HHS Public Access

Author manuscript

J Psychosom Res. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

J Psychosom Res. 2023 November ; 174: 111487. doi:10.1016/j.jpsychores.2023.111487.

Purpose in life and markers of immunity and inflammation: Testing pathways of episodic memory

Angelina R. Sutin, PhD[1], **Yannick Stephan, PhD**[2], **Martina Luchetti, PhD**[1], **Antonio Terracciano, PhD**[1]

[1]Florida State University College of Medicine

[2]Euromov, University of Montpellier

Abstract

Objective: This prospective cohort study examines whether purpose in life is associated with markers of immunity and inflammation and tests these markers as mediators between purpose and episodic memory.

Methods: Participants from the Venous Blood Study of the Health and Retirement Study reported on their purpose in life, had their blood assayed for markers of immunity and inflammation, and were administered an episodic memory task (*N*=8,999). Regression analyses tested the association between purpose and each marker. Prospective mediation analyses (*N*=6,092) tested whether these markers measured in 2016 were mediators between purpose measured in 2012/2014 and episodic memory measured in 2018.

Results: Higher purpose in life was associated with lower neutrophil counts (β=−.08, *p*<.001), lower ratio of neutrophils/lymphocytes (β=−.05, *p*<.001), and lower systemic immune inflammation index (β=−.04, *p*<.001); purpose was unrelated to monocyte, platelet, and lymphocyte counts or the ratio of platelets/lymphocytes (all *ns*). Purpose was associated negatively with c-reactive protein (β=−.07, *p*<.001), Interleukin-6 (β=−.08, *p*<.001), Interleukin-10 (β=−.07, *p*<.001), Interleukin-1ra (β=−.08, *p*<.001), and soluble Tumor Necrosis Factor Receptor 1 (sTNFR1; β=−.10, *p*<.001); purpose was unrelated to Transforming Growth Factor beta 1. These associations were largely not moderated by age, sex, race, ethnicity, and education. Lower neutrophils, Interleukin-6, and sTNFR1 were associated prospectively with better episodic memory and mediated the association between purpose and episodic memory.

Conclusion: Purpose in life is associated with markers of immunity and inflammation, some of which are one mechanism in the pathway between purpose and healthier episodic memory.

Address correspondence to: Angelina R. Sutin, Ph.D., Florida State University College of Medicine, 1115 W. Call Street, Tallahassee, FL 32306, (850) 645-0438 Fax: (850) 645-1773, angelina.sutin@med.fsu.edu.

Competing Interests

The authors have no competing interests to report.

Keywords

Purpose in life; Immunity; Inflammation; Episodic memory; Cognitive aging; Mechanism

Purpose is defined as the feeling that one's life is goal-oriented and driven (McKnight & Kashdan, 2009; Ryff, 1989). This aspect of well-being has been highlighted recently for its association with healthier cognitive outcomes across adulthood (Sutin, Luchetti, & Terracciano, 2021). Individuals higher in purpose, for example, tend to have better cognitive performance (Windsor et al., 2015), less cognitive decline (Kim et al., 2019), and lower risk of incident dementia (Sutin, Luchetti, et al., 2023). As such, there has been great interest in identifying pathways through which purpose is associated with healthier cognitive aging. Much of this work has focused on the relation between purpose and other risk factors for poor cognitive outcomes, including behavioral (e.g., physical activity; Sutin, Luchetti, et al., 2021b) and clinical (e.g., diabetes; Hafez et al., 2018) factors. Such mechanisms, however, do not explain all the association between purpose and dementia risk (Boyle et al., 2010; Sutin et al., 2021). To date, limited work has addressed the biological mechanisms that may operate in this pathway, compared to behavioral and clinical mechanisms.

Inflammation may be a promising biological pathway due to its association with psychological factors (Jones & Graham-Engeland, 2021; Luchetti et al., 2014), as well as health outcomes (Fioranelli et al., 2018), including dementia risk (Kinney et al., 2018). Emerging evidence suggests purpose is associated with healthier patterns of common markers of inflammation. Higher purpose, for example, is associated with lower c-reactive protein (CRP) (Steptoe & Fancourt, 2019), fewer soluble interleukin-6 (IL-6) receptors (Friedman et al., 2007), and lower IL-6 response to stress (Thoma et al., 2017). Purpose is also associated with less increase in CRP over time but is unrelated to development of unhealthy levels (Guimond et al., 2022). Previous work on purpose and inflammation has focused primarily on CRP and IL-6 (Boylan et al., 2020; Steptoe & Fancourt, 2019). Other inflammatory markers may also be associated with purpose.

Inflammation results, in part, from activation of peripheral immunity that is stimulated in response to threat. Peripheral immunity is composed of innate and adaptive immunity, which reflect immunity present from birth and immunity acquired from exposure to pathogens, respectively (Hoebe et al., 2004). Neutrophils, monocytes, and platelets are common markers of innate immunity, and lymphocytes are common markers of adaptive immunity. When the individual is healthy, these markers circulate at low levels to avoid risk of over proliferation but increase and activate cytokine (e.g., IL-6) release when needed to respond to threats to the body (Galea, 2021). These markers and the balance of innate to adaptive immunity have been associated with increased risk of Alzheimer's disease and related dementias (ADRD; van der Willik et al., 2019; Zhang et al., 2022). Purpose may be associated with lower levels of immunity and inflammatory markers because individuals higher in purpose tend to be healthier (Musich et al., 2018) and engage in behaviors that reduce inflammation (Sutin, Luchetti, et al., 2021b). If such markers are related to purpose, they may be one mechanism of the association between purpose and cognition. Thus, in addition to CRP and IL-6, the present research examines markers of innate and adaptive

immunity related to risk of incident dementia (van der Willik et al., 2019; Zhang et al., 2022) and other downstream cytokines associated with cognitive performance (Beydoun et al., 2019; Tegeler et al., 2016) that may contribute to the association between purpose and cognition.

Episodic memory is a cognitive function critical for daily life (Nyberg & Pudas, 2019). There are normative declines in episodic memory with aging (Salthouse, 2018) and loss of such memory is one defining characteristics of ADRD (Jahn, 2013). Purpose in life is associated consistently with better episodic memory when measured cross-sectionally (Sutin et al., 2022) and with lower risk of incident ADRD over time (Sutin, Luchetti, et al., 2023). Purpose in life may thus be a psychological resource that helps support better episodic memory and protect against cognitive impairment. Less is known, however, about the mechanisms that explain the association between purpose and better cognitive outcomes. As mentioned above, behavioral and clinical factors account for some but not all the association with healthier cognition (Boyle et al., 2010; Sutin et al., 2021). A better understanding of the physiological pathways that may contribute to this association is needed.

This study examines the association between purpose in life and markers of immunity and inflammation implicated in cognitive function and dementia risk. Given the previous research on CRP and IL-6 (Friedman et al., 2007; Steptoe & Fancourt, 2019), we expect purpose to be associated with lower levels of these markers and with other cytokines. Further, given that purpose is associated with lower risk of dementia, we expect that it will be associated negatively with the markers of immunity that have been shown to predict incident dementia, including innate immunity (neutrophils, monocytes, platelets), adaptive immunity (lymphocytes), and ratios of innate-to-adaptive immunity associated with dementia risk (neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, systemic immune inflammation index) (van der Willik et al., 2019; Zhang et al., 2022). We test whether these associations are moderated by sociodemographic characteristics (age, sex, race, ethnicity, education) because of demographic differences in both purpose in life (Mei et al., 2020) and immune function (Klein & Flanagan, 2016). Given that purpose tends to have similar associations with health outcomes across demographic groups (e.g., across males and females, relatively younger and older adults, etc.) (Sutin, Luchetti, et al., 2021a), we do not expect differences. Still, it is important to test empirically whether associations are similar or differ across demographic groups. Finally, we examine whether these markers of immune function mediate the prospective association between purpose in life and episodic memory function.

Method

Participants and Procedure

Participants were from the Health and Retirement Study (HRS; Sonnega et al., 2014), an ongoing study of adults in the United States aged 50 years and older and their spouse, regardless of age. The 2016 wave of HRS included a venous blood draw that was used to obtain detailed information on immune and other markers of health and aging that can be detected in blood. Purpose in life in HRS is assessed at every 2-year wave starting in 2006 but on only half the sample at a time (i.e., participants report on their purpose every four

years). To examine the association between purpose and the immune markers, the purpose in life assessment closest to the blood draw was selected for each participant (either concurrent in 2016 or the closest previous assessment). This analytic sample was used to evaluate the association between purpose and the immune and inflammatory markers and whether these associations were moderated by sociodemographic factors. A total of 8,794 participants had data on the immunity markers and purpose in life to be included in the analysis. Compared to those in the analytic sample, participants without data on immunity and/or purpose in life (n=1,140) were younger (d=.52, p<.001), had fewer years of education (d=.28, p<.001), more likely to be male (χ^2=7.15, p=.008), more likely to be Black (χ^2=179.96, p<.001), more likely to be an otherwise identified race (χ^2=146.21, p<.001), and more likely to be Hispanic ethnicity (χ^2=134.00, p<.001). A total of 8,999 participants had data on CRP and the cytokines and purpose in life to be included in the analysis. Compared to those in the analytic sample, participants without data (n=935) were younger (d=.65, p<.001), had fewer years of education (d=.32, p<.001), more likely to be male (χ^2=10.65, p<.001), more likely to be Black (χ^2=170.08, p<.001), more likely to be an otherwise identified race (χ^2=188.18, p<.001), and more likely to be Hispanic ethnicity (χ^2=196.97, p<.001).

We selected a different analytic sample to test the hypothesized mediation model. Specifically, assessments of purpose, immunity/inflammatory markers, and episodic memory were spaced out in time to have a temporal ordering of the underlying hypothesized mediation model. For this analysis, participants who reported on their purpose in life in either 2012 or 2014 were selected to examine the prospective association between purpose and the immune/inflammatory markers, measured 2–4 years later. The 2018 assessment of episodic memory was selected as the outcome. A total of 6,092 participants had the relevant data available to be included in the analysis. Compared to those in the analytic sample, participants without data (n=3,843) were younger (d=.13, p<.001), had fewer years of education (d=.09, p<.001), more likely to be male (χ^2=12.48, p<.001), more likely to be Black (χ^2=36.79, p<.001), more likely to be an otherwise identified race (χ^2=28.44, p<.001), and more likely to be Hispanic ethnicity (χ^2=8.76, p=.003).

Measures

Purpose in life.—The 7-item version of the Purpose in Life subscale from the Ryff Scales of Psychological Well-Being (Ryff, 1989) was used to measure sense of purpose. Participants rated items (e.g., “I have a sense of direction and purpose in my life”) on a scale from 1 (*strongly disagree*) to 6 (*strongly agree*). Items were scored in the direction of higher purpose and the mean takes across items.

Inflammatory markers.—Detailed information about blood collection, processing, assay, and quality control can be found in Crimmins and colleagues (2017). Briefly, venous blood was collected from participants, centrifuged in the field, and shipped overnight to the University of Minnesota for processing. Blood samples were assayed at the Advanced Research and Diagnostic Laboratory, a CLIA-certified laboratory at the University of Minnesota. Markers of peripheral immunity were derived from a complete blood count with differential using Sysmex XE-2100 (Sysmex America, Inc., Lincolnshire, IL). We focused on markers of innate (neutrophils, monocytes, platelets) and adaptive (lymphocytes)

immunity that have previously been associated with increased risk of ADRD (van der Willik et al., 2019; Zhang et al., 2022). We likewise focused on ratios of innate to adaptive immunity previously associated with increased ADRD risk: neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and the systemic immune inflammation index (SII), derived as neutrophils*platelets/lymphocytes. The immunity markers were winsorized to reduce skew: Neutrophil values equal to .00 were recoded to .4 (n=1) and values equal to 22.80 were recoded to 15.60 (n=1). Monocyte values equal to 0 were recoded to .1 (n=2) and values equal to 8.50 were recoded to 5.00 (n=1). Platelet values equal to 17 were recoded to 25 (n=1) and values equal to 916 were recoded to 849 (n=1). Lymphocyte values ≥8.50 were recoded to 7.90 (n=14). These markers were winsorized rather than transformed through another method (e.g., natural log) because the distribution was normal except for few cases on the distribution's tails. C-reactive protein was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN). A cytokine panel was used to measure Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin-1ra (IL-1ra), soluble Tumor Necrosis Factor Receptor 1 (sTNFR1), and Transforming Growth Factor beta 1 (TGFβ-1). These measures were derived from enzyme-linked immunosorbent assay (ELISA) Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). CRP and the cytokines were log transformed to normalize their distributions.

Episodic memory.—Participants were read a list of 10 words and recalled the words immediately and after a brief delay. The score was the sum of words correctly remembered across the two recalls (possible range=0–20).

Covariates.—Covariates were age in years (concurrent with the assessment of purpose), sex (0=male, 1=female), race (two dummy-coded variables that compared 1=Black and 1=Otherwise identified to 0=white), ethnicity (0=non-Hispanic, 1=Hispanic) and education in years.

Analytic Strategy

Linear regression was used to examine the concurrent association between purpose in life and the markers of inflammation and immunity. Specifically, each marker was regressed on purpose controlling for sociodemographic covariates and years since the assessment of purpose (i.e., 2016=0, 2014=2, etc.). Moderation was evaluated by testing an interaction between purpose and each sociodemographic covariate on each marker of immunity and inflammation. All interaction terms were tested in separate regression models. The mediational model was tested with the PROCESS macro (Hayes, 2018). Purpose assessed in 2012/2014 was tested as the predictor, episodic memory assessed in 2018 was tested as the outcome, and the immunity and inflammatory markers assessed in 2016 that were associated significantly with purpose from the first set of analyses were tested as simultaneous mediators, controlling for sociodemographic covariates and year of purpose assessment (2012 versus 2014).

Results

Table 1 shows the descriptive statistics for all study variables. Table S1 shows the correlations among all study variables. Purpose in life was associated with measures of peripheral inflammation that are most consistently associated with ADRD (Table 2): Participants who scored higher in purpose in life had lower neutrophil counts and lower ratio of neutrophils/lymphocytes and lower systemic immune inflammation index. Purpose was unrelated to monocyte, platelet, and lymphocyte counts and ratio of platelets/lymphocytes. Table 3 shows the results of the linear regressions for CRP and the cytokine panel. Consistent with expectations, purpose was associated negatively with CRP and IL-6. This negative association also extended to IL-10, IL-1ra, and sTNFR1. Purpose was unrelated to TGFβ−1. Of note, although we did not correct for multiple comparisons, applying a conservative Bonferroni correction of .004 (.05/13 immunity/inflammatory markers), all associations between purpose and the markers remained significant at this threshold. In addition, the pattern of associations was identical when inverse probability weighting was used to account for missing data on purpose in life (Supplemental Tables S2–S3). The pattern of association was also similar when participants with neutrophilia (n=197; Supplemental Table S4) or elevated CRP (n=821; Supplemental Table S5) were excluded from the analysis. The one exception was that purpose was no longer associated with SSI when participants with neutrophilia were excluded.

The observed associations were largely not moderated by sociodemographic factors. The only exception was IL-1ra, which was moderated by race, Hispanic ethnicity, and education. In each case, the association between purpose and lower IL-1ra was apparent across participants but was slightly stronger among white versus black participants (β=.03, p=.003), non-Hispanic versus Hispanic participants (β=.02, p=.034), and for participants with relatively higher versus relatively lower education (β=−.03, p=.003). These interactions, however, should be interpreted with caution until replicated because of the large number of interactions tested and the specificity to this inflammatory marker. There were no significant interactions on the other 12 markers, which indicated that the associations were similar across age, sex, race, Hispanic ethnicity, and education.

To test the mediation model (Figure 1), we focused on the immunity and inflammatory markers associated with purpose in the main analysis – neutrophil counts, neutrophil/lymphocyte ratio, systemic immune inflammation index, CRP, IL-6, IL-10, IL-1ra, sTNFR1 – as potential mediators since markers unrelated to purpose cannot be mediators of the association with episodic memory. Table 4 shows the results of the mediation model (the pattern of associations was identical when mediators were tested individually rather than simultaneously). Consistent with previous cross-sectional research in HRS (Sutin et al., 2022), purpose in life was associated prospectively with better episodic memory performance. Consistent with the (primarily cross-sectional) analysis reported above, purpose in life reported in 2012 or 2014 was associated prospectively with healthier levels of these inflammatory markers in 2016. Of these markers, neutrophils, IL-6, and sTNFR1 were associated prospectively with episodic memory: Lower levels of these markers in 2016 were associated with better episodic memory in 2018. These three markers also mediated a small part (collectively ~4.5%) of the association between purpose in life and episodic memory

measured four to six years later: Participants higher in purpose had better episodic memory in part through healthier levels of neutrophils, IL-6, and sTNFR1. The results were similar when participants with neutrophilia (Supplemental Table S6) or elevated CRP (Supplemental Table S6) were excluded from the analysis.

Discussion

The present research examined the association between purpose in life and markers of immunity and inflammation and tested these markers as mechanisms in the pathway from purpose to episodic memory. Across concurrent and prospective analyses, higher purpose was associated with lower levels of eight markers of immunity (neutrophil counts, neutrophil/lymphocyte ratio, systemic immune inflammation index) and inflammation (CRP, IL-6, IL-10, IL-1ra, sTNFR1). Further, lower neutrophil counts, Il-6, and sTNFR1 were associated with better episodic memory and were mediators of the purpose-memory association. The present research thus suggests that purpose is associated with healthier immunity and inflammatory profiles, which may be one mechanism through which purpose is associated with healthier cognitive outcomes over time.

Theoretical models of purpose in life and health suggest multiple mechanisms are likely to be in the pathway from purpose to better health-related outcomes (McKnight & Kashdan, 2009; Sutin, Luchetti, & Terracciano, 2021). Kim and colleagues (2019), for example, highlight behavioral, clinical, and biological factors as mechanisms that explain why purpose is associated with lower risk of cardiovascular disease. Within the domain of cognitive health, attention has focused primarily on testing behavioral (e.g., physical activity; Sutin, Stephan, et al., 2023) and clinical (e.g., hearing; Sutin et al., 2022) factors as mechanisms between purpose and cognitive function. Similar to cardiovascular disease (Kim et al., 2019), inflammation, as well as immunity, are likely to be significant mechanisms for cognitive health, since these markers are implicated in the development of dementia (Custodero et al., 2022; Zhang et al., 2022). The present research thus provides preliminary evidence for the role of these biological mechanisms and supports the examination of biological pathways, in addition to behavioral and clinical pathways, between purpose and healthier cognition.

Several mechanisms may explain why purpose is associated with healthier levels of immune and inflammatory markers. First, individuals with more purpose tend to be healthy (Musich et al., 2018), and thus peripheral immunity is more likely to be at healthier levels because the immune system does not need to be activated. Second, purpose is associated with more frequent engagement in physical activity (Sutin, Luchetti, et al., 2021b), which reduces levels of inflammation (Nieman & Wentz, 2019). Likewise, individuals higher in purpose are less likely to smoke (Konkolÿ Thege et al., 2009), which increases inflammation in the body (Shiels et al., 2014). Third, purpose may help protect against the development of psychological distress (Laird et al., 2019), which is also implicated in inflammatory processes (Osimo et al., 2019). As such, the healthier behavioral and clinical profiles of individuals higher in purpose may promote healthier levels of immunity and inflammation.

Previous research on purpose and inflammation has focused primarily on CRP and IL-6 (e.g., Boylan et al., 2020; Friedman et al., 2007; Steptoe & Fancourt, 2019). CRP and IL-6 are critical inflammatory markers associated with psychological factors, including personality (Luchetti et al., 2014) and psychological distress (Osimo et al., 2019). These two markers also tend to be responsive to stressors (Man et al., 2022), and elevated CRP and IL-6 may be markers of chronic stress (Rohleder, 2019). The present research replicates the association between purpose in life and lower CRP and IL-6 in a large sample and expands the association between purpose and healthier immunological profiles to markers of immunity, as well as additional markers of inflammation.

Immunity, particularly innate immunity, has been implicated in ADRD, and among these markers, neutrophils may be particularly important for cognitive function. Our mediation model supports their role in the pathway between purpose and memory function. Neutrophils are the first cells activated in response to injury (Chen et al., 2018). When functioning normally, neutrophils circulate in low levels and are cleared quickly after the initial inflammatory response (Liew & Kubes, 2019). With aging, however, neutrophils can remain in the blood stream longer than necessary, which can lead to a prolonged inflammatory state (Kolaczkowska & Kubes, 2013). Greater circulation increases risk that neutrophils will compromise the blood brain barrier (BBB) and stimulate inflammation in the brain (Sweeney et al., 2018). In rodent models, greater activation of neutrophils increases accumulation of neuropathology and impairs cognitive function, whereas experimental reduction of neutrophils improves cognitive performance (Zenaro et al., 2015). In humans, elevated neutrophils have been found in patients with Alzheimer's disease versus controls (Dong et al., 2018) and elevated levels, particularly compared to lymphocyte counts, have been found to increase risk of incident ADRD (Ramos-Cejudo et al., 2021; van der Willik et al., 2019; Zhang et al., 2022). Lower neutrophil counts may be one immunological mechanism that contributes to why individuals higher in purpose are at lower risk of ADRD. The mediation pathway observed for neutrophils, however, did not extend to other markers of innate or adaptive immunity.

Lower levels of IL-6 and sTNFR1 were likewise associated with purpose and better episodic memory. IL-6 and sTNFR1 are implicated in the inflammatory and cellular stress response (Galluzzi et al., 2018; Yan et al., 2018) and serve both pro-inflammatory and anti-inflammatory functions (Rose-John, 2018; Xin et al., 2006). Higher levels of Il-6 and sTNFR1 have been associated with the development of cardiovascular disease and cardiovascular events (Carlsson et al., 2018; Georgakis et al., 2020) and are associated with increased risk of premature mortality (Carlsson et al., 2014; Li et al., 2017). Purpose in life is also associated with better cardiovascular health (Kim et al., 2019), perhaps in part through healthier levels of IL-6 and sTNFR1. Cardiovascular factors are risk factors for ADRD (Li et al., 2019) and may be one pathway through which IL-6 and sTNFR1 impair cognition. IL-6 has further been implicated in cognitive decline among older adults (Bradburn et al., 2017). Similar to neutrophils, when chronically active, IL-6 can cross the BBB and increase risk of inflammation in the brain (Erickson & Banks, 2019). The hippocampus may be particularly sensitive to neuroinflammation (Montagne et al., 2015), which may result in lower episodic memory performance and increased risk of ADRD.

It is important to note that only three of the eight markers tested were significant mediators between purpose and episodic memory because five markers associated with purpose were unrelated to memory (IL-10, IL-1ra, CRP, NLR, SII). The inflammatory markers IL-10 and IL-1ra are thought to serve primarily anti-inflammatory functions, whereas IL-6 and sTNFR1 serve both anti- and pro-inflammatory functions (Rea et al., 2018). These different functions may contribute to the differential associations with incident dementia found in the literature (Miwa et al., 2016) and extend to episodic memory performance (i.e., IL-10 and IL-1ra were unrelated to memory and thus not mediators between purpose and memory). CRP is a non-specific marker and tends to indicate the presence of inflammation in the body (Sproston & Ashworth, 2018) that may not be predictive of cognitive function, as it was unrelated to episodic memory in the current analysis. The null relation between NLR and SII and episodic memory was surprising because these ratios are associated with increased risk of dementia (Zhang et al., 2022). These immunity measures may play less of a role in memory performance and become more important predictors when deficits surpass a threshold into impairment.

The present study had several strengths, including the large sample, the range of immune and inflammatory markers, and the prospective design. There are also limitations that could be addressed in future research. First, there was only one assessment of immune and inflammatory markers. Although we identified prospective associations between purpose and immunity/inflammation, the longitudinal association is more ambiguous. Second, and related, with only one venous blood assessment, it was not possible to examine bidirectional relations between purpose and the immunity/inflammatory markers. Purpose and the markers may shape the expression of each other over time. Third, our sample was limited to relatively older adults living in the United States and thus generalizability may be limited to this population. Future research could address the association between purpose and immunity/inflammation in a wider range of populations. Finally, the analyses were limited to the biomarkers available in the HRS resource, and other important markers (e.g., macrophages, other cytokines) were not available to examine their association with purpose.

Despite the limitations, the present research adds to the literature that purpose in life is associated with healthier patterns of immune function and inflammation, which, in turn, may be one pathway through which purpose supports better memory function. The present research suggests that both healthier immune function and less inflammation are independent mechanisms associated prospectively with better episodic memory and are modest biological factors in the pathway from purpose to healthier memory. This work is a step toward a more comprehensive model of purpose and cognitive health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Acknowledge of data use:

This study uses public data from the Health and Retirement Study, which is sponsored by the National Institute on Aging (NIA-U01AG009740) and conducted by the University of Michigan.

Funding:

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG074573. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

Beydoun MA, Weiss J, Obhi HK, Beydoun HA, Dore GA, Liang H, . . . Zonderman AB (2019). Cytokines are associated with longitudinal changes in cognitive performance among urban adults. Brain Behavior & Immunity, 80, 474–487. 10.1016/j.bbi.2019.04.027 [PubMed: 30981715]

Boylan JM, Cundiff JM, Fuller-Rowell TE, & Ryff CD (2020). Childhood socioeconomic status and inflammation: Psychological moderators among Black and White Americans. Health Psychology, 39(6), 497–508. 10.1037/hea0000866 [PubMed: 32212770]

Boyle PA, Buchman AS, Barnes LL, & Bennett DA (2010). Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. Archives of General Psychiatry, 67(3), 304–310. 10.1001/archgenpsychiatry.2009.208 [PubMed: 20194831]

Bradburn S, Sarginson J, & Murgatroyd CA (2017). Association of peripheral interleukin-6 with global cognitive decline in non-demented adults: A meta-analysis of prospective studies. Frontiers in Aging Neuroscience, 9, 438. 10.3389/fnagi.2017.00438 [PubMed: 29358917]

Carlsson AC, Juhlin CC, Larsson TE, Larsson A, Ingelsson E, Sundström J, . . . Arnlöv J (2014). Soluble tumor necrosis factor receptor 1 (sTNFR1) is associated with increased total mortality due to cancer and cardiovascular causes - findings from two community based cohorts of elderly. Atherosclerosis, 237(1), 236–242. 10.1016/j.atherosclerosis.2014.09.005 [PubMed: 25255422]

Carlsson AC, Ruge T, Kjøller E, Hilden J, Kolmos HJ, Sajadieh A, . . . Ärnlöv J (2018). 10-year associations between tumor necrosis ractor receptors 1 and 2 and cardiovascular events in patients with stable coronary heart disease: A CLARICOR (Effect of Clarithromycin on Mortality and Morbidity in Patients With Ischemic Heart Disease) Trial Substudy. Journal of the American Heart Association, 7(9). 10.1161/JAHA.117.008299

Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, . . . Zhao L (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204–7218. 10.18632/oncotarget.23208 [PubMed: 29467962]

Crimmins E, Faul J, Thyagarajan B, & Weir D (2017). Venous blood collection and assay protocol in the 2016 Health and Retirement Study 2016 Venous Blood Study (VBS). HRS Documentation Report. University of Michigan. https://hrs.isr.umich.edu/sites/default/files/biblio/HRS2016VBSDD_0.pdf

Custodero C, Ciavarella A, Panza F, Gnocchi D, Lenato GM, Lee J, . . . Solfrizzi V (2022). Role of inflammatory markers in the diagnosis of vascular contributions to cognitive impairment and dementia: a systematic review and meta-analysis. Geroscience, 44(3), 1373–1392. 10.1007/s11357-022-00556-w [PubMed: 35486344]

Dong Y, Lagarde J, Xicota L, Corne H, Chantran Y, Chaigneau T, . . . Elbim C (2018). Neutrophil hyperactivation correlates with Alzheimer's disease progression. Annals of Neurology, 83(2), 387–405. 10.1002/ana.25159 [PubMed: 29369398]

Erickson MA, & Banks WA (2019). Age-associated changes in the immune system and blood-brain barrier functions. International Journal of Molecular Science, 20(7). 10.3390/ijms20071632

Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, & Roccia MG (2018). Stress and inflammation in coronary artery disease: A review psychoneuroendocrineimmunology-based. Frontiers in Immunology, 9, 2031. 10.3389/fimmu.2018.02031 [PubMed: 30237802]

Friedman EM, Hayney M, Love GD, Singer BH, & Ryff CD (2007). Plasma interleukin-6 and soluble IL-6 receptors are associated with psychological well-being in aging women. Health Psychology, 26(3), 305–313. 10.1037/0278-6133.26.3.305 [PubMed: 17500617]

Galea I (2021). The blood–brain barrier in systemic infection and inflammation. Cellular and Molecular Immunology, 18, 2489–2501. 10.1038/s41423-021-00757-x [PubMed: 34594000]

Galluzzi L, Yamazaki T, & Kroemer G (2018). Linking cellular stress responses to systemic homeostasis. Nature Reviews Molecular Cellular Biology, 19(11), 731–745. 10.1038/s41580-018-0068-0 [PubMed: 30305710]

Georgakis MK, Malik R, Gill D, Franceschini N, Sudlow CLM, Dichgans M, & INVENT Consortium CIWG (2020). Interleukin-6 signaling effects on ischemic stroke and other cardiovascular outcomes: A Mendelian randomization study. Circulation: Genomic and Precision Medicine, 13(3), e002872. 10.1161/CIRCGEN.119.002872 [PubMed: 32397738]

Guimond AJ, Shiba K, Kim ES, & Kubzansky LD (2022). Sense of purpose in life and inflammation in healthy older adults: A longitudinal study. Psychoneuroendocrinology, 141, 105746. 10.1016/j.psyneuen.2022.105746 [PubMed: 35364478]

Hafez D, Heisler M, Choi H, Ankuda CK, Winkelman T, & Kullgren JT (2018). Association between purpose in life and glucose control among older adults. Annals of Behavioral Medicine, 52(4), 309–318. 10.1093/abm/kax012 [PubMed: 30084896]

Hayes AF (2018). Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Guilford Press.

Hoebe K, Janssen E, & Beutler B (2004). The interface between innate and adaptive immunity. Nature Immunology, 5(10), 971–974. 10.1038/ni1004-971 [PubMed: 15454919]

Jahn H (2013). Memory loss in Alzheimer's disease. Dialogues in Clinical Neuroscience, 15(4), 445–454. [PubMed: 24459411]

Jones DR, & Graham-Engeland JE (2021). Positive affect and peripheral inflammatory markers among adults: A narrative review. Psychoneuroendocrinology, 123, 104892. 10.1016/j.psyneuen.2020.104892 [PubMed: 33130406]

Kim ES, Delaney SW, & Kubansky LD (2019). Sense of purpose in life and cardiovascular disease: Underlying mechanisms and future directions. Current Cardiology Reports, 21, 135. [PubMed: 31673815]

Kim G, Shin SH, Scicolone MA, & Parmelee P (2019). Purpose in life protects against cognitive decline among older adults. American Journal of Geriatric Psychiatry, 27(6), 593–601. 10.1016/j.jagp.2019.01.010

Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, & Lamb BT (2018). Inflammation as a central mechanism in Alzheimer's disease. Alzheimer's & Dementia, 4, 575–590. 10.1016/j.trci.2018.06.014

Klein SL, & Flanagan KL (2016). Sex differences in immune responses. Nature Reviews Immunology, 16(10), 626–638. 10.1038/nri.2016.90

Kolaczkowska E, & Kubes P (2013). Neutrophil recruitment and function in health and inflammation. Nature Reviews Immunology, 13(3), 159–175. 10.1038/nri3399

Konkolÿ Thege B, Bachner YG, Kushnir T, & Kopp MS (2009). Relationship between meaning in life and smoking status: results of a national representative survey. Addictive Behaviors, 34(1), 117–120. 10.1016/j.addbeh.2008.09.001 [PubMed: 18842347]

Laird KT, Krause B, Funes C, & Lavretsky H (2019). Psychobiological factors of resilience and depression in late life. Translational Psychiatry, 9(1), 88. 10.1038/s41398-019-0424-7 [PubMed: 30765686]

Li H, Liu W, & Xie J (2017). Circulating interleukin-6 levels and cardiovascular and all-cause mortality in the elderly population: A meta-analysis. Archives of Gerontology and Geriatrics, 73, 257–262. 10.1016/j.archger.2017.08.007 [PubMed: 28866452]

Li XY, Zhang M, Xu W, Li JQ, Cao XP, Yu JT, & Tan L (2019). Midlife modifiable risk factors for dementia: A systematic review and meta-analysis of 34 prospective cohort studies. Current Alzheimer's Research, 16(14), 1254–1268. 10.2174/1567205017666200103111253

Liew PX, & Kubes P (2019). The neutrophil's role during health and disease. Physiology Review, 99(2), 1223–1248. 10.1152/physrev.00012.2018

Luchetti M, Barkley JM, Stephan Y, Terracciano A, & Sutin AR (2014). Five-factor model personality traits and inflammatory markers: New data and a meta-analysis. Psychoneuroendocrinology, 50, 181–193. 10.1016/j.psyneuen.2014.08.014 [PubMed: 25233337]

Man ISC, Shao R, Hou WK, Xin Li S, Yan Liu F, Lee M, . . . Lee TMC (2022). Multi-systemic evaluation of biological and emotional responses to the Trier Social Stress Test: A meta-analysis

and systematic review. Frontiers in Neuroendocrinology, 101050. 10.1016/j.yfrne.2022.101050 [PubMed: 36410619]

McKnight PE, & Kashdan TB (2009). Purpose in life as a system that creates and sustains health and well-being: An integrative, testable theory. Review of General Psychology, 13, 242–251. 10.1037/a0017152

Mei Z, Lori A, Vattathil SM, Boyle PA, Bradley B, Jin P, . . . Wingo AP (2020). Important correlates of purpose in life identified through a machine learning approach. American Journal of Geriatric Psychiatry. 10.1016/j.jagp.2020.09.018

Miwa K, Okazaki S, Sakaguchi M, Mochizuki H, & Kitagawa K (2016). Interleukin-6, interleukin-6 receptor gene variant, small-vessel disease and incident dementia. European Journal of Neurology, 23(3), 656–663. 10.1111/ene.12921 [PubMed: 26725994]

Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, . . . Zlokovic BV (2015). Blood-brain barrier breakdown in the aging human hippocampus. Neuron, 85(2), 296–302. 10.1016/j.neuron.2014.12.032 [PubMed: 25611508]

Musich S, Wang SS, Kraemer S, Hawkins K, & Wicker E (2018). Purpose in life and positive health outcomes among older adults. Population Health Management, 21(2), 139–147. 10.1089/pop.2017.0063 [PubMed: 28677991]

Nieman DC, & Wentz LM (2019). The compelling link between physical activity and the body's defense system. Journal of Sport Health Science, 8(3), 201–217. 10.1016/j.jshs.2018.09.009 [PubMed: 31193280]

Nyberg L, & Pudas S (2019). Successful memory aging. Annual Review of Psychology, 70, 219–243. 10.1146/annurev-psych-010418-103052

Osimo EF, Baxter LJ, Lewis G, Jones PB, & Khandaker GM (2019). Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychological Medicine, 49(12), 1958–1970. 10.1017/S0033291719001454 [PubMed: 31258105]

Ramos-Cejudo J, Johnson AD, Beiser A, Seshadri S, Salinas J, Berger JS, . . . Osorio RS (2021). The neutrophil to lymphocyte ratio is associated with the risk of subsequent dementia in the Framingham Heart Study. Frontiers in Aging Neuroscience, 13, 773984. 10.3389/fnagi.2021.773984 [PubMed: 34916927]

Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, & Ross OA (2018). Age and age-related diseases: Role of inflammation triggers and cytokines. Frontiers in Immunology, 9, 586. 10.3389/fimmu.2018.00586 [PubMed: 29686666]

Rohleder N (2019). Stress and inflammation - The need to address the gap in the transition between acute and chronic stress effects. Psychoneuroendocrinology, 105, 164–171. 10.1016/j.psyneuen.2019.02.021 [PubMed: 30826163]

Rose-John S (2018). Interleukin-6 family cytokines. Cold Spring Harbor Perspectives in Biology, 10(2). 10.1101/cshperspect.a028415

Ryff CD (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. Journal of Personality and Social Psychology, 57, 1069–1081.

Salthouse TA (2018). Trajectories of normal cognitive aging. Psychology and Aging. 10.1037/pag0000288

Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, . . . Chaturvedi AK (2014). Cigarette smoking and variations in systemic immune and inflammation markers. Journal of the National Cancer Institute, 106(11). 10.1093/jnci/dju294

Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, & Weir DR (2014). Cohort profile: The Health and Retirement Study (HRS). International Journal of Epidemiology, 43(2), 576–585. 10.1093/ije/dyu067 [PubMed: 24671021]

Sproston NR, & Ashworth JJ (2018). Role of c-reactive protein at sites of inflammation and infection. Frontiers in Immunology, 9, 754. 10.3389/fimmu.2018.00754 [PubMed: 29706967]

Steptoe A, & Fancourt D (2019). Leading a meaningful life at older ages and its relationship with social engagement, prosperity, health, biology, and time use. Proceedings of the National Academies of Science, 116(4), 1207–1212. 10.1073/pnas.1814723116

Sutin AR, Aschwanden D, Luchetti M, Stephan Y, & Terracciano A (2021). Sense of purpose in life is associated with lower risk of incident dementia: A meta-analysis. Journal of Alzheimer's Disease, 83, 249–258. 10.3233/JAD-210364

Sutin AR, Luchetti M, Aschwanden D, Stephan Y, Sesker AA, & Terracciano A (2023). Sense of meaning and purpose in life and risk of incident dementia: New data and meta-analysis. Archives of Gerontology and Geriatrics, 105, 104847. 10.1016/j.archger.2022.104847 [PubMed: 36347158]

Sutin AR, Luchetti M, Aschwanden D, Stephan Y, & Terracciano A (2022). Sense of purpose in life and markers of hearing function: Replicated associations across two longitudinal cohorts. Gerontology, 68(8), 943–950. 10.1159/000521257 [PubMed: 35114673]

Sutin AR, Luchetti M, Stephan Y, Strickhouser JE, & Terracciano A (2022). The association between purpose/meaning in life and verbal fluency and episodic memory: A meta-analysis of >140,000 participants from up to 32 countries. International Psychogeriatrics, 34, 263–273. 10.1017/S1041610220004214 [PubMed: 33612145]

Sutin AR, Luchetti M, Stephan Y, & Terracciano A (2021a). Purpose in life and motoric cognitive risk syndrome: Replicable evidence from two national samples. Journal of the American Geriatrics Society, 69(2), 381–388. 10.1111/jgs.16852 [PubMed: 32997804]

Sutin AR, Luchetti M, Stephan Y, & Terracciano A (2021b). Sense of purpose in life and motivation, barriers, and engagement in physical activity and sedentary behavior: Test of a mediational model. Journal of Health Psychology, 13591053211021661. 10.1177/13591053211021661

Sutin AR, Luchetti M, & Terracciano A (2021). Sense of purpose in life and healthier cognitive aging. Trends in Cognitve Science, 25(11), P917–919. 10.1016/j.tics.2021.08.009

Sutin AR, Stephan Y, Kekäläinen T, Luchetti M, & Terracciano A (2023). Purpose in life and accelerometer-measured physical activity among older adults. Psychology and Health, 1–15. 10.1080/08870446.2023.2200414

Sweeney MD, Sagare AP, & Zlokovic BV (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nature Reviews Neurology, 14(3), 133–150. 10.1038/nrneurol.2017.188 [PubMed: 29377008]

Tegeler C, O'Sullivan JL, Bucholtz N, Goldeck D, Pawelec G, Steinhagen-Thiessen E, & Demuth I (2016). The inflammatory markers CRP, IL-6, and IL-10 are associated with cognitive function--data from the Berlin Aging Study II. Neurobiology of Aging, 38, 112–117. 10.1016/j.neurobiolaging.2015.10.039 [PubMed: 26827649]

Thoma MV, Gianferante D, Hanlin L, Fiksdal A, Chen X, & Rohleder N (2017). Stronger hypothalamus-pituitary-adrenal axis habituation predicts lesser sensitization of inflammatory response to repeated acute stress exposures in healthy young adults. Brain Behavior and Immunity, 61, 228–235. 10.1016/j.bbi.2016.11.030 [PubMed: 27916659]

van der Willik KD, Fani L, Rizopoulos D, Licher S, Fest J, Schagen SB, . . . Ikram MA (2019). Balance between innate versus adaptive immune system and the risk of dementia: a population-based cohort study. Journal of Neuroinflammation, 16(1), 68. 10.1186/s12974-019-1454-z [PubMed: 30927918]

Windsor TD, Curtis RG, & Luszcz MA (2015). Sense of purpose as a psychological resource for aging well. Developmental Psychology, 51(7), 975–986. 10.1037/dev0000023 [PubMed: 26010384]

Xin L, Wang J, Zhang H, Shi W, Yu M, Li Q, . . . Li Z (2006). Dual regulation of soluble tumor necrosis factor-alpha induced activation of human monocytic cells via modulating transmembrane TNF-alpha-mediated 'reverse signaling'. International Journal of Molecular Medicine, 18(5), 885–892. [PubMed: 17016618]

Yan L, Zheng D, & Xu RH (2018). Critical role of tumor necrosis factor signaling in mesenchymal stem cell-based therapy for autoimmune and inflammatory diseases. Frontiers in Immunology, 9, 1658. 10.3389/fimmu.2018.01658 [PubMed: 30079066]

Zenaro E, Pietronigro E, Della Bianca V, Piacentino G, Marongiu L, Budui S, . . . Constantin G (2015). Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. Nature Medicine, 21(8), 880–886. 10.1038/nm.3913

Zhang YR, Wang JJ, Chen SF, Wang HF, Li YZ, Ou YN, . . . Yu JT (2022). Peripheral immunity is associated with the risk of incident dementia. Molecular Psychiatry, 27(4), 1956–1962. 10.1038/s41380-022-01446-5 [PubMed: 35079124]

Highlights

- Purpose in life is associated consistently with better physical and cognitive health
- Purpose was associated with markers of immunity and inflammation
- These markers are implicated in significant cognitive outcomes, such as dementia
- Immunity and inflammatory markers mediated between purpose and episodic memory

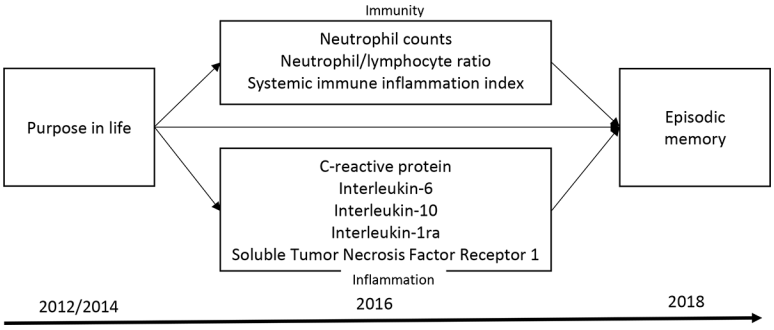

Figure 1.

Mediation model of the association between purpose in life measured in 2012/2014 and episodic memory measured in 2018 through three markers of immunity (neutrophil counts, neutrophil/lymphocyte ratio, systemic immune inflammation index) and five markers of inflammation (c-reactive protein, interleukin-6, interleukin-10, interleukin-1ra, soluble tumor necrosis factor receptor 1) measured in 2016.

Table 1

Descriptive Statistics for All Study Variables

Variable	Concurrent Sample	Prospective Sample
	Mean (*SD*) or % (*n*)	Mean (*SD*) or % (*n*)
Age (years)	67.48 (10.32)	67.55 (9.90)
Sex (female)	59.6% (5362)	60.4% (3682)
Race (Black)	16.7% (1503)	16.4% (1000)
Race (Otherwise identified)	8.1% (727)	8.1% (492)
Ethnicity (Hispanic)	13.2% (1192)	14% (854)
Education (years)	12.92 (3.09)	12.93 (3.06)
Purpose in life[a]	4.59 (.94)	4.63 (.92)
Immunity markers[b, c]		
Neutrophils (10^9/L)	3.93 (1.53)	3.89 (1.48)
Monocytes (10^9/L)	.56 (.22)	.56 (.22)
Platelets (10^9/L)	231.74 (65.40)	230.30 (63.45)
Lymphocytes (10^9/L)	2.02 (2.88)	1.98 (.91)
Neutrophils/Lymphocytes	2.26 (1.35)	2.21 (.91)
Platelets/Lymphocytes	132.21 (59.85)	130.29 (57.27)
Systemic immune inflammation index	524.37 (377.14)	509.48 (345.30)
C-reactive protein (mg/L)[d]	4.87 (10.80)	4.62 (10.01)
Cytokines[d]		
Interleukin-6 (pg/mL)	8.67 (68.76)	8.60 (68.33)
Interleukin-10 (pg/mL)	4.09 (7.81)	4.09 (9.08)
Interleukin-1ra (pg/mL)	605.24 (506.43)	601.94 (491.66)
sTNFR1 (pg/mL)	1888.16 (1629.51)	1844.42 (1510.95)
TGFβ-1 (pg/mL)	47804.65 (14767.42)	47721.44 (14645.68)
Episodic memorye	--	9.97 (3.44)

Note. N=8,999 for concurrent sample. N=6,091 for prospective sample. sTNFR1=soluble Tumor Necrosis Factor Receptor. TGFβ-1= and Transforming Growth Factor beta 1.

[a] Rated on a scale from 1 (*strongly disagree*) to 6 (*strongly agree*).

[b] N=8,794 for immunity markers and ratios.

[c] Raw means are reported in the Table; scores were winsorized for analysis.

[d] Raw means are reported in the Table; the natural log of the scores was used for analysis.

[e] Performance summed across immediate and delayed recall; possible range is 0–20.

Table 2

Association between Purpose in Life and Markers of Immunity

Predictor	Neutrophils		Monocytes		Lymphocytes		Platelets		NLR		PLR		SII	
	β	p	β	p	B	p	β	P	β	p	β	p	β	p
Age (years)	.01	.331	.08	<.001	−.18	<.001	−.16	<.001	.17	<.001	.08	<.001	.08	<.001
Sex (female)	−.05	<.001	−.15	<.001	.09	<.001	.25	<.001	−.10	<.001	.07	<.001	.02	.103
Race (Black)	−.16	<.001	−.09	<.001	.07	<.001	.00	.667	−.14	<.001	−.05	<.001	−.12	<.001
Race (Otherwise Ident)	−.03	.022	−.03	.011	.03	.010	.01	.579	−.04	<.001	−.03	.010	−.03	.009
Ethnicity (Hispanic)	−.01	.365	−.06	<.001	.02	.056	−.02	.182	−.02	.204	−.03	.015	−.02	.113
Education (years)	−.04	<.001	−.03	.012	−.06	<.001	.00	.910	.01	.214	.05	<.001	.01	.587
Time (years)[a]	−.01	.155	−.02	.163	.04	<.001	.03	.009	−.04	<.001	−.02	.130	−.02	.031
Purpose in life	−.08	<.001	−.01	.231	−.01	.228	.00	.760	−.05	<.001	.02	.128	−.04	<.001

N=8,794. Coefficients are standardized beta coefficients from linear regression. NLR=neutrophil/lymphocyte ratio.

PLR=platelet/lymphocyte ratio. SII=systemic immune inflammation index, derived as neutrophils*platelets/lymphocytes.

[a]Time refers to years since the assessment of purpose in life.

Table 3

Association between Purpose in Life and Markers of Inflammation

Predictor	CRP		IL-6		IL-10		IL-1ra		sTNFR1		TGFβ-1	
	β	p	β	p	β	P	β	p	β	p	β	p
Age (years)	−.02	.026	.18	<.001	.14	<.001	−.03	.020	.35	<.001	−.25	<.001
Sex (female)	.06	<.001	−.02	.056	−.05	<.001	.07	<.001	−.01	.449	.06	<.001
Race (Black)	.10	<.001	.11	<.001	.05	<.001	−.06	<.001	−.03	<.001	−.01	.438
Race (Otherwise Ident)	.00	.842	−.01	.360	−.02	.046	−.03	.004	−.03	.002	.00	.734
Ethnicity (Hispanic)	.02	.075	.03	.023	.03	.018	−.06	<.001	−.03	.013	.01	.404
Education (years)	−.06	<.001	−.05	<.001	−.04	<.001	−.08	<.001	−.09	<.001	−.01	.478
Time (years)	−.01	.380	−.02	.021	−.04	<.001	.00	.727	−.08	<.001	.08	<.001
Purpose in life	−.07	<.001	−.08	<.001	−.07	<.001	−.08	<.001	−.10	<.001	.02	.072

Note. *N*=8,999. CRP=c-reactive protein. IL=interleukin. sTNFR1=soluble tumor necrosis factor receptor 1. TGFβ-1=transforming growth factor beta 1.

Table 4

Analysis of Markers of Immunity and Inflammation as Mediators Between Purpose in Life and Episodic Memory

	Purpose to Immunity/ Inflammation (a path)		*Immunity/ Inflammation to Memory (b path)*		*Indirect Effect (a × b)*		*Direct Effect (c ′ path)*	*Total Effect (c path)*
	b (SE)	***p***	**b (SE)**	***P***	**Estimate (95% CI)**	***p***	**b (SE)**	**b (SE)**
Purpose in life							.42 (.04)	.44 (.04)
Mediators							*p*<.001	*p*<.001
Neutrophils	−.12 (.02)	<.001	−.11 (.04)	.002	.01 (.004, .025)	.006		
NLR	−.06 (.02)	<.001	.04 (.07)	.494	.00 (−.013, .006)	.513		
SII	−12.70 (4.85)	.009	.00 (.00)	.738	.00 (−.008, .006)	.757		
C-reactive protein	−.08 (.01)	<.001	.08 (.04)	.061	−.01 (−.015, .000)	.081		
Interleukin-6	−.07 (.01)	<.001	−.19 (.06)	.001	.01 (.004, .023)	.005		
Interleukin-10	−.04 (.01)	<.001	.08 (.10)	.438	.00 (−.011, .004)	.446		
Interleukin-1ra	−.05 (.01)	<.001	.14 (.09)	.138	−.01 (−.016, .002)	.151		
sTNFR1	−.05 (.01)	<.001	−.37 (.13)	.003	.02 (.004, .033)	.005		

Note. *N*=6,092. b=unstandardized beta estimate. SE=standard error. CI=confidence interval. NLR=neutrophil/lymphocyte ratio.

SSI=systemic immune inflammation index. Analysis controls for age, sex, race, ethnicity, education, and year of purpose assessment.