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Herpesviruses, Inflammatory Markers and Incident Depression in a Longitudinal Study of Detroit Residents

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Abstract

Background—Depression is predicted to become the leading cause of disability worldwide by 2030 and moreover, socioeconomic inequalities in depression persist. Herpesviruses, which are more prevalent among socioeconomically disadvantaged populations, subject to stress-induced reactivation and are associated with increased levels of pro-inflammatory cytokines implicated in the etiology of depression, may serve as novel risk factors for depression onset.

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Conflict of Interest
All authors declare no financial or other conflicts of interest related to the submitted manuscript.

Contributors
Drs. Simanek and Aiello conceived the study hypotheses and study design, Dr. Simanek conducted all statistical analyses and drafted the initial manuscript, Drs. Yolken, Uddin, Galea and Aiello as well as Ms. Cheng provided feedback on the draft and revisions and all authors have reviewed and approved the final version.

Methods—Data are from individuals in the Detroit Neighborhood Health Study tested for herpes simplex virus-1 (HSV-1) and cytomegalovirus (CMV) seropositivity/Immunoglobulin G (IgG) antibody levels (N=263) as well as interleukin-6 (IL-6) (N=245) and C-reactive protein (CRP) (N=236) levels and assessed for incident depression via the Patient Health Questionnaire-9. Linear and logistic regression models were used to examine associations between pathogen seropositivity/IgG antibody levels, pro-inflammatory markers and incident depression over approximately one-year of follow-up.

Results—For every one unit increase in CMV IgG antibody level, the odds of incident depression increased by 26% and individuals with IgG antibody levels in the highest quartile had over three times greater odds of incident depression (odds ratio 3.87, 95% confidence interval 1.47, 10.19), compared to those in the lower three quartiles. Neither CMV or HSV-1 seropositivity nor HSV-1 IgG antibody level were associated with IL-6 or CRP levels at Wave 1, nor were IL-6 or CRP levels associated with incident depression at Wave 2.

Conclusions—Further examination of the biological pathways linking CMV and depression are warranted.

Keywords

herpes simplex virus-1; cytomegalovirus; interleukin-6; C-reactive protein; incident depression

1. Introduction

Lifetime prevalence of major depressive disorder is estimated to be 16.6% among U.S. adults (Kessler et al., 2005) and importantly, depression is predicted to become the leading cause of disability worldwide by 2030 (WHO, 2004). Moreover, socioeconomic inequalities in depression prevalence and incidence persist in the U.S. (Gilman et al., 2013; Pabayo et al., 2014) and have been shown to worsen in older populations (Green and Benzeval, 2013). Given that the proportion of the U.S. population over the age of 65 is projected to grow to nearly 20% over the next four decades (Vincent and Velkoff, 2010), it remains important to identify novel biological risk factors for the onset of depression, particularly those which may be most salient among socioeconomically disadvantaged populations.

The adverse effects of psychosocial stress on immune function are well-documented (Webster Marketon and Glaser, 2008) and recent studies suggest that increased incidence of severe infection may serve as an important risk factor for the onset of depression (Goodwin, 2011; Benros et al., 2013). For example, Benros et al. found that increased hospitalization for infection was associated with greater risk of subsequent mood disorders (incidence rate ratio 1.62, 95% confidence interval (CI) 1.60, 1.64) in a large, population-based study of 3.65 million Danish individuals followed for over twenty years (Benros et al., 2013). Similarly, Goodwin et al. found that children whose parents reported they ever experienced, “a severe infection during the first year of life, needing antibiotics” had almost 4 times greater odds of major depression during childhood (Goodwin, 2011).

Debate regarding the directionality of the association between depression and inflammation (Howren et al., 2009) is ongoing, however, it has been hypothesized that infections may lead

to the onset of mood disorders in part via inflammatory pathways (Dantzer et al., 2008). For example, pro-inflammatory cytokines triggered in response to infection are known to induce symptoms referred to as “sickness behavior” that overlap with those of depression such as anhedonia, sleep disturbances, loss of appetite and fatigue (Dantzer et al., 2008). Indoleamine 2, 3-dioxygenase activity is also enhanced by cell-mediated cytokines, causing tryptophan to be metabolized along the kynurenine pathway, thereby depleting the levels of plasma tryptophan available for the synthesis of serotonin-a neurotransmitter important for mood regulation (Christmas et al., 2011). Furthermore, imbalances in the metabolites of kynurenine which serve as either N-methyl-D-aspartate agonists or antagonists, may also contribute to the etiology of depression onset via altering glutamatergic neurotransmission (Christmas et al., 2011).

While acute infections elicit a short-term inflammatory response, pathogens such as herpesviruses, which once acquired are never cleared from the body and capable reactivation (Glaser, 1994), have been hypothesized to lead to increased incidence of elevated pro-inflammatory cytokines over time (De Martinis et al., 2005). Indeed, a wealth of experimental and observational studies have shown that a wide array of stressors can trigger reactivation of herpesviruses such as herpes simplex virus-1 (HSV-1) and cytomegalovirus (CMV), via down-regulation of cellular immune processes, leading to the release of viral antigens into the circulation (Glaser, 1994). Immunoglobulin G (IgG) antibodies targeted against such pathogens have been shown to increase with leukocyte viral load (Kuo et al., 2008) as well as viral shedding in urine (Stowe et al., 2001), and importantly have also been found to be correlated with increased levels of pro-inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) (Nazmi et al., 2010; Bennet et al., 2012). Elevated levels of IL-6 and CRP have, in turn, been associated with increased risk of depression onset in several longitudinal studies as highlighted in a recent meta-analysis by Valkanova et al. (Valkanova et al., 2013). HSV-1 and CMV have further been linked to several chronic diseases with inflammatory etiology such as cerebrovascular disease (Elkind and Cole, 2006) with which depression commonly co-occurs or is a sequelae (Taylor et al., 2013). Taken together, we hypothesize that in addition to severe infections, chronic herpesvirus infections may also increase risk for depression onset, particularly among those undergoing increased levels of psychosocial stress.

To our knowledge, all previous studies examining the association between herpesviruses and depression have been cross-sectional (Trzonkowski et al., 2004; Miller et al., 2005; Phillips et al., 2008; Jaremka et al., 2013). Thus whether pathogens such as HSV-1 and CMV increase risk for the onset of *de novo* depression remains unknown. Furthermore, while it has been hypothesized that inflammatory pathways may play a key role in the etiology of depression (Trzonkowski et al., 2004; Miller et al., 2005), we are unware of any longitudinal studies that explicitly test whether pro-inflammatory cytokines mediate the association between herpesviruses and depression onset. The aims of this study are therefore to examine: 1) whether seropositivity and/or IgG antibody levels for HSV-1 and CMV are associated with incident depression over approximately one year of follow-up among those free of lifetime history of depression at baseline and 2) whether these associations are mediated by levels of the pro-inflammatory markers IL-6 and CRP at baseline, using data

from The Detroit Neighborhood Health Study (DNHS), a longitudinal study of individuals 18 years of age and older, living in Detroit, MI.

2. Methods

2.1. Study Population

A probability sample of 1547 individuals (aged ≥ 18 years) living within the Detroit city limits participated in a baseline telephone survey in Wave 1 of DNHS (2008–2009). Wave 1 survey participants were representative of the Detroit population in terms of age, gender, race, income, and educational attainment (ACS, 2009). More detailed information on sampling frame, recruitment procedures, and sample characteristics have been published previously (Uddin et al., 2010). All Wave 1 respondents were also given the opportunity to provide a venipuncture blood specimen or bloodspot sample, of which 501 (32.4%) participants provided venipuncture blood specimens. Compared to the overall sample, individuals who consented to the collection of venipuncture blood specimens were more likely to have lower income (p=0.02) and education level (p=0.02) and more likely to have had depression (p=0.01) in the past year at Wave 1. Of those providing a venipuncture sample, 263 (52.5%) were free of lifetime depression at Wave 1, re-interviewed about history of depression approximately one year later (mean 11.8 ± 1.3 months) during Wave 2 of the study and had non-missing values for covariates of interest. Of these individuals, 245 (93.2 %) had non-missing values for IL-6 and 236 (89.7 %) for CRP at baseline. All participants provided informed consent for participation and the study was approved by the University of Michigan Institutional Review Board.

2.2. Depression Outcome

Participants were interviewed at Wave 1 to ascertain information on history of lifetime depression using the Patient Health Questionnaire-9 (PHQ-9) which includes nine items corresponding to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder (Kroenke et al., 2001). During the Wave 1 interview, individuals were asked if there was ever a two-week period in their lifetime during which they were bothered by each item, scored from 0 (not at all) to 3 (nearly every day), with total scores ranging from 0 to 27. Consistent with previous studies (Uddin et al., 2010; Uddin et al., 2011), lifetime history of depression was considered present at Wave 1 if participants reported depressed mood or anhedonia and the cooccurrence of at least one additional symptom for ‘more than half the days’ in a 2-week period in their lifetime. One symptom, “thoughts that you would be better off dead or of hurting yourself in some way,” was included in the depression score if present, regardless of symptom duration. Individuals with lifetime history of depression at baseline (N=73) were excluded from the analyses and at Wave 2 the PHQ-9 was administered again to ascertain cases of incident depression with symptoms assessed in reference to a two-week period since last interview.

2.3. Blood samples and Virological Assays

Serum samples were frozen and stored at −70 C° and shipped on dry ice to the Stanley Neurovirology Laboratory of the Johns Hopkins University School of Medicine in Baltimore, Maryland to be tested for the presence and quantity of serum IgG antibodies to

CMV and HSV-1 via solid phase enzyme-linked immunosorbent assays (ELISAs), as described previously (Dickerson et al., 2003). For each sample, the antibody levels were expressed as ratio of the optical density of a test sample to that of a standard sample assayed in each test run. Individuals were categorized as seronegative for CMV or HSV-1 if their ratio value was <1.0 and seropositive if ≥1.0. Among those seropositive for CMV or HSV-1, IgG ratios were treated as continuous and also dichotomized as low (IgG antibody levels in the bottom 3 quartiles) versus high (IgG antibody levels in the upper quartile) to examine whether there was a dose-response relationship between IgG antibody level and the outcome. Serum levels of the pro-inflammatory markers IL-6 (pg/mL) and CRP (mg/L) were measured from frozen serum using the QuantiGlo Human IL-6 sandwich enzyme immunoassay kit (R & D Systems, USA) and the CRP Ultra Wide Range Reagent Kit (Genzyme, USA) at University of Michigan, following the manufacturer's recommended protocols. Individuals with values below the limit of detection for IL-6 (<0.50) (N=7) or CRP (<0.05) (N=13) were assigned values of 0.25 and 0.025, respectively. IL-6 and CRP levels were non-normally distributed and log transformed in analyses examining the association between CMV and HSV-1 seropositivity/IgG antibody level and IL-6 or CRP levels at Wave 1.

2.4. Covariates

Demographic and clinical characteristics of interest were collected via a telephone survey or home visit as previously described (Uddin et al., 2010). Covariates hypothesized to be potential confounders of the association between CMV and/or HSV-1 seropositivity/IgG antibody level and depression included age, gender, race, education level, annual income level, lifetime history of potentially traumatic events (PTEs), heavy alcohol use in the past month, smoking status, and use of anti-depressant, anti-anxiety and/or non-steroidal anti-inflammatory drugs (NSAIDS) at Wave 1 as these factors have been shown to predict both risk for depression (Hasin et al., 2005) and may also influence susceptibility and immune response to infection and/or inflammatory consequences of infection (Schillinger et al., 2004; Staras et al., 2006). Age in years at baseline was self-reported and treated as a continuous variable. Gender was dichotomized as female or male. Race was self-reported and individuals were categorized as White, African-American or Black or Other. Annual household income at baseline was self-reported in one of seven categories as pre-tax family income from all sources, and was categorized into tertiles as < $10,000, $10,000–34,999 and ≥ $35,000. Education level was self-reported and categorized as <High School, High School and >High School. Individuals were asked about history of 19 potentially traumatic events (PTEs) using the PTSD checklist (PCL-C) (Weathers F, 1996) and well as whether they experienced any 'other extraordinarily stressful event' in their lifetime at Wave 1. The total number of lifetime PTEs experienced by individuals (possible range 0-20) at Wave 1 was treated as continuous. Individuals were categorized according to smoking status (never, past or current) and alcohol use was self-reported as the average number of drinks individuals had on the days they drank in the past month. Individuals were categorized as heavy drinkers in the past month at Wave 1 if, on the days they drank, they consumed ≥ 4 drinks for women and ≥ 5 for men as done in previous studies (Karlamangla et al., 2006). Self-reported medication use was recorded and classified according to guidelines from the Center for Disease Control and Prevention Ambulatory Care Drug Database System (CDC, 2009)

and medication usage was dichotomized as currently taking anti-depressant, anti-anxiety and/or NSAID medications or no use of these medications.

2.5. Statistical Analysis

Statistical analyses were carried out using SAS, version 9.2 (SAS Institute, Cary, NC). Bivariate associations between CMV and HSV-1 seropositivity/ IgG antibody level at Wave 1, IL-6 and CRP levels at Wave 1, incident depression at Wave 2 and covariates of interest were estimated. Independent sample t-tests (two-tailed), Wilcoxon Rank-sum tests or one-way analysis of variance (ANOVA) for difference in mean were estimated for continuous variables. Pearson chi-square or Fisher's exact tests for independence of proportions, or Cochran-Armitage tests for trend for differences in proportions across categorical variables were estimated. Multiple linear regression models were used to examine whether CMV and HSV-1 seropositivity and continuous/dichotomized IgG antibody levels were associated with log IL-6 and CRP levels at Wave 1 among those re-interviewed at Wave 2. Logistic regression models were used to examine the associations between CMV and HSV-1 seropositivity and continuous/dichotomized IgG antibody level as well as IL-6 and CRP levels at Wave 1 and incident depression at Wave 2, among those free of lifetime depression at Wave 1.

Models were first adjusted for demographic characteristics including age, gender, race and annual income level and then for clinical and behavioral characteristics including number of lifetime PTEs, heavy drinking in the past month, smoking status and medication use at Wave 1. Last, models examining the association between CMV or HSV-1 seropositivity/IgG antibody level at Wave 1 and incident depression at Wave 2 were additionally controlled for IL-6 or CRP levels at Wave 1. Education level, while hypothesized as a potential confounder was highly correlated with income level and not associated with incident depression, and thus was not included in our adjusted models. Firth's bias correction (penalized maximum likelihood approach) was applied in some fully adjusted logistic regression models due to quasi-separation of data points. The PROCESS macro in SAS was used to estimate bias-corrected CIs for the indirect effect of CMV and HSV-1 seropositivity/IgG antibody level at Wave 1 on incident depression at Wave 2, through IL-6 and CRP levels at Wave 1 using 5000 bootstrap samples (Hayes, 2012). Last, we conducted sensitivity analyses in which we used PROC MULTTEST to adjust for multiple comparisons between each pathogen of interest (i.e., seropositivity, continuous IgG level and dichotomized IgG level for each pathogen) and incident depression, using the false discovery rate method described by Benjamini and Hochberg (Benjamini and Hochberg, 1995).

3. Results

3.1. Demographic and Clinical Characteristics

Demographic and clinical characteristics of participants at Wave 1 are shown in Table 1. All participants were between 19–91 years of age (mean 54.0 ± standard deviation (SD) 15.8), the majority of which self-reported their race as Black or African-American (81.4%). Fifty-eight percent were female, almost half reported ≤ high school education (44.9%) and 61.2%

of the study population reported annual income level of less than $35,000 per year. Approximately 13.3% of participants reported taking anti-depressant, anti-anxiety and/or NSAID medications at Wave 1, 63.9% reported being a current or former smoker and 6.8% reported heavy alcohol use in the past month at Wave 1. Individuals experienced a mean (±SD) of 4.8 (± 3.6) out of 20 possible PTEs in their lifetime at Wave 1 and 28 (10.7%) individuals reported first onset of depression at Wave 2. Nearly all (95.1%) participants were seropositive for HSV-1 and 76.4% were seropositive for CMV. The mean IgG antibody level among those seropositive for HSV-1 (N=250) was 5.9 ± 4.2 and for those seropositive for CMV (N=201) was 5.4 ± 2.5. Last, among those tested for IL-6 (N=245) and CRP (N=236) the mean IL-6 and CRP levels were 4.5 ± 7.2 pg/mL and 5.2 ± 7.9 mg/L, respectively.

In bivariate analyses, CMV seropositivity was statistically significantly associated with older age and female gender (see Table S1) while HSV-1 seropositivity was only marginally statistically significantly associated with older age (*P*=0.05) (see Table S2). Among those CMV seropositive, CMV IgG antibody level was statistically significantly higher among females and with older age (see Table S3) while older age and past or current smoking status were statistically significantly associated with HSV-1 IgG antibody level among those seropositive for HSV-1 (see Table S4). Female gender, older age, current smoking and lower number of lifetime PTEs were statistically significantly associated with increased IL-6 level at Wave 1 (see Table S5), whereas only female gender and current smoking were statistically significantly associated with higher CRP levels at Wave 1 (see Table S6). Lower annual income was the only covariate at Wave 1 that was statistically significantly associated with incident depression at Wave 2 (see Table S7).

3.2. Associations Between CMV and HSV-1 Seropositivity/IgG Antibody Levels and Log IL-6 and CRP Levels at Wave 1

The associations between CMV and HSV-1 seropositivity/IgG antibody levels and log IL-6 and CRP levels at Wave 1 are shown in Table 2. There were no statistically significant associations between CMV or HSV-1 seropositivity and log IL-6 or CRP levels, or between continuous or dichotomized CMV or HSV-1 IgG antibody levels and pro-inflammatory marker levels at Wave 1.

3.3. Associations between Pathogen Seropositivity/IgG Antibody Level, IL-6 and CRP levels at Wave 1 and Incident Depression at Wave 2

Table 3 shows the odds ratio (OR) (95% CI) for the associations between CMV and HSV-1 seropositivity and IgG antibody level as well as IL-6 and CRP levels at Wave 1 and incident depression at Wave 2. Neither CMV nor HSV-1 seropositivity at Wave 1 was associated with incident depression at Wave 2. Among those CMV seropositive at Wave 1, for every one unit increase in CMV IgG antibody level the odds of incident depression at Wave 2 increased by 26% (OR 1.26 (95% CI 1.04, 1.53)) after controlling for age, gender, race, annual income level, lifetime number of PTEs, heavy alcohol use in the past month, smoking status and medication use at Wave 1. Furthermore, compared to those with CMV IgG antibody levels in the lower three quartiles, the odds of incident depression at Wave 2 was over 3 times greater (OR 3.87 (95% CI 1.47, 10.19)), for individuals with IgG antibody

levels in the highest quartile, in the fully adjusted model (see Model 2, Table 3). After adjustment for multiple comparisons, the associations between continuous and dichotomized CMV IgG level and incident depression observed in model 2 remained statistically significant (P=0.02 and 0.02, respectively). There was no association between continuous or dichotomized HSV-1 IgG antibody level at Wave 1 and incident depression at Wave 2. We also found no association between IL-6 or CRP levels at Wave 1 and incident depression at Wave 2.

After additionally controlling for IL-6 or CRP level at Wave 1, the association between continuous CMV IgG antibody level at Wave 1 and incident depression at Wave 2 was slightly attenuated and only marginally statistically significant (P=0.05). The OR for incident depression for those with CMV IgG antibody level in the highest quartile compared to those in the lower three quartiles was attenuated by over 20%, after additional adjustment for IL-6 or CRP level at Wave 1, but remained statistically significant. The bias-corrected bootstrap CIs for the indirect effects of continuous CMV IgG antibody level on incident depression at Wave 2, through log IL-6 (ab=0.0015) or log CRP (ab=0.0039) level at Wave 1, were −0.0253, 0.0548 and −0.0138, 0.0565, respectively. For the indirect effects of dichotomized CMV IgG antibody level at Wave 1 on incident depression at Wave 2, through log IL-6 (ab=0.0084) and log CRP (ab=0.0211) level at Wave 1, the bias-corrected bootstrap CIs were −0.1520, 0.3208 and −0.0767, 0.3264, respectively.

4. Discussion

To our knowledge this is the first longitudinal study examining the association between herpesvirus seropositivity/IgG antibody level, inflammatory markers and incident depression. Neither CMV nor HSV-1 seropositivity at Wave 1 were associated with onset of depression at Wave 2. Among those seropositive for CMV, however, every one unit increase in IgG antibody levels at Wave 1 was associated with 26% greater odds of incident depression at Wave 2 and those with CMV IgG antibody level in the upper quartile had over three times higher odds of incident depression at Wave 2 compared to those with IgG antibody level in the lower three quartiles. These relationships remained statistically significant after adjustment for age, gender, race, annual income level, lifetime number of PTEs, heavy alcohol use in the past month, smoking status and medication use at Wave 1. A similar association between HSV-1 IgG antibody levels and incident depression was not observed. While the associations between continuous and dichotomized CMV IgG antibody levels and incident depression were attenuated after additional adjustment for IL-6 or CRP level at Wave 1, the indirect effects of these associations through IL-6 or CRP level were not statistically significant. Overall, our findings suggest a pathogen-specific effect of CMV on depression such that, among those seropositive for CMV, poor cell-mediated immune control of this pathogen may contribute to the onset of depression via mechanisms apart from increased levels of IL-6 or CRP.

We are unaware of any other studies that have examined the longitudinal association between CMV and HSV-1 seropositivity/IgG antibody levels and incident depression. Our findings are consistent however, with those from several recent cross-sectional studies examining these associations (Trzonkowski et al., 2004; Miller et al., 2005; Phillips et al.,

2008; Jaremka et al., 2013). For example, Phillips et al. assessed depression among an elderly cohort (mean age 73.6), using the General Health Questionnaire-28, finding that for every one unit increase in CMV IgG antibody titer, the odds of depression was 1.18 (95% CI 1.04, 1.33) times higher, among those seropositive for CMV, controlling for gender and anti-inflammatory medication use (Phillips et al., 2008). Trzonkowski et al., also found that elderly depressed individuals (assessed via DSM-IV criteria) had higher CMV IgG antibody levels compared to non-depressed controls (Trzonkowski et al., 2004).

Most recently, Jaremka et al. examined the cross-sectional association between loneliness, IgG antibody levels for CMV and Epstein Barr virus (EBV) (among seropositives) and elevated depressive symptoms (assessed with the Center for Epidemiological Studies (CES-D) scale) among 200 breast cancer survivors (Jaremka et al., 2013). The authors found that among CMV seropositive women, those with higher CMV IgG antibody levels were more likely to have a higher CES-D scores than those with lower CMV antibody titers, controlling for age, sleep quality, exercise levels, comorbidities, cancer stage and time since cancer treatment ended (Jaremka et al., 2013). Consistent with the hypothesis that stress-induced CMV reactivation may be an important risk factor for depression, the authors demonstrated that elevated CMV antibody titers partially mediated the association between loneliness and elevated depressive symptoms among this population (Jaremka et al., 2013). No such associations were identified for EBV, further supporting the pathogen-specific role of CMV in the etiology of depression (Jaremka et al., 2013).

To our knowledge, only one other study has examined the association between both CMV and HSV-1 seropositivity and depression (Miller et al., 2005). In contrast to our findings, Miller et al. found in unadjusted analyses that individuals in the highest tertile of depressive symptoms (assessed with the Beck Depression Inventory and Hamilton Rating Scale for Depression) were more likely to be seropositive for HSV-1 as well as CMV (Miller et al., 2005). Two studies also assessed pro-inflammatory marker levels including IL-6 and CRP (Trzonkowski et al., 2004; Miller et al., 2005). Trzonkowski et al. found that depressed individuals with elevated CMV IgG antibodies also had increased levels of IL-6 and TNF-α (Trzonkowski et al., 2004), whereas Miller et al. found that individuals in the highest tertile of depressive symptoms were also more likely to have elevated levels of CRP, but not IL-6 or tumor necrosis factor-α (TNF-α) (Miller et al., 2005).

In our study, neither IL-6 or CRP levels at Wave 1 were associated with incident depression at Wave 2, nor was the indirect effect of CMV IgG antibody level on depression onset through log IL-6 or CRP level at Wave 1 statistically significant. While results from a recent meta-analysis support the hypothesis that elevated levels of IL-6 and CRP precede the development of depressive symptoms (Valkanova et al., 2013), the effects were small and not all longitudinal studies have confirmed these associations (Milaneschi et al., 2009; Shaffer et al., 2011; Duivis et al., 2011; Baune et al., 2012). Valkanova et al. note that both IL-6 and CRP have a short half-life, and suggest that the inclusion of other markers of the cell-mediated immune response should be considered in future studies (Valkanova et al., 2013). Moreover, some studies suggest that elevated levels of other pro-inflammatory cytokines, besides IL-6 and CRP, may be most important for predicting depression onset (Milaneschi et al., 2009; Baune et al., 2012).

Importantly, most previous longitudinal studies examining the association between pro-inflammatory markers and depression have been conducted among older populations and/or individuals from specific geographic regions (Milaneschi et al., 2009; Baune et al., 2012; Valkanova et al., 2013). Furthermore, study populations in several previous studies were restricted to individuals with a history of chronic co-morbid conditions such as coronary heart disease (Duivis et al., 2011) or acute coronary syndromes (Shaffer et al., 2011). For these reasons, comparison of findings across studies is challenging and population differences could explain the lack of association between pro-inflammatory markers and incident depression observed in our study. Taken together, although we did not identify that IL-6 or CRP levels at Wave 1 were statistically significant mediators of the association between CMV IgG antibody level and depression in our study, we cannot rule out that CMV influences depression onset via inflammatory pathways. Future studies of healthy individuals spanning broader age ranges in which repeated measures of CMV IgG antibody levels, a wider array of inflammatory markers and other markers of cell-mediated immune activation are collected are needed to clarify the physiological pathways by which CMV influences depression onset.

The pathogen-specific effect of CMV observed in our study, may also reflect the fact that CMV, more so than HSV-1, has been implicated in the etiology of cerebrovascular disease-a chronic disease of aging for which depression is a well-established sequelae (Taylor et al., 2013). For example, CMV has been identified in the brains of those experiencing vascular dementia (Lin et al., 2002) and associated with hypertension (Haarala et al., 2012) as well as stroke (Tarnacka et al., 2002), whereas there are fewer studies demonstrating that HSV-1 is associated with these outcomes. It is possible therefore, that CMV may uniquely influence the onset of depression via exerting pathogen-specific effects which lead to sub-clinical vascular damage in the brain. Indeed, 42.7% of participants included in our sample reporting they had ever been told by a doctor that they had “high blood pressure or hypertension” and 11.8% reported lifetime history of “heart attack or stroke” at Wave 1 of the study.

In ancillary analyses, we additionally controlled for a modified Charlson comorbidity index (Charlson et al., 1987) in fully adjusted models examining the association between continuous/dichotomized CMV IgG antibody level at Wave 1 and incident depression at Wave 2. Individuals were assigned one point for lifetime history of each of the following conditions: heart attack or stroke, congestive heart failure or heart disease, pain in legs from a blockage of the arteries, diabetes, chronic obstructive pulmonary disease, ulcer disease, liver disease, and dementia and two points for history of kidney failure and cancer. In these analyses, the association between continuous CMV IgG antibody and incident depression was largely unchanged (OR 1.27, 95% CI 1.04, 1.54) while the association between dichotomized CMV IgG antibody level and incident depression was slightly attenuated (OR 3.57, 95% CI 1.31, 9.72) but remained statistically significant (data not shown). While these findings may reflect that history of chronic conditions such as cerebrovascular disease lie on the causal pathway between CMV and incident depression, the examination of individual chronic diseases as mediators of these associations is outside the scope of the present study.

CMV, more so than other herpesviruses, has also been associated with oligoclonal T-cell expansion leading to increased numbers of highly differentiated CD8+ T cells specific for

CMV (Pawelec et al., 2009). Indeed, CMV seropositivity has been hypothesized as a potential driver of immunosenescence characterized by an inverted CD4:CD8 T cell ratio, a decreased number of naïve T cells, an increased number but decreased diversity and function of memory T cells and the accumulation of late-stage differentiated T cells (Pawelec et al., 2009). Importantly, recent animal and human studies suggest that T cell function may play an important role in the development of depression (Miller, 2010). In the study by Trzonkowski et al., the authors found that in addition to having elevated CMV IgG antibody levels, depressed individuals also had a higher percentage of CD28-CD57+ cells than those without depression (Trzonkowski et al., 2004). Overall, CMV has been implicated in the etiology of several chronic diseases of aging that have been linked to depression which may explain the pathogen-specific effect of elevated CMV IgG antibody levels on depression onset observed in our study. Future studies are therefore warranted that aim to further elucidate the pathogen-specific mechanisms by which CMV, in particular, may increase risk for depression onset.

There are some limitations to our study. Our study population was drawn from a population-based representative sample of Detroit residents consisting of primarily middle-aged African-American individuals of low socioeconomic position (SEP) with high seroprevalence of HSV-1 and CMV. For this reason, generalizability of our findings may be limited to the Detroit population or similar populations in urban areas of the U.S. However, the prevalence of HSV-1 and CMV seropositivity has been shown to be similarly high among low SEP and African-American individuals in the US population (Schillinger et al., 2004; Staras et al., 2006). Moreover, given that race is a social construction and not a genetic distinction, there are no compelling reasons why the results in a primarily African-American population should be different than those one might observe in other populations.

While we did not assess depression via a clinical interview, we utilized the PHQ-9 consistent with previous studies by Uddin et al. (Uddin et al., 2010; Uddin et al., 2011) to identify and exclude individuals with a lifetime history of depression at baseline as well as to identify incident cases of depression at Wave 2. Use of the PHQ-9 for ascertaining cases of depression had good concordance with one-hour clinician-administered interviews conducted as part of a clinical reappraisal study using the Structured Clinical Interview for DSM-IV Disorders (SCID) for diagnosis of depression among 51 individuals randomly selected from the total sample. Specifically, the PHQ-9 had a sensitivity of 0.60, specificity of 0.93, positive predictive value of 0.67, negative predictive value of 0.90, and an area under the receiver operating characteristic (ROC) curve of 0.76— values comparable to well-established brief assessments for depression used in other community-based samples (Andrews and Peters, 1998).

Low sensitivity values for this instrument could mean we are potentially underestimating prevalence of lifetime history of depression at Wave 1. Indeed, a small proportion of individuals not categorized as having lifetime history of depression at Wave 1 were taking anti-depressant medications at baseline (N=6). It is possible these individuals were prescribed anti-depressant medications for off-label purposes; however this information was not ascertained in our study. Upon exclusion of these individuals from our analyses, the associations between continuous and dichotomized CMV IgG antibody level at Wave 1 and

incident depression at Wave 2 were however only slightly attenuated (<6%) compared to models controlling for medication use as a covariate, and remained statistically significant (data not shown). Furthermore, underestimation of the number of cases of incident depression at Wave 2 resulting from the use of the PHQ-9 will likely serve to bias our results toward the null. Nonetheless, this study represents the first longitudinal examination of the association between CMV and HSV-1 seropositivity/IgG antibody level and incident depression among those free of lifetime history of depression at baseline and the first to explicitly test whether these associations are mediated by levels of the pro-inflammatory markers IL-6 and CRP.

Overall, if CMV is causally associated with depression, prevention of primary CMV infection by the administration of a CMV vaccine may serve to lower the incidence of depression. Alternatively, interventions aimed at improving immune control of CMV such as antiviral medications and/or stress reduction may also be important for improving depressive symptoms among those already infected with CMV. Importantly, numerous population-based studies have demonstrated strong social gradients in seroprevalence (Dowd et al., 2009; Simanek et al., 2009) and immune control (Dowd and Aiello, 2009) of herpesviruses including CMV. For this reason, such interventions, if targeted among socioeconomically disadvantaged populations, may also serve to ameliorate socioeconomic inequalities in depression prevalence and incidence observed in the U.S. (Gilman et al., 2013; Green and Benzeval, 2013; Pabayo et al., 2014). Taken together, continued efforts to develop a CMV vaccine as well as future clinical trials aimed at evaluating the effectiveness of antiviral treatment for reducing depressive symptoms, particularly among populations most vulnerable to CMV reactivation, may therefore be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Study Sample Demographic and Clinical Characteristics

Baseline Characteristics	N=263
Age, years (mean ± SD)	54.0 ± 15.8
Gender, N (%)	
Female	151 (57.4)
Male	112 (42.6)
Race, N (%)	
White	36 (13.7)
Black or African-American	214 (81.4)
Other	13 (4.9)
Education Level, N (%)	
< High School	47 (17.9)
High School	71 (27.0)
> High School	145 (55.1)
Annual Income Level, N (%)	149 (55.2)
<$10000	61 (23.2)
$10000–34999	100 (38.0)
≥$35000	102 (38.8)
Medication Use[a], N (%)	
No	228 (86.7)
Yes	35 (13.3)
Smoking Status	
Never	95 (36.1)
Past	76 (28.9)
Current	92 (35.0)
Heavy Alcohol Use in Past Month[b], N (%)	
No	245 (93.2)
Yes	18 (6.8)
Lifetime Number of PTEs (mean ± SD)	4.8 ± 3.6
CMV Serostatus, N (%)	
Seronegative	62 (23.6)
Seropositive	201 (76.4)
CMV IgG Antibody Level (mean ± SD)[c]	5.4 ± 2.5
HSV-1 Serostatus, N (%)	
Seronegative	13 (4.9)
Seropositive	250 (95.1)
HSV-1 IgG Antibody Level (mean ± SD)[d]	5.9 ± 4.2
IL-6 Level (pg/mL) (mean ± SD)[e]	4.5 ± 7.2
CRP Level (mg/L) (mean ± SD)[f]	5.2 ± 7.9
Incident Depression at Wave 2, N (%)	

Baseline Characteristics	N=263
No	235 (89.3)
Yes	28 (10.7)

CMV; cytomegalovirus, HSV-1; herpes simplex virus-1, IgG; Immunoglobulin G, IL-6; interleukin-6, CRP; C-reactive protein, PTE; potentially traumatic event.

[a] Medication use refers to anti-anxiety, anti-depressant and/or non-steroidal anti-inflammatory drug use.

[b] Individuals were categorized as heavy drinkers if they consumed ≥ 4 drinks for women and ≥ 5 for men on average on the days they drank in the past month.

[c] IgG antibody levels among CMV seropositives only.

[d] IgG antibody levels among HSV-1 seropositives only.

[e] N=245, 18 individuals missing data on IL-6 levels.

[f] N=236, 27 individuals missing data on CRP levels.

Table 2

Associations Between Cytomegalovirus and Herpes Simplex Virus-1 Seropositivity/IgG Antibody Levels and Log Interleukin-6 and C-reactive Protein Levels at Wave 1 in the Detroit Neighborhood Health Study

	Log Interleukin-6 Level at Wave 1				Log C-reactive Protein at Wave 1			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	β (± SE)	P-value	β (± SE)	P-value	β (± SE)	P-value	β (± SE)	P-value
Cytomegalovirus								
Seropositivity[c]	−0.071 (0.14)	0.62	−0.109 (0.14)	0.45	0.246 (0.29)	0.40	0.194 (0.29)	0.50
IgG Antibody Level[d]	0.029 (0.03)	0.28	0.028 (0.03)	0.31	0.044 (0.06)	0.44	0.041 (0.06)	0.47
Low								
High	0.159 (0.15)	0.30	0.175 (0.15)	0.25	0.240 (0.32)	0.45	0.225 (0.32)	0.48
Herpes Simplex Virus-1								
Seropositivity[c]	0.397 (0.27)	0.14	0.317 (0.27)	0.24	0.543 (0.54)	0.31	0.480 (0.54)	0.37
IgG Antibody Level[e]	0.021 (0.01)	0.15	0.019 (0.01)	0.19	0.003 (0.03)	0.91	−0.005 (0.03)	0.86
Low								
High	0.110 (0.14)	0.43	0.087 (0.14)	0.53	−0.008 (0.28)	0.98	−0.082 (0.28)	0.77

IgG; Immunoglobulin G

[a] Model 1 adjusted for age, gender, race and annual income level at Wave 1.

[b] Model 2 additionally adjusted for lifetime number of potentially traumatic events, heavy alcohol use in past month, smoking status and and medication use at Wave 1.

[c] N=245 and N=236 for models examining the association between pathogen seropositivity and log interleukin-6 and log C-reactive protein level at Wave 1, respectively.

[d] N=188 and N=181 for models examining the association between cytomegalovirus IgG antibody level and log interleukin-6 and C-reactive protein level at Wave 1, respectively.

[e] N=233 and N=224 for models examining the association between herpes simplex virus-1 IgG antibody level and log interleukin-6 and C-reactive protein level at Wave 1, respectively.

Table 3

Associations Between CMV and HSV-1 Seropositivity/IgG Antibody Levels and Pro-Inflammatory Marker Levels at Wave 1 and Incident Depression at Wave 2 in the Detroit Neighborhood Health Study

	Odds Ratio (95% Confidence Interval)			
	Model 1[b]	**Model 2[c]**	**Model 3[d]**	**Model 4[e]**
CMV Serostatus (N=263)				
Seronegative	1.0	1.0	1.0	1.0
Seropositive	1.28 (0.43, 3.80)	1.36 (0.45, 4.09)	1.19 (0.38, 3.70)	1.15 (0.37, 3.60)
CMV IgG Antibody Level[f] (N=201)	1.23 (1.03, 1.48)[a]	1.26 (1.04, 1.53)[a]	1.22 (1.00, 1.48)	1.22 (1.00, 1.48)
Low	1.0	1.0	1.0	1.0
High	3.59 (1.39, 9.26)[a]	3.87 (1.47, 10.19)[a]	2.99 (1.09, 8.22)[a]	2.94 (1.06, 8.15)[a]
HSV-1 Serostatus (N=263)				
Seronegative	1.0	1.0	1.0	1.0
Seropositive	0.54 (0.13, 2.29)	0.52 (0.12, 2.26)	0.49 (0.11, 2.19)	0.51 (0.11, 2.25)
HSV-1 IgG Antibody Level[g] (N=250)	1.01 (0.91, 1.12)	1.02 (0.93, 1.13)[h]	1.04 (0.94, 1.15)[h]	1.04 (0.94, 1.16)[h]
Low	1.0	1.0	1.0	1.0
High	0.81 (0.28, 2.32)	0.91 (0.34, 2.45)[h]	1.01 (0.37, 2.80)[h]	1.09 (0.39, 3.06)[h]
IL-6 Level (pg/mL) (N=245)	1.01 (0.96, 1.06)	1.02 (0.97, 1.07)	--	--
CRP Level (mg/L) (N=236)	0.99 (0.94, 1.05)	1.00 (0.95, 1.06)	--	--

CMV; cytomegalovirus, HSV-1; herpes simplex virus-1, IgG; Immunoglobulin G, IL-6; interleukin-6 and CRP; C-reactive protein.

[a] $P<0.05$

[b] Model 1 adjusted for age, gender, race and annual income level at Wave 1.

[c] Model 2 additionally adjusted for number of lifetime potentially traumatic events and anti-anxiety, anti-depressant and/or non-steroidal anti-inflammatory drug use, heavy alcohol use in the past month and smoking status at Wave 1.

[d] Model 3 additionally adjusted for IL-6 level at Wave 1 (N=245 for models with pathogen seropositivity, N=188 for model with CMV IgG antibody level and N=233 for models with HSV-1 IgG antibody level).

[e] Model 4 additionally adjusted for CRP level at Wave 1 (N=236 for models with pathogen seropositivity, N=180 for model with CMV IgG antibody level and N=224 for model with HSV-1 IgG antibody level).

[f] Analyses conducted among those seropositive for cytomegalovirus.

[g] Analyses conducted among those seropositive for herpes simplex virus-1.

[h] Firth bias correction (i.e., penalized maximum likelihood approach) applied due to quasi-separation of data points.