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A Longitudinal Study of the Association Between Persistent Pathogens and Incident Depression Among Older U.S. Latinos

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Abstract

Depression is estimated to affect more than 6.5 million Americans 65 years of age and older and compared with non-Latino whites older U.S. Latinos have a greater incidence and severity of depression, warranting further investigation of novel risk factors for depression onset among this population. We used data on 771/1,789 individuals ≥60 years of age from the Sacramento Area Latino Study on Aging (1998–2008) who were tested for cytomegalovirus (CMV), herpes simplex virus, varicella zoster, *Helicobacter pylori*, *Toxoplasma gondii*, and C-reactive protein (CRP) and interleukin-6 (IL-6) level. Among those without elevated depressive symptoms at baseline, we examined the association between each pathogen, inflammatory markers and incident depression over up to nearly 10 years of follow-up using discrete-time logistic regression. We found that only CMV seropositivity was statistically significantly associated with increased odds of incident depression (odds ratio [OR]: 1.38, 95% confidence interval [CI]: 1.00–1.90) in the total sample as well as among women only (OR: 1.70, 95% CI: 1.01–2.86). These associations were not mediated by CRP or IL-6 levels. Our findings suggest that CMV seropositivity may serve as an important risk factor for the onset of depression among older U.S. Latinos, but act outside of inflammatory pathways.

Keywords: Cytomegalovirus, Gender, Inflammation

Depression affects approximately 6.5 million Americans 65 years of age and older and is estimated to be the leading cause of disability worldwide by 2030 (1). Although compared with non-Latino whites and blacks, younger U.S. Latinos have similar or even lower prevalence of major depression (2), this pattern has been shown to reverse in older age (3). Moreover, U.S. Latinos who become depressed also experience more severe and more chronic depressive symptoms over time (3). Given the U.S. population is rapidly aging and the number of Latinos over the age of 60 is projected to increase at a rate almost three times as fast as non-Latino whites over the next several decades (4), it remains important to identify novel risk factors for depression onset among older U.S. Latinos, to both reduce the overall burden of depression as well as prevent the development of race/ethnic disparities in mental health in the United States in the coming years.

Age-related declines in immune function that increase susceptibility to novel infections and/or impair immunologic control of latent infections are well-documented (5), and a growing body of evidence has suggested that infection-mediated immune alterations, such as inflammation, may play a key role in the regulation of mood (6). For example, proinflammatory cytokines which may be triggered in response to infection have been hypothesized to alter serotonin production and glutamatergic neurotransmission via enhancing tryptophan metabolism (6). Pathogens which once acquired persist over time, such as herpesviruses, have been suggested to be particularly relevant to the onset of mood disorders in older individuals as such

infections are subject to reactivation with age-related declines in cell-mediated immune processes (7–9). *Helicobacter pylori*, a gram-negative bacteria which establishes chronic infection within the stomach has also been hypothesized to influence mood regulation via interactions at the "gut-brain" axis (10) and the persistent neurotropic pathogen, *Toxoplasma gondii* via directly invading and altering levels of dopamine and serotonin within the brain (11). *Helicobacter pylori* and *T gondii* have, however, been examined in relation to depression primarily among younger individuals (12–15). The majority of previous studies examining the association between persistent pathogens and depression have, moreover, been cross-sectional (7–9,14,15) and have yielded mixed findings (15–21) regarding the role of inflammation as a biologic mediator of these pathways. For these reasons, questions remain regarding the role of persistent pathogens in increasing risk for onset of depression in older individuals via inflammatory pathways. Several studies have demonstrated that U.S. Latinos are more likely to be seropositive for several persistent pathogens compared with non-Latino whites (22–24), thus assessment of the relationship between persistent pathogens and depression among this population subgroup is further warranted.

A parallel body of literature has demonstrated that women have a greater burden of depression prevalence and severity (25) and differences in inflammatory response between women and men has been hypothesized to play a key role in explaining such observations (26). A recent study of young- to middle-aged U.S. adults identified positive associations between pathogens including cytomegalovirus (CMV) and *H pylori* on mood disorders in women but a protective effect among men (15). The associations among women were not mediated, however, by levels of the proinflammatory cytokine, C-reactive protein (CRP) (15). Although some evidence suggests that there are differences in the effect of *T gondii* on behavioral changes between women and men (27), findings from studies examining the association between *T gondii* and depression among women separately have been mixed (12,13,28) and not assessed the role of inflammatory pathways. Overall, further investigation into whether there are differences in the association between a broad array of persistent pathogens and depression between women and men over time in older age and the role of inflammation as a relevant mediator of these associations is warranted.

The proposed study utilizes data from a subset of individuals in the Sacramento Area Latino Study on Aging (SALSA), a longitudinal study of nearly 1,800 elderly Mexican Americans who were tested for seropositivity and immunoglobulin G (IgG) antibody levels for five persistent pathogens (CMV, herpes simplex virus-1 (HSV-1), varicella zoster (VZV), *T gondii* and *H pylori*) and assessed for depressive symptoms over up to six follow-up visits spanning more than 9 years of follow-up. The objectives of this study are to examine whether (a) seropositivity for and/or IgG antibody level targeted against persistent pathogens are associated with incident depression, (b) whether elevated levels of the proinflammatory cytokines CRP and interleukin-6 (IL-6) at baseline partially mediate these associations, and (c) whether sex/gender is a modifier of these relationships.

Methods

Study Population

Beginning in 1998–1999, 1,789 elderly male and female Latino (95% of Mexican origin) individuals between 60 and 101 years of age, residing in the Sacramento Valley of California were recruited into the SALSA cohort and underwent a baseline in-home interview and medical exam, during which a trained bilingual health technician collected data on sociodemographics, medical history, medication usage, behavioral risk factors, cognitive and functional status, and depressive symptoms. In-home interviews were repeated at 12- to 15-month intervals, during which information on depressive symptoms as well as other sociodemographic and behavioral characteristics of interest were obtained. We restricted our analyses to 1,208 (70.1%) individuals who were free of elevated depressive symptoms and not taking anti-depressant medications at baseline. Among these individuals, 119 (9.9%) were missing data on baseline characteristics of interest including age, gender, nativity, acculturation score, annual household income level, education level, smoking status, alcohol consumption, or body mass index (BMI) kg/m^2 and excluded from all analyses. Of the remaining 1,089 individuals, 846 (77.7%) also had serum samples collected and tested for IgG antibodies targeted against CMV, HSV-1, VZV, *T gondii*, and *H pylori* as well as the proinflammatory cytokines IL-6 and CRP at baseline. Individuals with serum samples were significantly younger and more likely to be female compared with those without samples. Of these individuals, 75 (8.9%) individuals were lost to follow-up as of the first follow-up visit and excluded from longitudinal analyses. Individuals who were lost to follow-up as of the first visit were more likely to have lower education and income level compared with those not lost to follow-up. Among those included in our analytic sample (N = 771), loss to follow-up was 6.4%, 6.4%, 10.0%, 8.9%, and 10.5% in follow-up visits 2–6, respectively.

Approximately 26% of individuals included in our subsample were missing data on depressive symptoms or medication use during one or more home interviews between the baseline interview and loss to follow-up. We performed multiple imputation via the chained equations (MICE) package in R. MICE runs a series of regression models in which a missing variable is regressed on all other available variables, and then prediction models are used to impute missing values for that specific variable. Using this method, we imputed missing values for depressive symptoms or medication use at any interview preceding loss to follow-up via carrying out linear or logistic regression and then predictive mean matching or logistic regression prediction, respectively. We then averaged the estimates for the log odds ratio for depression yielded from 40 imputed data sets to obtain a final estimate for each association of interest. The estimated covariance incorporating within and between imputation variability was computed based upon methods by Rubin and Schenker (29).

The Sacramento Area Latino Study on Aging (SALSA) was approved by the Institutional Review Boards at the University of Michigan and the University of California at San Francisco and Davis.

Laboratory Analyses

Frozen (–80°C) serum samples were sent to the Stanley Laboratory of Developmental Neurovirology at Johns Hopkins University School of Medicine and tested for presence of IgG antibody levels to CMV, HSV-1, VZV, *H pylori*, and *T gondii* using a solid-phase enzyme-linked immunosorbent assays (ELISA) as described previously (30,31). Briefly, diluted aliquots of serum were reacted with antigen bound to a solid-phase surface. Quantification of IgG antibody levels for each pathogen was determined by reaction of bound antibodies with enzyme labeled anti-human IgG (30). Continuous IgG antibody levels were measured via optical density unit (ODU) values and individuals with ODU values <1.1 were categorized as

seronegative and those with ODU values ≥1.1 as seropositive for CMV, HSV-1, VZV, and *H pylori*. Continuous IgG levels for *T gondii* were assessed in international units (IU)/mL and the cut-point for seropositivity to *T gondii* was ≥10 IU/mL.

Baseline frozen (−70°C) serum samples were also analyzed for IL-6, and high-sensitivity CRP levels. IL-6 levels were determined by using the Quantiglo Chemiluminescent Immunoassay, QTA00B and Q6000B, respectively (R&D Systems, Minneapolis, MN). CRP protein levels were assayed with the CRP Ultra Wide Range Reagent Kit latex-enhanced immunoassay (Equal Diagnostics, Exton, PA).

Outcome

Depressive symptoms were assessed at baseline and each follow-up visit via the Center for Epidemiological Studies Depression Scale (CESD) (32), a 20-item screening questionnaire that has been widely used in Latino populations of all ages and levels of acculturation (33). Depressive symptoms scores range from 0 to 60 and scores of ≥16 are considered consistent with clinical depression (32). Individuals with CESD scores of ≥16 or whom were taking anti-depressant medications at baseline were categorized as depressed and excluded from longitudinal analyses. Individuals not excluded at baseline that reported elevated depressive symptoms (ie, CESD score of ≥16) or new use of anti-depressant medications at each subsequent follow-up interview were categorized as an incident case of depression as has been done in previous studies (34).

Covariates

Several characteristics were considered as potential confounders in our analyses as they have been associated with seropositivity or IgG antibody response to persistent pathogens as well as identified as risk factors for depression including age, gender, nativity, education level, income level, acculturation status, BMI, smoking status, alcohol use, and non-steroidal anti-inflammatory drug (NSAID) use (for analyses with proinflammatory cytokines only) in previous studies. Age in years at baseline was calculated from date of birth and was treated as continuous. Gender was self-reported, and individuals were categorized as male or female. Individuals self-reported the income level that best represented their total household income in the past month at baseline without deductions (<$1,000, $1,000–1,499, $1,500–1,999, $2,000–2,499, or $2,500 and more). State and country of birth was self-reported, and individuals were categorized as Mexican born, U.S. born or other. Marital status was self-reported as never married, married, widowed, divorced, separated, or living with someone as married. Acculturation status was measured at baseline with the Acculturation Rating Scale (ARSMA-II), an established measure of cultural orientation that assesses the dynamic acculturative process comprehensively along multiple dimensions, including those related to ethnic identity and co-ethnic social ties (35). Lower scores represent stronger Mexican orientation, whereas higher scores represent stronger Anglo orientation. Continuous scores were categorized into tertiles representing Mexican orientation (lowest tertile), bicultural orientation (middle tertile), and Anglo orientation (highest tertile). BMI (kg/m^2) was calculated from height and weight assessed at baseline and treated as continuous. Individuals also reported whether they were current, former, or never smokers and were categorized as ever or never smokers at baseline. Alcohol consumption was ascertained at baseline and individuals were categorized according to whether they currently drink wine, beer, and/or alcohol (yes vs no). Medication use was ascertained via a medicine cabinet inventory at baseline as well as each follow-up home visit and medications were classified according to the National Drug Coding Directory. Individuals were categorized according to whether they were currently taking anti-depressants or NSAIDs at baseline and each follow-up home visit (yes vs no).

Statistical Analyses

Statistical analyses were carried out using R3.1.1. We first estimated descriptive statistics (ie, mean [±standard deviation (*SD*)] for all continuous variables and proportion for all categorical variables) among individuals who were tested for pathogen seropositivity, free of depression at baseline, not missing data on any other covariates of interest and had data on depression collected during at least one follow-up visit (*N*= 771). Discrete-time logistic regression models were used to examine the association between pathogen seropositivity/IgG antibody level as well as IL-6 and CRP levels and incident depression among those free of depression at baseline (ie, CESD score <16 and no medication use). Models were first unadjusted, then adjusted for sociodemographic characteristics including age, gender, education level or income level, nativity, level of acculturation and marital status, and last for clinical characteristics including BMI (kg/m^2), smoking status, and alcohol use. Models examining the association between IL-6 and CRP levels at baseline and incident depression were additionally adjusted for NSAID use at baseline. To assess the mediating role of IL-6 and CRP levels in the pathway between pathogen seropositivity and IgG antibody level and incident depression we decomposed the total effect of pathogen serostatus or IgG level on incident depression into direct and indirect effects (ie, effect mediated via IL-6 or CRP level). The direct effect is the association between pathogen serostatus/IgG level and incident depression after adjustment for IL-6 or CRP level and the indirect effect is calculated as the difference between total effect (ie, association between pathogen serostatus/IgG level and incident depression without adjustment for IL-6 or CRP level) and the direct effect. Bootstrapping was used to compute the standard error and corresponding *p*-value for the indirect effect. We also repeated all analyses stratified by gender and also ran models including an interaction term between gender and the exposure (ie, pathogen seropositivity/IgG level or proinflammatory marker level).

Results

Demographic and clinical characteristics of the sample at baseline are shown in Table 1. The mean age of individuals at baseline was 69.4 (±6.2) years, 54.5% were female, 38.5% had a 12 or more years of education, and the majority of individuals (35.7%) had a household income level in the past month of <$1000. A total of 39.3% of individuals were Mexican-born, and the majority (62.8%) were married or living with someone as a spouse. The mean BMI (kg/m^2) of individuals at baseline was 29.9 (±5.8), 10.1% were current smokers, 59.4% consumed alcohol, 13.2% of individuals were currently taking NSAIDS, and the mean CESD score at baseline was 4.6 (±4.5). At baseline, 86.4%, 83.5%, 30.1%, 90.5%, and 37.1% were seropositive for HSV-1, CMV, VZV, *H pylori*, and *T gondii*, respectively and the mean (±*SD*) IgG antibody level for these pathogens were 2.4 (±1.2) ODU, 1.0 (±0.5) ODU, 2.1 (±1.0) ODU, 3.7 (±1.9) ODU, and 13.1 (±13.1) IU/mL, respectively. The mean log IL-6 and CRP values among individuals in the sample were 1.3 (±0.7) and 1.1 (±1.1), respectively. Over the mean 6.4 years of follow-up (range 0.8–9.4), a total of 336 (43.5%) individuals became an incident case of depression.

Table 1. Study Sample Demographic and Clinical Characteristics of Individuals from the Sacramento Area Latino Study on Aging

Characteristic	N= 771
Age (years), mean (± SD)	69.4 (± 6.2)
Gender, N (%)	
Male	351 (45.5)
Female	420 (54.5)
Education (years), N (%)	
0-11	474 (61.5)
12+	297 (38.5)
Household income level (past month), N (%)	
< $1000	275 (35.7)
$1000-1499	146 (18.9)
$1500-1999	96 (12.4)
$2000-2499	106 (13.8)
≥ $2500	148 (19.2)
Acculturation, N (%)	
Mexican-oriented	209 (27.1)
Bicultural	262 (34.0)
Anglo-oriented	300 (38.9)
Nativity Status, N (%)	
Mexican born	303 (39.3)
US born	428 (55.5)
Other	40 (5.2)
Marital Status, N (%)	
Single/Never Married	21 (2.7)
Married/Living With Someone as Spouse	484 (62.8)
Widowed	166 (21.5)
Divorced/Separated	100 (13.0)
Body mass index (kg/m^2), mean (± SD)	29.9 (± 5.8)
Smoking Status, N (%)	
Never	362 (47.0)
Former	331 (42.9)
Current	78 (10.1)
Alcohol Consumption, N (%)	
No	313 (40.6)
Yes	458 (59.4)
CESD score, mean (± SD)	4.6 (± 4.5)
Non-steroidal anti-inflammatory drug use	
No	669 (86.8)
Yes	102 (13.2)
Pathogen Seropositivity, N (%)	
Herpes simplex virus-1	666 (86.4)
Cytomegalovirus	644 (83.5)
Varicella zoster virus	232 (30.1)
Helicobacter pylori	698 (90.5)
Toxoplasma gondii	286 (37.1)
Pathogen IgG antibody level, mean (± SD)[a]	
Herpes simplex virus-1	2.4 (± 1.3)
Cytomegalovirus	1.0 (± 0.5)
Varicella zoster virus	2.1 (± 1.0)
Helicobacter pylori	3.7 (±1.9)
Toxoplasma gondii	13.1 (± 13.1)
Log interleukin-6 level, mean (± SD)	1.3 (± 0.7)
Log C-reactive protein level, mean (± SD)	1.1 (± 1.1)

Note. IgG; immunoglobulin G.

[a]Immunoglobulin G antibody levels measured in international units for *Toxoplasma gondii* and in optical density units for all other pathogens

The longitudinal association between pathogen seropositivity, IgG antibody level, and inflammatory marker levels at baseline and incident depression are shown in Table 2. In the total sample, individuals that were CMV seropositive at baseline had 1.38 (95% CI: 1.00–1.90; p = .0498) times the odds incident depression compared to those that were seronegative, in the fully adjusted model. Although there was a positive association between HSV-1 as well as *H pylori* seropositivity and incident depression, these associations were not statistically significant, and there were no associations between IgG antibody level for any pathogen and incident depression (Table 2). In the unadjusted models, for every 1 *SD* increase in log IL-6 level at baseline, the odds of incident depression increased by 16% (OR: 1.16, 95% CI: 1.05–1.28), however this association was not statistically significant in the fully adjusted model (OR: 1.09, 95% CI: 0.98–1.22). The association between CMV seropositivity and incident depression among the total sample was only slightly attenuated after control for log IL-6 or CRP but became marginally statistically significant (OR: 1.36, 95% CI: 0.98–1.88, p = .067 and OR: 1.38, 95% CI: 1.00–1.90, p = .0502, respectively). The indirect effects of CMV seropositivity and depression through IL-6 and CRP were not statistically significant (OR: 1.02, 95% CI: 0.98–1.04, p = .55 and OR: 1.00, 95% CI: 0.99–1.01, p = .86, respectively).

In stratified analyses, the association between CMV seropositivity and incident depression was only statistically significant among women (OR: 1.70, 95% CI: 1.01–2.86) and stronger compared to men (OR: 1.29, 95% CI: 0.96–1.73; p-value for interaction term = .3600) in fully adjusted models. There were, however, no statistically significant associations between seropositivity for any other pathogens or IgG antibody level for any pathogen and incident depression among women or men, nor any statistically significant interactions between pathogen seropositivity or IgG antibody level and gender (Supplementary Table 1). Among women, neither log IL-6 or log CRP level at baseline was statistically significantly associated with incident depression in fully adjusted models (Supplementary Table 1). While the association between CMV seropositivity and incident depression among women was slightly attenuated (HR: 1.65, 95% CI: 0.97–2.80) and no longer statistically significant after additional adjustment for log IL-6 level, the association was similar in magnitude and remained statistically significant after adjustment for log CRP level (HR: 1.71, 95%: 1.01–2.86). Moreover, the indirect effects through IL-6 and CRP were not statistically significant (HR: 1.03, 95%: 0.96–1.10 and HR: 0.99, 95% CI: 0.94–1.05, respectively). Among men, however, the association between log IL-6 and depression among men (OR: 1.11, 95% CI: 1.00–1.23), remained statistically significant after covariate adjustment (Supplementary Table 2). Given there were no statistically significant associations for pathogen seropositivity/IgG level and incident depression among men, we did not further test for mediation by log IL-6 or CRP level. There were no statistically significant interactions between inflammatory markers and gender.

Discussion

To our knowledge, this is the first study to examine the longitudinal association between numerous persistent pathogens and incident depression over up to nearly a decade of follow-up among older individuals, and moreover, to assess the mediating role of IL-6 and CRP level in these associations. CMV was the only pathogen for which seropositivity was statistically significantly associated with incident depression in the total sample. In stratified analyses, the association between CMV was, moreover, stronger and only statistically significant among women. There were, however, no statistically significant interactions between pathogen seropositivity or IgG antibody and gender. We also did not find evidence for mediation of the associations for CMV seropositivity and incident depression observed in

Table 2. Association Between Pathogen Seropositivity and Immunoglobulin G Antibody Level, Interleukin-6 and C-Reactive Protein Levels at Baseline and Incident Depression Among Individuals in the Sacramento Area Latino Study on Aging

	Odds Ratio (95% Confidence Interval)				
(N=771)	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 5[e]
Pathogens					
Serostatus					
Herpes simplex virus-1	1.25 (0.91, 1.72)	1.26 (0.91, 1.74)	1.31 (0.94, 1.81)	1.32 (0.95, 1.84)	1.32 (0.95, 1.84)
Cytomegalovirus	1.58 (1.15, 2.16)*	1.39 (1.01, 1.91)*	1.38 (1.00, 1.90)*	1.36 (0.98, 1.88)	1.38 (1.00, 1.90)*
Varicella zoster virus	0.97 (0.77, 1.21)	1.01 (0.80, 1.28)	1.00 (0.79, 1.27)	1.00 (0.79, 1.27)	1.00 (0.79, 1.27)
Helicobacter pylori	1.14 (0.78,1.66)	1.11 (0.76, 1.63)	1.07 (0.73, 1.57)	1.07 (0.73, 1.56)	1.06 (0.72, 1.55)
Toxoplasma gondii	1.09 (0.87, 1.36)	1.01 (0.80, 1.28)	1.00 (0.79, 1.27)	1.00 (0.79, 1.26)	1.00 (0.79, 1.27)
IgG Antibody Level					
Herpes simplex virus-1	0.99 (0.89, 1.10)	0.99 (0.89, 1.11)	1.00 (0.90, 1.12)	1.00 (0.89, 1.12)	1.00 (0.90, 1.12)
Cytomegalovirus	1.14 (1.04, 1.25)*	1.08 (0.98, 1.20)	1.08 (0.97, 1.19)	1.07 (0.96, 1.18)	1.07 (0.97, 1.19)
Varicella zoster virus	0.97 (0.87, 1.08)	1.01 (0.90, 1.12)	1.00 (0.90, 1.11)	1.00 (0.89, 1.11)	1.00 (0.89, 1.11)
Helicobacter pylori	0.96 (0.87, 1.07)	0.94 (0.84, 1.04)	0.93 (0.84, 1.04)	0.93 (0.84, 1.04)	0.93 (0.84, 1.04)
Toxoplasma gondii	1.03 (0.93, 1.15)	0.99 (0.89, 1.11)	0.98 (0.87, 1.09)	0.97 (0.87, 1.09)	0.98 (0.87, 1.09)
Pro-inflammatory Markers					
Log Interleukin-6	1.16 (1.05, 1.28)*	1.12 (1.01, 1.24)*	1.09 (0.98, 1.22)	NA	NA
Log C-reactive protein	1.09 (0.98, 1.22)	1.06 (0.95, 1.19)	1.03 (0.92, 1.17)	NA	NA

[a]Model 1 for pathogen seropositivity/immunoglobulin G antibody level and pro-inflammatory markers unadjusted.

[b]Model 2 for pathogen seropositivity/immunoglobulin G antibody level and pro-inflammatory markers adjusted for sociodemographic characteristics including age, gender, education level (for pathogen seropositivity) or income level (for pathogen IgG antibody level), nativity, level of acculturation and marital status.

[c]Model 3 for pathogen seropositivity/immunoglobulin G antibody level additionally adjusted for body mass index (kg/m^2), smoking status and alcohol use at baseline and for pro-inflammatory markers additionally adjusted for these factors as well as use of non-steroidal anti-inflammatory drugs at baseline.

[d]Model 4 for pathogen seropositivity/immunoglobulin G antibody level additionally adjusted for log interleukin-6 level.

[e]Model 5 for pathogen seropositivity/immunoglobulin G antibody level additionally adjusted for log C-reactive protein level.

*$p < 0.05$.

the total sample or among women by inflammatory markers. Our findings suggest that CMV seropositivity may be an important risk factor for onset of depression in older age among U.S. Latinos and moreover, that this pathogen may act through physiologic pathways outside of inflammation.

Previous studies have consistently identified an association between CMV and depression among middle-aged and older individuals, but findings for seropositivity versus IgG antibody level have been mixed (7,8,16,36). For example, Miller and colleagues (9) observed that older individuals (mean age: 61) in the highest tertile of depressive symptoms were more likely to be seropositive for CMV among a clinical cohort of individuals recovering from acute coronary syndrome, but did not assess IgG antibody level. In another cross-sectional study of older individuals (mean age: 73.6), Phillips and colleagues (7) identified that for every one unit increase in CMV IgG antibody level, odds of depression was 1.18 (95% CI: 1.04–1.33) times higher, but found no association for CMV seropositivity. Similarly, several cross-sectional studies conducted among middle-aged individuals found higher CMV IgG antibody level, but not CMV seropositivity, was associated with elevated depressive symptoms (36,37). We are only aware of one other longitudinal study that examined the association between CMV seropositivity as well as IgG antibody level and incident depression (16). In contrast to the present study, the authors found among a community-based sample of middle-aged (mean age: 54.0 ± 15.8 years) no association between CMV seropositivity and incident depression over approximately 1 year of follow-up but that CMV seropositive individuals with IgG antibody levels in the highest quartile at baseline had over three times the odds of incident depression during this period (16). It is possible that CMV seropositivity is a stronger predictor of depression onset in older individuals than small differences in IgG antibody level targeted against this pathogen in the context of overall age-related declines in antibody production.

Fewer studies have examined the association between HSV-1 and depression and have also reported conflicting findings (9,15,16). Although Miller and colleagues (9) observed that older individuals in the highest tertile of depressive symptoms were more likely to be seropositive HSV-1, Simanek and colleagues (16) found no association between HSV-1 seropositivity or IgG antibody level and incident depression in the Detroit Neighborhood Health Study (DNHS), nor among younger U.S. adults using data from the National Health and Nutrition Examination Survey (NHANES) III (15). Although some studies have found that older individuals with depression have lower markers of VZV-specific cell-mediated immunity, compared with controls (38), our findings of no association between VZV and depression are consistent with a previous study by Irwin and colleagues (39), in which the authors found no association between VZV antibody levels and depression. In another study by Chen and colleagues (40), the authors found that individuals ≥18 years of age in Taiwan with newly diagnosed herpes zoster had 1.49 times the rate of developing major depression, compared with controls. Given that herpes zoster may be linked to depression via both immune-related mechanisms as well as adverse psychological effects related to neuralgia, it is possible that had data on occurrence of herpes zoster been available in the present study, we would have also detected an association between VZV and depression among those experiencing this condition.

Studies examining the association between *T gondii* and depression have also yielded mixed results (12,14,41). For example, Groër and colleagues found among a small cohort of pregnant women that among those seropositive for *T gondii*, IgG antibody titer was positively correlated with higher depressive symptoms assessed via the

Profile of Mood States (POMS), after controlling for age and sex (12). In contrast, Alvarado-Esquivel and colleagues (13) recently found no association between *T gondii* seropositivity and depression in a small case–control study of pregnant women in Durango City, Mexico. Two other studies carried out in middle-aged population- and community-based samples also found no association between *T gondii* seropositivity and depression (14,41). Further studies are needed to fully understand the role of *T gondii* in the etiology of depression at different stages of the life course as to our knowledge, this is the first study to examine the relationship between this pathogen and depression in older individuals.

We are only aware of one other study to date that has examined whether there are sex/gender differences in the effect of persistent pathogens on depression (15). Simanek and colleagues (15) identified a positive association between seropositivity for *H pylori* and dysthymia among women (OR: 2.37, 95% CI: 1.07–5.24), but a protective effect of CMV and *H pylori* seropositivity on dysthymia and depression among men, and no association between HSV-1 seropositivity and any mood disorder outcomes among women or men. CMV IgG antibody level was also positively (although not statistically significantly) associated with mood disorders among women, but data were unavailable for men (15). In contrast, in the present study, we did not identify an association between *H pylori* seropositivity among women or men. Simanek and colleagues (15) hypothesized that variation in the influence of *H pylori* on the production of endocrine hormones linked to depression such as ghrelin may serve to explain the differences in the association between *H pylori* and depression that was observed among young- to middle-aged U.S. women and men. Given that ghrelin levels have been shown to decline with age (42), it is possible that any differences in the association between *H pylori* and depression attributable to ghrelin production, may wane as individuals age. Overall, future studies are needed that elucidate whether ghrelin production, as well as other pathways, are relevant mechanisms by which *H pylori* may influence mood and whether these mechanisms differ between women and men across the life course.

The contribution of CMV to alterations to the T-cell compartment of the adaptive immune system may also serve to explain the more consistent finding of an association between this pathogen and depression across studies as well as the stronger effects observed among women. Among individuals who are CMV seropositive, oligoclonal expansion of memory cells targeted against this pathogen results in a large proportion of terminally differentiated effector T cells that are CMV-specific and thus CMV seropositivity has been implicated as key driver of aging of the adaptive immune system (43). Indeed, Aiello and colleagues recently found among a subset of middle-aged individuals in DNHS, that compared with CMV seronegative individuals, those who were CMV seropositive had a 3.80 unit (95% CI: 2.46–5.14) increase in log CD4 effector (CCR7–CD45RA+CD27–CD28–)/naïve (CCR7+CD45RA+CD27+CD28+) (E/N) ratio and a 1.15 unit (95% CI: 0.28–2.02) increase in log CD8 E/N ratio (44). Similar associations were not, however, detected for HSV-1 (data not published). A growing number of studies also suggest that T-cell activation may play an important role in the etiology of depression (45), with recent animal-based models pointing to mechanisms outside of inflammation such as via depletion of circulating amino acids necessary for tryptophan production through the accumulation in activated T cells (46). Taken together, further investigation into whether the observed effects of CMV on depression may be partially explained by the pathogen-specific effects of CMV infection on immune cell aging, particularly among women, is warranted.

While inflammation has been hypothesized as a key biologic mediator linking infection to depression onset, and CMV seropositivity was statistically significantly positively correlated with log IL-6 levels among the total sample (p = .0040) and among women (p = .0270), neither CRP or IL-6 levels at baseline were statistically significantly associated with incident depression among the total sample, or among women. It is possible that, as recently observed in the English Longitudinal Study of Aging (47), sustained elevations in inflammation over time is a more important predictor of depression onset, than levels of CRP or IL-6 measured at a single time point or that other proinflammatory markers are more salient indicators of depression risk over long periods of follow-up (19). Our findings are consistent, however, with several other recent studies that have not found evidence to support a mediating role of inflammation in the association between herpesviruses or *H pylori* and depression (15,16). Taken together with findings from previous studies, our study suggests that pathogens such as CMV may influence the onset of depression via mechanisms outside of inflammatory pathways. In addition to influencing alterations to the T-cell compartment, CMV is neurotropic, and thus may exert direct damage in regions of the brain in which morphological changes have been implicated in the etiology of depression such as the amygdala and hippocampus (48).

A few limitations to our study should be considered. First, other persistent pathogens which have also been hypothesized to play an important role in the etiology of depression such as HSV-2 and Epstein Barr virus (9,36), were not assessed in SALSA. In addition, there is potential selection bias in our sample as compared with the total sample free of depression at baseline, individuals included in our analyses were statistically significantly younger, more likely to be female, to have higher education and income level, to be Mexican-born, to be less Mexican-oriented, to have lower CESD scores and to be less likely to use NSAIDS. While some of these characteristics (ie, female gender, being Mexican-born) are associated with increased prevalence and worse immune control of persistent pathogens, others (ie, higher education and income level) are associated with lower prevalence and better immune control of such pathogens. Taken together with the fact that individuals included in our analyses had lower CESD scores, our results are likely biased toward the null. In addition, the proportion of individuals seropositive for VZV was relatively low (ie, 30.1%) which may indicate this population is not representative of the general U.S. Mexican American population in terms of past exposure to this pathogen (49) and that our findings for this pathogen should be interpreted with caution. Last, while researchers have argued that seronegative individuals should be excluded from analyses of IgG antibody level to better differentiate effects of elevated immune response from seropositivity, due to limited sample size, we estimated the association between IgG antibody level and depression among the entire analytic sample. In sensitivity analyses excluding seronegative individuals, we also found, however, no association between IgG level for any pathogen and incident depression (data not shown). Despite any study limitations, this is, to our knowledge, the largest and first longitudinal study to date to examine the association between a wide array of persistent pathogens, inflammation and incident depression over several years of follow-up and therefore improves upon previous cross-sectional studies in which there is temporal ambiguity regarding the direction of the association between such infections and the onset of depression. In addition, while the generalizability of our findings is limited to older

U.S. Latinos, this is the first study to examine these relationships among this rapidly growing proportion of the older U.S. population and serves to shed light on the role of persistent pathogens as a novel risk factor that may explain changes in the epidemiology of depression among this subgroup of the population later in life.

Conclusions

Our findings suggest that CMV may be associated with onset of depression among older individuals in the United States, particularly those who identify as Latino and to a greater extent among women than men but may act outside of inflammatory pathways to trigger onset of this condition. Continued efforts to develop vaccines targeted against herpesviruses such as CMV as well as future clinical trials aimed at evaluating the effectiveness of antiviral treatment for reducing depressive symptoms, among older individuals seropositive for CMV, may therefore be warranted. Moreover, given that prevalence of this pathogen has been found to be higher among U.S. Latinos (23), targeting of such interventions to older individuals of this population subgroup may also serve to prevent the development of race/ethnic disparities in depression among older individuals in the United States in the coming decades.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of interest

None declared.

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