self-reported psychological stress, including perceived racial discrimination, depressive symptoms, and exposure to childhood adversity, in relation to herpes virus antibody titers [29–37]. Similarly, in this study, general perceived stress, as measured by Cohen's PSS, was positively associ-

ated with EBV antibody titers [29–32]. Through our conceptual framework, we hypothesized that a relationship between perceived stress and EBV titers would be impacted by perceived social support, Appalachian self-identity, and behavioral health factors.

Although our conceptual model hypothesized that perceived social support may modify the impact of perceived stress on EBV titers, we did not observe this in our data. We also predicted that, like social support, Appalachian identity would modify the impact of perceived stress on EBV titer level. Again, our data did not support this hypothesis. Studies have demonstrated that a strong ethnic identity is associated with a healthy sense of self and can be protective against stressors [38, 39]. Thinking

of a strong Appalachian identity as similar to a strong ethnic identity, this identity was hypothesized to therefore be protective. In our study, however, even though all participants lived within the area defined as Appalachia only, around half identified as Appalachian. This could be a reason why this relationship was not identified. The use of other terms such as “rural” or “mountain” may have better captured this identity. An alternative hypothesis is that Appalachian self-identity may be linked to lower self-reported perceived stress than we have reported in the unadjusted results. Lastly, Appalachian self-identity is a relatively new construct that needs further study [21]. As stated in the introduction, Appalachian identity is a very complex concept, so that one simple question cannot capture any nuances.

Perceived stress was significantly associated with sleep quality, BMI, current tobacco smoking status, and Appalachian self-identity, but not with drug use or binge-drinking. No mediating effects of sleep quality, BMI, binge-drinking, or current drug use were observed in the relationship between perceived stress and EBV titer level.

In this particular study, the models do not control for education level and marital status because of the lack of clinical utility of these characteristics in this particular age range. As the age range in this study was as young as 18 years, not all participants had yet had the opportunity to reach their education attainment or be at the point for marriage. Similarly, socioeconomic status was a hard characteristic to capture in this population. In this transitional life age range, income was not a particularly good measurement as many in this age group are transitioning to first jobs and financial independence.

Because of the complex interplay of all of these psychological and behavioral factors as well as the fact that our study only looked at a snapshot in time, the relationship could only be hypothesized between these variables and EBV titer level. Most significantly, our results indicate the high prevalence of mental and behavioral health problems in the Appalachian community, and also that there is an association with EBV titer level. As higher EBV antibody titers have been associated with EBV-associated malignancies, the Appalachian community may be at a higher risk for cellular transformation events. This indicates the importance of the Appalachian population getting better access to preventative health care and mental health resources, in order to get these modifiable risk factors under control and possibly decrease their EBV titer levels.

The other concern for this age group of women residing in Appalachia Ohio is their ability to respond to vaccines for the prevention of diseases associated with hu-

man papillomavirus (HPV) infections such as cervical cancer. Stress, whether measured as the exposure to major life events, perceived stress, or negative affect, has been found to be inversely associated with the antibody response to a variety of vaccinations [40–43], implying that people experiencing stress have a reduced capacity to mount an immune response to a vaccine. The hepatitis B series of 3 inoculations had a very similar population target in the past when infants were not immunized. In 1 study, the series was given to 48 second-year medical students on the third day of a 3-day examination series [44]. Students seroconverting after the first injection (25%) were significantly less stressed and anxious than those who did not seroconvert. In addition, students who reported greater social support demonstrated a stronger immune response to the vaccine at the time of the third inoculation, as measured by antibody titers to hepatitis B surface antigen and the blastogenic response to an HBsAg peptide [44]. The stress of graduate school does not compare to the stress of growing up and living in Appalachian areas. If stress does lead to immune dysregulation as we report in this study, then young adult women residing in Appalachia Ohio may not have the same immune response to HPV vaccines.

In summary, perceived stress among women residing in Appalachian Ohio is high and is associated with higher EBV titers. These higher titers may represent immune dysregulation. Greater perceived social support was associated with lower EBV titers. Our hypothesized relationship of health behaviors and Appalachian self-identity did not impact the relationship between perceived stress and EBV titers.

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Disclosure Statement

The authors have no conflict of interest to declare.

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