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Relations of optimism and purpose in life to immune markers in aging

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ABSTRACT

Objective: Optimism and purpose in life are associated with improved health outcomes. More information is needed on biological mechanisms, including immunosenescence. We investigated if psychological well-being is associated with healthier immunosenescence-related measures including naïve and terminally differentiated $CD4^+$ and $CD8^+$ T cell percentages, $CD4^+$:$CD8^+$, and cytomegalovirus (CMV) IgG response.

Methods: Participants were adults over age 50 from the Health and Retirement Study. Optimism was measured using the Life Orientation Test Revised. Purpose in life was assessed using the subscale from the Ryff psychological well-being measure. We examined the cross-sectional associations of optimism and purpose in life with measures of T cell subsets using linear regression and with CMV IgG using ordered logit regression, controlling for potential confounding factors.

Results: The final analytic sample ranged from 7250 to 7870. After adjusting for sociodemographic factors, a 1-SD increment in optimism was associated with the percentage of naïve $CD4^+$ T cells increasing by 0.6 (95%CI 0.2%, 1.0%). A 1-SD increment in purpose in life was associated with the percentage of naïve $CD4^+$ T cells increasing by 0.9 (95%CI 0.5%, 1.3%) after adjusting for sociodemographic factors and the association was maintained after further adjustments for health conditions, depression, and health behaviors. For naïve $CD8^+$ T cell percentages, CD4:CD8 ratios, and CMV IgG antibodies, associations were seen only in models that adjusted for age. No significant associations were seen in any models for the terminally differentiated $CD4^+$ and $CD8^+$ T cells.

Conclusions: We found associations of optimism and purpose in life with naïve $CD4^+$ T cell percentages.

1. Introduction

The proportion of the world's population aged 65 and over increased from 6% in 1990 to 9% in 2019 and is projected to reach 16% by 2050 [1]. As the population ages, the burden of chronic diseases is also expected to increase. Various factors contribute to the rise in diseases in older adults, including age-related physiological dysfunction in tissues, organs, and systems [2]. In particular, age-related changes in the immune system (i.e., immunosenescence) [3] contribute to the etiology of various age-related diseases, including neurodegenerative diseases, rheumatoid arthritis, cancer, cardiovascular disease, type 2 diabetes, and infectious diseases [4,5]. Identifying modifiable factors that may decelerate immune aging could inform future interventions to lower the risk of diseases that occur with age.

Societies are increasingly interested in strategies to promote healthy aging and delay the onset of age-related diseases. However, most research has focused on identifying risk factors for disease and ill-health like genetics, smoking, and sedentary behaviors [6–8]. Recent studies suggest positive psychosocial factors, such as positive psychological well-being, are associated with better health [9,10]. Optimism and purpose in life are facets of psychological well-being that have consistently been associated with better health, as measured by decreased cardiovascular disease risk, mortality, and longer life [9]. Optimism is the generalized tendency to expect good outcomes [11], while purpose

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in life is the extent to which individuals feel their lives have meaning, purpose, and direction [12]. As research suggests psychological well-being can be modified with intentional interventions [13,14], investigating its association with immunosenescence may inform interventions promoting healthy aging. Understanding the link between psychological well-being and immunosenescence may also provide insight into mechanisms linking psychological well-being and better physical health.

Immunosenescence impacts both the innate and adaptive immune system, particularly causing functional changes in T cells. Age-related changes in T cells include a decrease in naïve T cells, an increased pool of effector memory T cells, and an inversion in the $CD4^+$: $CD8^+$ ratio [15–18]. These changes can be attributed to thymic involution (i.e., progressive shrinkage of the thymus with age), leading to fewer naïve T cells, and exposure to immunological insults, resulting in the accumulation of memory T cells [19–21]. Furthermore, studies suggest that antigenic stimulation throughout life can expand memory and effector T cell subsets, increasing pathogen-specific highly differentiated T cells [22]. Infection with cytomegalovirus (CMV), a highly prevalent latent herpesvirus, may significantly contribute to immunosenescence [23–25]. Multiple studies have shown CMV seroprevalence is associated with an increased risk of various age-related diseases, including cardiovascular diseases [26] and all-cause mortality [15,27,28].

Accumulating evidence suggests that psychological well-being is associated with improved subsequent health outcomes including greater longevity and healthier aging [9,10], however, limited studies have investigated the role of immunosenescence in these associations.

Prior work examining the association between psychological well-being and immune cell numbers (e.g., $CD4^+$ T cells, $CD8^+$ T cells, natural killer cells), has generally focused on young populations with small sample sizes [29–31]. Few studies have directly assessed CMV IgG response in relation to psychological well-being, but studies investigating the association with negative psychological factors show higher levels of distress (e.g., depression), are associated with increased CMV IgG levels [32–35]. Research also shows socioeconomic and racial and ethnic differences in T cell subsets and CMV IgG antibodies, with lower socioeconomic status and minoritized racial and ethnic categories associated with higher CMV IgG response [36,37]. A prior study in 138 older adults found higher psychological resources including a range of well-being elements was associated with lower T lymphocyte terminal maturity [38]. Limited studies have investigated the associations between optimism and purpose in life and T cell subsets, and CMV IgG antibodies in large and diverse samples, and assessed whether these associations are seen across socioeconomic and racial and ethnically diverse groups.

Using data from the Health and Retirement Study (HRS) 2016 Venous Blood Study, we investigated the cross-sectional association between psychological well-being (i.e., optimism and purpose) and markers of immunosenescence. Following prior work [17,36], we focused on T cell subsets and CMV IgG levels as measures associated with immunosenescence. We tested the hypotheses that higher levels of psychological well-being would be associated with: (1) higher percentages of naïve $CD4^+$ and $CD8^+$ T cells, lower percentages of terminally differentiated effector memory $CD4^+$ T and $CD8^+$ T cell percentages (TemRA), and higher proportion of $CD4^+$ T cells relative to $CD8^+$ T cells (CD4:CD8 ratio); (2) lower levels of CMV IgG antibodies. We considered a range of potential confounders including sociodemographic factors, baseline health conditions, and depressive symptoms as they have been previously associated with psychological well-being, T cell subsets, and CMV IgG antibodies [15,36,39,40]. As prior research suggests that the benefits of psychological well-being are seen across diverse populations, we investigated these associations across socioeconomic and racial and ethnic groups.

2. Methods

2.1. Study population

Data are from the Health and Retirement Study (HRS), a nationally representative cohort of U.S. adults aged 50 years and older. In 2014, a random 50% of the cohort had the enhanced face-to-face interview and the remaining 50% had it in 2016. We combined data from 2014 and 2016 to assess psychological well-being and other covariates. Participants completed a self-administered survey on psychosocial topics that they returned by mail to the University of Michigan. In 2016, all respondents who completed an interview wave were asked to consent to a venous blood draw with the exception of proxy respondents and nursing home residents [41]. Trained phlebotomists collected blood samples during home visits. Detailed information on HRS data collection is available on their website (http://hrsonline.isr.umich.edu/) [42]. Participants were excluded from the current analysis if they were cohort ineligible or in nursing homes ($N = 200$), had no assessment of optimism or purpose ($N = 1688$ had no assessment on either of the measures), missing 4 or 5 (out of 6) items on the optimism measures for analyses for optimism ($N = 23$), missing 4 to 6 (out of 7) items on the purpose measure for analyses for purpose ($N = 22$), missing on one or more of the T cell subsets ($N = 670$) for analyses of T cell subsets, and missing information on CMV IgG antibodies ($N = 67$) for analyses for CMV IgG. The final analytic sample was 7250 for optimism and T cell subset analyses, 7853 for optimism and CMV analyses, 7262 for purpose and T cell subset analyses, and 7870 for purpose and CMV analyses. The study used de-identified data and was exempt from institutional review board review by Harvard T.H. Chan School of Public Health. Informed consent was obtained orally from all HRS participants [43].

2.2. Measures

Optimism was assessed in 2014 or 2016 using the 6-item Life Orientation Test Revised (LOT-R), a measure shown to have good validity and reliability [44]. Participants indicated their agreement with each item, ranging from 1 (strongly disagree) to 6 (strongly agree). Optimism can be represented by endorsing positively worded statements while rejecting negatively worded statements [45]. Therefore, the 6 items were summed to obtain a total optimism score ranging from 6 to 36. Negatively framed items were reverse-coded, with higher scores reflecting higher optimism levels. The measure had high internal consistency reliability in this sample (Cronbach's α=0.75). For those missing $\leq$3 items ($N = 356$), missing values were replaced with the mean of the existing items [46]. We considered optimism as a standardized continuous measure (z-score) and also categorized it into quartiles based on the distribution in the sample to assess potential discontinuous threshold effects. We also created 3-item subscales for optimism and pessimism by summing the three positively worded items for optimism and the three negatively worded items for pessimism. The subscale scores had Cronbach's α =0.82 for optimism and 0.72 for pessimism.

Purpose in life was assessed in 2014 or 2016 using the 7-item subscale from the Ryff Measures of Psychological Well-being, which has been validated [47]. Participants rated their levels of agreement on a 6-point Likert scale from 1 (strongly disagree) to 6 (strongly agree). The 7 items were summed for a total score ranging from 7 to 42. Negatively framed items were reverse-coded, with higher scores reflecting higher levels of purpose. The measure had high internal consistency reliability in this sample (Cronbach's α=0.76). For those missing $\leq$3 items ($N = 252$), missing values were replaced with the mean of the existing items [46]. The score was also considered as a standardized continuous measure (z-score) and a quartile score.

T lymphocyte distributions were assessed in 2016 via the proportion (range 0 to 1) as well as counts of naïve $CD4^+$ and $CD8^+$ T cells ($CD3^+$/$CD19^-$/$CD45RA^+$/$CCR7^+$/$CD28^+$), terminally differentiated (TemRA) $CD4^+$ and $CD8^+$ T cells ($CD3^+$/$CD19^-$/$CD45RA^+$/$CCR7^-$/$CD28^-$), and

the ratio of $CD4^+$ to $CD8^+$ T cell counts ($CD4^+$ T cells divided by the count of $CD8^+$ T cells) [48]. Proportions were calculated using the corresponding parent population as denominators (e.g., naïve $CD4^+$ T cells = naïve $CD4^+$ T cells/total $CD4^+$ T cells). The immune cell subsets were identified using minor modifications to the standardized protocol by the Human Immunology Project. All flow cytometry measurements were performed on an LSRII flow cytometer or Fortessa X20 instrument (BD Biosciences).

CMV seropositivity. Primary infection with CMV often occurs early in life, followed by cycles of reactivation throughout the life course. However, both the primary infection and reactivation of CMV are usually asymptomatic in healthy individuals [49,50]. Chronic CMV infection likely contributes to deteriorative age-related changes in the immune system as a significant proportion of the adaptive immune system is required to keep the virus in a quiescent state [21]. Elevated CMV IgG antibody levels among seropositive individuals indicate an initial response to primary infection, or the inability to maintain the virus latent after the primary infection [20,36]. CMV seropositivity was assessed in 2016 using IgG antibodies to CMV in the serum using a Roche e411 immunoassay analyzer (Roche Diagnostics Corporation), with a lower detection limit of 0.015 U/mL. Following prior work, we categorized individuals with CMV-IgG <0.5 U/mL as seronegative, and those ≥ 0.5 U/mL as seropositive, including borderline responses. We then categorized seropositive individuals into tertiles according to the distribution in this sample, with seronegative individuals as the reference group [36]. The majority of the participants ($N = 5500$, 70%) were seropositive for CMV.

Covariates were all self-reported in 2014 or 2016. They include sociodemographic factors including age (continuous), sex (male, female), race and ethnicity (non-Hispanic White, Black, Hispanic/Latino, Other), education (less than high school, some high school, some college or associate degree, college graduate or more), total wealth (in U.S. dollars), and marital status (married or committed relationship, divorced or single, widowed). We assessed health conditions via a count of the number of conditions reported, which included hypertension, cancer, stroke, type 2 diabetes, cardiovascular disease, lung disease, and arthritis. Depressive symptoms were assessed using a summary score from the modified 8-item Center for Epidemiologic Studies Depression Scale. For secondary analyses, depression was dichotomized using ≥4 as the cut point indicating probable depression [51]. Health behaviors, including smoking (never, former, current smoker), alcohol consumption (non-drinker, 1–4 drinks/day, 5+ drinks/day), and exercise frequency (never, 1–3 times/month, 1 time a week, ≥ once/week, every day) were self-reported. Body mass index (BMI) was calculated from self-reported height and weight in kg/m^2.

2.3. Statistical analysis

First, we examined the distributions of covariates by level of optimism and purpose separately. To evaluate cross-sectional associations with T cell subsets, we used linear regression. Due to the non-normal residuals of some of the T cell outcomes (i.e., $CD4^+$ TemRA and CD4:CD8 ratio), standard errors were obtained via bootstrapping with 1000 replications. Considering optimism and purpose separately, we used four sets of models for each outcome measure. Model 1 adjusted for age; Model 2 additionally adjusted for other sociodemographic factors (sex, race and ethnicity, education, wealth, and marital status); Model 3 additionally adjusted for other potential confounders including health conditions and depressive symptoms; Model 4 additionally included health behaviors (smoking, exercise, and alcohol consumption) and BMI, which could be confounders or factors that lie on the pathway between psychological well-being and T cell subsets. As CMV infection plays an important role in determining the distribution of T cell subsets, CMV seropositivity was also included in Models 3 and 4 for the analyses of T cell outcomes. To evaluate cross-sectional associations with CMV IgG response, we used ordered logit regression to estimate the relative odds of being in a higher category of CMV IgG by levels of psychological well-being, using the same four sets of models.

We conducted the following as secondary analyses; first, we tested for interactions by race and ethnicity (i.e., White, Black, Hispanic/Latino), education, wealth, and sex. Second, as depression is an important potential confounder, we investigated associations among those with no depression. Third, using the same modeling strategy as described above, we ran separate models for the optimism and pessimism subscales of the LOT-R. Fourth, for the T cell outcome analyses, we also tested for interaction by CMV serostatus as CMV serostatus is a strong predictor for immunosenescence. Fifth, as CMV serostatus and CMV reactivation are different phenomena, we separately assessed these associations with optimism and purpose using logistic regression for CMV serostatus (seropositive vs. seronegative) and linear regression for CMV IgG levels among seropositive individuals. All analyses were conducted using R version 4.2.2.

3. Results

On average, the participants were 70 years old (standard deviation [SD] = 10), and the age range was 51 to 107 years. The mean optimism score was 27 (SD = 6) and the mean purpose score was 32 (SD = 7) (Appendix 1). The sample was 59% female and consisted of 70% White, 16% Black, and 12% Hispanic/Latino individuals. Participants with higher levels of optimism and purpose had higher levels of education and wealth, and were less likely to have health conditions and depression (Table 1).

3.1. Facets of psychological well-being and T cell subsets

The mean proportions for the T cell subsets were 0.44 (SD 0.18) for naïve $CD4^+$ T cells, 0.23 (SD 0.16) for naïve $CD8^+$ T cells, 0.04 (SD 0.06) for $CD4^+$ TemRA cells, and 0.46 (SD 0.22) for $CD8^+$ TemRA cells. The mean CD4:8 ratio was 3.86 (SD 2.98). Results from regressing T-cell subsets on optimism and purpose are shown in Fig. 1 and Fig. 2, respectively (full regression results in Tables A.1–10). For optimism, after adjusting for age (Model 1), a 1-SD increment in optimism was associated with the percentage of $CD4^+$ naïve T cells increasing by 1.4 (β=0.014, 95%CI = 0.010, 0.018), the percentage of $CD8^+$ naïve T cells increasing by 0.5 (β=0.005, 95%CI = 0.002, 0.009), and a 0.12 unit rise in levels of the ratio of $CD4^+$ to $CD8^+$ T cells (β=0.124, 95%CI = 0.054, 0.194). This association remained significant after additionally adjusting for sociodemographic factors (Model 2) for $CD4^+$ naïve T cells (β=0.006, 95%CI = 0.002, 0.010) but not for the other immune cell parameters. When we additionally included health conditions, depression, CMV IgG (Model 3), health behaviors, and BMI (Model 4) in the models, associations were substantially attenuated. Further, we did not find significant associations for any of the models for $CD4^+$ and $CD8^+$ TemRA cells. For purpose, after adjusting for age (Model 1), a 1-SD increment in purpose was associated with the percentage of $CD4^+$ naïve T cells increasing by 1.4 (β=0.014, 95%CI = 0.010, 0.018), the percentage of $CD8^+$ naïve T cells increasing by 0.7 (β=0.007, 95%CI = 0.003, 0.011), and a 0.12 unit rise in levels of the ratio of $CD4^+$ to $CD8^+$ T cells (β =0.121, 95%CI = 0.055, 0.191). For $CD4^+$ naïve T cells, associations remained significant in all subsequent models (Model 2 [β=0.009, 95%CI = 0.005, 0.013], Model 3 [β=0.005, 95%CI = 0.001, 0.009], and Model 4 [β=0.005, 95%CI = 0.000, 0.009). Significant associations were not evident after further adjustments for covariates for $CD8^+$ naïve T cells and the CD4:8 ratio. For $CD4^+$ and $CD8^+$ TemRA, we observed no significant associations for any of the models (Model 1 for $CD4^+$ TemRA [β= − 0.001, 95%CI = -0.002, 0.000] and $CD8^+$ TemRA [β= − 0.005, 95%CI = -0.010, 0.000]). Results for analysis with T cell subset counts are shown in Fig. A.1–2. Findings were largely similar to the analysis with proportions, although Model 1 for $CD8^+$ naïve T cells showed negative associations when analyzed as counts; however, with further adjustments for covariates, the findings aligned with those using

Table 1
Sample characteristics by quartiles of optimism and purpose in life in the Health and Retirement Study.

	Optimism				Purpose in life			
	Q1 $N = 2104$	Q2 $N = 1617$	Q3 $N = 2036$	Q4 $N = 1493$	Q1 $N = 1897$	Q2 $N = 2041$	Q3 $N = 1608$	Q4 $N = 1716$
Optimism/Purpose, mean (SD)	19.9 (3)	25.5 (1)	30.0 (1)	34.5 (1)	24 (3)	31 (2)	36 (1)	40 (1)
Demographics								
Age, mean (SD)	69 (10)	70 (10)	70 (10)	70 (10)	71 (10)	70 (10)	70 (9)	69 (9)
Female (%)	1207 (57)	932 (58)	1236 (61)	932 (62)	1130 (60)	1198 (59)	951 (59)	1029 (60)
Race								
White (%)	1377 (65)	1085 (67)	1493 (73)	1088 (73)	1290 (68)	1477 (72)	1131 (70)	1161 (68)
Black (%)	351 (17)	256 (16)	297 (15)	220 (15)	238 (13)	282 (14)	256 (16)	335 (20)
Hispanic (%)	309 (15)	219 (14)	193 (10)	151 (10)	303 (16)	213 (10)	187 (12)	175 (10)
Other (%)	66 (3)	56 (4)	50 (3)	33 (2)	61 (3)	69 (3)	34 (2)	44 (3)
Married (%)	1175 (56)	996 (62)	1303 (64)	986 (66)	1057 (56)	1226 (60)	1044 (65)	1147 (67)
Education								
<High School (%)	491 (23)	291 (18)	177 (9)	104 (7)	469 (25)	285 (14)	176 (11)	133 (8)
High School (%)	1174 (56)	879 (54)	1098 (54)	715 (48)	1030 (54)	1126 (55)	840 (52)	872 (51)
≥ College (%)	417 (20)	436 (27)	745 (37)	653 (44)	380 (20)	616 (30)	574 (36)	691 (40)
Wealth, mean (SD), per US $1000s	290 (666)	395 (907)	538(1052)	642 (1114)	285(746)	436 (863)	536(1090)	605 (1203)
Health conditions								
CESD, mean (SD)	2.2 (2)	1.4 (2)	0.9 (2)	0.6 (1)	2.3 (2)	1.3 (2)	0.9 (2)	0.7 (1)
Chronic conditions, mean (SD)	2.1 (1)	2.0 (1)	1.8 (1)	1.6 (1)	2.2 (1)	2.0 (1)	1.8 (1)	1.6 (1)
BMI, mean (SD)	29.5 (6)	29.0 (7)	28.6 (6)	28.3 (6)	29.5 (7)	29.0 (6)	28.6 (6)	28.4 (6)
Health behaviors								
Currently smoking (%)	323 (15)	183 (11)	167 (8)	89 (6)	285 (15)	193 (10)	151 (9)	130 (8)
Moderate alcohol intake (1–4 drinks/day) (%)	665 (32)	566 (35)	851 (42)	663 (44)	572 (30)	791 (39)	657 (41)	737 (43)
Healthy physical activity (>1× per week) (%)	744 (35)	688 (43)	1044 (51)	835 (56)	619 (33)	905 (44)	837 (52)	962 (56)

Note:
Optimism was categorized into the following quartiles: 6≤Q1≤23, 23 < Q2≤27, 27 < Q3≤32, 32 < Q4≤36
Purpose in life was categorized into the following quartiles: 7≤Q1≤27, 27 < Q2≤33, 33 < Q3≤37, 37 < Q4≤42.
Abbreviations: Q = quartile, SD = standard deviation, CESD = modified 8-item Center for Epidemiologic Studies Depression Scale, BMI=Body Mass Index.

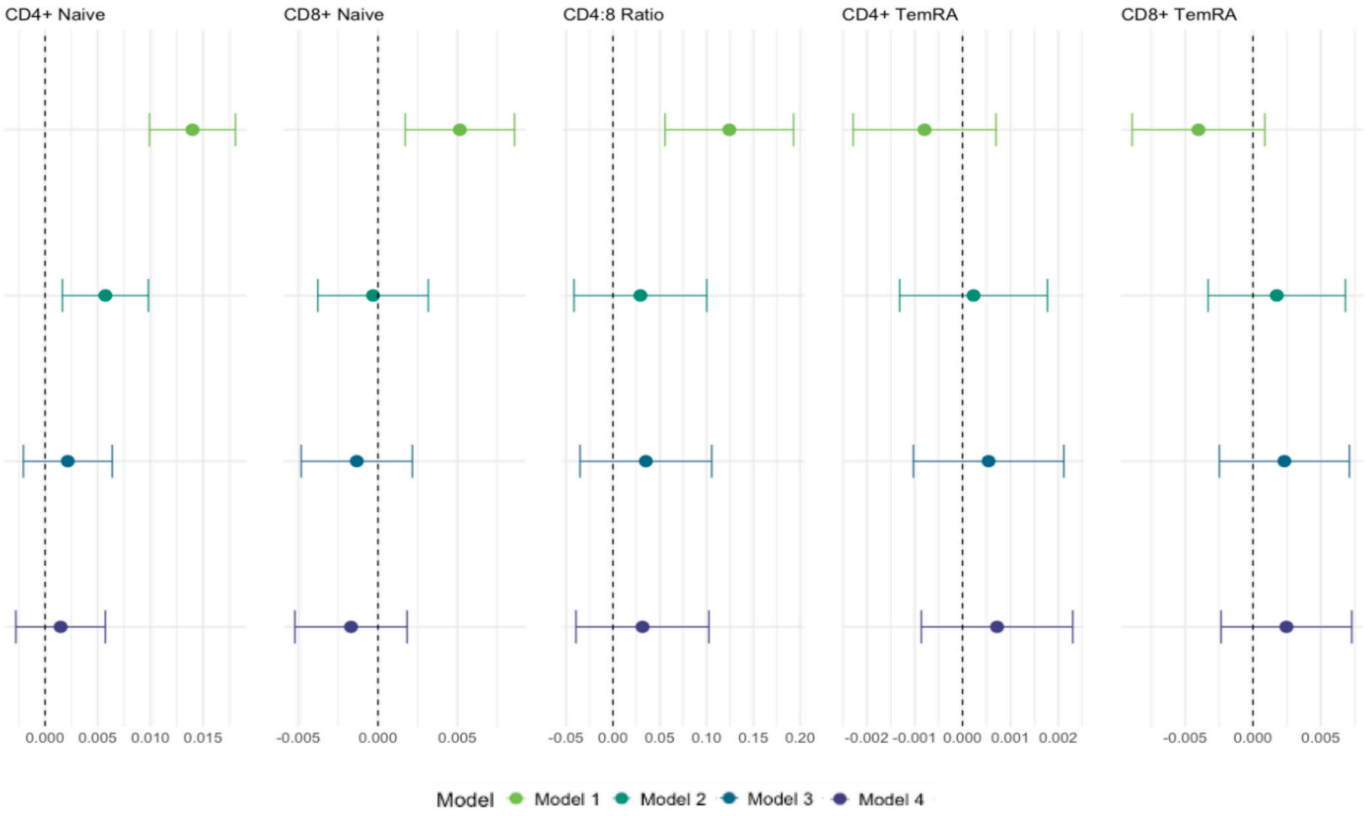

Fig. 1. Regression coefficients and 95% CIs for the association between optimism and T cell subsets in proportions ($N = 7250$).

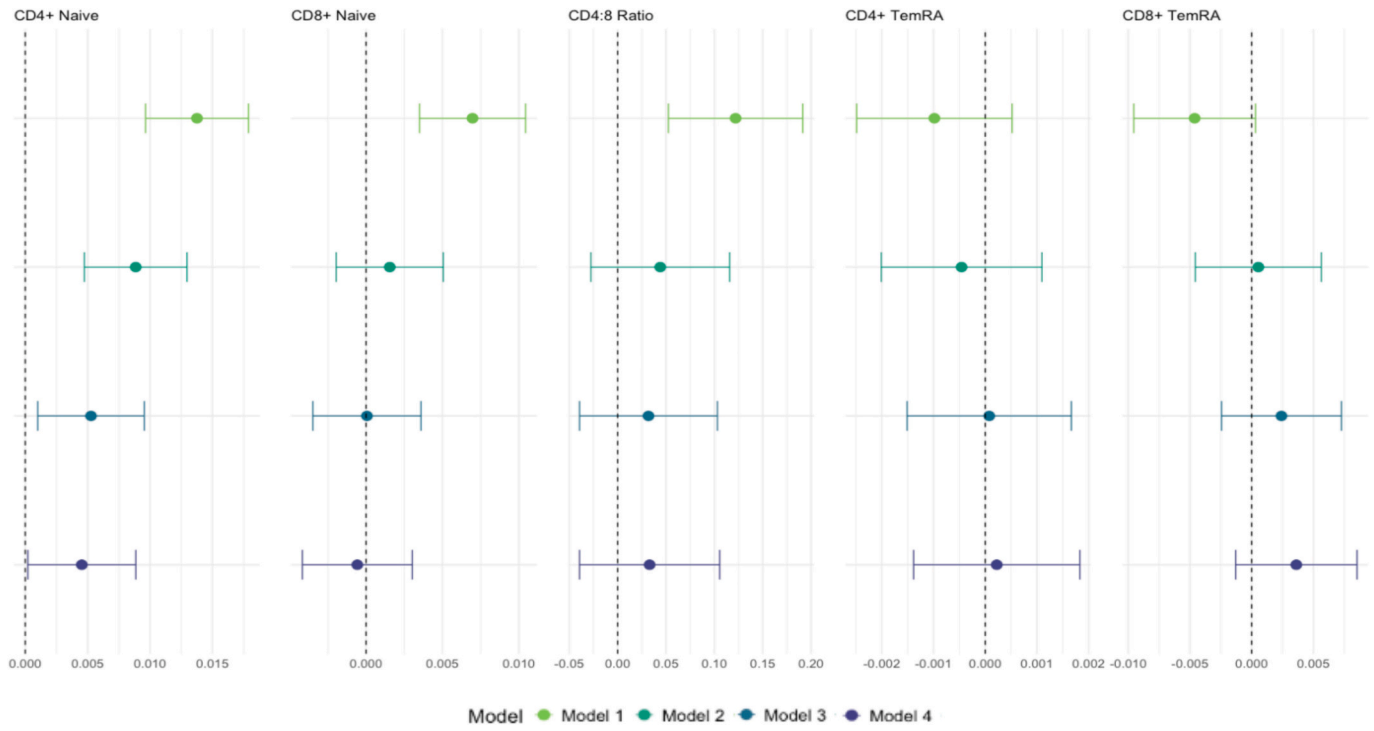

Fig. 2. Regression coefficients and 95% CIs for the association between purpose in life and T cell subsets in proportions ($N = 7262$).

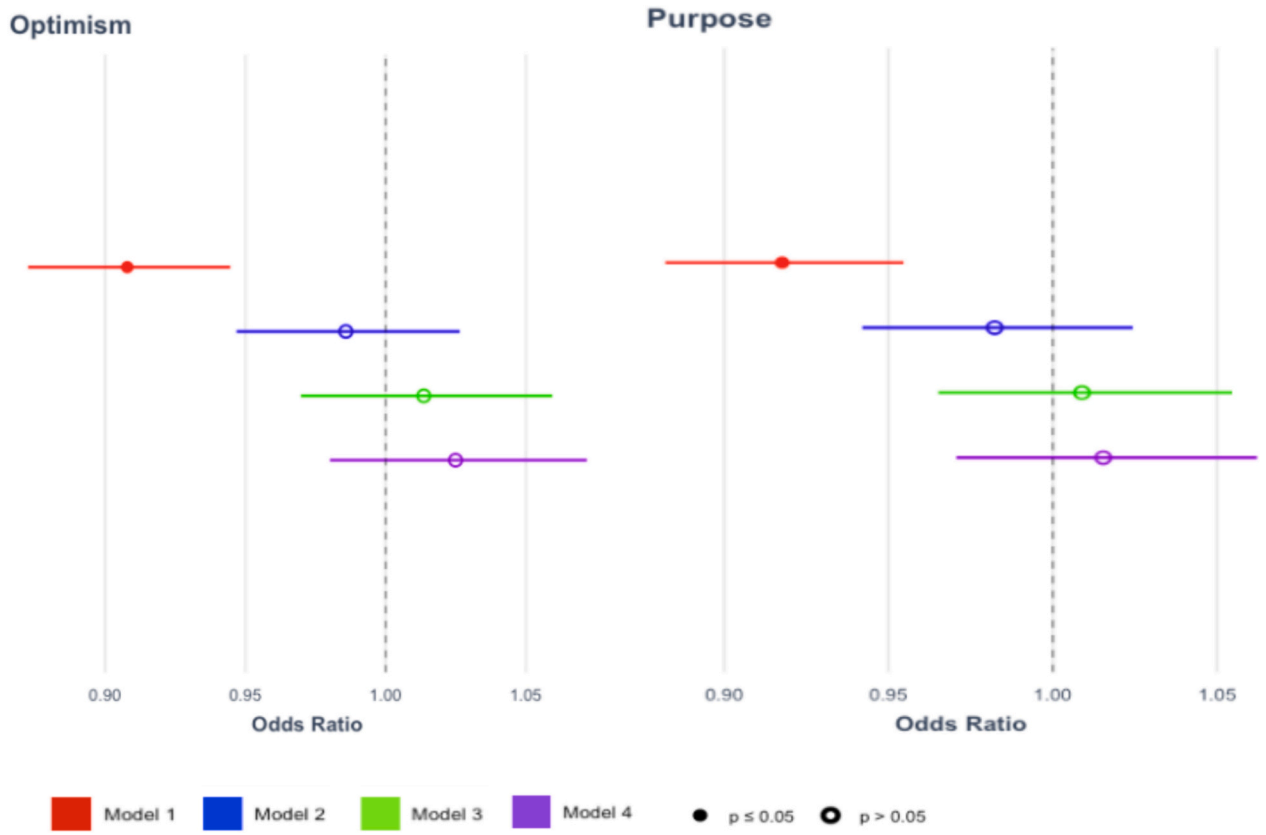

Fig. 3. Odds ratios for the association between optimism/purpose in life and being in a higher category of cytomegalovirus IgG ($N = 7853$ for optimism, $N = 7870$ for purpose).

proportions.

3.2. Facets of psychological well-being and CMV IgG

The mean CMV IgG level was 325 antibody U/mL (SD 363) for the full sample. Among seropositive individuals, the mean CMV IgG levels in each tertile was 109, 399, and 883 antibody U/mL. The results of the ordered logit regression for optimism, purpose, and CMV IgG are shown in Fig. 3. For optimism, a 1-SD increment in optimism was associated with 9% lower odds of being in a higher category of CMV-IgG (odds ratio [OR] = 0.91 [95%CI 0.87, 0.94]) after adjusting for age. For purpose, a 1-SD increment in purpose was associated with 8% lower odds of being in a higher category of CMV-IgG (OR = 0.92 [95%CI 0.88, 0.95]) after adjusting for age. Further adjustment in subsequent models attenuated all associations for optimism and purpose.

3.3. Secondary analysis

We found no evidence for interactions between optimism/purpose and race and ethnicity, education, wealth, and sex ($p > 0.05$). In analyses excluding those with depression (remaining $N = 6288$ for optimism, $N = 6299$ for purpose), the findings were comparable to the initial results. Given the different patterns of findings across T cell subsets and prior work suggesting differential decline rates with age in naïve $CD4^+$ and naïve $CD8^+$ T cells, we examined how T cell subsets were distributed with age and other sociodemographic factors. Fig. A.3 shows distributions of T cell subsets by age. We found that the distribution of $CD8^+$ T cells is strongly patterned by age, with older individuals having lower proportions of naïve $CD8^+$ T cells (distributions by other covariates shown in Fig. A.4–7). Analysis considering optimism and pessimism subscales showed slightly stronger associations with pessimism (Fig. A.8–11). We found no evidence of statistically significant interactions between optimism/purpose and CMV serostatus for any T cell outcomes. Results from the logistic regression for CMV seropositivity and linear regression for CMV IgG levels among seropositive individuals were also comparable to the initial findings (Fig. A.12–15).

4. Discussion

In this national sample of US adults over age 50, we found higher levels of optimism and purpose were not robustly associated with most immune measures evaluated after adjustment for age. However, associations were seen for naïve $CD4^+$ T cells, and for purpose, associations were maintained even after adjustments for a wide range of covariates. In models adjusting for age, a 1-SD increment in optimism/purpose was associated with the percentage of $CD4^+$ naïve T cells increasing by 1.4, which is equivalent to about 34% of the magnitude of the association between smoking status (never versus current smoker) and $CD4^+$ naïve T cells (−3.8%), adjusting for age. Associations of optimism and purpose with lower CMV IgG antibodies were not evident after adjusting for multiple covariates. We found no evidence of interactions by sex, race and ethnicity, and socioeconomic differences, which is consistent with prior work suggesting associations between optimism/purpose and health are similar across diverse groups [52,53]. However, sociodemographic factors were important confounders for the association between psychological well-being and measures of immunosenescence. Future research should account for these factors and investigate potential mediating effects of optimism and purpose for associations between sociodemographic factors and indicators of immunosenescence. Our findings are in line with prior work that investigated the cross-sectional associations between psychological well-being and immune cells, and found consistent associations for $CD4^+$ T cells [29,30,54].

The different associations with psychological well-being for naïve $CD4^+$ T cells and $CD8^+$ T cells may be due to the age range of this sample. Prior research indicates that the decline in naïve $CD8^+$ T cell numbers with thymic involution starts earlier than naïve $CD4^+$ T cells, with a significant decrease in the naïve $CD8^+$ T cell compartment observed in most individuals by age 65 [55]. In contrast, naïve $CD4^+$ T cell subsets show a more modest decline where the percentage of naïve $CD4^+$ T cells is sufficiently sustained at ages 65–75 and maintained for another two to three decades with homeostatic proliferation (i.e., a compensatory mechanism for the decline in thymic output) of the cells [55]. Given that participants in this study were on average age 70, many may have already experienced declines in $CD8^+$ T cells, while the $CD4^+$ T cells remained relatively stable, which may explain the patterning by age in the distribution of $CD8^+$ T cells. The limited variability in the $CD8^+$ T cells may have made it harder to observe associations for $CD8^+$ T cells.

We observed no significant associations for optimism or purpose with the terminally differentiated cells. One explanation is the secondary nature of the process by which these cells begin to proliferate. Although the accumulation of terminally differentiated T cells may signal immunosenescence, evidence suggests that the invasion of these cells is a secondary phenomenon to fill the space left by the reduction of the naïve T cells [55]. Thus, concentrations of these cells may be more variable in an older population with a broad range of ages and thereby harder to observe in relation to psychological or other more distal factors. Some researchers have further suggested the changes in the memory T cell pool may not offer a direct evidence for decline in cellular immune function per se and that it is the naïve T cell compartment that holds the key to our understanding of cellular immune decline with old age [56].

The mechanisms that underlie the link between psychological well-being and changes in the immune system are unclear, but several plausible processes can be considered. These include direct biological effects, moderating effect of psychological well-being on stress and biological responses to stress, and changes in health behaviors that promote healthier immune function. One potential biological process that may play a role is oxidative stress, which can affect the functions and differentiation of T cells [57]. T cell survival depends on low concentrations of reactive oxygen species (ROS) and the accumulation of ROS can lead to T cell apoptosis or necrosis [57]. Research suggests higher levels of psychological well-being are associated with higher levels of serum antioxidants [58], which can reduce the harmful effects of oxidative stress and play a protective role in the immune system. Prior research has linked facets of psychological well-being with autonomic function [59] and identified a close relationship between the autonomic nervous system and the immune system. Neurotransmitters such as catecholamines (i.e., dopamine, norepinephrine, epinephrine) have potent immunomodulating properties [60]. For example, naïve $CD4^+$ T cells strongly express high affinity saturable β_2-adrenergic receptors, which are regulated as T-lymphocytes differentiate [61]. Future research should assess more directly whether psychological well-being is associated with these processes.

Several studies also suggest optimism or purpose can moderate the effect of psychological stress on the immune system by reducing levels of stress experienced or mitigating its severity [29–31]. Additional mechanisms could operate through downstream effects on health behaviors including diet, exercise, and sleep. For example, studies have shown diet affects immune function, with fiber-rich diets associated with better immune response compared to high-fat, low-fiber diets [62]. Exercise has been shown to modulate both the number and activity of $CD4^+$ T cells, with an increase in $CD4^+$ T cells observed in athletes' blood after training [63]. These health behaviors have also been associated with psychological well-being [64].

This study has multiple strengths. It was conducted in a national sample of older U.S. adults with a large sample size, allowing us to adjust for a broad range of potential confounders. With rich data on different measures of immunosenescence, we were able to assess multiple indicators of immunosenescence. We also investigated two facets of psychological well-being and its link to immunosenescence. This study also has several limitations. It employed a cross-sectional design due to data

availability. Future research should investigate the longitudinal associations between psychological well-being and indicators of immunosenescence. Although the HRS oversampled racial and ethnic minorities, these groups were less represented in this sample. Therefore, we could not use more detailed categorizations of race and ethnicity. We also assessed associations for a limited number of age-related changes in immune cells relevant to immunosenescence.

In conclusion, we found associations of two facets of psychological well-being, optimism and purpose in life, with naïve $CD4^+$ T cell percentages. Future research should explore whether immunosenescence is a potential mechanism linking psychological well-being and physical health. As prior work has suggested that optimism and purpose are modifiable with active intervention [13,14], they may be novel targets for interventions aiming to decelerate immune aging and promote healthy aging.

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CRediT authorship contribution statement

Hayami K. Koga: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Francine Grodstein:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **David R. Williams:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Dawn L. Demeo:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Laura D. Kubzansky:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation.

Declaration of competing interest

none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.111851.

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