There is a strong relation between socioeconomic position and health outcomes, although the mechanisms are poorly understood. The authors used data from 1,503 California participants in the 1998–1999 Sacramento Area Latino Study on Aging aged 60–100 years to ask whether socioeconomic position is related to immune function as measured by the body’s ability to keep latent herpesvirus antibody levels in a quiescent state. Individuals with lower educational levels had significantly higher levels of immunoglobulin G antibodies to cytomegalovirus and herpes simplex virus type 1. The odds ratio for being in a higher tertile of cytomegalovirus antibodies was 1.54 (95% confidence interval: 1.18, 2.01) for those in the lowest educational group, and the odds ratio for being in a higher tertile of herpes simplex virus type 1 was 1.63 (95% confidence interval: 1.25, 2.13). The relation between education and cytomegalovirus and herpes simplex virus type 1 antibody levels remained strong after controlling for baseline health conditions, smoking status, and body mass index. This is the first study known to show a relation between socioeconomic position and immune response to latent infection. It provides suggestive evidence that modulation of the immune system via latent infections may play a role in the observed associations between socioeconomic position and disease.

Although the relation between socioeconomic position and health outcomes is well established in many contexts, the physical mechanisms linking socioeconomic position and health are poorly understood. Plausible explanations such as health behaviors and access to health care have failed to adequately clarify the gradient (1). Increasingly, social scientists are incorporating biomarkers into research to better identify and test mechanisms by which socioeconomic position can get “under the skin” and damage an individual’s physiological well-being (2).

There is evidence that individuals with lower educational levels and incomes are more likely to experience both chronic and acute stressors in their lives through their physical, financial/occupational, and sociocultural environments (3, 4). This stress, in turn, is thought to impact health outcomes via sustained activation of stress-related autonomic and neuroendocrine responses and impaired immunity. Chronically elevated cortisol levels is one commonly suggested mechanism through which low socioeconomic position may damage health. Recent work linking cortisol to socioeconomic position has produced mixed results, providing little direct evidence that stress-related biologic alterations explain the relation between socioeconomic position and health (2, 5–9).

Chronic inflammation has also been suggested as a potential mechanism through which psychosocial stress may
A promising alternative to examining neuroendocrine markers such as cortisol or inflammatory markers such as CRP in the socioeconomic position–stress relation is to measure a surrogate indicator of immune system functioning, such as the body’s ability to keep latent herpesvirus antibody levels in a quiescent state. Critical reviews of the psychoneuroimmunology literature support a strong and consistent relation between stress and increased antibody response to herpesviruses (22). Specifically, increases in herpesvirus antibody titers have been linked to academic stress in medical students and military cadets (23), caregiving for a family member with Alzheimer’s disease (24), involvement in a poor-quality marriage (22), anticipation of space flight by astronauts (25), traumatic life events (26), and psychological traits of loneliness and anxiety (27). Evidence of reactivation from other causes includes cases of immunosuppression such as human immunodeficiency virus infection, organ transplants, and chemotherapy (28–30).

Exposure to herpesviruses such as cytomegalovirus (CMV) and herpes simplex virus type 1 (HSV-1) is nearly ubiquitous in early life (31). Although infection with CMV and HSV-1 often passes undiagnosed because of the asymptomatic properties of these viruses, they persist in the infected host for life, with an increasing risk of subclinical reactivation during old age (32, 33). Stress-related changes in cellular immunity can facilitate subclinical herpesvirus reactivation. Levels of immunoglobulin G antibodies to CMV and HSV-1 have therefore been used as indirect measure of alterations in immune function in response to stress (24, 26).

Recent work suggests that stress-induced viral reactivation of CMV may reduce the capacity of the immune system to respond to other challenges (34). CMV infection has even been called the “driving force” behind age-related alterations to the T-cell immune system (32). Both CMV and HSV-1 have been linked to inflammatory processes, cardiovascular disease, cognitive outcomes, and Alzheimer’s disease (35–38). Given this evidence, CMV and HSV-1 provide a unique opportunity to examine a specific immunologic pathway through which socioeconomic position may affect chronic health conditions.

There are clear age, gender, race/ethnicity, and socioeconomic gradients associated with HSV-1 and CMV seropositivity status (31, 39). Ethnic differences in seropositivity to HSV-1 and CMV were found in the Third National Health and Nutrition Examination Survey, where 85.1 percent of Mexican Americans were found to have antibodies to HSV-1, compared with 74.1 percent of non-Hispanic Blacks and 64.7 percent of non-Hispanic Whites (39). Age-adjusted seroprevalence rates for CMV were 81.7 percent for Mexican Americans, 75.8 percent for non-Hispanic Whites, and 51.2 percent for non-Hispanic Whites (31).

Despite the evidence on seropositivity, it is unclear whether social gradients model immune response among infected individuals. There are no studies of which we are aware that have examined the existence of social disparities in immune response to latent infections in aging US populations. This is an important question, since differentials in antibody response may provide a biologic indicator of the socioeconomic gradient in cell-mediated immunity. This study examined the relation between socioeconomic position, as measured by level of education, and serum levels of antibodies to persistent CMV and HSV-1 infection. We also compared the herpesvirus results with models testing the associations between education and cortisol and education and CRP, two biomarkers frequently implicated as mediators of the socioeconomic position–health gradient.

MATERIALS AND METHODS

Study population

Participants were drawn from the Sacramento Area Latino Study on Aging (SALSA), an ongoing prospective cohort study of community-dwelling Mexican Americans aged 60–100 years at baseline in 1998–1999. A subsample of participants (n = 1,561) from the SALSA cohort (N = 1,789) for whom blood samples for CMV, HSV-1, CRP, and cortisol were available were included in the analyses. Individuals for whom blood samples were missing were more likely to be in the lowest education (39.1 percent vs. 31.2 percent, p = 0.0019) and lowest income (53.1 percent vs. 43.6 percent, p < 0.0001) categories but did not differ in age or sex. Fifty-eight observations for which data on dependent variables or covariates were missing were dropped, leaving 1,503 observations. Details of the SALSA study have been discussed previously, and all analyses were approved by the Institutional Review Board at the University of Michigan and the University of California, Davis (40).

Measures

Baseline data for SALSA began to be collected in 1998 with a 2-hour interview at the participant’s home. Information
on years of education, household income, medical history, and duration and date of diagnoses for 35 health conditions was gathered. Clinical evaluations were used to measure blood pressure, weight/height, and waist/hip ratios. Participants were asked to fast on the assigned day of the blood draw. A trained phlebotomist went to the home of the participant to collect a single fasting morning blood sample, which was processed within 4 hours of collection. Resulting serum and plasma samples were stored at −70°C until analysis.

A commercially available enzyme-linked immunosorbent assay immunoglobulin G detection system (Wampole Laboratories, Princeton, New Jersey) was used to analyze the level (expressed as optical density units) of immunoglobulin G antibody to HSV-1 and CMV in frozen serum samples. Each 96-well enzyme-linked immunosorbent assay kit contained controls and internal calibrations. Following manufacturer instructions, we assessed samples for the level of immunoglobulin G antibody signal as expressed by the mean optical density value. The sensitivity and specificity of the assay for HSV-1 are reported to be 97.1 percent and 96.8 percent, respectively; for CMV, the sensitivity and specificity are reported to be 99.0 percent and 94.0 percent, respectively.

A commercially available in vitro diagnostic test was used for the quantitative determination of CRP (CRP Ultra Wide Range Reagent Kit latex-enhanced immunoassay, Equal Diagnostics, Exton, Pennsylvania). The manufacturer’s instructions were followed, and CRP levels were determined by an automated analyzer using a prepared calibration curve. With the highly sensitive method, the kit provides a range of measurable CRP from 0.05 mg/liter to 80.0 mg/liter.

Serum cortisol from the single fasting morning blood sample was measured by using an automated chemiluminescence assay (ACS:180; Bayer HealthCare, Leverkusen, Germany). The manufacturer’s instructions were followed, and total cortisol levels were determined by an automated analyzer using a standardized calibration curve. The assay measures serum cortisol concentrations up to 75 μg/dl, with a minimum detectable concentration of 0.20 μg/dl.

Continuous levels of antibody to CMV and HSV-1 were included in regression models and were divided into tertiles for ordered logit models, as were cortisol and CRP (CRP was log-transformed because of skewness). A modified Charlson index was used to control for chronic health conditions. The Charlson index uses a weighting system for each condition category based on the adjusted risk of 1-year mortality (41). A higher score reflects a more severe burden of comorbidity. Weights were assigned for having myocardial infarction, congestive heart failure, stroke, dementia, liver disease, diabetes, renal disease, any malignancy, and leukemia or lymphoma, and points for each condition were summed to create the final score, as previously described (41). Information on current infections and some immune-related conditions such as rheumatoid arthritis and human immunodeficiency virus was not available. To assess whether the effects of these immune-related conditions or current infections influenced our results, we created two medication variables to represent whether an individual was taking any drugs near the time of the blood sample used as treatments for 1) concurrent infection (i.e., antibiotics, cold medicines, antivirals, antiretrovirals) or 2) autoimmune disorders (i.e., corticosteroids, immunologic agents, immunomodulators, antiarthritics).

**Statistical analyses**

Linear regression models were used to test the relation between continuous years of education and yearly income with continuous CMV, HSV-1, CRP, and cortisol values. Education was examined continuously and was also divided into three categories based on the distribution of education in this sample (0–3 years, 4–11 years, ≥12 years). Gross monthly household income was measured in three categories (<$1,000, $1,000–2,000, >$2,000).

Ordered logit models were used to test the relation between categorical levels of education and income with tertile values of CMV, HSV-1, CRP, and cortisol. Other covariates included in each model were age, sex, whether the respondent was born in the United States, household size, Charlson comorbidity index, smoking status (never, former, current), and an indicator for a body mass index of >30 kg/m². The autoimmune medication variable was not significantly associated with any of the biomarkers. Although use of infection medication was associated with higher CRP, its inclusion did not alter the relation between HSV-1 and CRP. Medication variables were thus excluded from final models.

**RESULTS**

Demographics and other characteristics of the SALSA sample are shown in table 1. When the clinical cutpoints designated by the enzyme-linked immunosorbent assay test kits were used, 97.0 percent of the study subjects showed signs of prior infection with CMV, and 98 percent showed prior infection with HSV-1. The biomarkers showed some associations with one another; positive correlations were found between CMV and Ln(CRP) (r = 0.139, p < 0.001) and Ln(CRP) and cortisol (r = 0.103, p ≤ 0.001), and between CMV and HSV-1 (r = 0.139, p < 0.001). Cortisol was not significantly associated with CMV or socioeconomic position, and Ln(CRP) was not associated with HSV-1.

Figure 1 shows the age-adjusted associations between education and antibody levels of CMV and HSV-1 based on linear regression models. A strong and significant relation between more years of education and lower antibody levels to CMV(r = −0.14, p < 0.001) and HSV-1 (r = −0.14, p < 0.001) was observed. Although monthly household income was a significant predictor of CMV and HSV-1 in models without education (data not shown), it was not significant after including education and was therefore excluded from final models. Figure 2 shows the age-adjusted associations of education with Ln(CRP) and cortisol based on linear regression models. A much weaker relation between education and these biomarkers was observed, and the effect estimates were not statistically significant (Ln(CRP); r = −0.02, p = 0.46; cortisol: r = −0.01, p = 0.69). Income
was not associated with CRP or cortisol by itself or jointly with education and was thus excluded from final models.

Table 2 shows results for the ordered logit models of CMV, HSV-1, and level of education. Results were similar for both markers, whereby individuals with less education showed significantly higher levels of antibody. For individuals with 0–3 years of education, the odds were 1.54 (95 percent confidence interval: 1.18, 2.01) and 1.63 (95 percent confidence interval: 1.25, 2.13) of being in a higher tertile of CRP. The Charlson index and being a former smoker were both associated with greater odds of being in a higher tertile of cortisol, whereas obesity was associated with reduced odds of being in a higher tertile of cortisol.

**DISCUSSION**

Our study demonstrated a significant relation between lower levels of education and increased CMV and HSV-1 antibody levels among Mexican Americans in the United States. This study represents an important new direction for researchers investigating the biophysical mechanisms connecting socioeconomic position and health outcomes. The finding of an association between CMV and HSV-1 immunoglobulin G antibody levels and education, which remained after adjustment for existing health conditions and health behaviors, suggests that modulation of the immune system, possibly due to stress, may be a pathway through which socioeconomic position affects future health outcomes.

Our results are consistent with previous research linking low socioeconomic position and susceptibility to upper respiratory infections in humans (42), suggesting that psychological stress associated with low socioeconomic position can down-regulate various aspects of cellular immune response. In contrast to these previous studies, measuring the relation between social status and primary infection of rhinoviruses, our study examined lifelong latent infections believed to play important roles in chronic diseases of aging (35–38).

Numerous studies have documented an inverse association between socioeconomic position and several chronic inflammation–associated conditions such as cardiovascular disease and dementia (43–45). The biologic pathways that mediate these associations have not been thoroughly characterized. The social gradient in cardiovascular disease persists even after adjustment for health behaviors and many clinical indicators, suggesting that other processes may be involved (46, 47). It is possible that immune response to latent infection may explain some of the socioeconomic gradients in cardiovascular disease and possibly other inflammatory–associated conditions.

Even though our findings are not consistent with several studies reporting a significant relation between CRP and socioeconomic position, they are consistent with findings that health-related behaviors such as smoking and obesity are strongly related to CRP and may moderate the relation with socioeconomic position in many contexts. Our findings regarding cortisol add to growing evidence that different measures of cortisol are not consistently related to socioeconomic position.
position across surveys and thus may not be a robust marker for examining the relation between socioeconomic position, stress, and health outcomes. Studies have shown that glucocorticoids can enhance HSV-1 and CMV infection in vitro and in animal models (48, 49). However, our results showed no correlation between these infections and a single measurement of cortisol. Infections with HSV-1 and CMV have been implicated as stimulators of CRP production (50).

FIGURE 1. Association between education and antibody levels, Sacramento Area Latino Study on Aging, California, 1998–1999. Shown are the fitted values of separate regressions of A) cytomegalovirus (CMV) and B) herpes simplex virus type 1 (HSV-1) immunoglobulin G (IgG) antibody levels as optical density units on years of education, adjusted for age. Dotted lines, 95% confidence intervals.

FIGURE 2. Association between education and C-reactive protein (CRP) and cortisol levels, Sacramento Area Latino Study on Aging, California, 1998–1999. Shown are the fitted values of separate regressions of A) the natural log of CRP and B) serum cortisol on years of education, adjusted for age. Dotted lines, 95% confidence intervals.
Only CMV was significantly correlated with CRP in our data, and inclusion of CRP did not moderate the relation between CMV and education. This finding suggests that the pathways between education and the biomarkers examined in this study may be independent.

Our results regarding the socioeconomic gradient in antibody response support and expand upon results from a nationally representative sample showing that income and education are associated with HSV-1 seropositivity. The rates of seroprevalence in our study were comparable to those for Mexican Americans aged 60 years or older in the Third National Health and Nutrition Examination Survey, where prevalence has been reported to be 97.2 percent for HSV-1 and 91.3 percent for CMV (31, 39).

The immunologic tests generally used to categorize seropositivity to HSV-1 and CMV are based on predesignated clinical cutoffs. We chose to include all subjects, regardless of clinical cutoffs, since analyses with or without the few subjects who were seronegative for CMV (3 percent) or HSV-1 (2 percent) led to the same results. The decision to include all subjects in our final analyses was also based on the high prevalence of these infections in our study population and the concern that clinically appointed cutoffs may be overly stringent (51). We think it is important in the future to not focus solely on seropositivity cutoffs, since continuous levels of immunoglobulin G antibody may provide information on intensity of exposure, subclinical reactivation, and immune response to these highly prevalent infections.

Although antibody response may provide insight into a social gradient in immune response, there are potential limitations associated with the use of viral antibodies as a marker. For example, increased levels of immunoglobulin G–specific antibodies may indicate recent primary infection. However, this possibility was unlikely in our study population since both initial infection as well as reinfection with HSV-1 and CMV commonly occur at young ages.

### TABLE 2. Ordered logit models*: odds ratios for being in a higher tertile of CMV† and HSV-1† by education, Sacramento Area Latino Study on Aging, California, 1998–1999

<table>
<thead>
<tr>
<th>Covariate</th>
<th>CMV Model 1</th>
<th>CMV Model 2</th>
<th>HSV-1 Model 1</th>
<th>HSV-1 Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Education: ≥12 years</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Education: 4–11 years</td>
<td>1.22</td>
<td>0.96, 1.54</td>
<td>1.22</td>
<td>0.96, 1.55</td>
</tr>
<tr>
<td>Education: 0–3 years</td>
<td>1.54</td>
<td>1.18, 2.01</td>
<td>1.63</td>
<td>1.25, 2.13</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.06</td>
<td>0.98, 1.15</td>
<td>1.02</td>
<td>0.95, 1.11</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.22</td>
<td>0.99, 1.52</td>
<td>1.05</td>
<td>0.85, 1.30</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.23</td>
<td>0.90, 1.71</td>
<td>0.97</td>
<td>0.71, 1.34</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m²</td>
<td>0.95</td>
<td>0.78, 1.15</td>
<td>0.80</td>
<td>0.66, 0.97</td>
</tr>
</tbody>
</table>

* All models were adjusted for age, sex, household size, and place of birth.
† CMV, cytomegalovirus; HSV-1, herpes simplex virus.

### TABLE 3. Ordered logit models*: odds ratios for being in a higher tertile of CRP† and serum cortisol by education, Sacramento Area Latino Study on Aging, California, 1998–1999

<table>
<thead>
<tr>
<th>Covariate</th>
<th>CRP Model 1</th>
<th>CRP Model 2</th>
<th>Cortisol Model 1</th>
<th>Cortisol Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Education: ≥12 years</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Education: 4–11 years</td>
<td>1.05</td>
<td>0.83, 1.32</td>
<td>1.06</td>
<td>0.82, 1.37</td>
</tr>
<tr>
<td>Education: 0–3 years</td>
<td>1.31</td>
<td>0.99, 1.71</td>
<td>1.05</td>
<td>0.77, 1.42</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.23</td>
<td>1.13, 1.33</td>
<td>1.17</td>
<td>1.06, 1.28</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.30</td>
<td>1.04, 1.61</td>
<td>1.28</td>
<td>1.00, 1.62</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.02</td>
<td>1.45, 2.82</td>
<td>1.08</td>
<td>0.75, 1.57</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m²</td>
<td>1.86</td>
<td>1.53, 2.27</td>
<td>0.79</td>
<td>0.63, 0.98</td>
</tr>
</tbody>
</table>

* All models were adjusted for age, sex, household size, and place of birth.
† CRP, C-reactive protein.
This study identified a social gradient in immune response to HSV-1 and CMV. Our results provide suggestive evidence that modulation of the immune system via persistent infections may play a role in the observed associations between socioeconomic position and disease. Research on the reactivation of herpesviruses is among the strongest and most consistent experimental evidence of a relation between stress and the immune system (22), suggesting that stress may have played a role in our results. Other possibilities cannot be excluded however, such as the likelihood that individuals of lower socioeconomic position have higher antibody levels because of a lifelong burden of exposure to these infections. Further research is needed to clarify the associations between socioeconomic position, stress, immune response, and disease.

ACKNOWLEDGMENTS

Funding for the Sacramento Area Latino Study on Aging parent study was aided by a grant from the National Institute on Aging, National Institutes of Health (AG12975). This work utilized the Chemistry Core of the Michigan Diabetes Research and Training Center funded by grant NIH5P60 DK20572 from the National Institute of Diabetes and Digestive and Kidney Diseases. The authors also acknowledge the Robert Wood Johnson Health and Society Scholar program at the University of Michigan for funding the viral testing and for financial support of J. B. Dowd. Conflict of interest: none declared.

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Am J Epidemiol 2008;167:112–120