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Childhood environments and cytomegalovirus serostatus and reactivation in adults

Denise Janicki-Deverts [a,*], Sheldon Cohen [a], William J. Doyle [b], Anna L. Marsland [c], Jos Bosch [d,e]

[a] Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213, USA
[b] Department of Otolaryngology/ENT, Children's Hospital of Pittsburgh, Pittsburgh, PA 15224, USA
[c] Department of Psychology, University of Pittsburgh, Pittsburgh, PA 15260, USA
[d] Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands
[e] School of Sport and Exercise Sciences, University of Birmingham, Birmingham, United Kingdom

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ABSTRACT

Childhood adversity, defined in terms of material hardship or physical or emotional maltreatment has been associated with risk for infection with cytomegalovirus (CMV) among children and adolescents, and with CMV reactivation in children and adults. The present study examined whether different dimensions of childhood experience—those pertaining to socioeconomic status (SES), physical environment, or family relationships—relate differentially to CMV serostatus and reactivation during adulthood. Participants were 140 healthy adults, aged 18–55 years (41% female; 64% white). Childhood environments were assessed retrospectively and included family SES (parental housing tenure); childhood neighborhood environment (urban residence; physical conditions; safety; and social atmosphere); residential exposures (parental smoking and physical condition of home); and family relationships (parental divorce; warmth; harmony; dysfunction; parental bonding). Approximately 39% ($n = 53$) of participants were CMV+. In individual analyses controlling for age, sex, race, body mass, current adult SES and smoking status, fewer years of parental home ownership, having a parent who smoked, and living in a poorly maintained or unsafe neighborhood each were associated with greater odds of infection with CMV. By comparison, in individual analyses limited to CMV+ participants, less family warmth, less harmony, greater dysfunction, and suboptimal parental bonding each were related to higher antibody levels, independent of the aforementioned covariates. Findings were not attributable to current adult perceptions of psychological stress or relative levels of emotional stability. These results suggest that different types of childhood adversity may be associated with differential effects on CMV infection and latency.

1. Introduction

Exposures to unfavorable physical and psychosocial environments during early life reliably have been associated with increased risk of morbidity and premature mortality during adulthood (Cohen et al., 2010; Miller et al., 2011). One pathway through which childhood experiences have been hypothesized to influence adult health involves long-term dysregulation of the immune system. Several studies have shown childhood adversity, defined in terms of material hardship or physical or emotional maltreatment, to be associated with poor immune response in adults. Much of this work has examined circulating markers of inflammation as the outcome. Early socioeconomic disadvantage, for example, has been associated with relatively elevated concentrations of circulating pro-inflammatory cytokines (Carroll et al., 2011) and C-reactive protein (CRP; Phillips et al., 2009; Pollitt et al., 2007) at midlife. Lower socioeconomic status (SES) during childhood and adolescence also has been associated with increased likelihood of developing acute upper respiratory illness—a process partly attributable to the activity of pro-inflammatory cytokines, following exposure to a virus that causes the common cold (Cohen et al., 2004, 2013). Similarly, accumulated exposure to parental abuse and/or neglect during early life, has been related to elevated levels of interleukin [IL]-6 among both healthy adults (Danese et al., 2007) and women with breast cancer (Janusek et al., 2013). Early adversity has also been found to interact with current adult life stress, amplifying the detrimental effects of current stress on

* Corresponding author. Tel.: +1 412 268 3295; fax: +1 412 268 3294.
E-mail address: djanicki@andrew.cmu.edu (D. Janicki-Deverts).

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inflammation (Kiecolt-Glaser et al., 2011) and local response to a basal cell carcinoma tumor (Fagundes et al., 2012).

Another aspect of adult immunity that appears to be influenced by unfavorable exposures during early life involves the processes implicated in establishing resistance to reactivation of latent viruses. Among young adult (mean age 29 years) participants in the National Longitudinal Study on Adolescent Health (Add Health) who had detectable antibody to Epstein Bar Virus (EBV), lower parental SES assessed during adolescence was associated with higher blood antibody levels (Slopen et al., 2013). However, a re-analysis of these same data using a different cut-off of antibody levels for defining serostatus failed to find an association between adversity and antibody levels (Dowd et al., 2013b). By comparison, in a sample of female breast cancer survivors who were seropositive for EBV and/or cytomegalovirus (CMV), higher scores on a retrospective summary measure of childhood adversity (including for example death of a parent, parental marital discord, lacking a close relationship with at least one adult) were associated with elevated levels of antibody against both viruses (Fagundes et al., 2013). Finally, among adolescents who were seropositive for herpes simplex virus type 1 (HSV-1), institutional rearing and physical abuse during childhood each were associated with elevated HSV-1 antibody levels relative to demographically similar controls (Shirtcliff et al., 2009).

Although provocative, these studies have limitations. The two analyses of the Add Health data produced inconsistent results, and the association between childhood adversity and antibody levels in the Fagundes et al. (2013) sample was based on a female clinical population. The Shirtcliff et al. (2009) sample, too, was drawn from two special populations (children adopted from Eastern European and Chinese orphanages; adolescents with a history of physical abuse). Moreover, although the adolescent study examined whether the association of early adversity with antibody levels could be explained by higher rates of infection among the maltreated (groups did not differ in infection rates), neither of the two adult studies examined whether the same factors associated with elevated antibody levels also predict seropositivity.

In the present study, we use data from a sample of healthy adult male and female volunteers to elaborate upon the existing research on childhood adversity and latent virus infection and reactivation. Specifically, we focus on identifying which dimensions of childhood experience—those pertaining to socioeconomic, physical, or familial environments, are most crucial for individuals' initial risk for viral infection and which are associated with long-term effects on immunologic resistance to subsequent reactivation. We also examine whether any found associations are independent of the effects of adult SES. We examine CMV serostatus and antibody levels as our model of latent virus infection and reactivation. CMV is prevalent throughout the United States, with infection rates ranging from about 35% among young children to 90% among older adults (Staras et al., 2006). Until recently CMV infection and non-clinical reactivation were thought to be without symptoms among healthy adults, and associated with detrimental effects only in vulnerable populations. However, this view has changed, with CMV infection increasingly being considered a public health concern. Among adults, CMV seropositivity has been associated with increased mortality risk both in community samples with broad age ranges (Simanek et al., 2011; Gkrania-Klotsas et al., 2013) and in healthy older adults (Savva et al., 2013). Moreover, prenatal infection with CMV has been associated with increased risk of infant mortality and long-term disability (Ross et al., 2006). Elevated CMV antibody levels, as well, have been linked to increased mortality in older adults, and, in all age groups, to immune dysregulation characteristic of accelerated aging of the immune system (immunosenescence) including impaired vaccination responses (McElhaney et al., 2012; Turner et al., 2014), increased inflammation (Freeman, 2009; Qiu et al., 2008), impaired ability to proliferate to mitogens (Chidrawar et al., 2009), reduced telomere length (van de Berg et al., 2010), and reduced telomerase activity (Dowd et al., 2013a). Thus, gaining a better understanding into early life factors affecting risk for infection and reactivation of this virus may have important implications for public health and may contribute to understanding of the role of early life determinants of healthy aging (Nikolich-Zugich, 2008).

2. Materials and methods

2.1. Participants

Participants were drawn from a sample of 212 healthy volunteers aged 18–55 years from the greater Pittsburgh, PA area who were recruited by newspaper and posted advertisement to participate in a study of psychological and behavioral influences on resistance to the common cold. Each was paid $1000 for their participation in the parent study. The 140 men and women included in the present analyses comprised all participants with sufficient stored blood available for assessment of CMV antibodies. The study was conducted between 2007 and 2011 and was approved by the Institutional Review Boards of both Carnegie Mellon University and the University of Pittsburgh and all participants provided signed informed consent.

2.2. Procedures

Volunteers presenting for possible enrollment in the parent study underwent medical screenings and were excluded if they had been either treated in the past year or hospitalized in the past 5 years for psychiatric illness; had a history of major nasal or otologic surgery, respiratory disorders, or cardiovascular disease; had abnormal urinalysis, complete blood count, or blood enzymes; were currently pregnant or lactating; tested seropositive for human immunodeficiency virus; or were regularly taking medication other than birth control. The parent study was designed to examine social, psychological, behavioral, and biological factors that influence participants' susceptibility to developing upper respiratory illness following experimental exposure to a common cold virus (rhinovirus [RV] 39; Cohen et al., 2013). Thus, specific serum neutralizing antibody against RV39 was assessed at screening, and volunteers also were excluded if their RV39 antibody levels were >4 IU, which is considered protective against this virus.

All data included in this article were collected during the baseline period (before viral-challenge) of the parent study. Sera for CMV antibody assessments were obtained by standard venipuncture into serum separator tubes (see Cohen et al., 2013). Samples were spun for 10 min at 3500 rpm. Serum was placed into labeled 2-ml microcentrifuge tubes, and then stored at −70 °C until shipped on dry ice to the University of Birmingham School of Sport and Exercise Sciences, Behavioural Immunology Laboratory (Birmingham, United Kingdom) for CMV antibody assay.

Self-reported adult demographic data and current perceived stress were collected by questionnaire at the time of screening for the parent study and the entry physical exam, respectively. Self-report questionnaires assessing childhood environments and adult personality were administered on the same day as the blood draw for CMV antibody assessment.

2.3. Childhood environments

2.3.1. Childhood neighborhood environment

The Places You've Lived Interview is comprised of 15 items asking respondents to describe the place(s) in which they lived during