Consistent associations between measures of psychological stress and CMV antibody levels in a large occupational sample

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A B S T R A C T

Cytomegalovirus (CMV) is a herpes virus that has been implicated in biological aging and impaired health. Evidence, largely accrued from small-scale studies involving select populations, suggests that stress may promote non-clinical reactivation of this virus. However, absent is evidence from larger studies, which allow better statistical adjustment for confounding and mediating factors, in more representative samples.

The present study involved a large occupational cohort (N = 887, mean age = 44, 88% male). Questionnaires assessed psychological (i.e., depression, anxiety, vital exhaustion, SF-12 mental health), demographic, socioeconomic (SES), and lifestyle variables. Plasma samples were analyzed for both the presence and level of CMV-specific IgG antibodies (CMV-IgG), used as markers for infection status and viral reactivation, respectively. Also assessed were potential biological mediators of stress-induced reactivation, such as inflammation (C-reactive protein) and HPA function (awakening and diurnal cortisol). Predictors of CMV infection and CMV-IgG among the infected individuals were analyzed using logistic and linear regression analyses, respectively.

Confirming prior reports, lower SES (education and job status) was positively associated with infection status. Among those infected (N = 329), higher CMV-IgG were associated with increased anxiety (β = .14, p < .05), depression (β = .11, p < .06), vital exhaustion (β = .14, p < .05), and decreased SF-12 mental health (β = -.14, p < .05), adjusting for a range of potential confounders. Exploratory analyses showed that these associations were generally stronger in low SES individuals. We found no evidence that elevated inflammation or HPA-function mediated any of the associations.

In the largest study to date, we established associations between CMV-IgG levels and multiple indicators of psychological stress. These results demonstrate the robustness of prior findings, and extend these to a general working population. We propose that stress-induced CMV replication warrants further research as a psychobiological mechanism linking stress, aging and health.

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1. Introduction

There is convincing evidence that psychological stress impacts health, with the immune system likely playing an important mediating role (Miller et al., 2009; Segerstrom and Miller, 2004). An elegant in vivo paradigm to study the impact of stress on the immune system is the reactivation of latent herpes viruses, such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), or cytomegalovirus (CMV) (Glaser and Kiecolt-Glaser, 1997, 2005). These infections are distinctive because the host is unable to completely eliminate the virus, establishing a life-long competition between the pathogen and the host immune system (Sinclair, 2008). In immune competent...
individuals, the virus mostly remains in a dormant (i.e., low-replicating) state, denoted as latency. However, when immune control is weakened, the virus begins to replicate, which in turn stimulates memory B lymphocytes to increase the output of virus-specific IgG antibody. This increase results in the seemingly paradoxical observation that higher antibody levels reflects poorer immune control of the virus (Glaser and Kiecolt-Glaser, 1994; Kuo

The current study focused on psychosocial factors related to CMV infection status and CMV-IgG levels (reflecting reactivation of the virus). CMV is a highly prevalent β-herpes virus which asymptptomatically infects between 30% and 90% of the population in developed countries (Staras et al., 2006). Prevalence of CMV increases nearly linearly with age (Crough and Khanna, 2009; Staras et al., 2006) and with lower socioeconomic status (SES) (Dowd et al., 2009; Enders et al., 2012; Mustakangas et al., 2000; Simonek et al., 2009). CMV has long been considered harmless to healthy immune competent host. More recently, this consensus has been revised on the basis of studies that have associated this virus with increased mortality, especially among older adults (Gkrania-Klotsas et al., 2012; Pawelec et al., 2012; Simonek et al., 2011; Strandberg et al., 2009; Savva et al., 2013). These epidemiological findings are complemented by studies showing correlations between CMV infection and poor health outcomes, such as the development of metabolic and cardiovascular diseases (Cheng et al., 2009; Haarala et al., 2012; Hjelmesaeth et al., 2004; Nabipour et al., 2006), autoimmune disease (Söderberg-Nauclér, 2012; Varani and Landini, 2011) some cancers (Dziurzynski et al., 2012; Michaelis et al., 2009), as well as cognitive decline and poor functional status (Aiello et al., 2006; Gow et al., 2013; Moro-García et al., 2012).

One prominent explanation for these health effects pertains to the possible role of CMV in accelerating aging of the immune system, a process denoted as immunosenescence (Pawelec et al., 2009; Turner et al., 2014). Indeed, studies show that CMV infection and CMV-IgG levels are associated with markers of impaired immunity that characterize aging. These include impaired vaccination responses (McElhaney et al., 2012; Turner et al., 2014), increased inflammation (Freeman, 2009; Qiu et al., 2008), selective accumulation of T-lymphocytes with impaired responsiveness to mitogens (Chidrawar et al., 2009), reduced telomere length (van de Berg et al., 2010), and reduced telomerase activity (Dowd et al., 2013). Together these findings suggest that research identifying factors that predict CMV infection status and reactivation may significantly contribute to understanding the determinants of healthy aging (Nikolich-Zugich, 2008).

Psychological stress has been identified as one of the factors that can drive subclinical CMV replication, representing a potential mechanism linking stress, immunity and aging (Bosch et al., 2012). In one of the earliest studies, Lycke et al. (1974) found that hospital psychiatric patients had higher CMV-IgG than healthy controls. Subsequent confirmations were provided by naturalistic stress studies involving caregiving (Pariante et al., 1997), spaceflight (Mehta et al., 2000), academic exams (Glaser et al., 1985; Måtalla et al., 2000; Sarid et al., 2004), post-traumatic stress disorder (PTSD) (Uddin et al., 2010), and childhood adversity (Dowd et al., 2012; Fagundes et al., 2013). Studies assessing self-reported stress confirmed these associations, and helped to further characterize the psychological variables involved. For example, studies in older adults identified depression and anxiety as factors associated with higher CMV-IgG (Phillips et al., 2008; Trzonkowski et al., 2004). In a cohort of cardiovascular patients, Appels et al. (2000a) found higher CMV antibody levels among those reporting vital exhaustion (VE), a state characterized by lack of energy, increased irritability, and feelings of demoralization (Appels et al., 2000b; Appels and Mulder, 1988). Related, higher levels of

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1 To date only 4 studies had an N > 50, two of which involved cancer patients or survivors Fagundes et al. (2012); Jaremka et al. (2012) two studied older adults Bennett et al. (2012); Phillips et al. (2008).
tired and worn out (Cronbach's a = .79). The 12-item Health Survey (SF-12), version 2, evaluated subjective quality of life on two dimensions – physical and mental health. For the purpose of this study only the latter subscale was analyzed. Higher scores (range 0–100) indicate better well-being (Ware et al., 1996). Sleep quality was measured by the Jenkins Sleep Problems Scale (Jenkins et al., 1998). Higher scores indicate increased difficulty falling asleep (Cronbach's α = .81 and .82, respectively). The 9-item Shortened Maastricht Exhastion Questionnaire (MQ) measured vital exhaustion (VE), which is reflective of lack of energy, increased irritability, and feelings of demoralization (Kopp et al., 1998). Higher scores indicate increased vital exhaustion (Cronbach's α = .91). The 12-item Health Survey (SF-12), version 2, evaluated subjective quality of life on two dimensions – physical and mental health. For the purpose of this study only the latter subscale was analyzed. Higher scores (range 0–100) indicate better well-being (Ware et al., 1996). Sleep quality was measured by the Jenkins Sleep Problems Scale (Jenkins et al., 1988), which assessed the frequency of four common sleep disturbances (6-point Likert scale) within the last month (ranging from "not at all" to "22–31 nights"), including trouble falling asleep, waking up at night, trouble staying asleep, and waking feeling tired and worn out (Cronbach's α = .79).

2.4. Socio-demographic and lifestyle data

Demographic data (e.g., age, gender, and marital status), SES indicators (job status, education level, and net monthly income), and health behaviors (e.g., smoking, alcohol, physical activity, and diet) were obtained by questionnaires previously validated in the MONICA study (Jönsson et al., 1999). Participants were identified as current smokers by self-report and smoking frequency was assessed as the number of cigarettes smoked per day. Alcohol consumption was assessed as the cumulative number of alcoholic beverages, specified in mean grams of alcohol per week.

2.5. Cytomegalovirus (CMV) antibody levels

Fasted blood samples were taken by venipuncture in ethylene-diaminetetraacetic acid (EDTA) coated tubes (Vacutainer, BD, Plymouth, UK). Plasma was obtained by centrifugation and stored in small aliquots at −80 °C until analysis. Evidence of CMV infection (serostatus) was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) (BioCheck, Inc., CA, USA) according to manufacturer instructions. Participants with a borderline seropositive result, classified as a calculated index score > 0.85 and <1.15, were retested. If they remained borderline (N = 16), subjects with index scores above and below 1.00 were considered positive (CMV+) and negative (CMV−), respectively, which is consistent with manufacturer instructions. The sensitivity, specificity, and accuracy of the test were reported as 95%, 97%, and 96%, respectively. Because the BioCheck assay is not recommended for quantitative determination of antibody levels, CMV-IgG levels in CMV+ individuals were again measured by a commercially available ELISA kit (Genesis Diagnostics Ltd., Cambridge, UK) according to the manufacturer's instructions. The company-reported within-assay and between assay imprecision was <12%.

2.6. Inflammation

Analysis of high sensitivity C-reactive protein (CRP) was performed by immunonephelometry using a Behring Nephelometer II (High Sensitivity CRP, Dade Behring). The detection limit for CRP was 0.015 mg/L, with intra-assay and inter-assay CV% < 10%. All analyses were done at Synlab (Leinfelden, Germany).

2.7. HPA activity

Salivary cortisol was analyzed using a cortisol luminescence immunoassay (sensitivity = 0.008 µg/dL; intra-CV% = 4.5%, IBL International GmbH, Hamburg, Germany) and were performed at the lab of Prof. Kirschbaum, at the Dept. of Biopsychology, TU
Dresden, Germany. To obtain a cortisol awakening response (CAR) participants were instructed to collect saliva immediately upon awakening and 30 min after awakening (Wüst et al., 2000) using time-labeled saliva collection tubes (polyester salivette, Sarstedt, Germany). The participants were provided with a diary to record the exact collection times. Further samples were collected at 2 h post-awakening, at 6:00 p.m., and at 10:00 p.m. to calculate diurnal cortisol area under the curve (AUC) (Golden et al., 2011). Participants were instructed to store the saliva samples in their refrigerator or freezer overnight. On return, all samples were immediately frozen at −20 °C until assay (within 8 weeks).

2.8. Statistical analysis

First, t-tests and χ² analyses were used to test for differences in covariates of interest between CMV+ and CMV− individuals. Binary logistic regression was used to calculate odds ratios (OR) and corresponding 95% CIs of CMV infection, adjusting for age and gender. CMV-IgG levels (among CMV+ individuals) were log-transformed to approximate a normal distribution. Linear regression analyses were then conducted to test the associations of socio-demographic and psychological stress measures with CMV-IgG levels. Potential confounders (e.g., age, gender, demographics, lifestyle, SES) were entered as covariates. Additional adjustments were performed to test cortisol and CRP (log-transformed), as potential mediators of the psychological stress-CMV-IgG relationship. The CAR was calculated as the difference between the cortisol value at awakening and the value 30 min after awakening (Kunz-Ebrecht et al., 2004a). Diurnal cortisol AUC was calculated according to the trapezoid rule described elsewhere (Pruessner et al., 2003). Lastly, analyses were stratified by education level and job status to test for SES differences in immune response to psychological stress. Analyses were carried out with SPSS version 19 (IBM-SPSS, Chicago, IL, USA).

### Table 2

<table>
<thead>
<tr>
<th>Socio-demographic factors</th>
<th>% CMV+</th>
<th>OR (95% CI)</th>
<th>Pr(&gt;Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College/University</td>
<td>30</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Vocational training</td>
<td>41</td>
<td>1.47</td>
<td>(0.87–2.49)</td>
</tr>
<tr>
<td>Completed apprenticeship</td>
<td>38</td>
<td>1.41</td>
<td>(0.92–2.15)</td>
</tr>
<tr>
<td>No higher education</td>
<td>75</td>
<td>5.92</td>
<td>(1.75–20.06)</td>
</tr>
<tr>
<td>Job status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Division/Dept manager</td>
<td>32</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Project Leader/process manager</td>
<td>34</td>
<td>1.03</td>
<td>(0.47–2.23)</td>
</tr>
<tr>
<td>Skilled worker (non-managerial)</td>
<td>36</td>
<td>1.26</td>
<td>(0.61–2.58)</td>
</tr>
<tr>
<td>Semi-skilled worker</td>
<td>60</td>
<td>3.05</td>
<td>(1.18–7.85)</td>
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<tr>
<td>Income</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4000 €/mo</td>
<td>36</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>2500–4000 €/mo</td>
<td>38</td>
<td>1.18</td>
<td>(0.68–2.02)</td>
</tr>
<tr>
<td>1500–2500 €/mo</td>
<td>37</td>
<td>1.22</td>
<td>(0.71–2.09)</td>
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<tr>
<td>&lt;1500 €/mo</td>
<td>36</td>
<td>1.15</td>
<td>(0.57–2.55)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single (incl. divorced &amp; widowed)</td>
<td>30</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Married</td>
<td>41</td>
<td>1.49</td>
<td>(1.04–2.14)</td>
</tr>
<tr>
<td>Smoking</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>1.00</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
<td>1.79</td>
<td>(1.29–2.49)</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Psychological stress factors</th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (HADS)</td>
<td>.105</td>
<td>.912−1.21</td>
<td>.503</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>.979</td>
<td>.929−1.23</td>
<td>.346</td>
</tr>
<tr>
<td>Mental health score (SF-12)</td>
<td>.905</td>
<td>.804–1.04</td>
<td>.283</td>
</tr>
<tr>
<td>Vital exhaustion (MQ)</td>
<td>.803</td>
<td>.735–1.19</td>
<td>.503</td>
</tr>
<tr>
<td>Sleep disturbances (jenkins)</td>
<td>.927</td>
<td>.927−1.23</td>
<td>.356</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age and gender. Model 2: Model 1 with additional adjustment for education, job status, marital status, and smoking. Significant at *p < .05, **p < .01, & *p = .06.

### Table 3

3.1. Predictors of CMV infection status

As shown in Table 1 and 329 (37%) participants were CMV+. On average, CMV+ individuals were older, more likely to be married, and had lower education and job status (Table 1). CMV+ individuals were also more likely to be current smokers, but infection status was unrelated to the quantity smoked. These associations remained significant after adjustment for age and gender (Table 2). Other lifestyle-related factors, such as alcohol intake, BMI, and activity levels were not associated with CMV infection status. Measures of psychological stress, including anxiety, depression, vital exhaustion, and SF-12 mental health scores were also not associated with CMV infection (see Table 2).

3.2. Predictors of CMV-specific IgG antibody levels

Increased HADS anxiety and depression, vital exhaustion, and lower SF-12 mental health scores were all significantly associated with increased CMV-IgG in CMV+ individuals, adjusting for age and gender (Table 3). After subsequent adjustment for predictors of CMV infection status (i.e., marital status, job status, education, smoking), these associations remained significant with the exception of depression, which was slightly attenuated (β = .108, p = .06) (see Table 3). For illustrative purposes, Fig. 1 presents the average scores for each of these psychological parameters by three antibody tertiles (low, middle, and high CMV-IgG), showing a near-linear trend for all parameters.

Notably, none of the factors that predicted serostatus (i.e., education, job status, marital status, or smoking) were predictors of CMV-IgG level (Table 3). Other lifestyle factors (i.e., alcohol intake, BMI, waist-to-hip ratio, and activity level) were likewise not significantly associated with CMV-IgG level (all p > .10; analyses not shown).

3.3. Mediation by inflammation and HPA activity

In light of evidence from in vitro and clinical studies, we aimed to determine if cortisol levels and inflammation were (1) associated with CMV reactivation, and (2) might act as potential pathways linking stress and CMV reactivation. We found no evidence that cortisol levels, either measured as cumulative daily cortisol output (AUC), or CAR, was associated with CMV infection or reactivation (all p > .10). Similarly, systemic inflammation, measured as serum CRP, was not significantly associated with infection status or CMV-IgG. Unsurprising therefore, when HPA parameters and
CRP were added to the multivariate model, the association between psychological variables and CMV-IgG was unaffected.

3.4. Exploratory analyses: SES moderates the associations between psychosocial stress and CMV-IgG level

Table 4 presents analyses of the relationship between psychological predictors (anxiety, depression, vital exhaustion, SF-12 mental health) and CMV-IgG stratified by education and job status. Linear regressions revealed substantially larger associations among those with lower education (apprenticeship or less) or lower job status (no managerial responsibility), which only in these groups reached statistical significance (adjustment for age and gender). However, formal tests of group × stress interaction did not reach significance (for all p > .10).

4. Discussion

CMV reactivation has been associated with impaired health and identified as a possible causal factor in the age-related decline of immune function. Psychological stress may be a determinant of CMV reactivation. The present study revealed consistent associations between measures of psychological stress and CMV-IgG in a large occupational sample. Higher anxiety, depression, vital exhaustion, and lower subjective mental health were all associated with elevated CMV-IgG levels in CMV+ individuals, but these factors were not associated with being infected per se. In contrast, lower SES was associated with increased odds of infection, but not with CMV-IgG levels. These associations withstood adjustment for a range of lifestyle and demographic variables. Overall, then, these findings suggest that stress-induced CMV reactivation is a
robust phenomenon that can be readily replicated in a general population sample, extending what is known for other herpesviruses (e.g., HSV, EBV) to a species which has increasingly become a cause of public health concern (Gkrania-Klotsas et al., 2012; Roberts et al., 2010; Strandberg et al., 2009).

As noted by others (e.g., Aiello et al., 2009; Fagundes et al., 2012), most prior studies in this area lacked a systematic assessment of well-being and stress (or, at least, did not present the data). The current study utilized several validated measures, and the consistency across measures is therefore a novel finding in its own right. This consistency contributes to the recurrent debate on whether specific psychological factors or a general “negative affectivity” (NA) factor are better able to account for the health effects of stress (Cohen et al., 1995; Joiner et al., 1996; Marsland et al., 2001). While both viewpoints have received ample support, the results presented here appear more in line with the latter. It is also conceivable that a specific component of the shared variance, other than or in addtion to NA, is driving the observed associations. For example, there is substantial overlap observed between the vital aspects of depressive symptomatology and VE (Vroege et al., 2013; Roest et al., 2013).

The current literature on psychosocial factors and CMV reactivation hinges on the assumption that CMV-IgG levels are reflective of viral activity. While this assumption has received empirical verification (Besson et al., 2006; Kuo et al., 2008; van Zanten et al., 1995), and is consistent with what has been established for other herpesviridae (e.g., EBV, HSV), there are additional factors that may affect virus-specific antibody levels. For example, repeated infection with different strains of the same virus (denoted as super-infection) may likewise elevate CMV-IgG levels (Novak et al., 2008; Ross et al., 2010). In light of the pattern of results, super-infection would seem less likely as an alternative explanation: if elevated antibody levels reflected repeated infection, it can logically be expected that at least some of the factors that predicted infection (e.g., SES, marital status) would also predict CMV-IgG levels. That was not the case here. While it is conceivable that other factors, like genetic background, may co-determine antibody levels, and thereby confound the observed association, we are not aware of any research identifying such extraneous factors. Hence, reactivation is, at present, the most likely explanation for elevated CMV-IgG levels in distressed individuals (Glaser and Kiecolt-Glaser, 1994; Kuo et al., 2008). Longitudinal studies linking temporal changes in mood and distress with fluctuation in CMV-IgG may further corroborate this idea (Faulkner and Smith, 2009; Stowe et al., 2007; Strachan et al., 2011).

The results showed that the association between CMV-IgG and psychological stress was strongest in low-SES individuals (job status, education), and virtually absent in high-SES employees. While previous studies have singularly explored a possible stress-CMV or a SES-CMV association, our investigation is the first to provide preliminary evidence that these predictors may interact. This finding adds to a small but growing literature demonstrating that SES can moderate the associations between stress and health. For example, in 5-year longitudinal study, Carroll et al. (2003) observed that cardiovascular reactivity to acute stress was a stronger predictor of blood pressure at follow-up among low-SES subjects than among high-SES subjects. Low SES has also been found to predict exaggerated stress reactivity of the immune (Brydon et al., 2004) and HPA-system (Gruenewald et al., 2006; Kunz-Ebrecht et al., 2004b). The exact mechanism responsible may involve exposure to more severe stressors (Grzywacz et al., 2004) or, alternatively, the same stressors having a larger impact due to impaired coping resources (Kristenson et al., 2004). The idea of impaired coping may translate to the biological level in the form of higher allostatic load (Seeman et al., 2010), which is consistent with the aberrant acute stress responses observed in low-SES individuals (McEwen and Seeman, 1999).

The current findings were not consistent with data demonstrating associations between lower SES and increased CMV-IgG levels in a nationally representative U.S. sample (Dowd and Aiello, 2009). This may be due, in part, to the more restricted SES range of this occupational cohort. Specifically, in the cohort analyzed by Dowd and Aiello many had less than high school education while in the present study >95% had more than high school education. By including the lowest SES groups, associations with CMV-IgG levels might involve factors linked to significant and prolonged deprivation, including distress (cf. Fiscella and Franks, 1997).

Inflammation has been shown to promote CMV reactivation in vitro (O’Connor and Murphy, 2012) and in experimental animal studies (Cook et al., 2006), but an association was not observed in the present study. This finding adds to a body of somewhat confusing evidence whereby some studies confirm an association between CMV and inflammation (e.g., Aiello et al., 2006; Fagundes et al., 2012; Roberts et al., 2010; Turner et al., 2014), but others do not (e.g., Bartlett et al., 2012; Bennett et al., 2012; Schmaltz et al., 2005).

Glucocorticoids have likewise been shown to cause CMV reactivation in vitro (Forbes et al., 1990; Tanaka et al., 1984b). However, we did not observe an in vivo association between CMV-IgG and cortisol secretion, measured as the cortisol awakening response, diurnal cortisol AUC, or rate of cortisol decline. The lack of an association with diurnal HPA activity appears to contrast with the literature on EBV reactivation in vivo (Cacioppo et al., 2002; Glaser et al., 1994; Stowe et al., 2000). The reasons for this difference remain speculative at this point, but might reflect an intrinsic difference between the two viruses, which may explain the weak association between CMV and EBV antibody levels observed previously (Fagundes et al., 2012; Ling et al., 2003; Rahman et al., 1989). Also, considering the single day “snapshot” assessment of cortisol release in the present study, these findings should perhaps be
followed up by more long-term assessments – for example via hair cortisol levels (cf. Stalder et al., 2013).

An important target for further research is also to determine the directionality between stress and viral reactivation. Naturalistic studies (e.g., academic stress, space flight) (Glaser et al., 1999, 1985; Mehta et al., 2000) as well as in vitro studies (Prösch et al., 2000) provided evidence that stress and stress hormones may drive viral replication. However, while less well-explored, there is also data to support a reverse causality, whereby CMV reactivation causes psychological changes. This neurological effect may occur due to CMV-induced inflammatory mediators not measured here (e.g., TNF-α, IL-6, IL-1, IFN-γ) that can act directly on the brain (Aldendorf et al., 2012). Indirectly, CMV-induced inflammation may cause psychological changes by cytokine signaling, via afferent nerve fibers, and participate in pathways known to be involved in the development of anxiety, depression, and vital exhaustion (Goodkin and Appels, 1997; Raison et al., 2006; Silverman et al., 2007).

The present sample involved a disproportionate number of males (88%), which limits the generalizability of our findings to women. However, exploratory analyses did not provide an indication that associations were markedly different in women, and adjusting for gender also did not impact the results. Another potential limitation is that the sample was taken from a working population, and is subject to the ‘healthy worker’ phenomenon – the sample is enriched for those with a higher physical and psychological resilience more likely to stay in the work force (Sterling and Appels, 1997; Rector et al., 2012). Such selection may possibly result in an underestimation of the associations between distress and CMV reactivation due to a restriction of range (implying that very high distress scores will be relatively absent). Finally, future studies may test if the observed associations would generalize to any of the other herpes viruses, such as Epstein-Barr virus, Herpes Simplex or Varicella-Zoster virus (Glaser and Kiecolt-Glaser, 2005).

In conclusion, in one of the largest studies to-date we observed remarkably consistent associations between CMV-specific IgG antibody levels, taken to signify viral reactivation, and measures of psychological stress. These associations withstood adjustment for a range of confounding variables, including those that were predictive of CMV infection, and tended to be stronger in those with lower SES. Inflammation and HPA activity, as measured in the preseroconversion period, predicted CMV infection, and tended to be stronger in those with higher SES. Inflammation and HPA activity, as measured in the preseroconversion period, predicted CMV infection, and tended to be stronger in those with higher SES.

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