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

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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.

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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-

trol sera that were commercially prepared (Microgen Laboratories, La Marque, TX, USA; Bion Enterprises, Park Ridge, IL, USA) were utilized to determine IgG antibody titers to EBV viral capsid antigen (EBV-VCA), EBV early antigen (EBV-EA), and HSV-1 as described previously (Peek et al., 2009). The majority of participants were seropositive for EBV (99.7%), HSV-1 (99.7%), and CMV (82.8%); however, a total of 251 participants were not seropositive for one of the herpesviruses and were subsequently removed from the analyses. Each of the four indicators of viral reactivation was z-standardized and then averaged to form an overall indicator of reactivation of herpesviruses.

2.2.3. Inflammation

Standard enzyme-linked immunosorbent assay (ELISA) methods were utilized to measure CRP, TNF-receptor 1 (TNF-r1), and IL-6. TNF-r1 was utilized instead of TNF-α given that TNF- α has a short half-life of approximately 15 min and TNF-r1 is more easily detectible than TNF- α (e.g., Stowe et al., 2012b). Furthermore, TNF-r1 has been described as a surrogate marker of TNF- α (e.g., Schröder et al., 1995). Each indicator of inflammation was z-standardized and values were averaged in order to form an overall indicator of inflammation.

2.2.4. Control variables

During the interview, participants provided self-reports of their age and sex. Furthermore, a body mass index (BMI) was calculated for each participant after measuring height and weight before blood was drawn. These variables were chosen to be covariates in our analyses given evidence that age, sex, and body mass index are associated with SRH (e.g., Cheng et al., 2013; Wang and Arah, 2015). Additionally, age, sex, and BMI are associated with reactivation of herpesviruses and inflammation (Bennett et al., 2012; Dowd et al., 2008; Hinojosa et al., 2009; Stowe et al., 2012b, 2010; Suarez, 2008). We also included socioeconomic status (i.e., participant reported number of years of education; Fagundes et al., 2012b, 2014) as a covariate in ancillary analyses given evidence that socioeconomic status is associated with SRH, herpesvirus reactivation, and inflammation (e.g., Stowe et al., 2010; Wang and Arah, 2015).

2.3. Analytic strategy

SPSS statistical software (IBM, 2012) was utilized for all analyses. A one-way analysis of variance was conducted in order to examine group differences by race/ethnicity. Bivariate correlations between primary study variables were also calculated. A linear regression was conducted to evaluate how SRH was associated with antibody titers and inflammation above and beyond age, sex, race/ethnicity, and BMI. A mediation analysis, which included generating a 95% confidence interval for the indirect effect using 5000 bootstrap samples (Hayes, 2013) to examine if antibody titer levels explained the association between SRH and inflammation, was also conduced.

3. Results

As seen in Table 1, a one-way analysis of variance revealed that non-Hispanic White participants were significantly older than U.S. born Hispanics, foreign born Hispanics, and non-Hispanic Blacks. Foreign born Hispanics were significantly younger than non-Hispanic Black participants. Non-Hispanic Whites had significantly lower BMIs than non-Hispanic Blacks. EBV-VCA was significantly higher in non-Hispanic Blacks as compared to foreign born Hispanics. EBV-EA was significantly lower in foreign born Hispanics as compared to non-Hispanic Whites, U.S. born Hispanics, and non-Hispanic Blacks. Non-Hispanic Whites demonstrated significantly lower HSV-1 than U.S and foreign born Hispanics, and non-Hispanic Blacks. CRP was significantly higher in non-Hispanic Blacks as compared to U.S. and foreign born Hispanics. Non-Hispanic Whites demonstrated significantly higher TNF-r1 than foreign born Hispanics and non-Hispanic Blacks.

Bivariate correlations (see Table 2) revealed that better SRH was associated with lower antibody titers. The association between better SRH and lower antibody titers remained when controlling for age, sex, race/ethnicity, and body mass index (see Table 3). Similarly, better SRH was associated with lower inflammation before and after control variables were entered into the model, replicating prior findings (e.g., Christian et al., 2013). As seen in Fig. 1, poorer self-reported health was associated with higher inflammation and reactivation of herpesviruses partially mediated this association as a significant indirect effect was identified. Such findings were replicated when utilizing a single-item from the general health scale

Table 1
Means and standard deviations for demographic, viral, and inflammatory characteristics of participants.

	All	non-Hispanic White	U.S. born Hispanic	Foreign born Hispanic	non-Hispanic Black
N	1208	411	457	206	134
Age	52.78 (16.05)	57.30 (15.48)	52.48 (16.01)[c]	45.19 (14.56)[c,d]	51.55 (15.37)[c,e]
Female, %	62.50	59.35	62.36	64.56	68.66
BMI	30.61 (7.15)	30.09 (7.58)	30.83 (6.71)	29.40 (5.33)	33.12 (8.57)[c,d]
Self-reported health	61.87 (24.06)	58.77 (25.30)	64.03 (22.95)[c]	67.88 (22.16)[c]	54.83 (24.26)[d,e]
C-reactive protein	13.63 (16.44)	14.09 (17.04)	12.83 (14.13)	11.99 (17.90)	14.47 (19.21)[d,e]
Tumor necrosis factor-r1[b]	1839.31 (1297.86)	2006.22 (1564.52)	1846.17 (1256.73)	1598.71 (864.74)[c,d]	1683.51 (1060.64)
Interleukin−6[b]	1.99 (4.91)	1.87 (3.94)	2.03 (5.68)	1.64 (3.41)	2.73 (6.46)
Epstein bar virus-VCA[a]	8.95 (1.46)	8.99 (1.54)	8.97 (1.41)	8.67 (1.44)	9.16 (1.43)[e]
Epstein bar virus-EA[a]	4.00 (1.22)	4.07 (1.23)	3.98 (1.23)	3.73 (1.10)[c,d]	4.23 (1.25)[e]
Herpes simplex virus−1[a]	9.41 (1.27)	9.14 (1.49)	9.52 (1.16)[c]	9.57 (1.06)[c]	9.62 (1.12)[c]
Cytomegalovirus[a]	1.87 (0.47)	1.88 (0.49)	1.87 (0.48)	1.81 (0.43)	1.90 (0.47)
Reactivation of herpesviruses	0.02 (0.59)	0.01 (0.60)	0.03 (0.60)	−0.10 (0.49)[d]	0.13 (0.59)[e]
Inflammation	0.01 (0.63)	0.05 (0.64)	−0.01 (0.65)	−0.11 (0.55)[c]	0.10 (0.67)[e]

Note: VCA = viral capsid antigen; EA = early antigen; reactivation of herpesviruses = z-standardized and combined variables for Epstein bar virus-VCA, Epstein bar virus-EA, herpes simplex virus-1, and cytomegalovirus; Inflammation = z-standardized and combined variables for c-reactive protein, tumor necrosis factor-receptor 1, and interleukin-6.

[a] $\log_2$ antibody titers (Epstein bar virus-VCA, Epstein bar virus-EA, Herpes simplex virus-1) or O.D. units (cytomegalovirus).
[b] Units (mg/dL).
[c] Significantly different from non-Hispanic White.
[d] Significantly different from U.S. born Hispanic.
[e] Significantly different from foreign born Hispanic.

Table 2
Pearson correlation coefficients between self-rated health, reactivation of herpesviruses, and inflammation.

Variable	1	2	3	4	5	6	7	8	9
1. Self-rated health	–								
2. Reactivation of herpesviruses	– .12**	–							
3. Inflammation	– .16**	.18**	–						
4. Epstein bar virus-viral capsid Antigen	– .05*	.62**	.07**	–					
5. Epstein bar virus-early antigen	– .05	.56**	.15**	.09**	–				
6. Herpes simplex virus-1	– .10**	.60**	.09**	.16**	.10**	–			
7. Cytomegalovirus	– .08**	.56**	.10**	.14**	.07*	.10**	–		
8. C-reactive protein	– .13**	.12**	.65**	.05	.08**	.09**	.06*	–	
9. Tumor necrosis factor-receptor 1	– .15**	.13**	.64**	.07*	.10**	.07**	.08**	.12**	–
10. Interleukin-6	– .03	.09**	.65**	.02	.11**	.02	.07*	.13**	.13**

Note: Reactivation of herpesviruses = average of z-standardized values for Epstein bar virus viral capsid antigen, Epstein bar virus early antigen, herpes simplex virus-1, and cytomegalovirus; Inflammation = average of z-standardized values for c-reactive protein, tumor necrosis factor-receptor 1; and interleukin-6. * p < .05; ** p < .01.

Table 3
Linear regressions of self-rated health predicting reactivation of herpesviruses and inflammation.

	Reactivation of herpesviruses	Inflammation
Model 1	– .12**	– .16**
Model 2	– .08**	– .14**
Model 3	– .07*	– .11**

Note: * $p < .05$; ** $p < .01$. Standardized Betas are presented. Model 1: unadjusted. Model 2: adjusted for age, sex, race/ethnicity. Model 3: adjusted for age, sex, race/ethnicity, body mass index.

on the SF-36 that is often utilized to measure self-reported health when brevity is needed (e.g., Jylhä, 2009). All findings remained significant with socioeconomic status included as an additional covariate in ancillary analyses.

4. Discussion

This is the first study to our knowledge that demonstrates poorer SRH is associated with elevated antibody titers to herpesviruses. Such findings are in line with prior research indicating that those with high antibody titers have poor health outcomes (Steptoe et al., 2007). Moreover, the literature is extended via results indicating that antibody titers partially mediated the association between SRH and inflammation, a well-known association in the literature (e.g., Christian et al., 2013). Indeed, those with poorer cellular immune system control over viral latency demonstrate higher production of proinflammatory cytokines (Fagundes et al., 2012a; Simanek et al., 2011; Stassen et al., 2006), and this process is important for SRH given present study findings. Accordingly, future work may benefit from incorporating measures of herpesviruses reactivation into studies of SRH in order to develop a better understanding of how SRH is associated with morbidity and mortality.

Findings provide further evidence that individuals are able to accurately report their health to some extent. Indeed, SRH was associated with reactivation of latent herpesviruses and inflammation, consistent with the hypothesis that individuals may be able to sense immune dysregulation (Kaplan and Camacho, 1983). SRH is consistently associated with use of physician services and mortality (e.g., Miilunpalo et al., 1997), indicating that individuals tend to be accurate when reporting on their health. It will be important to measure SRH, antibody titers, inflammation, and health outcomes in future longitudinal studies to elucidate present study findings.

EBV and CMV reactivation reflect poorer cellular immune system control over viral latency and they are influenced by different mechanisms. *In vivo* studies indicate that certain neuroendocrine interactions influence some herpesviruses differently than others (Glaser et al., 1985; Kiecolt-Glaser et al., 1984; Kiecolt-Glaser and Glaser, 1987; Yang et al., 2010). Indeed, latent EBV and CMV had different patterns of reactivation during academic stress and space flight (Matalka et al., 2000; Mehta et al., 2000). Accordingly, it is likely that the neuroendocrine system is an important mechanism underlying associations between self-reported health and immune markers which should be examined in future research.

The cross-sectional design of the current study limited our ability to examine the interplay between SRH, antibody titers, and inflammation over time. This is important to elucidate in future longitudinal research studies given that heightened inflammation is associated with increased sickness behaviors (e.g., Dantzer and Kelley, 2007). Furthermore, a large proportion of our sample was older, a time which is already marked by dysregulated immunity (e.g., Aw et al., 2007). It is important to evaluate associations between SRH, reactivation of herpesviruses, and inflammation among younger populations to provide a better understanding of the time course of present study findings. Additionally, we utilized the 5-item measure of self-reported health as opposed to the frequently utilized single-item measure (e.g., Jylhä, 2009) given evidence that multi-item measures demonstrate better predictive validity than single-item measures (e.g., Gardner et al., 1998; Wanous et al., 1997). However, findings were consistent when including the single-item from the SF-36 as an independent variable as opposed to the 5-item version, suggesting that present study findings can be integrated into the literature in which both single- and multi-item measures of self-reported health are utilized.

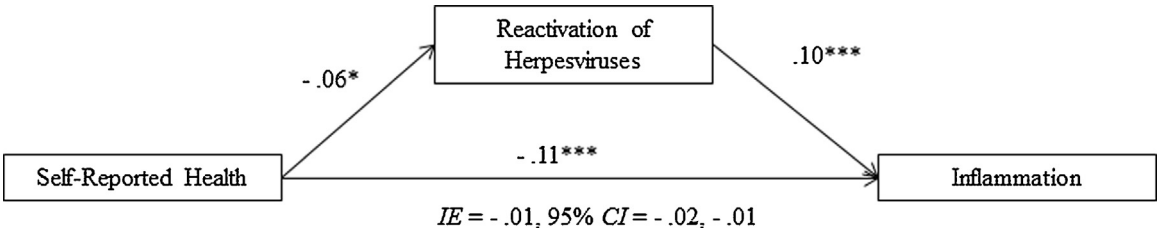

Fig. 1. The association between self-reported health and inflammation through reactivation of herpesviruses. *Note*. Standardized regression coefficients are reported. IE = indirect effect; CI = confidence interval. Control variables (not pictured) include participant age, sex, and body mass index. *$p < .05$. **$p < .01$. ***$p < .001$

5. Conclusions

Current findings add to our growing understanding of the association between SRH and immune dysfunction. Poorer SRH was associated with higher reactivation of herpesviruses, providing an extension to the literature. Moreover, reactivation of herpesviruses partially mediated the association between SRH and inflammation. As such, SRH is associated with increased reactivation of herpesviruses that may, in turn, trigger inflammatory responses that are involved in a number of age related diseases.

Conflicts of interest

None.

Contributors

K.W.M was involved in data analysis and manuscript writing for the present study. C.P.F, M.K.P, and R.P.S provided critical feedback and edited the manuscript. V.V assisted with data analysis and manuscript editing.

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