

Title: Life Course Social Disadvantage and the Aging Immune System:
Findings from the Health and Retirement Study

Word Counts:

Abstract: 228

Main Text: 4,303

Number of References: 67

Data Elements in Main Text: 4

Abstract

Objectives: Previous research has documented a consistent association between current socioeconomic status (SES) and cytomegalovirus (CMV). Early life is likely a critical period for CMV exposure and immune development, but less is known about early life socioeconomic factors and CMV, particularly in older age populations. Using data from the Health and Retirement Study, we investigated the association between life course socioeconomic disadvantage and CMV serostatus and IgG response at older age.

Methods: Using ordered logit models, we estimated associations between several measures of socioeconomic disadvantage and the odds of being in a higher CMV IgG response category in a sample of 8,168 respondents aged 50+ years.

Results: We found a significant association between educational attainment and CMV IgG response. Those with less than a high school education had 2.00 (95% CI: 1.67, 2.40) times the odds of being in a higher CMV category compared to those with a college degree or greater. In addition, we also observed a significant association with parental education and CMV response. Individuals with parents having 8 years or less of schooling had 2.32 (95% CI: 2.00, 2.70) times the odds of higher CMV response compared to those whose parents had greater than a high school education.

Conclusion: CMV IgG levels in older adults are associated with both early life and adult SES. Life course socioeconomic disadvantage may contribute to disparities in immunological aging.

Key Words: immune aging, persistent infections, socioeconomic disadvantage, life course studies

36

37 **Introduction**

38

39 Disparities by social factors in age-related physical decline and disease onset have been
40 widely described (Adler & Rehkopf, 2008; Adler & Stewart, 2010; Mensah, Mokdad, Ford,
41 Greenlund, & Croft, 2005). Immune dysfunction across the life course is a potential mechanism
42 underlying these disparities (Roberts, Haan, Dowd, & Aiello, 2010; A. M. Simanek, Dowd, &
43 Aiello, 2008). Specifically, exposure to infections during sensitive periods in early life may
44 promote later chronic disease through early programming of immune and inflammatory
45 responses (Jennifer Beam Dowd, Zajacova, & Aiello, 2009; McDade, 2005b; Meier et al., 2016).
46 Existing evidence suggests that persistent infections such as cytomegalovirus (CMV) are
47 associated with chronic diseases ranging from cancers to cardiovascular disease to cognitive
48 decline and dementia (Allison E Aiello, Chiu, & Frasca, 2017; Allison E Aiello et al., 2006; J. B.
49 Dowd et al., 2009; Liu et al., 2006; Patel et al., 1995; Schmaltz et al., 2005; Walboomers et al.,
50 1999).

51 Numerous studies have suggested that CMV infection and immune response to CMV (as
52 measured by Immunoglobulin G (IgG) antibody levels) may play a critical role in the process of
53 immune aging and age-related declines in health overall, including all-cause mortality (A. Aiello,
54 Simanek, Stebbins, & Dowd, 2018; A. E. Aiello et al., 2017; Feinstein et al., 2016; Pawelec et
55 al., 2005; A. Simanek, Dowd, Zajacova, & Aiello, 2015; A. M. Simanek et al., 2011). CMV
56 seropositivity and IgG antibody levels increase significantly with age (Fulop, Larbi, & Pawelec,
57 2013; Wikby et al., 2005). However, studies have also found similar age-associated alterations in
58 the immune compartment due to CMV in younger populations (Karrer, Mekker, Wanke, Tchang,
59 & Haeberli, 2009; Weinberger et al., 2007), suggesting that higher CMV IgG antibody levels can

be utilized as an indirect marker of lowered cell-mediated immunity, independent of age (A. Aiello & Dowd, 2012; A. Aiello et al., 2018). This is also supported by studies showing that CMV is associated with telomere shortening and telomerase activity, further suggesting CMV's role in cellular aging (A. Aiello et al., 2017; Jennifer B Dowd et al., 2017).

Primary infection with CMV often occurs early in life (Colugnati, Staras, Dollard, & Cannon, 2007) and is followed by cycles of reactivation of the virus throughout the life course (Fulop et al., 2013) (**Figure 1**). Each cycle of reactivation requires substantial immune resources to force the virus into a quiescent state, effectively aging the immune system (Fulop et al., 2013; Weinberger et al., 2007). Higher CMV IgG antibody levels among those who are seropositive, therefore, reflect either an initial response to primary infection or an impaired ability to keep CMV latent in the many cell types where it resides after initial infection.

We draw upon life course theories of social status and health to conceptualize the link between life course social disadvantage and CMV response in late life (Figure 1), focusing both on sensitive period and cumulative disadvantage models. While a formal test of these theories is not possible given the available data, we nevertheless find that these models are helpful in framing the processes we believe may be at work. In the sensitive period model, early life stress exposures may have lasting impacts on CMV response in late life because of reduced investment in the immune system in early life, particularly cell-mediated immunity which may have enduring consequences for immune aging across the life course (Barker, 1998; Ben-Shlomo & Kuh, 2002; McDade, 2005a). Such a model would predict that early life social disadvantage would accelerate the pace of immune aging leading to poor immune control of CMV in late life, independent of adult disadvantages.

A cumulative disadvantage model predicts that early life disadvantage is critical to adult

health due to an accumulation of disadvantage across the life course—disadvantage in early life leads to increased risk of disadvantage at later stages, increasing disease risk at all life stages (Dannefer, 1997, 2003; Ferraro & Shippee, 2009; O'Rand, 1996). In the current study, disadvantage in early life would be reproduced across time producing widening inequalities in both socioeconomic status (SES) and the pace of immune aging among older individuals (Crystal, Shea, & Reyes, 2017). Accordingly, those who experience multiple time points of socioeconomic disadvantage across the life course would have an accelerated pace of immune aging leading to poor immune control of CMV in late life. Therefore, we might expect experiences of more recent disadvantage to be more strongly associated with adult immune response to CMV than experiences of disadvantage in early life.

Moreover, it is likely that SES is fundamental both in determining likelihood of initial exposure to and infection with CMV (McDade, 2005a, 2005b), as well as determining the frequency with which cycles of reactivation occur (**Figure 1**). We use parental education as a proxy measure of early life social disadvantage. Individuals who grow up in households with low parental education have been shown to have an increased likelihood of poor housing conditions, less access to material resources, and neighborhood environments that limit access to healthcare compared with individuals who grow up in households with a higher level of parental education (Galobardes, Lynch, & Smith, 2007)—all of which could increase exposure to CMV. Studies among U.S. children have found that lower parental SES and minority race/ethnicity were associated with a higher prevalence of infections, including CMV (J. B. Dowd et al., 2009; Gares, Panico, Castagne, Delpierre, & Kelly-Irving, 2017). This same trends hold for adult SES in which lower socioeconomic status (SES) in adulthood is associated with a higher prevalence of persistent infection with CMV and other persistent pathogens in both the U.S. and U.K. (A. E.

Aiello et al., 2009; J. Dowd, Aiello, & Alley, 2009; A. M. Simanek et al., 2008; A. Zajacova, Dowd, & Aiello, 2009)

SES also is also likely an important predictor of reactivation of CMV through the stress process. Social stress theory posits that individuals experiencing social disadvantage are differentially exposed to chronic stress (Pearlin, 1989), which may result in increased physiological wear and tear on several body systems (R.-P. Juster, McEwen, & Lupien, 2010), including the immune system. Indeed, Ferraro posits that stress accumulation throughout the life course is a key mechanism for explaining how cumulative inequality accelerates the aging process (Ferraro & Shippee, 2009). Thus, we posit that via chronic stress, social disadvantage may result in poorer immune control of CMV (i.e. more frequent cycles of reactivation of the virus). This would be evidenced by higher circulating IgG antibodies to CMV at a given time point (Glaser & Kiecolt-Glaser, 1994; Kuo et al., 2008; Rector et al., 2014; Van Zanten et al., 1995). Indeed, studies have found that chronic stress is associated with increased inflammation (Friedman & Herd, 2010; Pollitt et al., 2008) and changes in immune function (Fagundes et al., 2012; Janicki-Deverts, Cohen, Doyle, Marsland, & Bosch, 2014), specifically cell-mediated immune function. In addition, higher CMV IgG antibody levels have been observed with stressors such as academic testing (Glaser, 2005) and acute hospital care (Clari et al., 2013). One recent study found that consistently experiencing disadvantage at multiple time points (i.e., cumulative disadvantage) across the life course was associated with higher IgG antibodies to CMV and other persistent pathogens in a population based study of older Latinos (Meier et al., 2016).

Using a life course framework, we hypothesize that social disadvantage in both early- and late-life will be associated with poor immune response to CMV in late life. Though formal tests

of life course theories are limited by the availability of longitudinal SES markers, we believe employing a life course framework can nonetheless provide a helpful lense through which to understand the processes at work. Furthermore, while existing studies suggest that SES across the life course may influence patterns of CMV infection and immune response critical for health in late life, population-based studies on life course SES and later-life CMV infection in U.S. population-based studies of aging have been scarce. Using newly released biomarker data from the Health and Retirement Study (HRS), the current study investigates the association between life course social disadvantage and CMV IgG antibodies among a nationally representative sample of aging adults.

Methods

Study Population

Data come from the Health and Retirement Study (HRS), the largest on-going nationally representative longitudinal survey of older adults in the U.S. The HRS began in 1992 with over 22,000 adults ages 50+ years at baseline, with follow-up every two years. Additional details on HRS design and methods have been previously described (F. T. Juster & Suzman, 1995; Sonnega et al., 2014).

Our analysis used existing demographic and social data from the 1998, 2014, and 2016 waves combined with the newly released immunological data from the 2016 Venous Blood Sample (VBS) (Crimmins, 2017). A total of 20,912 individuals participated in the HRS 2016 survey, of whom 16,056 were panel respondents. All panel respondents in the 2016 interview were asked to participate in the VBS. The 2016 refresher sample (born between 1960-1965) were not eligible for the VBS. Of the panel participants, 61.9% consented to and participated in the

VBS (n = 9,934). Our analysis included those who were deemed eligible based on the criteria below. Of the 9,934 participants, 7.5% were excluded based on having a survey weight of zero (n = 745). In HRS, weights of zero are assigned to deceased respondents, respondents residing in nursing homes, and those who are deemed age ineligible. In our sample, those with zero weights were deemed age ineligible, born after 1959. Another 6% were excluded due to missing data on parental education (N = 606). Those missing data on CMV were also excluded (0.7% of the sample, n = 74) and 1.3% were excluded because of missing data on other covariates (n = 139). Finally, we only included those categorized as non-Hispanic Black, Hispanic, or non-Hispanic White, yielding a final sample size of 8,168. Details of construction of the study sample are in **supplementary figure 3**.

Measures

Adult SES was measured using participant education level and current household income.

Education was categorized as less than high school, high school diploma or equivalent, some college, or college graduate and above (reference group). Household income was based on the continuous variable of household income to poverty ratio (IPR).

Childhood SES was measured using parental education. The highest level of education from either parent was used to construct parental education. The final parental education variable was a four-level variable comparing those with less than 8 years of education, those with 9-11 years of education, and those with a high school diploma to those with greater than a high school education.

CMV Seroprevalence and CMV IgG response were measured using IgG antibodies to CMV in serum using the Roche e411 immunoassay analyzer. The lower limit of detection was 0.015 antibody units per milliliter (U/mL). Results were reported as nonreactive (<0.5 U/mL),

borderline (0.5 to <1.0 U/mL), or reactive (≥ 1.0 U/mL). Those with a borderline response were classified as seropositive for CMV. For analytical purposes we first examined seropositives (≥ 0.5 antibody U/mL) and seronegatives (< 0.5 antibody U/mL). We then split the seropositives into tertiles of CMV antibody response using seronegatives as the reference group. The mean (standard error) CMV antibody response for seronegatives was 0.10 (0.0006) U/mL. The mean (standard error) CMV antibody response for tertile 1 was 107.07 (2.10) antibodies U/mL, 401.25 (3.01) for tertile 2, and 888.19 (8.86) for tertile 3.

Covariates included continuous age in years, gender (men/women), and race/ethnicity. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, or Hispanic.

Statistical Analyses

All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). Descriptive statistics characterized the study population overall. Ordered logit models were used to estimate the relative odds of being in a higher category of CMV IgG response by adult SES (i.e. educational attainment and IPR), and childhood SES. Model 1 estimated the association of adult SES and CMV IgG levels controlling for age, gender, and race/ethnicity. Model 2 further adjusted for childhood SES by incorporating parental education, which we expected to be a life course predecessor of adult SES. Finally, model 3 estimated the direct association of childhood SES and CMV IgG response, without adult SES. All analyses were weighted with the 2016 Venous Blood Sample weights.

Sensitivity Analyses

Several sensitivity analyses were performed. First, based on the different distribution and

rewards of educational attainment by race/ethnicity for these cohorts (Fischer & Hout, 2006), we explored differences in the association between SES and CMV response by race/ethnic group. Next, we used a latent variable of childhood SES constructed by Vable et al. to conduct a sensitivity analysis incorporating multiple dimensions of the childhood socioeconomic environment to provide a more robust measure of childhood social disadvantage (Vable, Gilsanz, Nguyen, Kawachi, & Glymour, 2017). Notably, the childhood SES index was only constructed for a sub-sample of HRS (N= 6,264), thus precluding us from using it in the primary analysis. Further details and all results are presented in the supplementary material.

Results

Sample Characteristics

Overall, 65% of the sample was seropositive for CMV (see **table 1**). A greater proportion of non-Hispanic Blacks (32%) and those with less than a high school education (33%) were classified in the highest tertile of CMV IgG antibody response. This is contrasted with the percentage of non-Hispanic Whites and those with a college education or above who had 19% and 15%, respectively classified in the highest tertile of CMV antibody response. The same pattern held was observed for parental education as well where those with the lowest parental education levels were more likely to be in the highest tertile of CMV antibody response. Additionally, those with a lower mean household income to poverty level were more likely to be classified in the highest tertile of CMV antibody response. The complete demographic and socioeconomic characteristics of our study population are described in **table 1**.

Ordered Logit Results

We found statistically significant associations between level of educational attainment and CMV IgG response tertiles across models. In model 1, we observed an educational gradient in CMV IgG response whereby those with less education had higher odds of being in a higher CMV response category compared to those with less education. For example, those with less than a high school education had 2.00 (95% CI: 1.67, 2.40) times the odds of being in a higher CMV response category compared to those with a college degree or greater (model 1; **figure 2a**). In models controlling for parental education, the association between participant educational attainment and CMV response was attenuated (model 2). There were no statistically significant associations observed between household income to poverty ratio and CMV response category.

We next examined the association between childhood SES, as measured by parental education, and CMV IgG tertiles, both with and without adjustment for adult SES (**figure 2b**). Across models, there was a significant association between parental education and CMV response that remained when controlling for adult SES (models 2, 3). Controlling for adult SES, individuals with parents with 8 years or less of schooling had 2.32 (95% CI: 2.00, 2.70) times the odds of being in a higher CMV response category compared to those with parents having greater than a HS education (model 3). Full results of the regression analyses are found in **table 2**.

Sensitivity Analyses

In sensitivity analyses, we examined whether the association between SES and CMV response differed by race/ethnicity. First, we tested the statistical significance of a two-way interaction term of education*race/ethnicity in a model including education attainment, household income to poverty ratio, age, gender, race/ethnicity, and parental education. The interaction term was not statistically significant ($P = 0.12$). Nonetheless, given the substantial literature documenting differences in the burden of CMV by race/ethnicity, we examined

race/ethnic-stratified models. Demographic characteristics stratified by race/ethnicity are presented in **supplementary table 3**. Among non-Hispanic Blacks and Hispanics, there were lower proportions of college education, lower household income, and lower levels of parental education compared to Whites. However, due to the small proportion of the sample that were classified as non-Hispanic Black (9.48%) or Hispanic (8.57%) inferences regarding the association between SES and CMV response were limited. For non-Hispanic Blacks, we only observed a significant association comparing those with less than a high school education to those with college or above, and only in model 1 (**supplementary table 4**). For non-Hispanic Whites the association between educational attainment and CMV response followed a consistent dose response pattern across models. There was no significant association between educational attainment and CMV response for those classified as Hispanic across models.

We next examined the association between childhood SES, as measured by parental education, and CMV IgG tertiles, both with and without adjustment for adult SES. For non-Hispanic Blacks, Hispanics, and non-Hispanic Whites, there was a significant association between parental education and CMV response that remained when controlling for adult SES, though this association was more consistently observed among non-Hispanic Whites. The race-ethnicity-stratified analyses suggest that the findings with regards to SES and CMV response are largely reflective of patterns among non-Hispanic Whites. However, conclusions are tempered by the small sample sizes of race-ethnic stratified models.

We next replicated our models using the latent variable of childhood SES that incorporated multiple dimensions of childhood social capital, financial capital, and human capital elements. Notably, this variable was only available on a subset of the study population. We found similar associations whereby childhood SES was significantly associated with an

increased odds of being in a higher CMV response category, net of adult SES (**supplementary tables 5 and 6**).

Discussion

Using a nationally representative aging cohort, we examined associations between life course SES and CMV IgG levels to better clarify the relationship between life course social processes and immune aging. We found strong associations (ORs ranging from 1.52 to 2.00) between adult educational attainment and CMV IgG levels, but no association with adult income. We also found evidence of both direct and indirect associations between childhood SES and CMV IgG levels. Our results suggest that early life social status, including parental education and one's own educational attainment, may shape the aging immune system. Overall, poor immune control may be one mechanism by which life course social disadvantage contributes to disparities in age-related decline and early mortality.

Our results are consistent with existing studies documenting associations between low SES and both CMV seropositivity and CMV IgG levels, although we find differences depending on the measure of SES examined (Cannon, Schmid, & Hyde, 2010; Feinstein et al., 2016). While we observed a significant association between adult educational attainment and CMV IgG levels, we did not observe a statistically significant association between household IPR and CMV IgG levels. This is consistent with a study among an elderly Hispanic population that reported a significant association between more years of education and lower CMV IgG levels, but no association for household income when controlling for education. In the U.S., a study examining adults aged 25 years and older found that education was more strongly associated with CMV IgG levels for women, while for men income was a stronger predictor (Jennifer Beam Dowd &

Aiello, 2009). It is likely that current income does not reflect life course SES as well as educational attainment in our largely retired cohort, and thus may not be as relevant a predictor of CMV level for older adults. Educational attainment is generally a more stable indicator of SES over the adult lifespan and reflects access to myriad resources such as income, neighborhood resources, and health-promoting behaviors, which likely explains its stronger association with CMV IgG in our sample (Link & Phelan, 1995; Anna Zajacova & Lawrence, 2018).

The association between adult educational attainment and CMV response, net of parental education, suggests there may be a cumulative disadvantage process at work in which low adult educational attainment is a proxy of an underlying accumulation process of disadvantage. However, given that we were not able to employ longitudinal measures of social disadvantage and immune markers in the current study, a formal test of this theory was not feasible.

It may also be that the educational patterns are explained by considering the timing and duration of infection with CMV. Research has documented that socially disadvantaged populations (i.e., racial/ethnic minorities and/or low SES populations) are more likely to be infected with CMV at a younger age (Colugnati et al., 2007), and therefore live with the virus for a longer period of time. Thus, if an individual is already infected with CMV at an early age, the indirect protections afforded by educational attainment (i.e. reduced exposure to infection, living in less crowded conditions, increased access to nutritious foods) may have less of an impact for these groups. The current findings support this hypothesis: we found strong independent associations between parental education and CMV response, net of participant educational attainment. This is also consistent with other studies examining the childhood social environment and CMV. In the nationally representative NHANES III study, children from low SES households and children of minority race/ethnicity status had a higher likelihood of CMV

seroprevalence (Bate, Dollard, & Cannon, 2010). However, Meier et al. found that the childhood environment, measured by parental education, occupation, and food availability as a child, was only significantly associated with adult CMV IgG levels through its influence on adult SES in a largely Latino sample 60-101 years old at baseline (Meier et al., 2016). Importantly, this would support a sensitive period model in which experiencing disadvantage in early life is an important predictor of late life immune status, regardless of adult SES attainment. Future studies with improved social and environmental measures can help clarify the timing of these life course processes and their impact on both CMV seropositivity and CMV IgG levels.

In sensitivity analyses, we found some evidence that the association between educational attainment and CMV antibody response differed by race/ethnicity. However, these inferences were limited by the small proportion of the sample that was classified as non-Hispanic Black or Hispanic. Whereas Black participants had an overall higher predicted probability of CMV response than Whites, there was less of an educational gradient in CMV response among Blacks (i.e. higher education did not seem to confer the same magnitude of benefit with regards to CMV response among Blacks compared to Whites) (**supplementary table 4**). A growing body of research has documented the differential returns to health at equal levels of education among racial/ethnic minority groups, particularly Blacks in the U.S.(Assari, 2018) and across health outcomes. Fundamental cause theory, for example, predicts that disadvantaged race/ethnic groups may realize fewer economic and health benefits from equivalent levels of education due to constrained resources and opportunities (Link & Phelan, 1996). Further, prior research also suggests that different baseline levels of exposures (e.g. quality education) and outcomes (e.g. higher baseline levels of CMV) across minority groups are central to understanding these patterns (Fuller-Rowell, Curtis, Doan, & Coe, 2015; Gaydosch, Schorpp, Chen, Miller, & Harris,

2018; Hayward, Hummer, & Sasson, 2015; Ward et al., 2019). For example, educational attainment was lower among Blacks for the HRS cohorts, and differences in educational quality were substantial for cohorts raised in the Jim Crow era (Fischer & Hout, 2006). Our findings support these hypotheses: Blacks had a higher predicted probability of CMV compared to Whites but there was not a consistent association between educational attainment and CMV response for Blacks in contrast to Whites. These findings suggest that there is another force driving the trends we see in CMV response among racial/ethnic minorities. Future studies would benefit from examining these trends in cohorts with larger proportions of racial/ethnic minority populations which would lend the statistical power to detect these associations.

More broadly speaking, higher overall pathogen burden (i.e. infection with multiple persistent pathogens such as CMV) has been proposed as one mechanism linking SES to accelerated biological aging overall (A. E. Aiello et al., 2009; A. Zajacova et al., 2009). A recent study reported higher pathogen burden, measured as a latent variable accounting for both number and combinations of several persistent pathogens, was associated with a significant increase in the respondent's number of pre-clinical deficits (a measure of accelerated biological aging) (Noppert, Aiello, O'Rand, & Cohen, 2018). Moreover, a study using the Whitehall II Heart Scan Study found that herpesvirus co-infections were associated with significant declines in leukocyte telomere length prospectively over three years, and that CMV seemed to be the most important driver of these declines (Jennifer B Dowd et al., 2017). These studies highlight the potential role of persistent pathogens in the wear and tear of multiple biological systems, leading to disparities in age-related disease.

While we believe that this study offers important insights into the relationship of SES and CMV across the life course, it is not without limitations. The data on CMV was only collected at

one point in time in HRS, and thus examining how CMV IgG levels change over the life course is not yet possible. Additionally, there could be misclassification of individuals as seronegative or seropositive, but our use of ordered categorical IgG levels should mitigate any bias resulting from such misclassification. While we believe our use of a life course framework is an important contribution of this work, the measure of parental education is based on self-reports from the respondents much later in life, and thus may suffer from recall bias. As with most observational studies, the association of social factors with CMV cannot be interpreted as causal and is best interpreted as a description of the social distribution of this important marker of immunological aging, which likely arises from a variety of life course causal mechanisms. Finally, while CMV IgG levels are a commonly used proxy for immune function, future studies would benefit from the inclusion of additional phenotypic and function immune markers such as t-cell surface markers, stimulation, and proliferation endpoints.

In conclusion, this study contributes to the growing body of literature showing the association between social disadvantage and biological processes occurring across the life course. In particular, our findings highlight a link between social disadvantage across the life course and a biomarker related to immunity. Given that aging of the immune system is a critical predictor of age-related decline and disease development, our results suggest that social disadvantage may influence the pace of these processes. There have been several efforts focused on developing a vaccination for CMV (Schleiss, 2016), which could reduce transmission of CMV in the total population. However, in order for vaccination efforts to impact the socioeconomic disparities observed in CMV infection, critical attention would need to be paid to the equitable distribution of such a vaccine. Among older age race/ethnic minorities CMV antibody response may be a reflection of both earlier age at infection and altered immune

response to CMV from differential burden of life course stressors (Williams, Yu, Jackson, & Anderson, 1997). To that end, interventions that target upstream life course socioeconomic determinants of immunity and infection will likely have the biggest impact on age-related changes in immunity. Therefore, it will be critical to continue to consider the importance of life course social resources for improving health in older age, in combination with ongoing clinical vaccine interventions for preventing CMV infection.

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Tables and Figures

Table 1. Weighted distribution of baseline sociodemographic characteristics of eligible HRS participants, stratified by CMV response category (N = 8,168).

| Demographic Characteristics | Total | % CMV Seronegative (35.29%) | % CMV Tertile 1 (22.04%) | % CMV Tertile 2 (21.51%) | % CMV Tertile 3 (21.09%) |
|-----------------------------------|--------------|-----------------------------|--------------------------|--------------------------|--------------------------|
| Education | | | | | |
| Less than HS | 11.6 | 12.34 | 26.73 | 28.23 | 32.64 |
| HS Grad | 31.35 | 31.06 | 23.24 | 21.34 | 24.31 |
| Some College | 27.21 | 38.13 | 21.99 | 20.18 | 19.63 |
| College Grad | 29.84 | 46.06 | 19.03 | 20.28 | 14.57 |
| HH Income to Poverty Ratio | | | | | |
| Mean HH IPR | 5.81 (0.12) | 6.74 (0.20) | 5.52 (0.26) | 5.79 (0.31) | 4.61 (0.17) |
| Parental Education | | | | | |
| 8 years or less | 21.68 | 15.04 | 27.34 | 27.33 | 30.24 |
| 9-11 years | 12.98 | 22.16 | 25.03 | 25.16 | 27.50 |
| HS grad | 37.44 | 41.77 | 20.38 | 19.39 | 18.44 |
| Greater than HS | 27.89 | 48.46 | 18.80 | 18.13 | 14.59 |
| Race/Ethnicity | | | | | |
| Black | 9.48 | 11.55 | 27.91 | 28.23 | 32.30 |
| Hispanic | 8.57 | 7.09 | 31.48 | 31.16 | 30.18 |
| White | 81.95 | 40.99 | 20.39 | 19.73 | 18.85 |
| Age (years) | | | | | |
| Age | 66.59 (0.14) | 64.64 (0.20) | 67.86 (0.30) | 67.56 (0.29) | 67.55 (0.34) |
| Gender | | | | | |
| Female | 54.69 | 46.78 | 52.30 | 58.16 | 66.81 |
| Male | 45.31 | 53.20 | 47.70 | 41.8 | 33.1 |

Weighted means and standard errors are reported for continuous variables. Weighted frequency distributions are reported for categorical variables.

Note: Higher CMV tertile indicates higher CMV IgG antibody response.

Table 2. Ordered logit analyses estimating the odds of being in the next sequentially higher CMV IgG response category by both adult SES and parental education in the Health and Retirement Study, Venous Blood Sample 2016 (N = 8,168).

| Variable | Model 1 | | Model 2 | | Model 3 | |
|--|-------------|-------------------|-------------|-------------------|-------------|-------------------|
| | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI |
| Educational Attainment | | | | | | |
| Less than HS Education | 2.00 | 1.67, 2.40 | 1.52 | 1.26, 1.85 | . | |
| HS Education | 1.51 | 1.32, 1.74 | 1.27 | 1.10, 1.47 | . | |
| Some College | 1.19 | 1.04, 1.38 | 1.10 | 0.95, 1.27 | . | |
| College grad or above (ref) | | | | | | |
| Household Income to Poverty Ratio | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 | . | |
| Parental Education | | | | | | |
| 8 years or less | . | | 2.01 | 1.71, 2.37 | 2.32 | 2.00, 2.70 |
| 9-11 years | . | | 1.90 | 1.59, 2.28 | 2.11 | 1.78, 2.52 |
| HS grad | . | | 1.18 | 1.03, 1.36 | 1.27 | 1.11, 1.45 |
| Greater than HS (ref) | | | | | | |
| Race | | | | | | |
| Non-Hispanic Black | 2.54 | 2.19, 2.95 | 2.30 | 1.99, 2.66 | 2.39 | 2.07, 2.75 |
| Hispanic | 2.34 | 1.99, 2.75 | 1.90 | 1.60, 2.25 | 2.07 | 1.76, 2.44 |
| Non-Hispanic White (ref) | | | | | | |
| Age (Years) | 1.02 | 1.02, 1.03 | 1.01 | 1.01, 1.02 | 1.02 | 1.01, 1.02 |
| Gender (Female vs Male) | 1.63 | 1.47, 1.81 | 1.63 | 1.47, 1.81 | 1.65 | 1.49, 1.83 |

Significant results at alpha = 0.05 are bolded.

Model 1 includes race/ethnicity, adult SES, age, and gender. *Model 2* includes race/ethnicity, adult SES, parental education, age, and gender. Those with a college education or higher are the reference group.

Model 3 includes race/ethnicity, parental education, age, and gender. Having at least one parent with greater than a high school education is the reference group.

Figure 1. Conceptual framework describing how socioeconomic status may be associated with CMV IgG response.

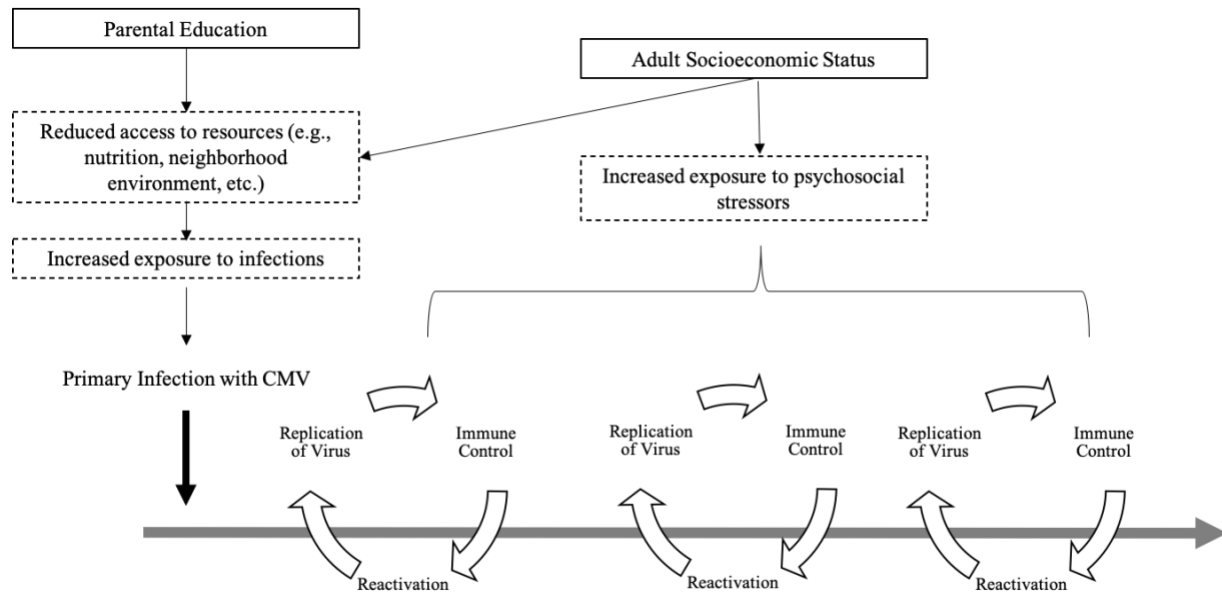
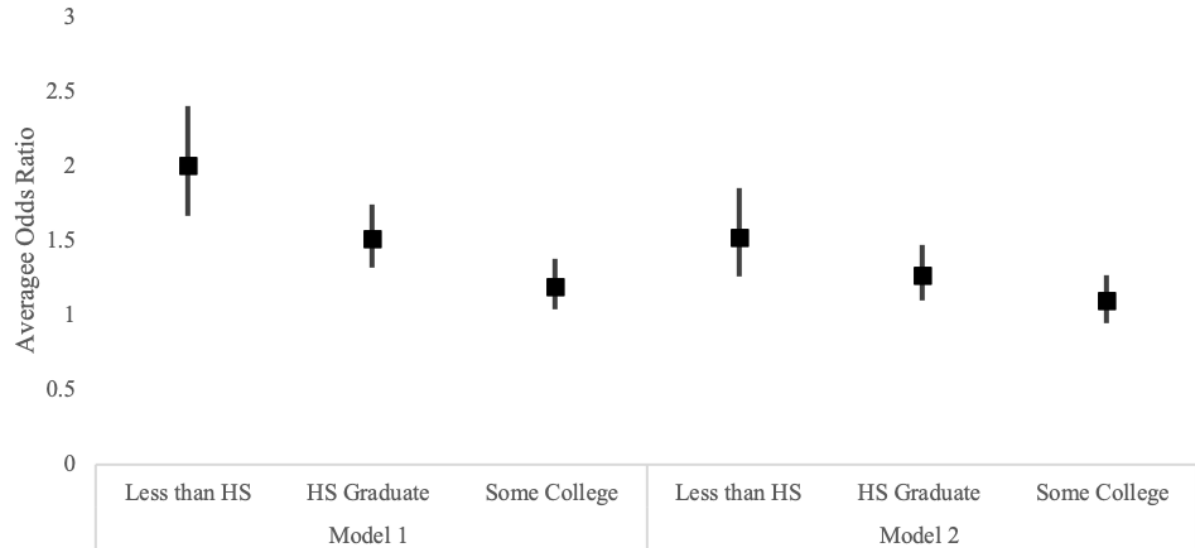
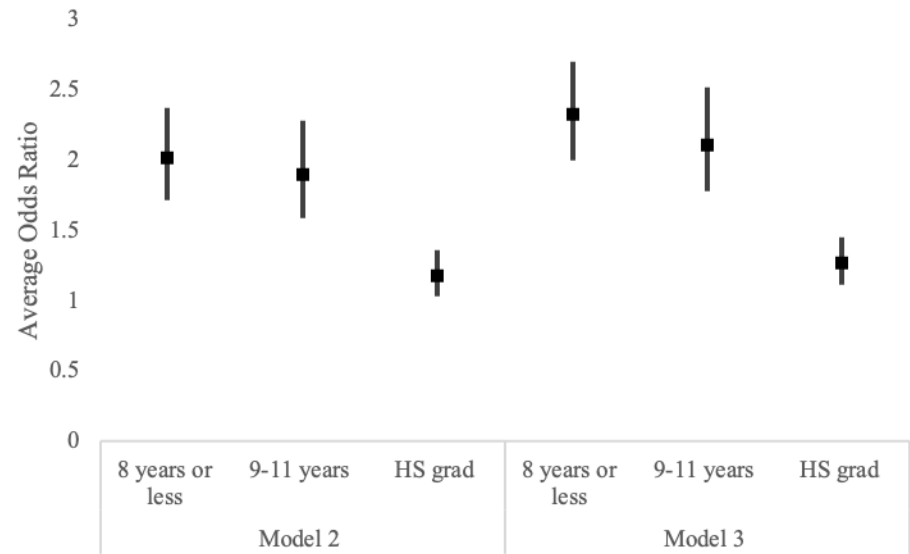


Figure 2a. Estimated relative odds ratio of being in the next sequentially higher CMV IgG response category by adult SES in the Health and Retirement Study, Venous Blood Sample 2016.



Note: *Model 1* includes adult SES, race/ethnicity, age, gender, and marital status; *Model 2* includes adult SES, race/ethnicity, age, gender, marital status, and parental education. Those with a college education or greater are the reference group.

Figure 2b. Estimated relative odds ratio of being in the next sequentially higher CMV IgG response category by parental education in the Health and Retirement Study, Venous Blood Sample 2016.



Note: *Model 2* includes adult SES, race/ethnicity, age, gender, marital status, and parental education; *Model 3* includes race/ethnicity, age, gender, marital status, and parental education. Having a least one parent with greater than a high school education is the reference group.

Supplementary Material

Supplementary Table 3. Weighted distribution of baseline sociodemographic characteristics of eligible HRS participants, stratified by race/ethnicity (N = 8,168).

| Demographic Characteristics | Black (9.48%) | Hispanic (8.57%) | White (81.95%) |
|------------------------------------|--------------------------|-----------------------------|---------------------------|
| Age (years) | | | |
| Age | 65.29 (0.25) | 66.10 (0.27) | 66.90 (0.13) |
| Gender | | | |
| Female | 58.10 | 55.87 | 54.17 |
| Male | 41.90 | 44.13 | 45.83 |
| Education | | | |
| Less than HS | 20.90 | 46.28 | 6.90 |
| HS Grad | 31.90 | 25.50 | 31.89 |
| Some College | 29.39 | 18.82 | 27.83 |
| College Grad | 17.73 | 9.39 | 33.37 |
| HH Income to Poverty Ratio | | | |
| HH IPR | 3.16 (0.09) | 3.02 (0.14) | 6.41 (0.12) |
| Parental Education | | | |
| 8 years or less | 31.88 | 71.15 | 15.33 |
| 9-11 years | 18.73 | 6.20 | 13.02 |
| HS grad | 35.71 | 12.80 | 40.22 |
| Greater than HS | 13.68 | 9.85 | 31.42 |
| CMV Serostatus | | | |
| % CMV Seronegative | 11.56 | 7.17 | 41.03 |
| % CMV Tertile 1 | 27.91 | 31.48 | 20.39 |
| % CMV Tertile 2 | 28.23 | 31.16 | 19.73 |
| % CMV Tertile 3 | 32.30 | 30.18 | 18.85 |

Weighted means and standard errors are reported for continuous variables. Weighted Frequencies are reported for categorical variables.

Supplementary Table 4. Ordered logit analyses estimating the odds of being in the next sequentially higher CMV IgG response category by both adult SES and parental education, stratified by race/ethnicity in the Health and Retirement Study, Venous Blood Sample 2016 (N = 8,168).

| Variable | Model 1 | | | | | | Model 2 | | | | | | Model 3 | | | | | |
|-----------------------------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|
| | Black | | Hispanic | | White | | Black | | Hispanic | | White | | Black | | Hispanic | | White | |
| | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI |
| Educational Attainment | | | | | | | | | | | | | | | | | | |
| Less than HS Education | 1.67 | 1.01, 2.76 | 1.58 | 0.91, 2.74 | 2.21 | 1.75, 2.80 | 1.34 | 0.80, 2.23 | 1.11 | 0.59, 2.06 | 1.68 | 1.31, 2.15 | . | . | . | . | . | |
| HS Education | 1.33 | 0.84, 2.11 | 1.29 | 0.72, 2.34 | 1.51 | 1.30, 1.75 | 1.16 | 0.73, 1.84 | 1.01 | 0.53, 1.94 | 1.28 | 1.09, 1.49 | . | . | . | . | . | |
| Some College | 0.96 | 0.60, 1.52 | 1.09 | 0.62, 1.94 | 1.20 | 1.03, 1.40 | 0.88 | 0.56, 1.38 | 0.96 | 0.52, 1.77 | 1.11 | 0.95, 1.30 | . | . | . | . | . | |
| College grad or above (ref) | | | | | | | | | | | | | | | | | | |
| Household Income to Poverty Ratio | | | | | | | | | | | | | | | | | | |
| | 0.99 | 0.94, 1.04 | 0.99 | 0.96, 1.02 | 1.00 | 0.99, 1.01 | 0.99 | 0.94, 1.04 | 0.99 | 0.96, 1.02 | 1.00 | 0.99, 1.01 | . | . | . | . | . | |
| Parental Education | | | | | | | | | | | | | | | | | | |
| 8 years or less | . | . | . | . | . | . | 2.46 | 1.54, 3.92 | 2.48 | 1.40, 4.42 | 1.96 | 1.63, 2.36 | 2.70 | 1.79, 4.05 | 2.66 | 1.57, 4.50 | 2.28 | 1.92, 2.71 |
| 9-11 years | . | . | . | . | . | . | 2.06 | 1.35, 3.14 | 2.14 | 0.96, 4.79 | 1.85 | 1.52, 2.26 | 2.20 | 1.48, 3.27 | 2.15 | 1.01, 4.58 | 2.08 | 1.72, 2.52 |
| HS grad | . | . | . | . | . | . | 1.27 | 0.85, 1.90 | 1.68 | 0.83, 3.41 | 1.15 | 0.99, 1.34 | 1.32 | 0.90, 1.92 | 1.63 | 0.82, 3.25 | 1.24 | 1.08, 1.44 |
| Greater than HS (ref) | | | | | | | | | | | | | | | | | | |
| Age (Years) | 1.01 | 0.99, 1.02 | 1.02 | 1.00, 1.03 | 1.02 | 1.02, 1.03 | 1.00 | 0.98, 1.01 | 1.01 | 0.99, 1.03 | 1.02 | 1.01, 1.02 | 1.00 | 0.98, 1.02 | 1.01 | 1.00, 1.03 | 1.02 | 1.01, 1.02 |
| Gender (Female vs Male) | 1.74 | 1.29, 2.34 | 1.53 | 1.12, 2.09 | 1.64 | 1.46, 1.84 | 1.77 | 1.32, 2.37 | 1.56 | 1.14, 2.15 | 1.63 | 1.45, 1.84 | 1.77 | 1.33, 2.36 | 1.58 | 1.15, 2.17 | 1.65 | 1.47, 1.86 |

Significant results at alpha = 0.05 are bolded.

Model 1 includes adult SES, age, and gender. *Model 2* includes adult SES, parental education, age, and gender. Those with a college education or higher are the reference group. *Model 3* includes parental education, age, and gender. Having at least one parent with greater than a high school education is the reference group.

Childhood SES Latent Construct:

To further investigate the association with childhood SES we used a latent variable constructed by Vable et al. using scales of childhood social capital, financial capital, and human capital.⁴⁰ These measures were retrospectively reported and ask participants to report information from when they were aged 16 years and below. The social capital scale was composed of two factors: maternal investment and family structure. The financial capital scale captured both financial resources (e.g. financial status, father occupation, etc.) and financial instability (e.g. receiving financial help, moving, bankruptcy, etc.). Finally, the human capital scale was composed of mother's and father's years of education. Each scale were standardized and averaged. The final index was the average of all three scales and standardized for interpretability. Individuals were assigned a continuous score on the variable. We reverse-coded the variable such that a higher score indicated increased disadvantage.

Supplementary Table 5. Ordered logit analyses estimating the odds of being in the next sequentially higher CMV IgG response category by both adult SES and childhood SES in the Health and Retirement Study, Venous Blood Sample 2016 (N = 6,109).

| Variable | Model 1 | | Model 2 | | Model 3 | |
|--|-------------|-------------------|-------------|-------------------|-------------|-------------------|
| | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI |
| Educational Attainment | | | | | | |
| Less than HS Education | 2.01 | 1.65, 2.46 | 1.68 | 1.36, 2.08 | . | |
| HS Education | 1.54 | 1.32, 1.79 | 1.38 | 1.18, 1.61 | . | |
| Some College | 1.21 | 1.03, 1.42 | 1.13 | 0.96, 1.33 | . | |
| College grad or above (ref) | | | | | | |
| Household Income to Poverty Ratio | | | | | | |
| | 1.00 | 0.99, 1.01 | 1.00 | 0.99, 1.01 | . | |
| Childhood SES Index (higher =more disadvantaged) (continuous) | | | | | | |
| | . | | 1.20 | 1.12, 1.28 | 1.28 | 1.20, 1.36 |
| Race/Ethnicity | | | | | | |
| Non-Hispanic Black | 2.23 | 1.89, 2.64 | 2.09 | 1.77, 2.47 | 2.18 | 1.85, 2.57 |
| Hispanic | 2.07 | 1.71, 2.51 | 1.79 | 1.47, 2.19 | 1.98 | 1.64, 2.39 |
| Non-Hispanic White (ref) | | | | | | |
| Age (Years) | | | | | | |
| | 1.02 | 1.02, 1.03 | 1.02 | 1.02, 1.03 | 1.02 | 1.02, 1.03 |
| Gender | | | | | | |
| Female | 1.63 | 1.45, 1.83 | 1.64 | 1.46, 1.84 | 1.68 | 1.50, 1.88 |
| Male (ref) | . | | . | | . | |

Significant results at alpha = 0.05 are bolded.

Model 1 includes adult SES, race/ethnicity, age, and gender. *Model 2* includes adult SES, childhood SES, race/ethnicity, age, and gender. Those with a college education or higher are the reference group. *Model 3* includes childhood SES, race/ethnicity, age, and gender.

Supplementary Table 6. Ordered logit analyses estimating the odds of being in the next sequentially higher CMV IgG response category by both adult SES and childhood SES for the sample stratified by race/ethnicity in the Health and Retirement Study, Venous Blood Sample 2016 (N = 6,109).

| Variable | Model 1 | | | | | | Model 2 | | | | | | Model 3 | | | | | |
|---|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|----------|------------|
| | Black | | Hispanic | | White | | Black | | Hispanic | | White | | Black | | Hispanic | | White | |
| | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI | Estimate | 95% CI |
| Educational Attainment | | | | | | | | | | | | | | | | | | |
| Less than HS Education | 2.23 | 1.34, 3.73 | 1.68 | 0.74, 3.81 | 2.04 | 1.60, 2.61 | 1.93 | 1.13, 3.29 | 1.64 | 0.68, 3.92 | 1.69 | 1.31, 2.17 | . | . | . | . | . | . |
| HS Education | 1.39 | 0.85, 2.26 | 1.44 | 0.63, 3.30 | 1.53 | 1.30, 1.79 | 1.24 | 0.76, 2.03 | 1.42 | 0.61, 3.28 | 1.36 | 1.15, 1.60 | . | . | . | . | . | . |
| Some College | 1.36 | 0.83, 2.22 | 1.20 | 0.50, 2.87 | 1.18 | 0.99, 1.40 | 1.29 | 0.79, 2.12 | 1.18 | 0.49, 2.87 | 1.10 | 0.92, 1.30 | . | . | . | . | . | . |
| College grad or above (ref) | | | | | | | | | | | | | | | | | | |
| Household Income to Poverty Ratio | | | | | | | | | | | | | | | | | | |
| | 0.95 | 0.90, 1.00 | 0.98 | 0.94, 1.03 | 1.00 | 0.99, 1.01 | 0.95 | 0.90, 1.00 | 0.98 | 0.94, 1.03 | 1.00 | 0.99, 1.01 | . | . | . | . | . | . |
| Childhood SES Index (higher =more disadvantaged) (continuous) | | | | | | | | | | | | | | | | | | |
| | . | . | . | . | . | . | 1.18 | 0.98, 1.41 | 1.02 | 0.83, 1.26 | 1.21 | 1.12, 1.31 | 1.29 | 1.09, 1.52 | 1.10 | 0.92, 1.32 | 1.30 | 1.21, 1.40 |
| Age (Years) | | | | | | | | | | | | | | | | | | |
| | 1.01 | 0.99, 1.03 | 1.01 | 0.99, 1.04 | 1.03 | 1.02, 1.03 | 1.01 | 0.99, 1.03 | 1.01 | 0.99, 1.04 | 1.02 | 1.02, 1.03 | 1.01 | 0.99, 1.04 | 1.02 | 0.99, 1.04 | 1.03 | 1.02, 1.03 |
| Gender | | | | | | | | | | | | | | | | | | |
| Female | 1.67 | 1.20, 2.35 | 1.91 | 1.30, 2.82 | 1.62 | 1.42, 1.83 | 1.68 | 1.20, 2.36 | 1.92 | 1.30, 2.83 | 1.62 | 1.43, 1.84 | 1.74 | 1.24, 2.45 | 1.99 | 1.35, 2.93 | 1.66 | 1.46, 1.88 |
| Male (ref) | | | | | | | | | | | | | | | | | | |

Significant results at alpha = 0.05 are bolded.

Model 1 includes adult SES, race/ethnicity, age, and gender. Model 2 includes adult SES, childhood SES, race/ethnicity, age, and gender. Those with a college education or higher are the reference group. Model 3 includes childhood SES, race/ethnicity, age, and gender.

Supplementary Figure 3. Sample flow chart showing how the study sample was derived. Final study sample, N = 8,370.

