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

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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 helper and CD8+ T cytotoxic/T regulatory and CD8+ T helper/T regulatory) 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 helper/T regulatory. 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 helper/T regulatory and CD8+ T helper/T regulatory 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; Pellicano et al., 2012; Sundelof 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; Sundelof 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

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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; Lueng et al., 2015; Pellican 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⁻ T₉/T₉M and CD4⁻ T₉/T₉M. 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., 2016; Moss and Khan, 2004). The immune system’s inability to suppress CMV viral replication indicates poor immune functioning. In elderly adults, 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 (Bate et al., 2016; 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 (Lovdén 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 (socio-demographic 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), and dementia, using an approach adopted in many HRS-based studies of cognitive status (Chen and Zissimopoulos, 2018; Crimmins et al., 2016, 2021; Langa et al.,
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 and immune biomarkers 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 quantified 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) category variable based on seropositivity and antibody level. The lab positivity combined with CMV IgG antibody levels. Our CMV was a 4-category variable including 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/T and CD8^+ T/T.

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 APOE ε4 alleles. Age was based on birthdate provided by respondents. Sex was categorized into male or female. APOE ε4 allele information was provided by the Health and Retirement Study. We included number of APOE ε4 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 APOE ε4 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/T) 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 ε4 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 ε4 alleles was 0.3.

The mean albumin level was 4.0 U/L. The mean logCRP 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 seropositive or borderline. IgG antibody levels were 0.9–245.2 for respondents in the 1st tertile, 245.3 to 589.9 in the 2nd tertile, and 589.1 to 1817.0 in the 3rd tertile. The mean CD4^+ T/T level was 1.0, and the mean CD8^+ T/T 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).

| Dementia Status | Mean (SD) | Percent | Range |
|----------------|-----------|---------|-------|
| Normal         | 83.1%     | 56–100  |       |
| Cognitive Impairment without Dementia (CIND) | 13.6% |       |
| Dementia | 3.3% |       |

| Demographic Characteristics | Mean (SD) | Percent | Range |
|-----------------------------|-----------|---------|-------|
| 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 ε4                     | 0.3 (0.5) |         | 0–2   |

| Inflammation                | Mean (SD) | Percent | Range |
|-----------------------------|-----------|---------|-------|
| Albumin                     | 4.0 (0.3) | 2.2–5.5 |       |
| CRP (log)                   | 0.8 (1.0) | –6–1.6 | 5.5   |
| Neutrophil/Lymphocyte Ratio (NLR) | 2.3 (1.2) | 0.0–24.2 |       |
| Num of High-Risk z scored Cytokine | 1.3 (1.1) | 0.5   |

| Quartiles | Mean (SD) | Percent | Range |
|-----------|-----------|---------|-------|
| Neutrophil/Lymphocyte Ratio (NLR) | 2.3 (1.2) | 0.0–24.2 |       |
| Num of High-Risk z scored Cytokine | 1.3 (1.1) | 0.5   |

| Immune Functioning Indicators | Mean (SD) | Percent | Range |
|-------------------------------|-----------|---------|-------|
| CMV Seronegative and Borderline | 37.0% |         |       |
| CMV Seropositive 1st Tertile (0.9–245.2 IgG Antibody) | 21.0% |         |       |
| CMV Seropositive 2nd Tertile (245.3–589.9 IgG Antibody) | 21.0% |         |       |
| CMV Seropositive 3rd Tertile (589.1–1817.0 IgG Antibody) | 21.0% |         |       |
| CD4^+ T/T                  | 1.0 (0.7) | 0.0–7.1 |       |
| CD8^+ T/T                  | 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+ Tn/Tm, but found lower CD8+ Tn/Tm 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+ Tn/Tm and a positive association with CD8+ Tn/Tm. We found a negative association between CD4+ Tn/Tm and CIND. We found no statistically association with CIND for CD8+ Tn/Tm 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 first tertile. Additionally, CD4+ Tn/Tm and CD8+ Tn/Tm 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 underlines 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              | 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 | 2.27 |
| Num of High-Risk t-scored Cytokine Quartiles | 1.55* | 1.50, 1.60 | 1.43* | 1.40, 1.45 | 1.26 | 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 |
| TNFRI 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+ Tn/Tm | 0.99 | 0.98, 1.00 | 0.98 | 0.98, 0.99 | 0.98 | 0.98, 0.98 |
| CD8+ Tn/Tm | 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.
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+ T5/T6 and CD8+ T5/T6) before accounting for race/ethnicity and educational levels. However, the multinomial logistic regression results were mixed. CD4+ T5/T6 was negatively associated with poor cognitive status (CIND and dementia), while CD8+ T5/T6 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+ T5/T6 across cognitive status, and lower levels of CD8+ T5/T6 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 minority 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 Aj40/42, 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.

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Declaration of competing interest

None.

Data availability

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

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Appendix A. Supplementary data

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

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