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Physical activity, sedentary behaviors, and Epstein-Barr virus antibodies in young adults

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HIGHLIGHTS

- The effect of physical activity (PA) on cell-mediated immunity is unclear.
- This effect of PA on health outcomes may be confounded by sedentary behaviors (SB).
- We studied the associations between PA, SB, and EBV antibody levels.
- PA and SB are associated with EBV antibody levels.

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ABSTRACT

This study aimed to elucidate the associations between physical activity, sedentary behaviors, and Epstein-Barr virus (EBV) antibody levels (as an indirect marker of cell-mediated immunity, CMI). This study made use of a 14-year longitudinal study with a representative sample of adolescents in the US. A total of 3361 participants (42.1% male) aged 11 to 21 years at baseline who completed Wave I (1994–1995), Wave III (2001 − 2002), and Wave IV (2008) surveys of the National Longitudinal Study of Adolescent Health (Add Health) were analyzed. Physical activity and sedentary behaviors at Waves I and III were assessed using interviewer-administered questionnaire. EBV viral capsid antigen (VCA) IgG antibody levels at Wave IV were analyzed from dried blood spot assays. Adjusted for confounders, among males, one additional day spent per week on strenuous sports at Wave III were associated with a decrease of 4.09 AU/ml in EBV antibody levels ($p = 0.012$), while one additional hour spent per week viewing videos at Wave I was associated with an increase of 0.83 AU/ml in EBV antibody levels ($p = 0.026$). Among females, one additional day spent per week on individual sports at Wave III were associated with a decrease of 4.63 AU/ml in EBV antibody levels ($p = 0.014$), while sedentary behaviors were not associated with EBV antibody levels. To conclude, physical activity and sedentary behaviors were associated with CMI among males and physical activity was associated with CMI among females.

1. Introduction

The level of Epstein-Barr virus (EBV) antibody is not only the aetiological agent responsible for infectious mononucleosis [1], but its serological response is also an indirect marker of psycho-social stress [2] and failure of cell-mediated immunity (CMI) [3,4]. An elevated level of EBV antibody is an indirect marker of CMI. Most EBV infection occurs in childhood [5] and the virus persists in the body for life. The maintenance of EBV in a latent state relies on the functionality of CMI, and CMI limits EBV reactivation and prevents future systemic disease [6]. Elevated EBV antibodies are the result of a failure of CMI to prevent the reactivation of the latent EBV [7], and research has demonstrated that EBV reactivation was associated with delayed-type hypersensitivity, an indicator of the CMI [8].

Although physical activity is a modifiable lifestyle factor that can protect against and alleviate various morbidities [9], it may also be effective in improving our CMI [10]. However, the association between EBV antibody levels and physical activity is unclear. Studies have shown that prolonged and intense exercise were not associated with CMI among male triathletes [11]. In addition, acute eccentric exercise, i.e. lateral raise exercise, did not improve CMI response to influenza vaccination among young adults [12]. Other studies showed that young Caucasian athletes had lower EBV IgG antibody levels than their non-athletes counterparts [13], and Tai Chi was effective in increasing CMI to varicella zoster virus (VZV) among elderly subjects [14]. It is hypothesized that these contradictory findings were confounded by time spent sitting or sedentary behaviors, which are negatively associated with

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time spent undertaking physical activities and also independently associated with increased mortality [15]. This study aimed to elucidate the associations between physical activity, sedentary behaviors, and EBV antibody levels using a representative sample of young adolescents in the US from a 14-year longitudinal study (National Longitudinal Study on Adolescent Health, Add Health 1994–2008). We hypothesized that EBV antibody levels would be negatively associated with physical activity and positively associated with sedentary behaviors.

2. Methods

2.1. Participants

The National Longitudinal Study of Adolescent Health (Add Health) is a longitudinal study of adolescents of grade 7 to 12 in United States at 1994–1995 (Wave I), and three follow-ups were conducted at 1996 (Wave II), 2001–2002 (Wave III), and 2008 (Wave IV). The sample of the Add Health included 80 nationally representative high schools and one single randomly chosen feeder school from the 60 high schools that did not have a 7th grade in the United States. All schools were selected through a systematic sampling method. A total of 134 schools (79%) agreed to participate and 90,118 adolescents in grades 7 to 12 completed an in-school questionnaire in 1994–1995 (Wave I). A subgroup of 20,475 completed an in-home interview, and for this subgroup a parent or guardian was invited to complete a parent-in-home questionnaire. A total of 4564 participants provided publicly available and valid EBV data collected at 2008 (Wave IV), and EBV seronegative participants, defined as those with bottom 10% of EBV antibody values, were removed from the analysis [16,17], leaving the eligible sample of 4107. Parental consent was obtained at Wave I and written consent from the participants was obtained at Waves III and IV. This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill, and further details of the study can be found on the Add Health official Website (http://www.cpc.unc.edu/projects/addhealth/).

2.2. EBV viral capsid antigen (VCA) titers

EBV viral capsid antigen (VCA) IgG (AU/ml) was analyzed from blood spot samples at Wave IV when the participants were 25–35 years old (mean age 28.3, SD 1.8). The details of the assays can be found elsewhere [18]. In summary, field interviewers collected capillary whole blood from the participants' middle or ring finger, and seven blood drops were collected using blood collection card (Whatman 903 Protein Saver). Dried blood spots were shipped to the University of Washington Department of Laboratory Medicine for assay using indirect ELISA [19]. The within-assay and between-assay coefficients of variation were 3.9% and 10.2% respectively [18]. Blood spot samples with high between-duplicate differences were re-assayed in duplicate if possible. High linear association of EBV measures of dried blood spot with serum samples was demonstrated in 162 samples (Pearson correlation = 0.95). High reliability of the EBV measures was demonstrated by a 2-week test-retest reliability of ICC = 0.97 in a sub-group of 100 random samples.

2.3. Physical activity and sedentary behaviors

Leisure time physical activity and sedentary behaviors at Waves I and III were assessed using an interviewer-administered questionnaire (used and validated in other studies [20]). At Wave I, physical activity was assessed with the question "During the past week, how many times did you play an active sport, such as baseball, softball, basketball, soccer, swimming, or football?" (Not at all, 1 or 2 times, 3 or 4 times, and 5 or more times). At Wave III, physical activity was assessed with the question "In the past seven days, how many times did you participate in strenuous team sports?", "In the past seven days, how many times did you participate in individual sports?", and "In the past seven days, how many times did you walk for exercise?". At both Waves I and III, sedentary behaviors were assessed with the questions "How many hours a week do you watch television?", "How many hours a week do you watch videos?", and "How many hours a week do you play video or computer games?" Among the 4107 eligible sample, those who provided valid data in all physical activity and sedentary behaviors variables at both Waves I and III (n = 3361) were included in the final sample.

2.4. Demographic characteristics, socioeconomic status, and lifestyle behaviors

A number of potential confounders measured at Wave I were included in this study. These confounders included demographic characteristics (age, sex, race), socioeconomic status (annual household income, parental education level), and lifestyle behaviors (smoking and sex habits). Additive regression was used to impute missing confounder data using the package *Hmisc* of R (http://biostat.mc.vanderbilt.edu/Hmisc).

2.5. Statistical analysis

Given the significance difference of EBV antibody levels across sex (shown in Section 3), all analysis was stratified by sex. Descriptive statistics were presented by quartiles of EBV. To assess the association between physical activity, sedentary behaviors and CMI, linear regression was used with EBV VCA IgG antibody titers (AU/ml) as the outcome variable, and all physical activity and sedentary behavior variables collected in Waves I and III as the independent variables. Backward elimination procedure of level of significance 0.2 (that is, backward selection regression with exit p-value of >0.2) was used to determine the confounders to be adjusted [21]. Both crude regression slopes of physical activity and sedentary behaviors and those adjusted for confounders were reported.

3. Results

A total of 3361 participants were included in the analysis. The EBV VCA IgG antibody levels in this sample were 166.3 (SD 97.8) AU/ml. A significant difference ($p < 0.001$) was found between male (151.9 (SD 91.8) AU/ml) and female (176.8 (SD 103.9) AU/ml) participants.

The demographic characteristics of the Add Health 1994–2008 male sample (n = 1416, 42.1%) is shown in Supplementary Table S1. Those who spent more hours viewing videos at Wave I, with a lower annual household income, a father did not have a college degree, and being Black or African were more likely to be in the fourth quartile of EBV VCA IgG antibody levels, while those who spent more hours viewing videos at Wave III were more likely to be in the second and third quartiles. The demographic characteristics of the Add Health 1994–2008 female sample (n = 1945, 57.9%) was shown in Supplementary Table S2. Those who spent more hours viewing videos at Wave I, spent fewer days playing strenuous and individual sports at Wave III, and being White were less likely to be in the fourth quartile of EBV VCA IgG antibody levels.

Linear regression and adjustment for confounders performed in the male participants (Table 1) showed that one additional day spent per week performing strenuous sports at Wave III were associated with a decrease of 4.09 AU/ml in EBV antibody levels ($p = 0.012$), while one additional hour per week spent viewing videos at Wave I was associated with an increase of 0.83 AU/ml in EBV antibody levels ($p = 0.026$), after adjusting for confounders. Linear regression and adjustment for confounders performed in the female participants (Table 2) showed that one additional day per week spent on individual sports at Wave III were associated with a decrease of 4.63 AU/ml in EBV antibody levels ($p = 0.014$). On the other hand, sedentary behaviors were not associated with EBV antibody levels.