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The effect of self-reported health on latent herpesvirus reactivation and inflammation in an ethnically diverse sample

Kyle W. Murdock[a], Christopher P. Fagundes[a,b,c,*], M. Kristen Peek[d], Vansh Vohra[a], Raymond P. Stowe[e]

[a] Department of Psychology, Rice University, 6500 Main Street, Houston, TX 77005, USA
[b] Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030, USA
[c] Department of Psychiatry, Baylor College of Medicine, One Baylor Plaza - BCM350, Houston, TX 77030, USA
[d] Department of Preventative Medicine and Community Health, The University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555, USA
[e] Microgen Laboratories, 903 Texas Avenue, La Marque, TX 77568, USA

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ABSTRACT

Self-rated health (SRH) is a reliable predictor of health outcomes including morbidity and mortality. Immune dysregulation is one hypothesized mechanism underlying the association between SRH and health outcomes. Indeed, poorer SRH is associated with greater inflammation. The association between SRH and reactivation of latent herpesviruses is unknown, representing an important gap in the literature given that reactivation of latent herpesviruses leads to enhanced inflammation. The present study addressed this important gap in the literature by examining associations between SRH, inflammation (i.e., peripheral cytokines in the blood), and reactivation of latent herpesviruses among a sample of 1208 individuals participating in the Texas City Stress and Health Study. Participants completed a self-report measure of SRH and a blood draw. Results indicated that higher SRH was associated with lower reactivation of latent herpesviruses and inflammation. Moreover, reactivation of latent herpesviruses partially mediated the association between SRH and inflammation. Accordingly, findings add to our growing understanding of the association between SRH and immune dysfunction.

Contents

* Corresponding author at: Rice University, BRC 773, 6500 Main Street, Houston, TX 77005, USA.
E-mail addresses: christopher.fagundes@rice.edu, cpfagundes@mdanderson.org (C.P. Fagundes).

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1. Introduction

Individuals are able to report valuable information about their own health. A growing body of literature suggests that the people's subjective determination of their global health status is strongly linked to subsequent morbidity and mortality. Such findings have been replicated among various age ranges (e.g., Larsson et al., 2002; Nybo et al., 2003), ethnic groups (e.g., Nielsen et al., 2008; Yu et al., 1998), and patient populations (e.g., Bosworth et al., 1999; Jylhä, 2009; Kaplan and Camacho, 1983). Interoceptive (i.e., originating within the body) sensations associated with the immune and endocrine systems are hypothesized to explain why individuals are able to accurately report their global health status (Kaplan and Camacho, 1983). The present study focused on how self-reported health (SRH) is associated with reactivation of latent herpesviruses among a large and ethnically diverse sample.

When the immune system is dysregulated, people generally exhibit greater disease susceptibility, inflammation, and latent herpes virus reactivation (e.g., Fagundes et al., 2013; Jaremka et al., 2013; Shirtcliff et al., 2009). Herpesviruses create latent infections which largely remain dormant among infected cells for the rest of their lives; however, the virus can be reactivated in those cells and replicate (Cacioppo et al., 2002; Glaser and Kiecolt-Glaser, 1994; Yang et al., 2010).

Maladaptive alterations in cellular immune function can enhance herpesvirus reactivation and replication, resulting in elevated herpesvirus antibody titers (Steptoe et al., 2007; Glaser and Kiecolt-Glaser, 2005, 1994). For example, organ transplant patients have elevated herpesvirus antibody titers (Gray et al., 1995). Although usually asymptomatic, elevated herpesvirus antibody titers reflect poor cellular immune system control over viral latency (Glaser and Kiecolt-Glaser, 1994). Psychological stress can also dysregulate cellular immunity, and enhance latent herpesvirus reactivation (Glaser and Kiecolt-Glaser, 1994). Importantly, chronically stressed low SES individuals have higher antibody titers to latent herpesviruses (Stowe et al., 2010). Additionally, dementia caregivers had greater herpes simplex virus type 1 (HSV-1) antibody titers compared with demographically matched controls (Glaser and Kiecolt-Glaser, 1997).

The vast majority of the literature on reactivation of herpesviruses has focused on the Epstein—Barr virus (EBV), cytomegalovirus (CMV), and HSV-1 because these herpesviruses are ubiquitous in adulthood (e.g., Simanek et al., 2009; Steptoe et al., 2007; Stowe et al., 2010). Being seropositive for multiple herpesviruses does not always lead to problematic symptoms; however, greater herpesvirus burden, evidenced by continuous levels of antibody titers for each pathogen, is associated with higher inflammation (e.g., Nazmi et al., 2010; Zhu et al., 2000). Indeed, elevated antibody titers to herpesviruses can promote increases in inflammatory markers such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (Fagundes et al., 2012a; Simanek et al., 2011; Stassen et al., 2006). One consequence of elevated inflammation is increased risk of disease, especially in older adults (Steptoe et al., 2007). In particular, older adults who have chronically elevated proinflammatory cytokines are at greater risk for some cancers, cardiovascular disease, and type II diabetes, among other diseases of older adulthood (Ershler and Keller, 2000; Libby, 2007).

The association between SRH and herpesvirus antibody titers has yet to be examined. Given that people's subjective determination of their health status is related to inflammation (e.g., Christian et al., 2013; Undén et al., 2007) and subsequent morbidity and mortality risk, and latent herpesvirus reactivation reflects poor cellular immune function that can promote elevated levels of inflammation, a link between SRH and herpesvirus antibody titers is likely. Therefore, we expected that poorer SRH would be associated with higher antibody titers to herpesviruses. Additionally, we sought to replicate the association between SRH and inflammation and examine if antibody titers partially explained (or mediated) this association.

2. Material and methods

2.1. Participants and procedure

Data were obtained from the Texas City Stress and Health Study, which was part of a larger study focusing on the health of Hispanic individuals by the Center for Population Health and Health Disparities. An exhaustive listing of households in Texas City, Texas was created and households were classified as non-Hispanic White, U.S. born Hispanic, Foreign born Hispanic, and non-Hispanic Black (Peek et al., 2010). One in eight non-Hispanic White and non-Hispanic Black households were selected for the study, with one adult aged 25+ randomly selected from the household. One adult aged 25–64 was randomly selected from all U.S. and foreign born Hispanic households that did not have an adult aged 65+. All U.S. and foreign born Hispanic adults aged 65+ were selected for participation. Informed consent was obtained from all participants, and the protocol was approved by the University of Texas Medical Branch Institutional Review Board.

Approximately 80% of individuals who were selected to participate in the study agreed to be interviewed in their homes, yielding a sample size of 2706. Of those, 1459 individuals elected to provide blood samples for the present study. A total of 251 individuals were excluded due to being seronegative for one or more herpesviruses (described below), yielding a final sample of 1208. A trained phlebotomist drew blood between 9:00 and 12:00 in the morning at the participant's household or a centrally located clinic. Blood samples were centrifuged to obtain plasma, and were batch analyzed to minimize variation between assays (described in detail below).

2.2. Measures

2.2.1. Self-reported health

The RAND SF-36 (SF-36) is a 36-item measure containing eight multi-item subscales: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, pain, general well-being, social functioning, and general health (Ware and Sherbourne, 1992). The SF-36 is a widely utilized measure evidencing strong psychometric characteristics (Ware and Sherbourne, 1992). The five item general health subscale was utilized as an indicator of SRH in the present study. All items on the general health subscale include five response choices ranging from 1 to 5 which are recoded to reflect a scale ranging from 0 to 100 such that higher scores are associated with more optimal functioning.

2.2.2. Reactivation of herpesviruses

CMV immunoglobulin G (IgG) antibody levels were evaluated using enzyme immunoassay (Biocheck, Foster City, CA) as described previously (Stowe et al., 2012a). Substrate slides and con-