Brain, Behavior, & Immunity - Health 26 (2022) 100559

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Links between inflammation and immune functioning with cognitive status among older Americans in the Health and Retirement Study

Mateo P. Farina [a,*], Jung Ki Kim [a], Mark D. Hayward [b], Eileen M. Crimmins [a]

[a] Leonard Davis School of Gerontology, University of Southern California, USA
[b] Population Research Center and Department of Sociology, University of Texas at Austin, USA

ARTICLE INFO

Keywords:
Dementia
biomarkers
inflammation
immune functioning

ABSTRACT

Elevated inflammation and poor immune functioning are tied to worse cognitive health. Both processes are fundamental to aging and are strongly implicated in the development of age-related health outcomes, including cognitive status. However, results from prior studies evaluating links between indicators of inflammation and immune function and cognitive impairment have been inconsistent due to biomarker selection, sample selection, and cognitive outcome. Using the Health and Retirement Study (HRS), a nationally representative study of older adults in the United States, we assessed how indicators of inflammation (neutrophil-lymphocyte ratio (NLR), albumin, CRP, IL6, IL10, IL-1Ra, sTNFR1, and TGFβ1) and immune functioning (CMV, $CD4^+$ T_N/T_M, and $CD8^+$ T_N/T_M) are associated with cognitive status. First, to examine the association between each biomarker and cognitive status, we tested whether markers of inflammation and immune functioning varied across cognitive status categories. We found that dementia and cognitive impairment without dementia (CIND) were associated with elevated inflammation and poorer immune functioning across biomarkers except for $CD4^+$ T_N/T_M. Next, we estimated multinomial logistic regression models to assess which biomarkers would continue to be associated with dementia and CIND, net of each other. In these models, albumin, cytokines, CMV, $CD4^+$ T_N/T_M, and $CD8^+$ T_N/T_M are associated with cognitive status. Because poor immune functioning and increased inflammation are associated with cognitive impairment, improving immune functioning and reducing inflammation may provide a mechanism for reducing ADRD risk in the population.

1. Introduction

Researchers have investigated the role of age-related physiological changes to better understand the etiology of cognitive impairment. Inflammation and immune functioning are key predictors of cognitive aging and Alzheimer's disease and related disorders (ADRD) (Bettcher and Kramer, 2014; Pellicanò et al., 2012; Sundelöf et al., 2009; Walker Keenan et al., 2017; Wichmann et al., 2014). While inflammation and immune function are interrelated, most studies have observed them separately (Kim et al., 2018; Ng et al., 2018; Stebbins et al., 2020; Sundelöf et al., 2009). Studying them together may help clarify how these processes are related to cognitive impairment, net of each other, which will identify robust and important biomarkers of cognitive aging in population health research. In addition, existing studies are mostly limited to non-representative community or clinical samples and have yielded inconsistent results. Thus, the independent effects of physiological dysregulation due to greater inflammation and worse immune functioning on cognitive status and the generalizability to the population are largely still unknown. Our study examines the associations of multiple inflammation and immune functioning indicators in a nationally representative sample to better understand the biological underpinnings of cognitive impairment and dementia.

People with cognitive impairment and dementia have elevated inflammation. Pathways that link inflammatory processes to cognitive impairment can be through brain structural changes from neurodegeneration and cardiovascular dysfunction. Inflammation can lead directly to neurodegeneration through the activation of immune cells in the brain, which release neurotoxic enzymes (Glass et al., 2010). Additionally, researchers have found greater amyloid plaque deposits and more neurofibrillary tangles with increased levels of inflammation, which are considered two important neuropathological correlates of Alzheimer's disease (Lue et al., 1996). Increased inflammation is also associated with cognitive impairment through other vascular health conditions, such as stroke and atherosclerosis (Hansson, 2005; McColl

* Corresponding author.
E-mail address: mfarina@usc.edu (M.P. Farina).

https://doi.org/10.1016/j.bbih.2022.100559
Received 7 November 2022; Accepted 11 November 2022
Available online 13 November 2022

et al., 2009).

To evaluate the link between inflammation and cognitive health risk, researchers have often used CRP or individual cytokines. However, results for CRP have not been consistent, even though it has been one of the most widely used and available biomarkers of inflammation. Researchers have found CRP to be positively, negatively or not associated with cognitive impairment (Kim et al., 2018; Schmidt et al., 2002). In contrast, results from proinflammatory cytokines are more consistent in their links to cognitive status. Researchers have generally found strong associations of IL6 and TNF-alpha with cognitive impairment. Additional markers of systemic inflammation linked to cognitive outcomes include albumin levels and the neutrophil/lymphocyte ratio (NLR). Albumin levels have been found to have a negative association with cognitive impairment (Llewellyn et al., 2010). NLR has been tied to both cardiovascular conditions (Imtiaz et al., 2012)—important risk factors for ADRD (Shah et al., 2014; Xue et al., 2017) - and to dementia incidence (Sayed et al., 2020; Zhang et al., 2013). Altogether, these markers have shown elevated risk of poor cognitive health outcomes with greater inflammation.

In addition to inflammation, immunosenescence (or poor immune functioning) has been linked to worse cognitive status. Immunosenescence and inflammation, however, are interconnected. Immunosenescence can lead to chronic low-grade inflammation (Santoro et al., 2021), through the inability to control infection that leads to deterioration of the adaptive immune system and upregulation of the innate immune system that can lead to neuroinflammation. Researchers have also tied this inflammatory response in the brain to changes in the distribution and reactivity of immune cells in the blood (Britschgi and Wyss-Coray, 2007; Martorana et al., 2012). One of the most widely used and available markers to study immunosenescent and cognitive aging has been T-cell counts. Prior research has largely used the CD4/CD8 ratio of less than 1 as indicative of poor immune functioning, and this has been shown to have a strong association with cognitive impairment (Doty et al., 2015; Lueg et al., 2015; Pellicanò et al., 2012; Unger et al., 2018). However, the CD4/CD8 ratio as a marker of immune functioning has been tied to seropositivity of CMV, and does not appear to reflect age-related changes in immune functioning among CMV seronegative individuals, limiting its broader applicability to the non-seropositive population (Thyagarajan et al., 2022). To address this limitation, two new markers of age-related immune functioning have been suggested based on T-cell subsets that appropriately reflect age-related changes in the immune system that could increase vulnerability to age-related chronic conditions: $CD8^{+}$ T_N/T_M and $CD4^{+}$ T_N/T_M. Although these measures have not yet been applied to cognitive functioning or status, these measures indicating naïve T-cells have been found to be related to several later life health outcomes such as mortality, multimorbidity, and biological age (Ramasubramanian et al., 2022).

In addition to T-cell indicators of immunosenescence, gerontologists have often relied on cytomegalovirus (CMV) seropositivity as an indicator of poor immune functioning (Thyagarajan et al., 2022). To study poor immune functioning among older adults, CMV may be a good indicator because 1) it is a virus in the herpesvirus family, meaning that once the infection is acquired, it cannot be cleared from the body but rather must be suppressed by the immune system and 2) there is a high prevalence of infection in the population which increases with age (Bate et al., 2010; Moss and Khan, 2004). The immune system's inability to suppress CMV viral replication indicates poor immune functioning. In evaluating the association of CMV seropositivity with worse cognitive health, research has found that compared to seronegative older adults, older adults with CMV seropositivity had a greater risk of vascular dementia, Alzheimer's disease, and cognitive decline (Barnes et al., 2015; Lin et al., 2002; Stebbins et al., 2020; Westman et al., 2014).

Moreover, social characteristics are important to consider when evaluating the association of inflammation and poor immune functioning with cognitive health. Racially minoritized populations (namely, Blacks and Hispanics) and people with lower levels of education are more likely to have cognitive impairment, but are also more likely to have elevated inflammation and poor immune functioning (Lövdén et al., 2020; Zhang et al., 2016). Therefore, when evaluating the association between inflammation and immune functioning and cognitive impairment, sociodemographic characteristics should be accounted for, as other factors associated with race and ethnicity, or education may be contributing to the biomarker associations with cognitive status.

In this study, we investigated the association between poor cognitive status and inflammation and immune functioning. Our study used the 2016 Venous Blood Study (VBS) of the Health and Retirement Study, which collected several biomarkers of inflammation and immunosenescence that were not previously available in large nationally representative studies of the U.S. older adult population. We evaluated how markers of inflammation and immunosenescence are associated with worse cognitive functioning and investigated whether these associations are influenced by sociodemographic composition. By considering multiple markers, we sought to clarify whether specific inflammation and immune functioning biomarkers were more robust to examining cognitive health status differences in the population.

2. Data and methods

2.1. Study population

The data come from the Health and Retirement Study, a nationally representative longitudinal study of adults 50+ in the United States. The biomarker data come from the 2016 Venous Blood Study (VBS) of the HRS. Respondents were ages 56 and over, were not living in a nursing home, provided responses to the 2016 core interview, and had agreed to, and completed, blood collection. Blood collection was completed by phlebotomists and took place in respondents' homes about 2 months after the 2016 core interview. Blood was centrifuged in the field and sent cold for assay at the Advanced Research & Diagnostics Laboratory at the University of Minnesota, with more than 90% arriving within a 24-hour period (Crimmins et al., 2017). Tests needing to be done with fresh samples (e.g., neutrophil and lymphocyte counts) were done immediately; remaining samples were aliquoted and frozen, and the remainder of the assays were done using frozen serum samples (Crimmins et al., 2017). A detailed descriptions of the protocols and procedures for collection, assays, and quality are provided in other documentation, and information on biomarkers used in this study is available as supplementary information (see description S1) (Crimmins et al., 2017; Thyagarajan et al., 2018).

The total VBS analytical sample consists of 9,187 respondents with non-zero VBS weights. Of these respondents, 6,710 had no missing biomarker information. The analytical sample was further reduced to 5,959 due to missing information from other model covariates (sociodemographic characteristics, APOE *e4* allele information, or cognitive measures). The largest reduction in sample size was due to missing information on APOE *e4* alleles – the HRS has collected and distributed genetic information from a smaller subsample. However, sensitivity analysis excluding information on APOE *e4* alleles found similar patterns to ones presented here, indicating that the smaller analytical sample with APOE *e4* inclusion was not biasing the results. Those who were missing did not differ in age, sex and educational attainment; they were more likely to be African American and less likely to be white. The HRS provided weights for the biomarker sample to adjust for sampling probability and non-response, which allows for estimates to be nationally representative.

2.2. Cognitive status measurement

Cognitive status was classified as normal cognitive functioning, cognitive impairment without dementia (CIND), anddementia, using an approach adopted in many HRS-based studies of cognitive status (Chen and Zissimopoulos, 2018; Crimmins et al., 2016, 2021; Langa et al.,

2017; Liu et al., 2020). Classification was based on a summary score derived from a series of cognitive tests: 10-word immediate (0–10) and delayed recall (0–10) tests of memory, a serial 7s subtraction test (0–5) of working memory and counting backwards (0–2) to assess attention and processing speed. Summary scores of cognitive functioning based on these tests range from 0 to 27 and are used to classify cognitive status into normal (12–27), CIND (7–11), and dementia (0–6) (Crimmins et al., 2011). These data came from the imputed cognitive scores based on 2016 HRS core interview.

2.3. Inflammation and immune biomarkers

Inflammation levels were indicated by levels of albumin, high-sensitivity C-reactive protein (CRP), the neutrophil count to lymphocyte count ratio (NLR) (Balta et al., 2016; Chung et al., 2020) and a summary measure of the number of cytokines out of 5 that are in the highest risk quartile: IL6, TNFR1, IL10, TGF Beta, and IL-1Ra. To combine cytokine measures, first, we standardized each cytokine to adjust for differences in variances across measures. Next, we quartiled each cytokine and dichotomized each measure to indicate highest risk group: 1 – highest quartile, 0 – otherwise. We also evaluated whether a continuous measurement of the summed cytokines would have the same association. We found no difference between the continuous measure or the categorical measure.

Immunosenescence was indicated by Cytomegalovirus (CMV) seropositivity combined with CMV IgG antibody levels. Our CMV was a 4-category variable based on seropositivity and antibody level. The lab that processed the blood-based assays used any cutoff interval (COI) above 1 as indicative of seropositivity. Furthermore, level of CMV infection was indicated by the tertial of the IgG antibody level among those who were seropositive. High levels of IgG can reflect an inability to control a past infection, which may be indicative of immunosenescence. Our 4-category variable includes seronegative CMV, CMV seropositive and 1st tertile of IgG antibody levels, CMV seropositive and 2nd tertile of IgG antibody levels, and CMV seropositive and 3rd tertile of IgG antibody levels.

Immune functioning is also indicated by information on naïve cell subsets produced using cryopreserved PBMC samples and flow cytometry: $CD4^+$ T_N/T_M and $CD8^+$ T_N/T_M.

Descriptive information on the inflammatory and immune functioning biomarkers and assays are included in Supplementary Table 1.

2.4. Additional covariates

Models were also adjusted for age, sex/gender, and presence of APO*e4* alleles. Age was based on birthdate provided by respondents. Sex was categorized into male or female. APO*e4* allele information was provided by the Health and Retirement Study. We included number of APO*e4* alleles as important controls due to the strong association with ADRD risk (Huang et al., 2004; Slooter et al., 1998). For data collected from 2006 to 2010, saliva was collected from HRS participants, which was directly genotyped using a Taqman allelic discrimination SNP assay, where available, or imputed from preexisting genotype array data otherwise (Faul et al., 2021). We treat APO*e4 alleles* as a continuous measure.

2.5. Statistical analysis

We compared biomarker levels across the three cognitive status groups (dementia, CIND, and cognitively normal). We tested whether biomarker levels were significantly different for both those with dementia and those with CIND when compared to cognitively normal adults, using a chi-square and *t*-test. Biomarkers were tested separately. Next, we used multinomial logistic regression models to test biomarker associations and cognitive status, net of other biomarkers. For these analyses, all biomarkers were included together. We examined variance/covariance matrices to determine whether a further reduction of the biomarker subset was necessary. We found that covariances between biomarkers were relatively weak. The smallest covariance was −0.005 (neutrophil/lymphocyte ratio and $CD4^+$ T_N/T_M) and the strongest was −0.33 (albumin and CRP), indicating that biomarkers were not strongly colinear (see Supplementary Table 2). In the first model, all biomarkers were included along with controls for age, sex, and APOE *e4* alleles. In the second model, further adjustments for race/ethnicity and education were included to account for differences in race/ethnicity or education composition of the sample population.

3. Results

3.1. Sample characteristics

As shown in Table 1, the mean age in our sample was 68.7 years, a majority of the sample were female (54.3%), and most were non-Hispanic White or other (82.0%). About 9.3% identified as non-Hispanic Black and 8.7% identified as Hispanic. Approximately 43.4% had 12 or fewer years of schooling; 25.5% had between 13 and 15 years of schooling; and 31.1% had 16 years or more. The average number of APOE e4 alleles was 0.3.

The mean albumin level was 4.0 U/L. The mean logged CRP was 0.8. The average NLR was 2.27. And the average number of high-risk cytokine quartiles was 1.25. About 37% of respondents were CMV seronegative or borderline. IgG antibody levels were 0.9–245.2 for respondents in the 1st tertile, 245.3 to 588.9 in the 2nd tertile, and 589.1 to 1817.0 in the 3rd tertile. The mean $CD4^+$ T_N/T_M level was 1.0, and the mean $CD8^+$ T_N/T_M level was 0.4.

About 83.1% of the sample had normal cognitive functioning, 13.6% had CIND, and 3.3% had dementia.

Table 1
Analytical sample characteristics, HRS 2016 VBS (N = 5959).

	Mean (SD)	Percent	Range
Dementia Status			
Normal		83.1%	
Cognitive Impairment without Dementia (CIND)		13.6%	
Dementia		3.3%	
Demographic Characteristics			
Age	68.7 (9.1)		56–100
Female		54.3%	
Race/Ethnicity			
Non-Hispanic Whites and Others		82.0%	
Non-Hispanic Black		9.2%	
Hispanic		8.7%	
Education (Years)			
0–12		43.4%	
13–15		25.5%	
16+		31.1%	
APOE 4	0.3 (0.5)		0–2
Inflammation			
Albumin	4.0 (0.3)		2.2–5.5
CRP (log)	0.8 (1.0)		−1.6-5.5
Neutrophil/Lymphocyte Ratio (NLR)	2.3 (1.2)		0.0–24.2
Num of High-Risk z scored Cytokine Quartiles	1.3 (1.1)		0–5
Immune Functioning Indicators			
CMV Seronegative and Borderline		37.0%	
CMV Seropositive 1st Tertile (0.9–245.2 IgG Antibody)		21.0%	
CMV Seropositive 2nd Tertile (245.3–588.9 IgG Antibody)		21.0%	
CMV Seropositive 3rd Tertile (589.1–1817.0 IgG Antibody)		21.0%	
$CD4^+$ T_N/T_M	1.0 (0.7)		0.00–7.1
$CD8^+$ T_N/T_M	0.4 (0.4)		0.0–4.2

3.2. Descriptive information on inflammation, infection and immune markers

We found higher levels of inflammation and poorer immune functioning for people with some type of cognitive impairment (CIND or dementia) when compared to people who were cognitively normal. The means and confidence intervals of each biomarker by cognitive status are reported in Table 2. People with dementia or CIND had greater NLR, lower albumin levels, lower CRP levels, and a higher mean number of risk level cytokines.

We also found that people with dementia or CIND were more likely to be seropositive for CMV and report greater IgG levels. We found no differences in $CD4^+$ T_N/T_M, but found lower $CD8^+$ T_N/T_M levels among those with dementia or CIND.

3.3. Regression results

Next, we estimated two multinomial logistic regression models to test biomarker associations with cognitive impairment status when all are examined simultaneously and while controlling for sex and age (Model 1) and to test whether some of the associations between inflammation and immune functioning and cognitive impairment status are influenced by the demographic composition of the sample (Model 2). These results are presented in Table 3.

In the first model, we found statistically significant associations between cognitive impairment status and several of the inflammation and immune markers. Among inflammation markers, we found lower levels of albumin and high cytokine risk levels were associated with an increased likelihood of having dementia or CIND. Compared to cognitively normal respondents, a 1 U/L increase in albumin was associated with 62% lower risk of having dementia (RRR = 0.38, $p < .001$) and a 31% lower risk of having CIND (RRR = 0.69, $p < .001$). Each unit increase in the cytokine summary measure was associated with 20% increase in risk of having dementia and 17% increase in risk of having CIND (RRR = 1.20, $p < .05$ and RRR = 1.17, $p < .001$, respectively).

For immune markers, we found that CMV seropositive respondents were more likely to be classified as having dementia or CIND. For dementia, relative risk ratios (RRR) ranged from 3.37 to 3.65 ($p < .001$). For CIND, the relative risk ratio ranged from 1.65 to 2.04 ($p < .001$). We also found a negative association with dementia for $CD4^+$ T_N/T_M and a positive association with $CD8^+$ T_N/T_M. We found a negative association between $CD4^+$ T_N/T_M and CIND. We found no statistically association with CIND for $CD8^+$ T_N/T_M values.

In Model 2, we observed inflammation and immune functioning associations with cognitive status, after adjusting for race/ethnicity and education. As in Model 1, albumin levels and the cytokine summary score continued to be associated with greater likelihood of having dementia. These associations, however, were attenuated: for example, the relative risk ratio approached parity for albumin, increasing from 0.38 in Model 1 to 0.55 in Model 2. We, however, no longer found a statistically significant difference in albumin levels between those with CIND and cognitively normal adults. In contrast, the association between cognitive impairment status and number of high-risk cytokines remained largely unchanged.

For CMV, differences between the cognitively impaired and cognitively normal were largely attenuated. We did, however, observe a significant association between dementia and CMV positivity in the 1st tertile. Additionally, $CD4^+$ T_N/T_M and $CD8^+$ T_N/T_M were no longer associated with cognitive status, after adjusting for education level and race/ethnicity. These findings provide evidence that cognitive impairment status associated with CMV and albumin may be, in part, driven by inflammation and immune functioning differences found across education and race/ethnic categories.

4. Discussion

Our study examined the association between inflammation and immune functioning and cognitive status in a nationally representative study of older adults. Similar to existing studies, we found strong associations of greater inflammation and worse immune functioning with having CIND or dementia when compared to being cognitively normal. When these markers were included in the fully adjusted models, we found an increased likelihood of cognitive impairment on a more limited set of biomarkers. We also found some evidence that links between albumin, CMV, and T-cells biomarkers and cognitive status may be related to education levels and race/ethnicity.

Our results are consistent with other studies that have documented the strong association between increased inflammation and worse cognitive health outcomes (Bettcher and Kramer, 2014). We found that greater levels of inflammation as indicated by increased cytokine risk levels and lower levels of albumin were strongly associated with increased risk of having CIND or dementia, when compared to being cognitively normal. This finding aligns with previous work that has found a strong association of proinflammatory markers with neurodegeneration through worse brain structural changes such as lower hippocampal volume (Walker et al., 2017) or increasing vascular permeability which contributes to cerebrovascular disease and undermines white matter integrity.

Table 2
Mean (SD) or percent of inflammatory, infection, and immune markers by dementia status, adjusted for sex and age, HRS 2016 VBS (N=5959).

	With Dementia		CIND		Normal	
	Adjusted Mean	95% CI	Adjusted Mean	95% CI	Adjusted Mean	95% CI
Inflammation						
Albumin	3.91*	3.90, 3.92	3.94*	3.93, 3.94	3.97	3.97, 3.97
CRP (log)	0.82*	0.82, 0.83	0.83*	0.83, 0.83	0.84	0.84, 0.84
Neutrophil Lymphocyte Ratio (NLR)	2.46*	2.42, 2.50	2.38*	2.37, 2.40	2.27	2.26, 2.27
Num of High-Risk z scored Cytokine Quartiles	1.55*	1.50, 1.60	1.43*	1.40, 1.45	1.26	1.25, 1.26
IL6 Risk Quartile	0.30*	0.30, 0.31	0.28*	0.28, 0.29	0.25	0.25, 0.25
IL10 Risk Quartile	0.30*	0.29, 0.31	0.28*	0.28, 0.28	0.25	0.25, 0.25
IL-1Ra Risk Quartile	0.24*	0.24, 0.24	0.24*	0.24, 0.24	0.25	0.25, 0.25
TGFβ1 Risk Quartile	0.33*	0.32, 0.34	0.30*	0.29, 0.30	0.25	0.25, 0.25
TNFR1 Risk Quartile	0.38*	0.36, 0.40	0.33*	0.32, 0.33	0.25	0.25, 0.26
Immune Functioning						
CMV Seronegative and Borderline	10.61%*	4.94, 16.29	23.11%*	19.67, 26.55	39.96%	38.17, 41.75
CMV Seropositive 1st Tertile	30.10%*	22.56, 37.65	26.11%	22.67, 29.55	20.07%	18.65, 21.49
CMV Seropositive 2nd Tertile	27.84%	20.77, 34.91	23.29%	19.97, 26.61	20.80%	19.34, 22.26
CMV Seropositive 3rd Tertile	31.44%*	23.73, 39.14	27.49%*	23.91, 31.06	19.17%	17.73, 20.61
$CD4^+$ T_N/T_M	0.99	0.98, 1.00	0.98	0.98, 0.99	0.98	0.98, 0.98
$CD8^+$ T_N/T_M	0.27*	0.26, 0.29	0.31*	0.30, 0.32	0.36	0.36, 0.37

*$p < .05$ indicates difference from normal dementia status.

Table 3
Nested multinomial regressions of predicting dementia and cognitive impairment without dementia from individual inflammation and immune functioning biomarkers, HRS 2016 VBS (N = 5959).

	Model 1		Model 2	
	Dementia	CIND	Dementia	CIND
	RRR	RRR	RRR	RRR
Inflammation				
Albumin	0.38 [0.23, 0.61]***	0.69 [0.53, 0.91]**	0.55 [0.33, 0.92]*	0.86 [0.66, 1.14]
CRP (log)	1.11 [0.95, 1.29]	1.04 [0.96, 1.13]	1.05 [0.90, 1.22]	0.99 [0.91, 1.07]
Neutrophil Lymphocyte Ratio (NLR)	0.99[0.89, 1.12]	1.02 [0.96, 1.08]	1.08 [0.97, 1.20]	1.07 [1.00, 1.14]*
Number of High-Risk z scored Cytokine Quartiles	1.20 [1.04, 1.39]*	1.17 [1.09, 1.27]***	1.22 [1.06, 1.41]**	1.17 [1.08, 1.27]***
Immune Functioning				
CMV Status (Seronegative and borderline as reference)				
CMV 1st Tertile	3.37 [2.04, 5.57] ***	1.78 [1.42, 2.23] ***	1.87 [1.11, 3.15]*	1.22 [0.96, 1.54]
CMV 2nd Tertile	3.31 [1.98, 5.54] ***	1.65 [1.31, 2.08] ***	1.62 [0.94, 2.78]	1.09 [0.85, 1.39]
CMV 3rd Tertile	3.65 [2.19, 6.08] ***	2.04 [1.63, 2.56] ***	1.69 [0.99, 2.89]	1.26 [0.99, 1.61]
$CD4^+$ T_N/T_M	0.72 [0.55, 0.94]*	0.81 [0.71, 0.92]**	0.96 [0.74, 1.26]	0.98 [0.86, 1.12]
$CD8^+$ T_N/T_M	1.85 [1.21, 2.83]**	1.20 [0.93, 1.55]	1.12 [0.70, 1.80]	0.85 [0.64, 1.12]
Age	1.11 [1.09, 1.13]***	1.07 [1.06, 1.08]***	1.12 [1.10, 1.14]***	1.07 [1.06, 1.08]***
Female	0.93 [0.67, 1.28]	0.85 [0.72, 1.00]	0.82 [0.59, 1.14]	0.79 [0.67, 0.94]**
Race/ethnicity (NH White/other as Ref)				
NH Black			7.26 [4.67, 11.29]***	3.88 [3.00, 5.01]***
Hispanic			5.05 [3.26, 7.85]***	2.71 [2.10, 3.50]***
Education (13–15 yrs as Ref)				
0–12 yrs			3.03 [1.93, 4.77]***	2.01 [1.64, 2.47]***
16+ yrs			0.21 [0.08, 0.50]***	0.45 [0.34, 0.60]***
APOE4	1.38 [1.03, 1.86]*	1.36 [1.17, 1.58]***	1.41 [1.04, 1.93]*	1.35 [1.15, 1.58]***
Pseudo R^2	0.1778		0.2862	

***p < .001; **p < .01; *p < .05.

While the neurodegenerative pathways associated with inflammation have been well-researched, results from different studies have been inconsistent: showing either no association (Sundelöf et al., 2009), a positive association (Walker et al., 2017), or negative association (Metti et al., 2014). These results may be inconsistent due to the specific biomarkers used to measure inflammation. While we cannot dismiss these mixed findings outright, our study provides a more robust investigation of inflammation and cognitive status by drawing on a large nationally representative sample of older adults and incorporating several biomarkers simultaneously. We found worse levels of inflammation across all inflammatory markers among cognitively impaired individuals in the bivariate associations, but only albumin and high-risk cytokine quartiles were significant in the multivariate models. CRP, which had yielded mixed results in other studies (Hsu et al., 2017), was not statistically significant in the full models. These findings suggest that including specific inflammatory biomarkers may result in different conclusions on the links between inflammation and cognitive status. And these results provide some evidence that CRP may not be the strongest measure for understanding the association between cognitive impairment and inflammation. The lack of association between CRP and cognitive impairment may be due to CRP non-specificity when distinguishing between acute infection and chronic low-grade elevated inflammation levels.

Additionally, it is important to note that our findings do not clarify the causal role of inflammation. While growing evidence using animal models or longitudinal data has pointed to a causal link (Schmidt et al., 2002; Wichmann et al., 2014), reverse causation may be a factor: elevated inflammatory levels may be in response to damage or injury that had already occurred in the brain rather than antecedent to dementia (Schmidt et al., 2002). Therefore, the strong associations that we found between inflammation and cognitive impairment may be in part related to reverse causation, which our cross-sectional data cannot test. Longitudinal studies in the future will provide a more careful investigation of timing and further evidence that inflammation may lead to cognitive impairment. Nonetheless, the strong associations observed in this study provide evidence that inflammation may have an important role in identifying people with dementia in population health research and, potentially, for understanding the mechanisms related to dementia.

Regarding immune functioning, as expected, we found strong results from our analysis of CMV. Previous studies have found that cognitive impairment was linked closely with HIV, Herpes Simplex Virus, pneumonia, and CMV (Sochocka et al., 2017; Stebbins et al., 2020). These associations are primarily driven by increased risk of transition to dementia (Chiu et al., 2014; Sochocka et al., 2017), steeper declines in cognitive functioning (Nimgaonkar et al., 2016), and greater likelihood of being classified as having a cognitive impairment (Aiello et al., 2006). In line with previous work, in our study, respondents with CMV seropositivity were more likely to have CIND or dementia. This association remained robust even when adjusting for other associated inflammation or immune functioning biomarkers.

Lastly, in our evaluation of other immune functioning markers, we found significant associations between cognitive status and T-cell markers ($CD4^+$ T_N/T_M and $CD8^+$ T_N/T_M) before accounting for race/ethnicity and educational levels. However, the multinomial logistic regression results were mixed. $CD4^+$ T_N/T_M was negatively associated with poor cognitive status (CIND and dementia), while $CD8^+$ T_N/T_M was positively associated with dementia. Prior research evaluating these measures with chronological aging, biological aging, and chronic health conditions (cancer, diabetes, heart disease, and lung disease) has found negative associations with both T-cell markers, providing evidence that lower levels of these specific T-cell subsets are associated with poor aging outcomes (Thyagarajan et al., 2022). This mixed finding with cognitive status warrants additional investigation, but also provides some evidence that T-cell subsets may not be strong predictive biomarkers of cognitive status, especially when accounting for other inflammatory and immune functioning markers. In fact, in our analysis of means, we found no differences in $CD4^+$ T_N/T_M across cognitive status, and lower levels of $CD8^+$ T_N/T_M among those with dementia or CIND, which contrasts with the association found in the full models.

However, after adjusting for race/ethnicity and education, we found that the association between immune functioning markers and cognitive impairment weakened. CMV findings were mixed. T-cell markers were no longer associated with being cognitively impaired. This finding points to two potential explanations that require further investigation. Part of the association may be driven by the greater inflammation levels and worse immune functioning among people with lower levels of education and racial/ethnic minoritized populations that are at greater

risk of cognitive impairment. Or, the significant attenuation of their associations with cognitive impairment from prior models suggests that worse immune functioning may be an important pathway that elevates the risk of cognitive impairment for minoritized populations or people with lower levels of education.

While our study provides a significant contribution to understanding the association of inflammation and immune functioning with cognitive impairment in population-based surveys, it has some important limitations. First, our estimates may be conservative due to the disproportionate exclusion of people with dementia. Only 3.3% of our analytical sample had dementia, which is significantly below the 4.5% of HRS respondents aged 56 and older who had dementia in 2016. People with dementia are disproportionately excluded because 1) they are institutionalized or 2) require a proxy respondent. Both these conditions were part of the exclusion criteria for the VBS sample. Additionally, while we have included several biomarkers that have been recently included in population-based surveys, there are many additional neurodegenerative biomarkers that may be important to consider in future work, such as Ptau 181 and Aβ40/42, which are associated with ADRD pathology and neuroinflammation (Popp et al., 2017). Finally, the associations we observed are cross-sectional. Longitudinal analysis of dementia and CIND onset would increase our understanding of the potential causal relationships between these biological indicators and cognitive status.

Our study examines how inflammation and immune functioning are tied to cognitive impairment among older adults in the United States. It is one of the first studies to use extensive biological information and be generalizable to the US population. Both greater levels of inflammation and poorer immune functioning were tied to increased risk of cognitive impairment. However, some of the association with immune functioning may be tied to demographic composition, which requires further investigation to elevate the role of inflammation and immune functioning in minority health and health disparities. Understanding the role of inflammation and immune functioning may lead to improvements in cognitive health for the population by better understanding the role of biological risk more broadly, for which this study points to some potentially important biomarkers to understand these processes.

Funding

This research was supported by the National Institute on Aging (grant numbers P30 AG043073, R56 AG057778, T32 AG000037, P30 AG17265, R01 AG060110, K99AG076964); and infrastructure support from Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant number P2CHD042849).

Declaration of competing interest

None.

Data availability

The data are publicly available on the HRS website: https://hrs.isr.umich.edu/about.

Acknowledgements

Mateo P Farina wrote the manuscript and guided the analysis. Jung Ki Kim carried out the analysis. Mark D Hayward provided feedback on the conceptual model. Eileen M Crimmins wrote sections of the manuscript and guided the analysis. All authors participated in editing.

The HRS is a longitudinal project sponsored by the National Institute on Aging (NIA U01AG009740).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2022.100559.

References

Aiello, A.E., Haan, M.N., Blythe, L., Moore, K., Gonzalez, J.M., Jagust, W., 2006. The influence of latent viral infection on rate of cognitive decline over 4 years. J. Am. Geriatr. Soc. 54 (7), 1046–1054. https://doi.org/10.1111/j.1532-5415.2006.00796.x.

Balta, S., Celik, T., Mikhailidis, D.P., et al., 2016. The relation between atherosclerosis and the neutrophil–lymphocyte ratio. Clin. Appl. Thromb. Hemost. 22 (5), 405–411. https://doi.org/10.1177/1076029615569568.

Barnes, L.L., Capuano, A.W., Aiello, A.E., et al., 2015. Cytomegalovirus infection and risk of alzheimer disease in older Black and white individuals. J. Infect. Dis. 211 (2), 230–237. https://doi.org/10.1093/infdis/jiu437.

Bate, S.L., Dollard, S.C., Cannon, M.J., 2010. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. Clin. Infect. Dis. 50 (11), 1439–1447. https://doi.org/10.1086/652438.

Bettcher, B.M., Kramer, J.H., 2014. Longitudinal inflammation, cognitive decline, and Alzheimer's disease: a mini-review. Clin. Pharmacol. Ther. 96 (4), 464–469. https://doi.org/10.1038/clpt.2014.147.

Britschgi, M., Wyss-Coray, T., 2007. Systemic and acquired immune responses in Alzheimer's disease. In: International Review of Neurobiology, vol. 82. Neuroinflammation in Neuronal Death and Repair. Academic Press, pp. 205–233. https://doi.org/10.1016/S0074-7742(07)82011-3.

Chen, C., Zissimopoulos, J.M., 2018. Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. Alzheimers Dement Transl Res Clin Interv 4, 510–520. https://doi.org/10.1016/j.trci.2018.08.009.

Chiu, W.C., Tsan, Y.T., Tsai, S.L., Chang, C.J., Wang, J.D., Chen, P.C., 2014. Hepatitis C viral infection and the risk of dementia. Eur. J. Neurol. 21 (8) https://doi.org/10.1111/ene.12317, 1068-e59.

Chung, D., Lee, K.O., Choi, J.W., et al., 2020. Blood neutrophil/lymphocyte ratio is associated with cerebral large-artery atherosclerosis but not with cerebral small-vessel disease. Front. Neurol. 11. https://www.frontiersin.org/article/10.3389/fneur.2020.01022. (Accessed 17 May 2022).

Crimmins, E.M., Kim, J.K., Langa, K.M., Weir, D.R., 2011. Assessment of cognition using surveys and neuropsychological assessment: the health and retirement study and the aging, demographics, and memory study. J Gerontol Ser B 66B (Suppl. l_1), i162–i171. https://doi.org/10.1093/geronb/gbr048.

Crimmins, E.M., Faul, J., Thyagarajan, B., Weir, D., 2017. Venous blood collection and assay protocol in the 2016 health and retirement study venous blood study (VBS). https://hrsonline.isr.umich.edu/modules/meta/vbs/2016/desc/HRS2016VBSDD.pdf?_ga=2.171951269.408614381.1589823285-975920407.1589823285&_ga=2.171951269.408614381.1589823285-975920407.1589823285. (Accessed 12 November 2020).

Crimmins, E.M., Saito, Y., Kim, J.K., 2016. Change in cognitively healthy and cognitively impaired life expectancy in the United States: 2000–2010. SSM - Popul Health 2, 793–797. https://doi.org/10.1016/j.ssmph.2016.10.007.

Crimmins, E.M., Thyagarajan, B., Kim, J.K., Weir, D., Faul, J., 2021. Quest for a summary measure of biological age: the health and retirement study. *GeroScience*. Published online February 5. https://doi.org/10.1007/s11357-021-00325-1.

Doty, K.R., Guillot-Sestier, M.V., Town, T., 2015. The role of the immune system in neurodegenerative disorders: adaptive or maladaptive? Brain Res. 1617, 155–173. https://doi.org/10.1016/j.brainres.2014.09.008.

Faul J, Collins S, Smith J, Zhao W, Weir D. APOE and Serotonin Transporter Alleles – Early Release. Published online 2021.

Glass, C.K., Saijo, K., Winner, B., Marchetto, M.C., Gage, F.H., 2010. Mechanisms underlying inflammation in neurodegeneration. Cell 140 (6), 918–934. https://doi.org/10.1016/j.cell.2010.02.016.

Hansson, G.K., 2005. Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 352 (16), 1685–1695. https://doi.org/10.1056/NEJMra043430.

Hsu, P.F., Pan, W.H., Yip, B.S., Chen, R.C.Y., Cheng, H.M., Chuang, S.Y., 2017. C-reactive protein predicts incidence of dementia in an elderly asian community cohort. J. Am. Med. Dir. Assoc. 18 (3) https://doi.org/10.1016/j.jamda.2016.12.006, 277.e7-277.e11.

Huang, W., Qiu, C., von Strauss, E., Winblad, B., Fratiglioni, L., 2004. APOE genotype, family history of dementia, and alzheimer disease risk: a 6-year follow-up study. Arch. Neurol. 61 (12), 1930–1934. https://doi.org/10.1001/archneur.61.12.1930.

Imtiaz, F., Shafique, K., Mirza, S.S., Ayoob, Z., Vart, P., Rao, S., 2012. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int. Arch. Med. 5 (1), 2. https://doi.org/10.1186/1755-7682-5-2.

Kim, J.W., Stewart, R., Kang, H.J., et al., 2018. Longitudinal associations between serum cytokine levels and dementia. Front. Psychiatr. 9 https://doi.org/10.3389/fpsyt.2018.00606.

Langa, K.M., Larson, E.B., Crimmins, E.M., et al., 2017. A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Intern. Med. 177 (1), 51–58. https://doi.org/10.1001/jamainternmed.2016.6807.

Lin, W.R., Wozniak, M.A., Wilcock, G.K., Itzhaki, R.F., 2002. Cytomegalovirus is present in a very high proportion of brains from vascular dementia patients. Neurobiol. Dis. 9 (1), 82–87. https://doi.org/10.1006/nbdi.2001.0465.

Liu, H., Zhang, Z., won, Choi S., Langa, K.M., 2020. Marital status and dementia: evidence from the health and retirement study. J Gerontol Ser B 75 (8), 1783–1795. https://doi.org/10.1093/geronb/gbz087.

Llewellyn, D.J., Langa, K.M., Friedland, R.P., Lang, I.A., 2010. Serum albumin concentration and cognitive impairment. Curr. Alzheimer Res. 7 (1), 91–96.

Lövdén, M., Fratiglioni, L., Glymour, M.M., Lindenberger, U., Tucker-Drob, E.M., 2020. Education and cognitive functioning across the life span. Psychol. Sci. Publ. Interest 21 (1), 6–41. https://doi.org/10.1177/1529100620920576.

Lue, L.F., Brachova, L., Civin, W.H., Rogers, J., 1996. Inflammation, aβ deposition, and neurofibrillary tangle formation as correlates of Alzheimer's disease neurodegeneration. J. Neuropathol. Exp. Neurol. 55 (10), 1083–1088. https://doi.org/10.1097/00005072-199655100-00008.

Lueg, G., Gross, C.C., Lohmann, H., et al., 2015. Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. Neurobiol. Aging 36 (1), 81–89. https://doi.org/10.1016/j.neurobiolaging.2014.08.008.

Martorana, A., Bulati, M., Buffa, S., et al., 2012. Immunosenescence, inflammation and Alzheimer's disease. Longev. Heal. 1 (1), 8. https://doi.org/10.1186/2046-2395-1-8.

McColl, B.W., Allan, S.M., Rothwell, N.J., 2009. Systemic infection, inflammation and acute ischemic stroke. Neuroscience 158 (3), 1049–1061. https://doi.org/10.1016/j.neuroscience.2008.08.019.

Metti, A.L., Yaffe, K., Boudreau, R.M., et al., 2014. Change in inflammatory markers and cognitive status in the oldest-old women from the study of osteoporotic fractures. J. Am. Geriatr. Soc. 62 (4), 662–666. https://doi.org/10.1111/jgs.12739.

Moss, P., Khan, N., 2004. CD8+ T-cell immunity to cytomegalovirus. Hum. Immunol. 65 (5), 456–464. https://doi.org/10.1016/j.humimm.2004.02.014.

Ng, A., Tam, W.W., Zhang, M.W., et al., 2018. IL-1β, IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. Sci. Rep. 8 (1), 12050 https://doi.org/10.1038/s41598-018-30487-6.

Nimgaonkar, V.L., Yolken, R.H., Wang, T., et al., 2016. Temporal cognitive decline associated with exposure to infectious agents in a population-based, aging cohort. Alzheimer Dis. Assoc. Disord. 30 (3), 216–222. https://doi.org/10.1097/WAD.0000000000000133.

Pellicanò, M., Larbi, A., Goldeck, D., et al., 2012. Immune profiling of Alzheimer patients. J. Neuroimmunol. 242 (1–2), 52–59. https://doi.org/10.1016/j.jneuroim.2011.11.005.

Popp, J., Oikonomidi, A., Tautvydaitė, D., et al., 2017. Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults. Brain Behav. Immun. 62, 203–211. https://doi.org/10.1016/j.bbi.2017.01.020.

Ramasubramanian, R., Meier, H.C.S., Vivek, S., et al., 2022. Evaluation of T-cell aging-related immune phenotypes in the context of biological aging and multimorbidity in the Health and Retirement Study. Immun. Ageing 19 (1), 33. https://doi.org/10.1186/s12979-022-00290-z.

Santoro, A., Bientinesi, E., Monti, D., 2021. Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? Ageing Res. Rev. 71, 101422 https://doi.org/10.1016/j.arr.2021.101422.

Sayed, A., Bahbah, E.I., Kamel, S., Barreto, G.E., Ashraf, G.M., Elfil, M., 2020. The neutrophil-to-lymphocyte ratio in Alzheimer's disease: current understanding and potential applications. J. Neuroimmunol. 349, 577398 https://doi.org/10.1016/j.jneuroim.2020.577398.

Schmidt, R., Schmidt, H., Curb, J.D., Masaki, K., White, L.R., Launer, L.J., 2002. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia aging study. Ann. Neurol. 52 (2), 168–174. https://doi.org/10.1002/ana.10265.

Shah, N., Parikh, V., Patel, N., et al., 2014. Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: insights from the National Health and Nutrition Examination Survey-III. Int. J. Cardiol. 171 (3), 390–397. https://doi.org/10.1016/j.ijcard.2013.12.019.

Slooter, A.J.C., Cruts, M., Kalmijn, S., et al., 1998. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the rotterdam study. Arch. Neurol. 55 (7), 964–968. https://doi.org/10.1001/archneur.55.7.964.

Sochocka, M., Zwolińska, K., Leszek, J., 2017. The infectious etiology of Alzheimer's disease. Curr. Neuropharmacol. 15 (7), 996–1009. https://doi.org/10.2174/1570159X15666170313122937.

Stebbins, R.C., Noppert, G.A., Yang, Y.C., Dowd, J.B., Simanek, A., Aiello, A.E., 2020. Immune response to cytomegalovirus and cognition in the health and retirement study. Am. J. Epidemiol. https://doi.org/10.1093/aje/kwaa238 kwaa238.

Sundelöf, J., Kilander, L., Helmersson, J., et al., 2009. Systemic inflammation and the risk of Alzheimer's disease and dementia: a prospective population-based study. J Alzheimers Dis 18 (1), 79–87. https://doi.org/10.3233/JAD-2009-1126.

Thyagarajan, B., Barcelo, H., Crimmins, E., et al., 2018. Effect of delayed cell processing and cryopreservation on immunophenotyping in multicenter population studies. J. Immunol. Methods 463, 61–70. https://doi.org/10.1016/j.jim.2018.09.007.

Thyagarajan, B., Faul, J., Sithara, V., et al., 2022. Age-related differences in T-cell subsets in a nationally representative sample of people older than age 55: findings from the health and retirement study. J Gerontol Biol Sci 77 (5), 927–933. https://doi.org/10.1093/gerona/glab300.

Unger, M.S., Marschallinger, J., Kaindl, J., et al., 2018. Doublecortin expression in CD8+ T-cells and microglia at sites of amyloid-β plaques: a potential role in shaping plaque pathology? Alzheimers Dement 14 (8), 1022–1037. https://doi.org/10.1016/j.jalz.2018.02.017.

Walker, K.A., Power, M.C., Hoogeveen, R.C., et al., 2017. Midlife systemic inflammatory markers are associated with late-life brain volume: the ARIC study. Neurology 89 (22), 2262–2270. https://doi.org/10.1212/WNL.0000000000004688.

Walker Keenan, A., Power Melinda, C., Hoogeveen Ron, C., et al., 2017. Midlife systemic inflammation, late-life white matter integrity, and cerebral small vessel disease. Stroke 48 (12), 3196–3202. https://doi.org/10.1161/STROKEAHA.117.018675.

Westman, G., Berglund, D., Widén, J., et al., 2014. Increased inflammatory response in cytomegalovirus seropositive patients with Alzheimer's disease. PLoS One 9 (5). https://doi.org/10.1371/journal.pone.0096779.

Wichmann, M.A., Cruickshanks, K.J., Carlsson, C.M., et al., 2014. Long-term systemic inflammation and cognitive impairment in a population-based cohort. J. Am. Geriatr. Soc. 62 (9), 1683–1691. https://doi.org/10.1111/jgs.12994.

Xue, J., Huang, W., Chen, X., et al., 2017. Neutrophil-to-Lymphocyte ratio is a prognostic marker in acute ischemic stroke. J. Stroke Cerebrovasc. Dis. 26 (3), 650–657. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.010.

Zhang, R., Miller, R.G., Madison, C., et al., 2013. Systemic immune system alterations in early stages of Alzheimer's disease. J. Neuroimmunol. 256 (1), 38–42. https://doi.org/10.1016/j.jneuroim.2013.01.002.

Zhang, Z., Hayward, M.D., Yu, Y.L., 2016. Life course pathways to racial disparities in cognitive impairment among older Americans. J. Health Soc. Behav. 57 (2), 184–199. https://doi.org/10.1177/0022146516645925.