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Socioeconomic and race/ethnic differences in immunosenescence: Evidence from the Health and Retirement Study

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ARTICLE INFO

Keywords:
Geroscience
Immunosenescence
Population-based studies
Sociodemographic differences
Socioeconomic status
Race/ethnicity

ABSTRACT

Background: The COVID-19 pandemic has highlighted the urgent need to understand variation in immunosenescence at the population-level. Thus far, population patterns of immunosenescence have not well described.

Methods: We characterized measures of immunosenescence from the 2016 Venous Blood Study from the nationally representative U.S Health and Retirement Study (HRS) of individuals ages 50 years and older.

Results: Median values of the CD8+:CD4+, EMRA:Naïve CD4+ and EMRA:Naïve CD8+ ratios were higher among older participants and were lower in those with additional educational attainment. Generally, minoritized race and ethnic groups had immune markers suggestive of a more aged immune profile: Hispanics had a CD8+:CD4+ median value of 0.37 (95% CI: 0.35, 0.39) compared to 0.30 in non-Hispanic Whites (95% CI: 0.29, 0.31). Non-Hispanic Blacks had the highest median value of the EMRA:Naïve CD4+ ratio (0.08; 95% CI: 0.07, 0.09) compared to non-Hispanic Whites (0.03; 95% CI: 0.028, 0.033). In regression analyses, race/ethnicity and education were associated with large differences in the immune ratio measures after adjustment for age and sex.

Conclusions: Lower educational attainment and minoritized racial ethnic status were associated with higher levels of immunosenescence. This population variation may have important implications for both risk of age-related disease and vulnerability to emerging pathogens (e.g., SARS-CoV-2).

1. Introduction

Aging of the immune system (i.e., immunosenescence) is hypothesized to contribute to the etiology of many age-related diseases including cardiovascular diseases, cancers, type 2 diabetes mellitus, neurodegenerative diseases, frailty, and premature mortality (Olsson et al., 2001; Pawelec et al., 2006; Gkrania-Klotsas et al., 2013; Stassen et al., 2006). Immunosenescence has also been implicated in reduced immune response to vaccination among aging populations (Grubeck-Loebenstein et al., 2009). While there is growing evidence that differences in immune status may underlie many age-related diseases, few studies have examined population patterns of immunosenescence in older age (Klopack et al., 2022; Thyagarajan et al., 2021).

As individuals age, several functional changes occur in both the innate and adaptive immune systems including dysfunction in the T cell compartment (Thyagarajan et al., 2021; Domingues et al., 2020; Iwasaki and Grubaugh, 2020; Lucas et al., 2020), increasing chronic low-grade inflammation (i.e., ‘inflammaging’) and diminished ability to fight infections Bandaranayake and Shaw (2016). In addition, T cell ratios and cell surface markers change over time, including an inversion of CD4+:CD8+ T cell ratios, a decrease in naïve T cells, and an accumulation of effector memory T cells with limited function (Pawelec and Solana, 1997). Together, these age-related immune alteration form a phenotype of immunosenescence. Concurrently, antigenic stimulation across the life course drives expansion of memory and effector T cell subsets contributing to an increase in the number of pathogen-specific, highly differentiated T cells (Gruver et al., 2007). It is thought that cytomegalovirus (CMV) infection, in particular, may be a key driver of these
trends (Solana et al., 2012; Aiello et al., 2017). CMV is a highly prevalent herpesvirus infection in older age populations and has been implicated as a major driver of age-associated alterations to the T cell repertoire (Pawelec and Derhovanessian, 2011) with expansion of T cells specific for CMV and decreases in T cells specific to other pathogens over time (Kadambari et al., 2020).

We conceptualize immunosenescence as related to, but distinct from the well-characterized phenomenon of cellular senescence, a hallmark feature of aging (Kholsa et al., 2020). Cellular senescence refers to a cell fate in which cells experience irreversible cell growth arrest, become resistant to apoptosis, and leads to a highly pro-inflammatory cellular response (Kholsa et al., 2020; Gerdes et al., 2020; Palmer et al., 2019). Immunosenescence, in contrast, is a combination of cellular senescence occurring in immune cells specifically, and the associated phenotypic changes occurring in the immune system in general over the life course of an individual (Zhou et al., 2021).

Despite evidence that changes in immunity contribute to many of the hallmark diseases of aging, prior research on immunosenescence has relied on small, often non-representative samples (e.g., clinical cohorts) and investigated individual markers rather than employing multiple indicators across the immune system. Using newly released venous blood data collected in 2016 from the population-based U.S. Health and Retirement Study (HRS), we carried out a secondary data analysis of cohort data. Our study characterizes markers and ratios of T-cell immunosenescence in a population of individuals ages 56 years and older. We also examined other age-related immune cell markers of the adaptive (B-cells, Natural Killer cells) and innate (monocytes, lymphocytes, Natural Killer cells) immune system. Natural killer cells, while traditionally considered to be only part of the innate immune system, have more recently been found to have immunological memory, identifying them also as part of the adaptive immune system (Vivier et al., 2011). The objective of this paper is to assess the differences in these markers of immunosenescence by sociodemographic characteristics including age, sex, race/ethnicity, and educational attainment. Our analysis follows a recently published paper that described the distribution of the raw T cell variables in the HRS population (Thyagarajan et al., 2021). Our investigation builds upon this work by both employing novel ratio measures of T cell immunosenescence as well as giving critical attention to differences in these ratio measures by racial/ethnic categorizations, educational status, in addition to age and sex. As one of only a few population-based studies of immunosenescence, our study provides new insights into population variation in immunity, with implications for age-related disease, vaccine response, and vulnerability to pathogens, for example SARS-CoV-2.

2. Methods

2.1. Study population

Data come from the U.S. Health and Retirement Study (HRS), the largest on-going nationally representative longitudinal survey of older adults in the U.S. HRS began in 1992 and included over 22,000 adults over the age of 50 years at baseline and interviewed every-two years (Thyagarajan et al., 2021). Data collection consisted of face-to-face baseline interviews and primarily telephone interviews for follow-up waves, until 2006, when half the sample (alternated at each subsequent wave) was randomly assigned face-to-face interviews to enhance physical and biological measures. There were 22,343 individuals who participated in the 2015 core HRS survey. Of those participants, our study sample included those with who were eligible for the Venous Blood Study (VBS) (n = 15,509) (Grimmins et al., 2017). 11,974 individuals consented for the VBS and 9,933 had complete and valid test results consent rate = 78.5 %, completion rate = 65 %). Our analysis included individuals who 1) had survey weights > 0, 2) full covariate data, and 3) had data on at least one set of immune biomarkers required to calculate at least one ratio measure. We also excluded two individuals with extreme values on two of the ratio measures. The final sample size was 8,440. Additional details on how the study sample was derived is described in Supplemental Fig. S1.

2.2. Immune measures

Immunophenotyping was performed on the entire VBS sample. Further details on blood sample processing, laboratory assays, and the characterization of subtypes of T, B, monocytes, and natural killer (NK) cells are described in Thyagarajan et al. (2021). We focused on 10 specific cell subtypes: CD4+: (CD3+CD19-CD8-CD4+), naïve CD4+ (CD45RA+CD28-CD95-), terminally differentiated effector memory (EMRA) CD4+: (CD3+CD19-CD8-CD4+CD45RA+CCR7-CD28-), CD8+: (CD3+CD19-CD8+CD4), naïve CD8+ (CD3+CD19-CD8-CD4-CD45RA+CCR7+CD28-), EMRA CD8+: (CD3+CD19-CD8+CD4-CD45RA+CCR7-CD28-). IgD− Memory B Cells (CD3−CD19+IgD+CD27+), IgD− naïve B Cells (CD3−CD19+IgD−CD27+), NK Cells: CD56 Low (CD3−CD19-CD20-CD14+CD16+CD56LO), and NK Cells: CD56 High (CD3−CD19-CD20-CD14+CD16+CD56HI).

For the primary analyses, we used a continuous percentage measure for each cell type. The percentages were defined in terms of the proportion of the parent cell population. For example, the percentage of naïve CD4+ T cells was defined as the proportion of naïve CD4+ T cells out of the total CD4+ cell parent population.

We utilized several T-cell markers to create ratios measures of immunosenescence. CD4+:CD8+ T cell ratios have been widely used in clinical research to indicate immunocompromised health and this ratio known to decrease with age (Muller et al., 2015). In addition, we followed a previously published methods for creating ratios of T cell immunosenescence, developed by Aiello et al. (2016a), Aiello et al. (2016b) Following these approaches, we assessed the following ratios:

A. CD8+:CD4+
B. EMRA CD4+:Naïve CD4+
C. EMRA CD8+:Naïve CD8+

In order for interpretation of all three ratio measures to be consistent, we inversely coded the CD4+:CD8+ T cell ratio as CD8+:CD4+ . With this coding, for all ratio measures, higher median values can be interpreted as a more aged immune profile.

We also developed three ratio measures that have been less utilized in studies of immunosenescence and provide insights on both adaptive and innate immune changes with age:

D. Memory:Naïve B Cell (adaptive)
E. NK Cells CD56 Low to CD56 High (adaptive and innate)
F. Monocyte: Lymphocyte (innate)

The analyses using these ratio measures are included in the supplementary material.

For full details on which variables were used to create each ratio measure, see Supplemental Material.

We added a small constant 0.001 to all cell types to avoid dividing by a zero value, and all ratio measures were natural-log transformed prior to inclusion in regression models to account for skewness.

2.3. Cytomegalovirus

In addition, we examined whether continuous CMV IgG antibody levels mediate the relationship between sociodemographic factors and immunosenescence. The role of CMV in immunosenescence remains unclear. This large DNA virus may drive immunosenescence or interact biologically with the immune system in ways that accelerate immunosenescence. Alternatively, immunosenescence may lead to loss of immune control over CMV and subclinical reactivation. Importantly, CMV has known associations with socioeconomic factors at the population-
level (Aiello et al., 2016a; Noppert et al., 2021; Aiello et al., 2006; Dowd et al., 2012; Feinstein et al., 2016). CMV immunoglobulin (IgG) levels were measured in serum using the Roche e411 immunoassay analyzer. For the main statistical analyses, we utilized the continuous CMV IgG antibody levels setting those seronegative to a value of 0. As noted above, we added a small constant 0.001 to the CMV IgG antibody levels to avoid dividing by a zero value, and then we performed a natural-log transformation to account for skewness. We carried out two sensitivity analyses using alternative classifications of CMV to ensure our inferences were consistent across ways of modeling CMV. In the first, we used the continuous CMV IgG levels but restricted the analysis to only those CMV seropositive. In the second analysis, we used a binary indicator of CMV (seropositive versus seronegative).

### 2.4. Sociodemographic variables

Self-reported sociodemographic characteristics including age, sex, race/ethnicity, and educational attainment were collected in the 2016 core interview. We examined differences by age and sex given known changes in the immune system corresponding to both chronological age, and corresponding to sex hormone differences (Hagg and Jylhäva, 2021). Educational attainment was categorized as less than a high school diploma, high school diploma, some college, or a college diploma and higher. Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or Other Race, and sex was self-reported as either male or female. Of note, we recognize that there is significant variation within race/ethnic categories as to how individuals may identify themselves. Race/ethnic associations should be interpreted with this in mind. See the Supplementary Materials for additional details on how race/ethnicity was conceptualized and measured.

### 2.5. Statistical analyses

We calculated descriptive statistics for the study population overall and stratified by age group, sex, race/ethnicity, and educational attainment. We compared the median values and 95% confidence interval of each of the immune ratios by sociodemographic characteristic.

We ran a series of linear regression models to estimate the association between each sociodemographic characteristic and the three primary immune measures. **Model 1** included age and sex. **Model 2** included age, sex, and educational attainment. **Model 3** included age, sex, race/ethnicity, and educational attainment. Additionally, to investigate whether CMV partially mediates the association between the sociodemographic characteristics and immune outcomes, **Model 5** includes all covariates plus CMV IgG levels. The regression models estimate the change in the mean value of the log-transformed immune ratio measure associated with each category of sociodemographic group compared to a referent.

We carried out three sensitivity analyses. First, we compared an alternative construction of the three primary ratio measures. We first estimated the correlation between the proportion-based ratio measures and the count-based ratio measures. We then estimated Model 1 using the count-based ratio measures and compared the estimates to Model 1 when using the proportion-based ratio measures to ensure the associations were consistent when using cell counts. Second, we compared two alternative methods for measuring CMV to ensure our inferences were consistent across methods of modeling CMV. Finally, we estimated whether the observed associations varied when examining those 65 years and younger compared to those 66 years and older.

All analyses were weighted with the 2016 VHS weights and the statistical models accounted for the complex survey design. Observations missing values for one of the outcome measures were excluded from the analysis. The sample size for each outcome measure is displayed in Table 1. Statistical analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, North Carolina), and figures were generated in R.
3.2. Distribution of immune measures by sociodemographic characteristics

We compared the median values of each immune measure across age group, sex, race/ethnicity, and education (Table 2 and Fig. 1). As expected, the median values of the CD8+:CD4+, EMRA:Naive CD4+, and EMRA:Naive CD8+ ratios increased with age. For example, among those 56-65 years, the median CD8+:CD4+ value was 0.31 (95% CI: 0.29, 0.32) compared to the median of 0.37 (95% CI: 0.33, 0.41) among those 86+ years. Comparing the median values of the immune markers: Naive CD8+ ratio, those 56-65 years old had a median value of 1.44 (95% CI: 1.30, 1.57) compared to those 86+ with a median value of 6.71 (95% CI: 5.53, 7.88).

We also observed sex differences in the median values of each of the outcome measures. Females had lower median values for the CD8+:CD4+ and EMRA:Naive CD8+ ratios compared to men. For the CD8+:CD4+ ratio men had a median value of 0.34 (95% CI: 0.33, 0.35) compared to the median of 0.37 (95% CI: 0.33, 0.41) among those 86+ years. Comparing the median values of the EMRA:Naive CD8+ ratio, those 56-65 years old had a median value of 1.44 (95% CI: 1.30, 1.57) compared to those 86+ with a median value of 6.71 (95% CI: 5.53, 7.88).

Finally, we observed an educational gradient across all three immune measures with more education associated with lower values, suggesting a less aged immune profile. For example, those with less than a high school education had a median CD8+:CD4+ ratio of 0.39 (95% CI: 0.36, 0.41) compared to those with a college degree or higher with a value of 0.28 (95% CI: 0.27, 0.29). The same trend was observed for both the EMRA:Naive CD8+ ratio and the EMRA:Naive CD8+ ratio.

3.3. Associations between sociodemographic factors and immune function

Fig. 2 and Tables S1-S3 show the associations between sociodemographic characteristics and the immune ratios measures, adjusted for covariates. In model 1, we found that for each additional year of age, there was a higher mean value of all three ratio measures CD8+:CD4+, CD4+ EMRA:Naive ratio and CD8+ EMRA:Naive ratio when adjusted for sex. For example, a one-year increase in age was associated with 0.01 (95% CI: 0.004, 0.01) higher CD8+:CD4+ ratio. There were also statistically significant associations between sex and both the CD8+:CD4+ ratio and the CD8+:EMRA:Naive ratio, with females having a lower

| Table 2 |
| Distribution of immune measures by age group, sex, race/ethnicity and education attainment. |
| 56-65 | 66-75 | 76-85 | 86+ | Female | Male |
| CD8+:CD4+ Ratio | 0.31 (0.29, 0.32) | 0.31 (0.30, 0.33) | 0.35 (0.34, 0.36) | 0.37 (0.33, 0.41) | 0.30 (0.29, 0.31) | 0.34 (0.33, 0.35) |
| EMRA CD4+ : Naive CD4+ Ratio | 0.03 (0.027,0.033) | 0.037 (0.035,0.04) | 0.05 (0.04,0.05) | 0.06 (0.05,0.07) | 0.038 (0.035,0.04) | 0.035 (0.032,0.04) |
| EMRA CD8+ : Naive CD8+ Ratio | 1.44 (1.30, 1.57) | 2.49 (2.29,2.70) | 4.39 (4.09,4.69) | 6.71 (5.53, 7.88) | 1.96 (1.79, 2.12) | 2.56 (2.29, 2.74) |
| Memory: Naive B Cell Ratio | 0.16 (0.15,0.17) | 0.15 (0.14,0.16) | 0.16 (0.15,0.18) | 0.19 (0.16,0.22) | 0.15 (0.14,0.17) | 0.17 (0.16,0.18) |
| Natural Killer Cells CD56 Low to CD56 High Ratio | 142.24 | 154.96 | 176.98 (168.51, 185.45) | 200.26 | 146.32 (139.86, 152.79) | 160.34 (153.51, 167.16) |
| MLR | 0.27 (0.26,0.273) | 0.29 (0.28,0.30) | 0.33 (0.324,0.34) | 0.35 (0.33,0.37) | 0.27 (0.26,0.271) | 0.32 (0.31,0.32) |
| CMV, % Seropositive | 59.46 | 67.08 | 75.21 | 80.92 | 70.83 | 59.9 |
| CMV IgG Continuous Antibodies U/mL of blood (Among Seropositives) | 400.83 (369.47, 432.20) | 376.62 (340.18, 404.53) | 380.38 (356.24, 417.22) | 364.09 (290.96, 437.28) |
| Race/Ethnicity | Non-Hispanic Black Median (95% CI) | Hispanic Median (95% CI) | Other Race Median (95% CI) | Non-Hispanic White Median (95% CI) |
| CD8+ : CD4+ Ratio | 0.35 (0.33, 0.37) | 0.37 (0.35, 0.39) | 0.35 (0.31, 0.39) | 0.30 (0.29, 0.31) |
| EMRA CD4+ : Naive CD4+ Ratio | 0.08 (0.07, 0.09) | 0.07 (0.06,0.08) | 0.04 (0.03,0.05) | 0.03 (0.028, 0.033) |
| Memory: Naive B Cell Ratio | 1.84 (1.66, 2.02) | 3.21 (3.12,4.17) | 2.00 (1.77, 2.28) | 1.96 (2.03, 2.28) |
| Natural Killer Cells CD56 Low to CD56 High Ratio | 19.90 (18.85, 21.73) | 174.01 | 196.56 | 149.32 |
| MLR | 0.25 (0.24,0.25) | 0.25 (0.24,0.26) | 0.25 (0.23,0.26) | 0.300 (0.296, 0.304) |
| CMV, % Seropositive | 88.33 | 93.42 | 84.85 | 58.93 |
| CMV IgG Continuous Antibodies U/mL of blood (Among Seropositives) | 435.72 (387.51, 483.94) | 401.29 (361.52, 441.05) | 372.82 (245.70, 490.95) | 373.86 (352.74, 394.97) |

| Education |
| Less than HS | HS Grad | Some College | College + |
| Median (95% CI) | Median (95% CI) | Median (95% CI) | Median (95% CI) |
| CD8+ : CD4+ Ratio | 0.39 (0.36, 0.41) | 0.32 (0.31, 0.33) | 0.32 (0.30, 0.33) | 0.28 (0.27, 0.29) |
| EMRA CD4+ : Naive CD4+ Ratio | 0.064 (0.06, 0.07) | 0.04 (0.03,0.044) | 0.03 (0.029, 0.034) | 0.027 (0.02,0.03) |
| Memory: Naive B Cell Ratio | 0.17 (0.16, 0.19) | 0.15 (0.14,0.16) | 0.17 (0.16,0.18) | 0.16 (0.15,0.17) |
| Natural Killer Cells CD56 Low to CD56 High Ratio | 177.83 (167.44, 188.23) | 160.28 (150.38,170.18) | 147.42 (137.22,157.63) | 141.94 (134.69,149.51) |
| MLR | 0.26 (0.25,0.27) | 0.29 (0.28,0.30) | 0.29 (0.28,0.293) | 0.297 (0.289, 0.31) |
| CMV, % Seropositive | 87.98 | 69.68 | 62.65 | 54.35 |
| CMV IgG Continuous Antibodies U/mL of blood (Among Seropositives) | 437.13 (400.38, 474.89) | 396.02 (367.22,424.82) | 373.38 (342.58,404.19) | 340.27 (315.63,264.91) |
mean value compared to males. For the CD8+CD4+ ratio, females had a mean value 0.15 lower than males (95% CI: 0.19, 0.11) and for the CD8+ EMRA:Naive females had a mean value 0.36 lower than males (95% CI: 0.43, 0.29). The CD4+ EMRA:Naive ratio did not differ by sex.

Models 2 and 3 show the age- and sex-adjusted estimates for the associations between the immune ratio measures and education and race/ethnicity, respectively. For all three measures, higher educational attainment was associated with lower mean values on all immune measures, suggesting a less aged immune profile. The educational differences were most strongly observed for the EMRA:Naive CD4+ ratio where those with less than a high school education had a mean value 0.78 (95% CI: 0.65, 0.91) higher than those with a college degree or higher while those with some college had a mean value 0.15 (95% CI: 0.04, 0.27) higher than those with a college degree.

With those who self-identified as non-Hispanic White as the referent, all three immune ratios varied statistically significantly by racial and ethnic group. For all three ratio measures, a higher value is indicative of a more aged immune profile. For the CD8+CD4+ ratio, this contrast was most strongly observed comparing those who identified as Hispanic and those who identified as “Other” race/ethnicity to those who identify as non-Hispanic White: both those that identified as Hispanic and “Other” race/ethnicity had a mean value 0.19 (95% CI: 0.14, 0.24; 95% CI: 0.08, 0.29, respectively) higher compared to those that identified a non-Hispanic White. Those who self-identified as non-Hispanic Black had a mean EMRA:Naive CD4+ ratio 0.91 (95% CI: 0.78, 1.04) higher than those that identified as non-Hispanic White. The difference between those who identified as non-Hispanic Black and non-Hispanic Whites’ mean EMRA:Naive CD8+ ratio was not statistically significant, though those who identified as Hispanic had an elevated value (0.51 (95% CI: 0.41, 0.60)). In general, these associations were slightly attenuated when race/ethnicity and education were included in the same regression model (Model 4). See Fig. 2, Tables S1-S3 for all relevant measures of association.

After adding CMV IgG levels to the model (Model 5) many of the education and race/ethnicity estimates, though not all, were attenuated, indicating that CMV may be a direct or indirect link between social factors and immune aging.

We also replicated the analyses with the three additional immune ratio outcomes: memory:naive B cell ratio, NK cells CD56 low:CD56 high ratio, and monocyte:lymphocyte ratio. Associations with sociodemographic characteristics were mixed and not in a consistent direction. With new immune measures, we are cautious in interpreting how higher or lower values correspond to immunosenescence, but hope these estimates provide new descriptive information. Full results are available in supplemental Figs. S2-S3 and Tables S4-S6.

Finally, in sensitivity analyses we examined whether results were consistent when using cell count-based ratio measures as compared to proportion-based ratio measures. We first examined correlations between the 3 primary ratio measures comparing the measures...
constructed using a cell count-based ratio measure to those using the proportion-based ratio measures. The three measures were all highly correlated (see Supplementary Table S7). We then estimated Model 1 using the count-based ratio measures for the three primary immune outcomes and compared to it Model 1 using the proportion-based ratio measures. The regression results were generally very similar when using the count-based measure with the exception of the sex estimates for the EMRA:Naïve T cell measure (see Supplementary Table S8).

We also carried out sensitivity analyses with two alternative methods for measuring CMV to ensure our inferences were consistent across methods of modeling CMV. We estimated Model 5 for all three of the primary immune outcomes comparing if CMV was modelled using the continuous IgG levels setting seronegatives to zero, using the continuous IgG levels excluding seronegatives, and a CMV binary indicator (sero-positive versus seronegative). Inferences regarding the associations between the sociodemographic variables and the three main immune outcomes were consistent across all three ways of modeling CMV (see Supplementary Table S9).

Finally, in sensitivity analyses we also compared whether the observed associations differed comparing those under 66 years and those 66 years and above (see Supplementary Table S10). By and large, the estimates were similar in the two groups though the statistical power decreased given the lower sample sizes resulting in wider confidence intervals.

4. Discussion

The large variation in patterns of COVID-19 disease susceptibility and vaccination response to SARS-CoV-2 has highlighted the critical need to better understand population differences in adaptive and innate immunity. We identified statistically significant associations between sociodemographic factors and immunosenescence among individuals 56 years and older. We found differences in the levels of each immunosenescence ratio by age group, sex, race/ethnicity, and education, though the magnitude of the differences varied by immune measure and sociodemographic characteristic. Overall, those occupying more disadvantaged societal positions (i.e., minoritized race and ethnic groups and individuals with lower educational attainment) had indicators of more advanced immunosenescence compared to those in less disadvantaged positions.

The demographic predictors of the immune measures we described here have been assessed in only a few other population-based studies and these were smaller samples (Aiello et al., 2016a; Aiello et al., 2016b). Our results showed that sociodemographic factors, specifically race/ethnicity and education, were associated with large differences in immune measures even compared to those associated with chronological age. While there are few population-based studies of immunosenescence to compare these results to, there has been a wide body of research on CMV infection and immune response and demographic characteristics. CMV infection often happens early in the life course, and evidence suggests that structurally disadvantaged individuals are more likely to be infected at earlier ages and experience re-infection across the life course (Redeker et al., 2018; Dowd et al., 2009). All of these viral dynamics can result in structurally disadvantaged individuals exhibiting higher CMV IgG levels across the life course, with implications for many aging-related conditions, including immunosenescence. While some studies have examined CMV as a proxy measure of immunosenescence itself, we conceptualized it as a potential driver of immunosenescence and thus did preliminary analyses adjusting for CMV in our statistical models. We found that inclusion of CMV in the models resulted in partial, and in some cases full, attenuation of the estimates between the sociodemographic characteristic and the immune outcome measures, similar to previous studies. Kadambari et al., (2020); Aiello et al., (2016); Aiello et al., (2016); Bjornvik et al., (2022); Di Benedetto et al., (2015); Pawelec et al., (2012) Given the strong association of CMV with sociodemographic factors, more work on the causal role of CMV in these associations is warranted. Overall, these findings support earlier work on CMV and suggest an important role for the social environment in addition to chronological age in shaping immunosenescence at the population-level.

The social environment could accelerate immunological aging via several pathways. Socially disadvantaged individuals are more likely to encounter both infectious and other immune-taxing exposures across their life course. For example, social differences in housing, transportation, and occupations may lead to more infectious exposures, heightened by COVID-19. McClure et al., (2018) Living in disadvantaged neighborhoods can increase the quantity and frequency of exposure to pollution, noise, and psychosocial stressors that activate cortisol production via the HPA-axis, potentially interacting directly with immune cells (Zilioli et al., 2017). Indeed, previous research has shown that psychosocial trauma is associated with changes in these ratios in the same direction we identified, suggesting that psychosocial stressors may play a role in the association between disadvantage and immunosenescence (Aiello et al., 2016). If stressors age the immune system, our findings could have key implications for understanding the biological mechanisms linking disadvantage to poor health. Further research explicating stress-related pathways to immunosenescence are warranted.

We observed higher levels of T cell immunosenescence in racial and ethnic minorities and those with less education. Importantly, the magnitudes of these sociodemographic differences are large in comparison to the differences observed by age. For example, in Model 4, those with less than a high school education had a mean CD4+ EMRA: Naïve ratio value 0.47 (95% CI: 0.34, 0.61) higher than those with a college education or more. This is notably larger than the age-associated coefficient of 0.02 (95% CI: 0.02, 0.02), which represents the difference in CD4+ EMRA: Naïve ratio mean value for each additional year of age. In that same model, non-Hispanic Blacks had a mean ratio value 0.82 (95% CI: 0.69, 0.96) higher than compared to non-Hispanic Whites. It is particularly important to consider the chronic, life course nature of these social exposures, which may help explain the magnitude of these associations.

While this study significantly advances our understanding of population-level immunosenescence, there are several key limitations that should be considered. First, the immune measures are only measured at a single point in time. These data were all collected as part of the 2016 VBS; no longitudinal data are available. Thus, we cannot make inferences regarding life course trajectories of immune biomarkers or differential speed of immunosenescence. Second, measurement of T cell phenotypes in large-scale cohort studies is logistically demanding, and there is likely to be technical error introduced through the time it takes to process samples and cell loss. These markers are not only sensitive to the conditions under which they are collected and processed, but also sensitive to human variation at the time of collection (e.g., may be altered in response to acute illness). Moreover, the immune system is a complex and dynamic system. While our use of multiple immune measures is certainly a step forward in terms of previous studies, we still only utilize a limited set of immune measures representing only a small part of the larger immune system at a single point in time. Thus, we are limited in the inferences we can derive regarding the broader immune system dynamics at play. Future studies should continue to move towards a systems-based approach for understanding immune aging to better capture complexities in these processes. Related, despite using previously established methods for our T cell ratio measures, these ratios likely don’t capture the dynamic links between T cells, B cells, NK cells, macrophages, and lymphocytes. Development of measures that better capture interactions between these markers and how they evolve with aging could improve our models of immunosenescence.

While large and population-based, the HRS over-represents non-Hispanic Whites, thus our results are not fully generalizable to the U.S. population. There is also differential attrition by race/ethnicity, and our analytic sample only includes individuals who survived to age 56 and
enrolled in the study. An additional limitation is the possibility of selection bias though it is difficult to disentangle the direction of the bias. Generally, those who agree to enroll in studies such as this are healthier than the average population and experience less life disadvantage (Keyes et al., 2018). As a result, selection may be biasing associations between immunosenescence measures and sociodemographic variables. Future studies should investigate these relationships earlier in the life course, before individuals are dying of age-related diseases, to understand the extent of this bias. Finally, we documented preliminary evidence that one’s structural position in society is related to measures of immunosenescence. We conceptualize structural drivers or structural position as referring to the institutional- and policy-level conditions that affect health and disproportionally burden certain groups of the population versus others. Notably, our results are consistent with a recent investigation finding that experiencing stressful life events, trauma, and discrimination are associated with markers of advanced immune aging (e.g., higher terminally differentiated CD4+ T cells, lower naive CD8+ T cells, lower CD4+/CD8+ T cell ratio) Klopack et al. (2022). Future work should continue these sorts of investigations by examining socioeconomic differences within racial and ethnic groups, and specifically the role of stress, to understand the role of individual-level socioeconomic status in patterns of immunosenescence.

5. Conclusion

Our study describes the relationship between sociodemographic factors and key measures of immunosenescence in a large, population-based cohort. We found evidence that lower educational attainment and minoritized racial ethnic status was associated with higher levels of immunosenescence. While age has traditionally been thought of as the primary driver of immune differences, the magnitude of differences by sociodemographic factors observed, suggests that the social environment also plays an important role in aging the human immune system.

6. Statements

Contributors: AA conceived of the study. GN, RS, JD, and AA contributed to the study design. GN and RS prepared and conducted the data analysis and drafted the manuscript. RS and GN both performed code review to verify the underlying data. All authors critically revised the manuscript. All authors approved the final version of the manuscript.

Funding: GAN acknowledges support by the U.S. National Institutes of Health, National Institute on Aging R00AG062749. AEA and GAN acknowledge support from the National Institutes of Health, National Institute on Aging R01AG075719. JBD acknowledges support from the Leverhulme Trust (Centre Grant) and the European Research Council grant ERC-2021-CoG-101002587.

Data sharing: The Health and Retirement Study data are publicly available through https://hrs.isr.umich.edu/. The Venous Blood Study data are restricted but can be accessed through a data use agreement with the Health and Retirement Study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.10.019.

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