



# Social stressors associated with age-related T lymphocyte percentages in older US adults: Evidence from the US Health and Retirement Study

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Exposure to stress is a risk factor for poor health and accelerated aging. Immune aging, including declines in naïve and increases in terminally differentiated T cells, plays a role in immune health and tissue specific aging, and may contribute to elevated risk for poor health among those who experience high psychosocial stress. Past data have been limited in estimating the contribution of life stress to the development of accelerated immune aging and investigating mediators such as lifestyle and cytomegalovirus (CMV) infection. This study utilizes a national sample of 5,744 US adults over age 50 to assess the relationship of social stress (viz., everyday discrimination, stressful life events, lifetime discrimination, life trauma, and chronic stress) with flow cytometric estimates of immune aging, including naïve and terminally differentiated T cell percentages and the ratio of CD4<sup>+</sup> to CD8<sup>+</sup> cells. Experiencing life trauma and chronic stress was related to a lower percentage of CD4<sup>+</sup> naïve cells. Discrimination and chronic stress were each associated with a greater percentage of terminally differentiated CD4<sup>+</sup> cells. Stressful life events, high lifetime discrimination, and life trauma were related to a lower percentage of CD8<sup>+</sup> naïve cells. Stressful life events, high lifetime discrimination, and chronic stress were associated with a higher percentage of terminally differentiated CD8<sup>+</sup> cells. High lifetime discrimination and chronic stress were related to a lower CD4<sup>+</sup>:CD8<sup>+</sup> ratio. Lifestyle factors and CMV seropositivity partially reduced these effects. Results identify psychosocial stress as a contributor to accelerating immune aging by decreasing naïve and increasing terminally differentiated T cells.

socioeconomic status | immunosenescence | aging

Lifetime exposure to stressful conditions is a known risk factor for poorer health, increasing the risk for early onset of age-related disease and premature death (1–3). Models examining the mechanisms driving these effects have centered on the sequelae of repeated activation and prolonged activation of the sympathoadrenal and hypothalamic pituitary adrenal systems, leading to wear and tear at the biological level (4). Many have postulated that this wear and tear manifests at the cellular level, causing accumulation of DNA damage, increasing inflammation, shortening telomere length, and driving cellular aging (5, 6). Critically short telomere length within immune cells and cellular stress (e.g., DNA damage) can drive cells into a nonreplicating state termed cellular senescence (7, 8). In addition to localized tissue-specific aging (9), age-related changes in immune function contribute to systemic aging, organ failure, and premature mortality, making immunosenescence a critical player in aging and disease (10).

Age is a robust determinant of immune cell population composition (11, 12), with aging immune systems characterized by a reduced pool of naïve B and T cells, increased pool of terminally differentiated T cells, increased supply of CD8<sup>+</sup> cells relative to CD4<sup>+</sup> T cells, and increased systemic inflammation (13). However, there is substantial variance in the rate of these changes and consequent alterations in immune cell composition among older adults (14). Understanding the contributors to this variance is critical given that immune aging is associated with chronic diseases [e.g., cancer (15) and cardiovascular disease (16)], weakened response to acute infections, increased risk of pneumonia, reduced efficacy of vaccines (17), and organ system aging (10).

In the current study we focus on social stressors, that is, difficult or challenging circumstances (18) that arise from social position and experience that are expected to be stressful, that occur in adulthood. Past research has categorized stressors in various ways, often depending on discipline; however, stressors are typically distinguished by timescale (e.g., acute, daily hassles, life events, chronic stressors) (19). We distinguish

## Significance

As the world's population of older adults increases, understanding disparities in age-related health is essential. Age-related changes in the immune system play a critical role in age-related morbidity and mortality. This study assesses associations between social stress and immunophenotypes as immune age phenotype markers for the first time in a national sample of older US adults. This study helps clarify mechanisms involved in accelerated development of the immune age phenotype, including socioeconomic and lifestyle factors and cytomegalovirus infection and reactivation. This study also identifies important points of intervention that may be useful in addressing inequalities in aging.

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discrimination-related stressors from other stressors because past research suggests these stressors have distinct, independent effects on health (20–22). We also distinguish traumatic life events from other stressors, as is common in past research (19, 23, 24). Thus, we assess five stress variables that have been well established past research and are available in a large number of studies of health and aging (viz., stressful life events, chronic stress, everyday discrimination, lifetime discrimination, and life trauma). More information about these stressors is available in the *SI Appendix*.

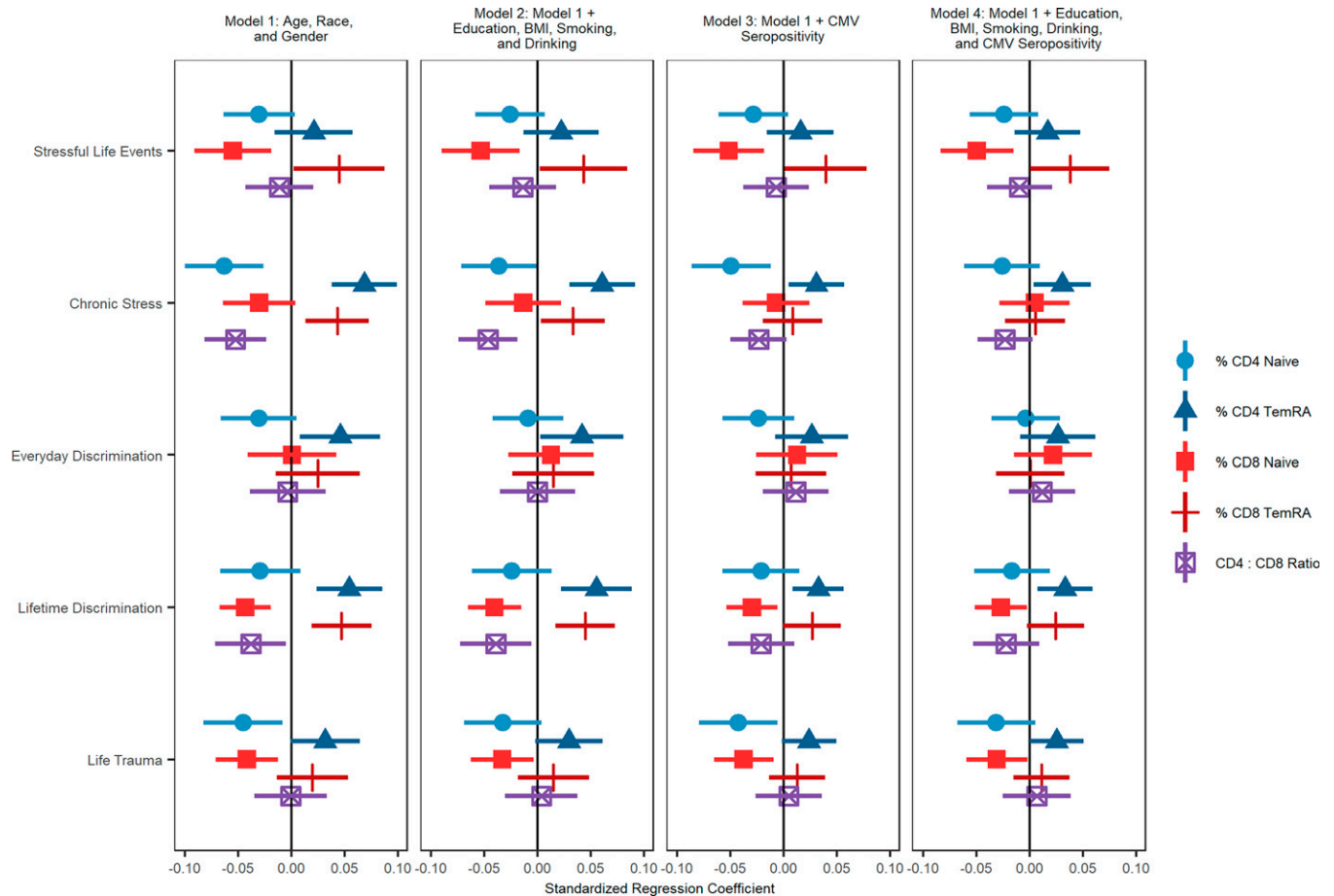
Social stress can modify the immune system in several ways, including increased inflammatory signaling and reduced antiviral responses (18, 25–27), suggesting that social stress may accelerate immune aging (28–38). However, past research has utilized small clinical and specialized samples, potentially limiting power to detect effects, power to assess mediators, and generalizability of results. In the present study, we utilized a nationwide sample of 5,641 US adults over the age of 50 to assess associations between five categories of social stress that have well established effects on health and enumerative measures of immunological aging, including naïve CD4<sup>+</sup> T cell percentages (CD4<sup>+</sup>/CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>+</sup>/CD28<sup>+</sup>), naïve CD8<sup>+</sup> T cell percentages (CD8<sup>+</sup>/CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>+</sup>/CD28<sup>+</sup>), terminally differentiated effector memory CD4<sup>+</sup> T cell percentages (TemRA; CD4<sup>+</sup>/CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>-</sup>/CD28<sup>-</sup>), terminally differentiated effector memory CD8<sup>+</sup> T cell percentages (CD8<sup>+</sup>/CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>-</sup>/CD28<sup>-</sup>), and the ratio of CD4<sup>+</sup> to CD8<sup>+</sup>

T cells. Analyses also assessed potential mediation of these associations by socioeconomic and lifestyle factors and cytomegalovirus (CMV) seropositivity.

## Results

Descriptive statistics are shown in *SI Appendix, Table S1*. The weighted sample is 55.2% female and has a median age of 68 y. Of the sample, 84.9% is non-Hispanic White, 6.9% is non-Hispanic Black, 5.8% is Hispanic, and 2.5% is non-Hispanic other race; 10.1% has less than 12 y of education, 30.7% has 12 y of education, 26.1% has 13 to 15 y of education, and 33.1% has 16 or more years of education. Of the sample, 9.4% are current smokers and 45.4% are former smokers, more than one-third of the sample is obese (36.1%), and 53.6% were nondrinkers. On average, participants reported relatively low everyday discrimination, 0.50 stressful life events, 0.65 incidents of lifetime discrimination, 1.09 life traumas, and a moderate level of chronic stress. There was substantial variance on all of these scales.

Results from nested analyses regressing T cell subset percentage/ratio on each stressor while controlling for age, sex, race/ethnicity, and various potential mediators (education, drinking, smoking, body mass index [BMI], and CMV serostatus), are shown in Fig. 1. Individual figures and tables for each predictor are shown in *SI Appendix, Figs. S1–S5 and Tables S2–S6*. All stress variables and immune outcomes variables were standardized to have a mean of 0 and SD of 1.



**Fig. 1.** Regression coefficients and 95% CIs from nested analyses regressing cell subset percentage/ratio on each stressor and mediators. All models control for age, race, and sex.

Experiencing more stressful life events was associated with a lower percentage of CD8<sup>+</sup> naïve T cells ( $b = -0.055$ , SE = 0.018,  $P = 0.004$ ) and a higher percentage of terminally differentiated CD8<sup>+</sup> T cells ( $b = 0.045$ , SE = 0.022,  $P = 0.044$ ). The association between terminally differentiated CD8<sup>+</sup> T cells and more stressful life events was reduced to nonsignificance after controlling for education, BMI, smoking, drinking and CMV seropositivity. The association between stressful life events and CD8<sup>+</sup> naïve T cell percentage remained statistically significant after controlling for all covariates ( $b = -0.049$ , SE = 0.017,  $P = 0.007$ ).

Experiencing greater chronic stress was related to a greater percentage of terminally differentiated CD4<sup>+</sup> ( $b = 0.068$ , SE = 0.016,  $P < 0.001$ ) and terminally differentiated CD8<sup>+</sup> T cells ( $b = 0.043$ , SE = 0.015,  $P = 0.007$ ), a lower percentage of CD4<sup>+</sup> naïve T cells ( $b = -0.063$ , SE = 0.019,  $P = 0.001$ ), and a lower ratio of CD4<sup>+</sup> to CD8<sup>+</sup> T cells ( $b = -0.053$ , SE = 0.015,  $P = 0.001$ ). The association between chronic stress and CD4<sup>+</sup> naïve T cells became nonsignificant after controlling for socioeconomic and lifestyle factors and CMV seropositivity. The associations between chronic stress and terminally differentiated CD8<sup>+</sup> T cells and the CD4:CD8 ratio were reduced to nonsignificance after controlling for CMV seropositivity. The association between chronic stress and terminally differentiated CD4<sup>+</sup> T cells ( $b = 0.031$ , SE = 0.014,  $P = 0.030$ ) remained significant even after adjusting for education, BMI, smoking, drinking, and CMV seropositivity.

Greater lifetime discrimination was related to having higher percentages of terminally differentiated CD4<sup>+</sup> ( $b = 0.054$ , SE = 0.016,  $P = 0.001$ ) and terminally differentiated CD8<sup>+</sup> T cells ( $b = 0.047$ , SE = 0.014,  $P = 0.002$ ), a lower percentage of CD8<sup>+</sup> naïve T cells ( $b = -0.043$ , SE = 0.012,  $P = 0.001$ ), and a lower CD4<sup>+</sup>:CD8<sup>+</sup> ratio ( $b = -0.038$ , SE = 0.017,  $P = 0.028$ ). The association between terminally differentiated CD8<sup>+</sup> T cells and greater lifetime discrimination was reduced to nonsignificance after controlling for education, BMI, smoking, drinking, and CMV seropositivity. The association between lifetime discrimination and the CD4<sup>+</sup>:CD4<sup>+</sup> ratio was reduced to nonsignificance after controlling for CMV seropositivity. The associations between lifetime discrimination and terminally differentiated CD4<sup>+</sup> ( $b = 0.033$ , SE = 0.013,  $P = 0.015$ ) and CD8<sup>+</sup> naïve ( $b = -0.027$ , SE = 0.013,  $P = 0.039$ ) T cell percentages were both substantially reduced by these mediators but remained statistically significant.

Experiencing more everyday discrimination was related to having a higher percentage of terminally differentiated effector memory CD4<sup>+</sup> T cells ( $b = 0.046$ , SE = 0.019,  $P = 0.022$ ). This association was reduced after accounting for CMV seropositivity.

Finally, experiencing a greater number of life traumas was related to a smaller percentage of CD4<sup>+</sup> naïve T cells ( $b = -0.045$ , SE = 0.019,  $P = 0.020$ ) and CD8<sup>+</sup> naïve T cells ( $b = -0.042$ , SE = 0.015,  $P = 0.007$ ). The association between CD4<sup>+</sup> naïve T cells and trauma was reduced to nonsignificance after controlling for education, BMI, smoking, and drinking, suggesting that these socioeconomic and lifestyle factors may mediate this association. Associations between life trauma and CD8<sup>+</sup> naïve T cells ( $b = -0.031$ , SE = 0.015,  $P = 0.042$ ) remained significant after including all covariates.

We also estimated models with interactions between stressors and sex and race/ethnicity, including all controls. There was only one statistically significant interaction. The effect of experiencing more lifetime discrimination on naïve CD8<sup>+</sup> T cell percentage was amplified for Hispanic respondents compared to non-Hispanic White respondents.

## Discussion

Using a national sample of older US adults, we found that exposure to social stress was associated with T cell distributions indicative of accelerated immune aging. Specifically, life trauma and chronic stress were associated with a lower percentage of CD4<sup>+</sup> naïve T cells, whereas everyday discrimination, lifetime discrimination, and chronic stress were associated with a greater percentage of terminally differentiated CD4<sup>+</sup> T cells. Stressful life events, lifetime discrimination and life trauma were associated with a lower percentage of CD8<sup>+</sup> naïve T cells, whereas stressful life events, lifetime discrimination, and chronic stress were significantly associated with a higher percentage of terminally differentiated CD8<sup>+</sup> T cells. Lifetime discrimination and chronic stress was associated with a lower CD4:CD8 ratio. These effects were all independent of chronological age, sex, and race/ethnicity.

All significant associations with CD4<sup>+</sup> naïve T cells were reduced to nonsignificance after controlling for socioeconomic and lifestyle factors (viz., education, smoking, BMI, and alcohol use) and CMV seropositivity, suggesting that this may be an important pathway by which stress affects CD4<sup>+</sup> T cell immunosenescence. This is consistent with past research suggesting that adiposity is associated with thymic involution (39) and research showing reduced percentages of CD4<sup>+</sup> naïve T cells in people with alcohol use disorder (40). Further research is needed to clarify how these factors affect naïve CD4<sup>+</sup> T cells.

Lifetime discrimination and chronic stress associations with terminally differentiated CD8<sup>+</sup> T cells and the CD4:CD8 ratio became nonsignificant after controlling for CMV seropositivity and the association between stressful life events and terminally differentiated CD8<sup>+</sup> T cells became nonsignificant after controlling for lifestyle and socioeconomic status factors and CMV seropositivity. This is consistent with past research showing that stress is associated with impaired immunological control of latent viruses like CMV (26). More stressed individuals may have reduced control over and more frequent activation of CMV, leading to an increase in memory T cells and decrease in the CD4:CD8 ratio (18, 41–43).

The percentage of CD8<sup>+</sup> naïve T cells remained significantly inversely associated with stressful life events, lifetime discrimination, and life trauma regardless of controls added to the model. This suggests that the accumulation of major negative events across the life course may have a direct effect on these naïve CD8<sup>+</sup> T cells, although future research may uncover mediating mechanisms that were not identified here. This finding is again consistent with the possibility that thymic involution may be accelerated by social stress [e.g., via chronic activation of the hypothalamic-pituitary-adrenal axis, which can accelerate thymic involution and thereby reducing naïve T cell development (25, 44)].

Finally, lifetime discrimination and chronic stress are associated with a greater percentage of terminally differentiated CD4<sup>+</sup> T cells, regardless of controls in the model. CD4<sup>+</sup> T cells play a critical role in cell-mediated immunity, producing cytokines that help direct the action of other cells. This compartment typically develops age-related changes later than the CD8<sup>+</sup> compartment (17); therefore, accelerated immune age phenotype in CD4<sup>+</sup> T cells may be particularly indicative of aging immunity. Research has shown these terminally differentiated CD4<sup>+</sup> T cells fail to optimally “help” B cell activation, produce more inflammatory cytokines, and have been implicated in cardiovascular disease (16). This cell subset may be of particular interest to researcher investigating stress and health (45).

The current study has several limitations. This is a study of community-dwelling older adults in the United States. Future studies using non-US samples are needed. Our sample represents a cohort of older adults exposed to various forms of stress, discrimination, and trauma that might not be representative of younger cohorts or groups not well represented in the US Health and Retirement Survey (e.g., indigenous peoples). The most recent reports of life events (viz., stressful life events, lifetime discrimination, and life trauma) were in 2012. Thus, these measures may miss events that took place between 2012 and 2016. Respondents with particularly high exposure to stress may have died before reaching older ages, potentially attenuating the effect of stress on immune function. Because immunotyping data are only available at one time point, it is impossible to establish temporal ordering of stress and immune variables. We are not characterizing age-related changes across all cell types in the immune system. We selected T cells because of their importance in immune aging (see supporting information). Future research is needed to characterize stress effects on age-related changes in other cell types (e.g., B cells, monocytes, natural killer cells). Additionally, we are not able to address all domains and time-scales of stressors. We focus on five well-established and widely used stress scales; however, future research should investigate other domains of stress (e.g., job stress, caregiver stress).

Despite these limitations, this study provides important insights on the role of social stress in immune aging, highlighting a key role for health behaviors and social-environmental conditions as correlates of naïve T cell decline as well as a distinctive association of stressors with higher terminally differentiated CD4<sup>+</sup> T cell percentages (i.e., independent of variables controlled for here). These results raise the possibility that interventions such as CMV vaccination and senolytic therapies might potentially help reduce social disparities in T cell immunologic aging (13). Interventions aimed at reducing stress or increasing resilience may be needed to address these inequalities.

## Materials and Methods

**Sample.** We utilize data from the US Health and Retirement Study (HRS) 2016 Venous Blood Study ( $n = 9,934$ ). Multiparameter flow cytometry was used to assess counts and percentages of 24 different types of immune cells using the standardized protocol by the Human Immunology Project (46) with minor modifications performed on an LSRII or a Fortessa ×20 flow cytometer (BD Biosciences). More detailed methods for this sample are published elsewhere (47–49).

This sample was designed to be representative of the US population when weighted. Stress scales were assessed as part of the psychosocial leave behind questionnaire at various waves. This questionnaire is given to a rotating random half of the core panel every other wave so that data are available for the full sample every 4 y. Two hundred participants were in a nursing home or were cohort ineligible in 2016, 614 participants were missing on one or more cell type, 3,233 participants were missing on one or more stressor, and 142 participants

were missing on one or more mediator or control variables. Thus, the final sample size is 5,744 (*SI Appendix, Fig. S6*).

**Measures.** T lymphocyte distributions were assessed following the protocol described above. We focus here on the percentage of naïve CD4<sup>+</sup> and CD8<sup>+</sup> T cells (CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>+</sup>/CD28<sup>+</sup>) and TemRA CD4<sup>+</sup> and CD8<sup>+</sup> T cells (CD3<sup>+</sup>/CD19<sup>-</sup>/CD45RA<sup>+</sup>/CCR7<sup>-</sup>/CD28<sup>-</sup>). We also assess the ratio of CD4<sup>+</sup> to CD8<sup>+</sup> T cells using the quotient of counts of these compartments. Highly skewed cell variables (skewness > 2; viz., CD4<sup>+</sup> TemRA and the CD4:CD8 ratio) were natural log transformed to approximate a normal distribution. These variables were standardized to have a mean of 0 and SD of 1 to ease comparison.

We utilize five well-established health-relevant measures of social stress: stressful life events (50), chronic stress (51), everyday discrimination (52), lifetime discrimination (52), and life trauma (53). Because everyday discrimination, stressful life events, lifetime discrimination, and life trauma assess life course or ongoing exposure to stress, we use the first available data from the years these measures were assessed (2006 to 2016 for everyday discrimination, 2008 to 2012 for stressful life events, and 2006 to 2012 for lifetime discrimination and life trauma). Because we are interested in assessing ongoing chronic stress, we only use data from the 2014 and 2016 leave behind questionnaire. More information on these measures is available in the *SI Appendix* and more detailed information is available elsewhere (54).

Socioeconomic and lifestyle factors were assessed using self-reports of education (categorized: 0 to 11 y, 12 y, 13 to 15 y, and 16+ years as the reference), self-reported smoking (categorized: current smoker, past smoker, and non-smoker as the reference), BMI (categorized:  $\geq 25$  and  $< 30$  overweight,  $\geq 30$  and  $< 35$  obese 1,  $\geq 35$  obese 2, and  $< 25$  normal and underweight as the reference), and alcohol use (categorized: 1 to 4 drinks per day drinking, 5+ drinks per day drinking, and nondrinker as the reference).

CMV seropositivity was assessed using IgG antibodies in serum with the Roche e411 immunoassay analyzer (Roche Diagnostics Corporation) (categorized: borderline, reactive, or nonreactive as the reference) (49).

In all models we control for chronological age, race/ethnicity (non-Hispanic Black, Hispanic, non-Hispanic other race, and non-Hispanic White as reference), and sex (male as reference).

**Plan of Analysis.** All stressors and T cell type percentages/ratios were standardized to have a mean of 0 and SD of 1 to ease comparisons across models. A series of nested linear regressions were estimated regressing each T cell type percentage/ratio first on controls, then on controls and socioeconomic and lifestyle factors, then on controls and CMV seropositivity, and finally on controls, socioeconomic and lifestyle factors and CMV seropositivity. All analyses were conducted in R 4.1.1 (55) using the survey package (56).

**Data Availability.** Anonymized data have been deposited in <https://hrsdata.isr.umich.edu/>. Study data are available (researchers must submit an application to <https://hrs.isr.umich.edu/about>).

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