Race/Ethnic and Educational Disparities in the Association Between Pathogen Burden and a Laboratory-Based Cumulative Deficits Index

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Abstract

Background Disparities in adult morbidity and mortality may be rooted in patterns of biological dysfunction in early life. We sought to examine the association between pathogen burden and a cumulative deficits index (CDI), conceptualized as a pre-clinical marker of an unhealthy biomarker profile, specifically focusing on patterns across levels of social disadvantage.

Methods Using the data from the National Health and Nutrition Examination Survey 2003–2004 wave (aged 20–49 years), we examined the association of pathogen burden, composed of seven pathogens, with the CDI. The CDI comprised 28 biomarkers corresponding to available clinical laboratory measures. Models were stratified by race/ethnicity and education level.

Results The CDI ranged from 0.04 to 0.78. Nearly half of Blacks were classified in the high burden pathogen class compared with 8% of Whites. Among both Mexican Americans and other Hispanic groups, the largest proportion of individuals were classified in the common pathogens class. Among educational classes, 19% of those with less than a high school education were classified in the high burden class compared with 7% of those with at least a college education. Blacks in the high burden pathogen class had a CDI 0.05 greater than those in the low burden class ($P < 0.05$). Whites in the high burden class had a CDI only 0.03 greater than those in the low burden class ($P < 0.01$).

Discussion Our findings suggest there are significant social disparities in the distribution of pathogen burden across race/ethnic groups, and the effects of pathogen burden may be more significant for socially disadvantaged individuals.

Keywords Pathogen burden · Racial disparities · Educational disparities · Biological aging

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Introduction

Inequalities in age-related declines and disease are well documented [1–3]. Age-related disease development is likely the result of accelerated wear and tear of multiple biological systems, much of which precedes the development of clinical disease. Indeed, the growing body of research in this area suggests that the pace of aging itself is unequally distributed in the population and that divergence in the pace of aging likely occurs early in the life course [4]. One potential mechanism driving the heterogeneity in the pace of aging is life course social disadvantage.

Social disadvantage is a broad term used to describe multiple aspects of inequality that an individual may experience that both shape access to resources and result in increased experiences of stress. These inequalities may be linked to features of an individuals' social identity (e.g.,

minority race/ethnicity, nativity status) and/or to an individual's social environment (e.g., socioeconomic status (SES), neighborhoods) [2, 5–7]. For example, those with lower education are more likely to experience increased social disadvantage through limited access to resources including neighborhood environments, health care, and occupational choices. Those of minority race/ethnicity status may also more likely to experience greater social disadvantage through a variety of pathways including experiences of discrimination interpersonally, institutionally, and societally.

Social disadvantage may impact biological processes of aging through several mechanisms. First, socially disadvantaged individuals may be more exposed to risk factors that lead to disease development. For example, individuals of lower SES are more likely to be exposed to air pollutants with known pathogenic effects (e.g., sulfur oxides, fine particulates, ozone) [8, 9]. Individuals of low SES are also more likely to live in disadvantaged neighborhoods with increased exposure to crime, unhealthy food environments, increased exposure to infections, and less access to outdoor space [8].

The stress process is a potential second mechanism operating in tandem with the previous pathway based on exposure. For many individuals, sustained social disadvantage results in prolonged exposure to stress, with a corresponding cascade of biological consequences. For example, the concept of allostatic load was coined to describe the wear and tear to several biological systems with repeated allostatic responses during periods of stress [10]. In their 2006 study, Geronimus et al. [11] using allostatic load, based on physiological biomarkers linked to stress, found that Blacks have higher allostatic load scores than their White peers throughout midlife. Using another measure of biological deterioration associated with stress, telomere length, Needham et al. [12] found evidence to suggest that individuals with less than a high school education had significantly shorter telomeres than individuals with a college education. Findings such as these point to an underlying biological vulnerability produced by social disadvantage. The biological vulnerability produced by chronic stress may also modify the effects of the aforementioned risk factors to which one is exposed. Socially disadvantaged individuals are therefore more likely to be exposed to risk factors for disease and have an inhibited ability to mitigate the effects of such exposures.

Our previous study focused on the development of the two measurements that could improve our understanding of biological pathways leading to an altered biomarker profile using data from the National Health and Nutrition Examination Survey (NHANES) [13]. The cumulative deficits index (CDI) is a summary measure incorporating data from 28 biomarkers that are commonly collected in standard laboratory biochemistry profiles (e.g., triglycerides, iron, sodium, etc.). Following previous work using this composite marker, we conceptualized the CDI as an indicator of an altered physiological profile on several important clinical indicators of overall health in human populations [13, 14]. Next, there is a body of research suggesting that infection with multiple, persistent pathogens can have a cumulative effect on health, because many of these persistent pathogens are lifelong, elicit an immune response, and stimulate circulation of inflammatory molecules [15–19]. Thus, following previous research, we developed a measure of overall pathogen burden intended to proxy the total load of persistent infections to which an individual is exposed.

We found significant differences in the distribution of the CDI by age, sex, race/ethnicity, and education in a relatively young cohort (20–49 years). We also saw significant associations with the pathogen burden measure and the CDI. While the findings from this report suggested underlying disparities in the distribution of the CDI by social factors, given the focus of the study on measurement, we were not able to delve into those disparities more thoroughly. In the current report, we used the measures of CDI and pathogen burden to do a more in-depth exploration of racial/ethnic and educational disparities in biological dysfunction. We hypothesized that individuals experiencing increased social disadvantage may have higher levels of pathogen burden, and this pathogen burden will produce worse outcomes on the CDI than individuals experiencing less social disadvantage.

Methods

Study Sample

The study sample was drawn from the continuous NHANES collected by the National Center for Health Statistics, 2003–2004 wave. NHANES is a cross-sectional, nationally representative survey of the health and nutritional status of the US non-institutionalized, civilian population aged 2 months and older. Details of the sampling strategy for the continuous NHANES can be found at https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx. We chose the 2003–2004 wave as it tested more infections than many other waves, and importantly included cytomegalovirus (CMV). CMV is a persistent infection, common in the population and for which there is a large body of evidence documenting the health consequences of persistent CMV infection [20–22].

Individuals participating in the NHANES provided information on a range of demographic characteristics based on an in-home interview and physical examination and laboratory studies performed at the mobile examination center.

Our study sample included 20–49 years old who participated in all three of the survey, physical examination, and laboratory studies. There were 14,623 participants in the 2003–2004 wave. Of those, 4980 participants were excluded

because they did not participate in the interview, physical examination, and laboratory studies in the 2003–2004 wave. An additional 6934 individuals were excluded for whom there was not complete pathogen sample information available in the 2003–2004 wave. The final sample included only those with complete covariate information (2003–2004 Wave Final $N = 2168$).

Laboratory Analyses

NHANES participants provided blood and urine samples as part of the laboratory component of the survey. These samples were tested for a standard biochemistry panel of markers such as albumin, calcium, hemoglobin, iron, etc. These data are then made publically available from NHANES. The laboratory information used to construct the CDI was based on the biomarkers assessed from blood serum. Additional details on the laboratory component of NHANES are provided in the supplement.

Measures

Construction of the Cumulative Deficits Index

Details regarding the construction of the CDI have been published previously (see [13]). Briefly, the CDI is composed of 28 biomarkers that are commonly collected in standard biochemistry panels (see supplementary table 1). Each biomarker was examined separately and was split into quartiles based on the distribution of that biomarker. Depending on the specific biomarker and whether high or low levels indicate dysfunction, individuals received a score of 1 if they were in the highest or lowest quartile. The final CDI was the sum of the score of each biomarker divided by the total number of biomarkers available for that participant. The CDI was constructed in this way as to detect those individuals at the higher/lower end of the normal range for each biomarker rather than simply using values that indicate current clinical dysfunction. Using this approach allowed us to develop a measure applicable to relatively younger populations; many of whom are not likely showing abnormal values for the biomarkers assessed.

An increase in the value of the CDI can be interpreted as an increase in the number of pre-clinical deficits, or as a proxy for an altered biomarker profile with implications for future disease development. The CDI should not be used directly for clinical practice. Rather, it is a tool for estimating population levels of biological alterations based on several clinical biomarkers of health.

Classification of Pathogen Burden

The deleterious effects of persistent pathogens on health have been well documented [15–17, 23]. Yet, the methods for appropriately capturing the total burden of these pathogens is a topic of continued study. A consistent theme in this work is the value of measurements that incorporate both the number of pathogens as well as the combination of pathogens an individual is infected with [24]. To that end, we used latent class methods that account for both of these elements to capture pathogen burden. The pathogen burden measure compiled data on the following seven infections: CMV, herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), human papillomavirus virus (HPV), syphilis, toxoplasmosis, and human immunodeficiency virus (HIV). Details on the pathogen measurements are provided in the supplement.

Using the latent class analyses, we classified individuals into pathogen burden subgroups. Classification methods are detailed in the previous manuscript (see [13]; supplementary tables 2 and 3). We followed the three-step inclusive-analyze approach proposed by Bray et al. [25] which first classifies individuals into latent classes and then regresses the outcome on the latent classes. We used three latent classes of pathogen burden based on both model fit indices and interpretability. We then assigned labels to the classes based on our assessment of their pathogen composition. The "low burden" class was characterized by having lower probabilities of seropositivity on all pathogens. Alternatively, the "high burden" class had higher probabilities of being seropositive to several of the pathogens tested. Finally, the "common pathogens" class was characterized by individuals with higher probabilities of seropositivity to common pathogens such as CMV and HSV-1. For statistical modeling, the low burden class was used as the referent.

Covariates

We controlled for covariates that are likely associated with either pathogen burden and/or the CDI. Demographic controls included age and sex. Age was analyzed as a continuous variable in years. Sex was binary coded as male or female. Health status characteristics included BMI and smoking status. BMI was examined categorically with those with a BMI less than 18.5 classified as underweight, 18.5–25 classified as normal, 25–30 classified as overweight, and greater than 30 classified as obese. Smoking status was classified as having ever smoked versus never smoked. We also used data on the number of chronic conditions an individual reported to include chronic disease burden as a covariate.

Analyses were stratified by race/ethnicity and education. Race/ethnicity was categorized according to the NHANES guidelines as non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, and other race. Education was treated categorically according to NHANES classifications as less than a high school

education, high school graduate, some college education, and college graduate and above.

Statistical Analyses

Regression Analyses

Linear regression models were constructed to examine the association between the latent categories of pathogen burden and the CDI, stratified by race/ethnicity and education. The difference in the mean CDI was estimated with the low burden group as the referent. Our previous work documents the weaker associations between other metrics of pathogen burden assessment (single pathogen associations and a pathogen burden summary score) and the CDI. Additionally, the results of the full models including race/ethnicity and education as covariates in the statistical models are detailed in the previous report.

We then tested two-way interactions between the latent classes and both race/ethnicity and education. Two sets of subsequent models were developed: one stratified by race/ethnicity and the other by educational attainment. For models stratified by race/ethnicity, models included controls for age, sex, BMI, smoking, chronic conditions, and education. For analyses stratified by education, models included controls for age, sex, BMI, smoking, chronic conditions, and race/ethnicity.

All regression analyses used appropriate sampling weights and adjustments to account for the complex survey design features. A two-side alpha of 0.05 was used to determine significance in all statistical analyses.

Statistical analyses were performed in SAS v.9.4 (Cary, NC).

Results

Sample Characteristics

The study sample comprised 2168 individuals aged 20–49 years old (mean age 34.9 years). The sample was 50% female and 69% non-Hispanic White. One-quarter of the study sample had a college education or greater, and 52% of the sample were classified as never smokers. Over half of the study population (64%) had a body mass index (BMI) greater or equal to 25 while one-quarter (25%) reported having been diagnosed with one or more chronic conditions (Table 1).

There were seven pathogens tested in the population. Over half of the study population (60%) were seropositive to HSV-1; 19%, seropositive to HSV-2; 25%, to HPV; 13%, seropositive to toxoplasmosis; 0.44%, to HIV; 52%, seropositive to CMV; and 2%, to syphilis.

Table 1 Population-weighted demographic and pathogen characteristics of the study population in the National Health and Nutrition Examination Survey, 2003–2004 ($N = 2168$)

	Wave 1 2003–2004 ($N = 2168$)
Age	
Mean age (SD)	34.9 (0.30)
Sex	*N* (%)
Female	1130 (50)
Race/ethnicity	
Non-Hispanic White	1045 (69)
Non-Hispanic Black	500 (12)
Mexican American	471 (10)
Other Hispanic	82 (4)
Other Race	70 (4)
Education	
Less than high school	484 (15)
High school graduate	569 (27)
Some college	676 (34)
College graduate and above	439 (25)
Ever smoker	
Yes	975 (48)
No	1193 (52)
Body mass index (BMI)	
Underweight (less than 18.5)	41 (2)
Normal (≥ 18.5, < 25)	703 (34)
Overweight (≥ 25, < 30)	709 (33)
Obese (≥ 30)	715 (31)
Chronic condition	
Any chronic condition	465 (25)
None	1703 (75)
Pathogens seropositivity	
Herpes simplex virus type 1	1397 (60)
Herpes simplex virus type 2	472 (19)
Human papillomavirus	542 (25)
Toxoplasmosis	296 (13)
Human immunodeficiency virus	13 (0.44)
Cytomegalovirus	1315 (52)
Syphilis	51 (2)

The chronic condition variable was based on participant report of physician diagnosis of one of the following conditions: arthritis, congestive heart failure, coronary heart disease, heart attack, stroke, emphysema, chronic bronchitis, liver condition, thyroid problem, or cancer

The Distribution of Latent Classes by Race/Ethnicity and Education

Latent class analyses were performed to classify individuals into pathogen burden categories identified in earlier research. The distribution of latent classes was significantly different across race/ethnic groups ($P < 0.0001$). Among non-

Hispanic Whites, 62% were classified in the low burden class, 30% as in the common pathogens class, and 8% in the high burden class (Fig. 1a). Conversely, among non-Hispanic Blacks, 25% were classified in the low burden class, 35% in the common pathogens class, and 40% in the high burden class. Among both Mexican Americans and other Hispanic groups, the largest proportion of individuals were classified in the common pathogens class.

The distribution of pathogen latent classes also differed significantly across educational categories ($P < 0.0001$) (Fig. 1b). As education increased, the proportion of individuals classified in the low burden class increased. Among those with less than a high school education, 26% of individuals were classified as low burden compared with 66% of those with college degrees and above. Conversely, the proportion of individuals classified in the high burden class was highest among those with less than a high school education (19%) compared with those with college degrees and above (7%).

CDI by Levels of Race/Ethnicity and Education

We then examined how the CDI differed by race/ethnicity and educational levels (Table 2). The mean CDI differed significantly by race/ethnicity. Non-Hispanic Whites had the lowest mean CDI with a value of 0.29, while the other Hispanics category had the highest CDI of 0.34 ($P = 0.01$). Those having a college degree or above had the lowest mean CDI of 0.28, while those with less than a high school education had a mean CDI of 0.33 ($P < 0.0001$). Descriptive statistics of the CDI for the full sample have been published previously [13].

Table 2 The mean CDI by race/ethnicity and educational levels for the National Health and Nutrition Examination Survey ($N = 2168$)

	N (%)	Mean CDI
Race/ethnicity		
Non-Hispanic Whites	1045 (69)	0.29 (0.003)
Non-Hispanic Blacks	500 (12)	0.32 (0.005)
Mexican Americans	471 (10)	0.33 (0.007)
Other Hispanics	82 (4)	0.34 (0.02)
Other	70 (4)	0.32 (0.01)
Education		
Less than high school	484 (15)	0.33 (0.006)
High school graduate	569 (27)	0.32 (0.006)
Some college	676 (34)	0.30 (0.005)
College grad and above	439 (25)	0.28 (0.006)

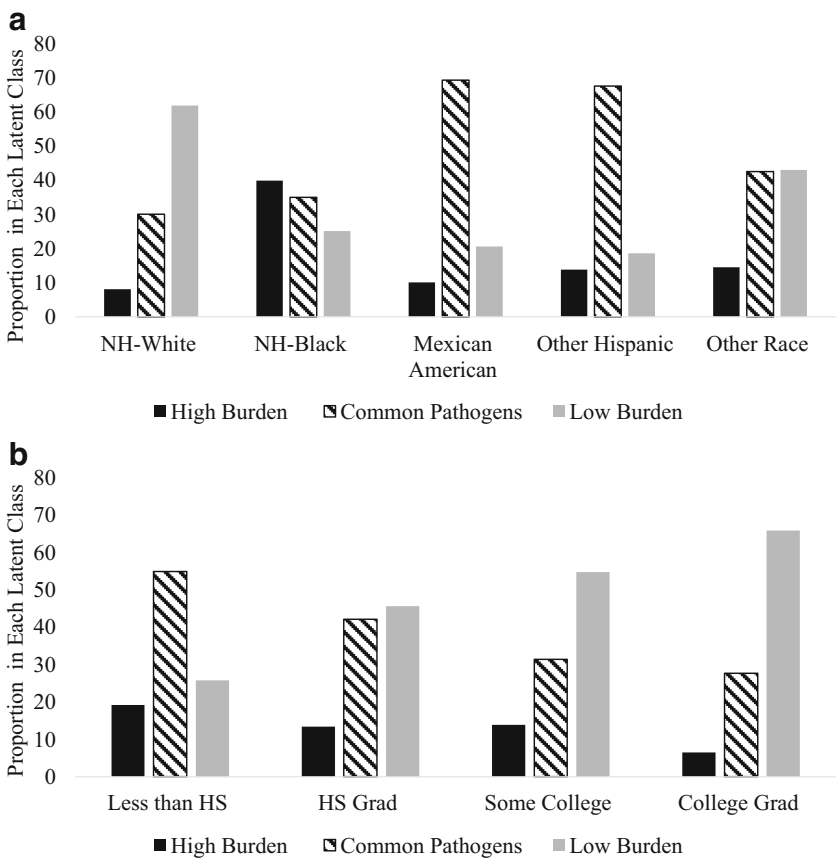

Fig. 1 **a** Distribution of the pathogen latent classes across levels of race/ethnicity for the National Health and Nutrition Examination Survey, 2003–2004 ($N = 2168$). **b** Distribution of the pathogen latent classes across levels of education for the National Health and Nutrition Examination Survey, 2003–2004 ($N = 2168$)

Association Between Race/Ethnicity, Education, and the CDI

Finally, we tested two-way interactions between the latent classes and both race/ethnicity and education (supplementary table 4). Both interaction terms were significant or borderline significant suggesting differences in the association of pathogen burden and the CDI by race/ethnicity and education (P for race/ethnicity = 0.06; P for education = 0.02). Thus, based on the statistical results and a priori hypotheses, we stratified the subsequent statistical models.

Significant associations between the CDI and the pathogen latent classes were observed for both non-Hispanic Whites and non-Hispanic Blacks in stratified analyses (Table 3). Among non-Hispanic Whites, those in the high burden class had a CDI 0.028 greater than those in the low burden class ($P = 0.05$). Among non-Hispanic Blacks, those in the common pathogens class had a CDI 0.045 greater than those in the low burden class; those in the high burden class had a CDI 0.049 greater than those in the low burden class ($P = 0.01$ and $P = 0.01$, respectively).

Among educational categories, there were significant associations between the CDI and the pathogen latent classes among high school graduates, those with some college education, and those with a college degree or higher (Table 4). Among high school graduates, those in the high burden class had a CDI 0.062 greater than those in the low burden class ($P < 0.001$); those in the common pathogens class had a CDI 0.045 greater than those in the low burden class ($P < 0.01$). Among those with some college education, those in the common pathogens class had a CDI 0.055 greater than those in the low burden class ($P < 0.0001$) while those in the high burden class had a CDI 0.032 greater than those in the low burden class ($P < 0.05$). Among those with college degrees or above, those in the common pathogens class had a CDI 0.030 greater than those in the low burden class ($P = 0.05$).

Sensitivity Analyses

In sensitivity analyses, we replicated the main analyses using the 2009–2010 wave. We found similar gradients in the mean CDI by race/ethnicity and education. In regression analyses, we did not observe consistent significant associations between pathogen burden and the CDI when stratified by race/ethnicity and education. We believe this is likely due to missing data on CMV in 2009–2010. Results of these analyses are reported in the supplementary material (supplementary tables 5 and 6).

Discussion

We applied a cumulative deficits approach to examine the role of social disadvantage on pathogen burden and multifactor marker of biological dysfunction labeled the cumulative deficits index (CDI). Our study yielded several important insights critical to understanding the ways in which social disadvantage may impact biological processes across the life course. First, we found that the CDI and the distribution of the pathogen burden latent classes differed significantly by race/ethnicity and educational level illustrating the underlying social structure of both pathogen burden and biological dysfunction. Second, based on the interaction analyses and the subsequent stratified models, we found that the effect of being in the high burden class of pathogen burden was worse for non-Hispanic (NH) Blacks and those of lower educational status than for NH Whites and those with a college education. Together, these findings suggest a social stratification underlying both the distribution of pathogen burden and the effects of pathogen burden on biological dysfunction, as measured by the CDI.

Persistent viruses, such as those in the herpesvirus family, are frequently subclinical without signs of severe illness at the time of infection [26–28]. Infection often occurs early in life leading to a process of latency and reactivation across the life

Table 3 Results of the regression analysis examining the association between the latent classes of pathogen burden and the cumulative deficits index stratified by race/ethnicity in the National Health and Nutrition Examination Survey 2003–2004

	Non-Hispanic Whites		Non-Hispanic Blacks		Mexican Americans		Other Hispanics		Other	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Intercept	0.25**	0.22, 0.27	0.23**	0.17, 0.28	0.20**	0.14, 0.26	0.19*	0.03, 0.35	0.33**	0.24, 0.42
Latent classes										
Low burden	Ref.		Ref.		Ref.		Ref.		Ref.	
Common pathogens	0.04**	0.02 0.06	0.05*	0.02, 0.08	0.025	− 0.002, 0.05	− 0.01	− 0.11, 0.09	0.04	− 0.03, 0.11
High burden	0.03*	0.01, 0.05	0.05**	0.01, 0.08	0.008	− 0.04, 0.05	− 0.02	− 0.13, 0.10	0.03	− 0.04, 0.10

Results of the full model controlling for the following covariates: age, sex, BMI, smoking, education, and chronic conditions

*$P < 0.05$; **$P < 0.01$

Table 4 Results of the regression analysis examining the association between the latent classes of pathogen burden and the cumulative deficits index stratified by education in the National Health and Nutrition Examination Survey 2003–2004

	Less than HS		HS grad		Some college		College graduate	
	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI	Coeff.	95% CI
Intercept	0.27**	0.22, 0.32	0.23**	0.19, 0.27	0.24**	0.19, 0.28	0.25**	0.19, 0.32
Latent classes								
Low burden	Ref.		Ref.		Ref.		Ref.	
Common pathogens	0.01	− 0.03, 0.04	0.05**	0.02, 0.07	0.05**	0.03, 0.07	0.030*	0.0001, 0.06
High burden	0.02	− 0.01, 0.05	0.06**	0.03, 0.09	0.03*	0.01, 0.06	− 0.01	− 0.06, 0.04

Results of the full model controlling for the following covariates: age, sex, BMI, smoking, race/ethnicity, and chronic conditions

*$P < 0.05$; **$P < 0.01$

course [29]. Each period of reactivation requires substantial immune resources to control the infection, effectively accelerating the pace of immunosenescence. This is born out in studies using various metrics of immunological aging. For example, herpesvirus coinfections are associated with significant declines in leukocyte telomere length prospectively over 3 years [30]. Studies of CMV, specifically, find that nearly 10% of CD4 and CD8 cells are devoted to CMV control [31–34], effectively aging the immune compartment.

We found that individuals with lower education and individuals of minority race/ethnicity were more likely to be in the high pathogen burden class. This is consistent with the growing body of research documenting the association between latent viruses and social status. Individuals of low SES have higher antibody titers to CMV, HSV-1, *Helicobacter pylori*, and *Chlamydia pneumoniae.* Moreover, children with lower family income and parental education and children of minority race/ethnicity have higher levels of infection with pathogens including Epstein-Barr virus (EBV), *H. pylori*, CMV, HSV-1, hepatitis B virus (HBV), and hepatitis A virus (HAV) [35–37].

Despite the number of studies suggesting an underlying social stratification process of latent viral infections, few studies have examined whether the association between social disadvantage and pathogen burden is consistent across SES groups of individuals. We found significant interactions between latent class membership and both race/ethnicity and education. These findings suggest that individuals experiencing greater social disadvantage were more likely to be in the high pathogen burden class and that being in the high burden class was associated with increased deficits for those individuals.

While the CDI is a not direct measure of clinical disease, we believe these findings are indeed clinically relevant since the CDI is composed of markers that are used to indicate the health of multiple systems in the body. For example, high triglycerides are related to cardiometabolic health and lower than normal iron levels can indicate anemia and blood disorders. Based on our index, a change in the detrimental direction in only one of these markers results in a change in the overall CDI. Therefore, the CDI provides a broad measure of changes in clinically relevant biomarkers that are used to navigate and identify health concerns in populations. For example, among non-Hispanic Blacks, a change in the CDI of 0.05 is roughly equivalent to an increase of 1.3 in the number of deficits for an individual. For a high school graduate, a change of 0.06 is roughly equivalent to an increase of 1.7 in the number of deficits. Increases in the number of deficits could then indicate that an individual has one or more body systems on a trajectory towards clinical dysfunction. In this way, we believe changes in the CDI are clinically significant because of their holistic impact on the probability of future disease development.

While the cross-sectional nature of the data does not allow for a formal adjudication of causal processes, evidence from prospective studies suggests that causal mechanisms could be at work. For example, a number of studies have found prospective evidence linking experiences of stress to subsequent increases in herpesvirus antibodies [38–44], suggesting that stress resulting from experiences of racism for racial/ethnic minorities and/or sustained low SES among those with less education may directly impact pathogen burden, and ensuing physiological wear and tear. Additionally, it may be that increased individual-level social disadvantage correlates with living in physical environments that both increase exposure to infectious pathogens (i.e., from crowded living conditions), and experiences of psychosocial stress (i.e., due to increased neighborhood crime or disorder) [45, 46].

Indeed, the stress literature bears this out. Sustained disadvantage has been associated with prolonged activation of the stress process [47]. Chronic stress is linked with higher levels of inflammation [48, 49] and diminished immune function [50, 51]. The seminal studies by Cohen et al. found that those reporting lower levels of subjective social status fared worse when exposed to a viral challenge than those of higher social status [52, 53]. The authors suggest that these findings may be partially mediated by health behaviors such as sleep duration

and quality, and other psychological traits serving as buffers that confer a greater ability to cope with stress. Vis-à-vis these hypotheses, individuals experiencing sustained social disadvantage may have fewer behavioral and psychological resources to cope with stress, and therefore, biological pressures such as those presented by persistent infections may have increased biological costs for these individuals.

While we believe this study provides critical insights into the biology of social disadvantage, it is not without limitations. First, the data are cross-sectional which limits our ability to establish a temporal sequence, and therefore causality. Future studies should investigate whether pathogen burden predicts increased deficits over time, and compare these trajectories among race/ethnic and educational sub-populations. Additionally, the data used are from 2003 to 2004. However, we do not believe overall trends in the prevalence of persistent infections or social disparities have significantly changed in the intervening years, suggesting these trends are generalizable to current populations. Indeed, evidence from other work in this area suggests that educational disparities in pathogen burden are widening (Stebbins, Noppert, Aiello et al., unpublished work 2019). Thus, we believe our estimates of the overall educational and race/ethnic disparities in pathogen burden may be an underestimate of current trends.

Our findings point to a strong role of the social environment in determining the distribution of pathogen burden as well as overall patterns of biological dysfunction. However, our ability to capture the social environment was limited by the data available in the NHANES. Testing of these relationships with datasets that offer more robust assessments of the social environment may further elucidate the mechanisms at work.

Finally, the variables used to construct both the CDI and the pathogen burden measure are not comprehensive. Other biological markers and infections may be critical to understanding these processes. Future replication studies are critical to better understand the biological processes at work.

In conclusion, we found evidence that individuals of lower education and individuals of minority race/ethnicity both had unhealthier biomarker profiles, as measured by the CDI, and were more likely to experience higher levels of pathogen burden. Perhaps, more importantly, the effects of high pathogen burden on biomarker profiles were worse for these groups. These findings point to underlying social processes that both put certain groups of individuals at higher risk for exposure to infections with fewer biological resources to buffer the effects of such infections. Notably, these findings were observed in a relatively young cohort before clinical disease typically manifests. Public health interventions that reduce pathogen load may address overall changes in biological dysfunction, reducing health disparities in the aging process.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Responsibilities of Authors This manuscript has not been submitted to more than one journal for simultaneous consideration and has not been published previously. No data have been fabricated or manipulated to support the conclusions. Consent to submit has been received explicitly from all co-authors. Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

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