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Investigating the Association of Inflammation Scores with Cognitive Function

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B.S., Johns Hopkins University, 2020

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Abstract

Investigating the Association of Inflammation Scores with Cognitive Function

By Ananya G. Reddy

Background: Mild cognitive impairment is a transitional stage between normal cognitive function and dementia. Previous research has investigated inflammatory markers in relation to cognition. However, individual inflammatory markers may not fully reflect the inflammatory state. As such, we aimed to assess the relationship between cognitive impairment using both individual inflammatory markers and composite measures of inflammation.

Methods: Participants in the English Longitudinal Study of Aging were used to investigate the cross-sectional (n=4228) as well two-year (n=3670) and ten-year (n=2604) longitudinal associations between inflammation at baseline and cognitive function. The association of memory, executive function, processing speed, and aggregate cognition was investigated with four biomarkers (high-sensitivity C-reactive protein (CRP), ferritin, fibrinogen, and white blood cell (WBC) count), as well as with two composite inflammation scores. Inflammation scores were calculated by classifying individual inflammatory biomarkers into quintiles, which were then summed. IS1 incorporated CRP, ferritin, and fibrinogen, while IS2 incorporated CRP, ferritin, fibrinogen, and WBC count. Age, sex, education, marital status, occupation, prevalent CVD or risk factors, and smoking were included as covariates.

Results: Higher serum ferritin was associated with better memory (B = 0.11, S.E. = 0.06) at baseline and higher WBC count was associated with worse processing speed (B = -1.35, S.E. = 0.65) at baseline. No other markers were associated with cognitive function at baseline. In the longitudinal analyses, no markers were associated with cognitive function after adjustment. Neither inflammation score was significantly associated with cognition after adjustment for covariates in the cross-sectional or longitudinal analyses.

Conclusions: In this analysis, systemic low-grade inflammation does not appear to be significantly associated with cognitive function, either cross-sectionally or longitudinally.

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Background

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a condition in which individuals have diminished memory and cognitive function beyond what is expected for their age that does not significantly affect daily function.[1, 2] MCI has been described as a "transitional state" between normal cognitive function and dementia, which is characterized by more severe memory impairment and cognitive dysfunction and has greater impact on the ability to independently carry out daily activities.[3] A study comparing those with MCI and those with Alzheimer's disease (AD) to healthy controls found that while memory was similarly impaired in MCI and mild AD, AD patients had greater impairment in other cognitive domains; additionally, the rate of cognitive decline in MCI was greater than in healthy individuals, but less than in those with AD.[3]

Criteria for a diagnosis of MCI includes 1) concern about changes in cognitive function from the patient, a knowledgeable other, or a clinician; 2) evidence of impairment in at least one cognitive domain assessed through neuropsychological testing; 3) preservation of independent functioning; and 4) no significant impairment in social or occupational functioning.[4] Additional characteristics, such as memory impairment or progressive cognitive decline, may suggest MCI is due to AD.[4]

Various tests are used to diagnose MCI, including the Memory Alteration Test, the Montreal Cognitive Assessment, and the Mini-Mental State Exam, among others.[5] Though studies have shown comparable accuracy in diagnosing MCI between neuropsychological tests, MCI has been shown to be a heterogenous condition, with impairment observed across several cognitive domains, including speed and attention, memory and learning, visuospatial function,

language, and executive function.[5, 6] A study of comprehensive neuropsychological batteries on patients with MCI has shown that most have impairment in more than one cognitive domain.[7]

MCI does not always progress to AD. A meta-analysis of 19 studies investigating conversion of MCI to AD found that the mean annual conversion rate was 10.25% (95% CI: 6.9%, 11.9%).[8] A separate meta-analysis of 25 studies investigating reversion from MCI to normal cognition found a reversion rate of 24.93% (95% CI: 18.38%, 29.97%).[9] Both meta-analyses had high heterogeneity, as estimates in the studies included varied significantly. However, individuals who revert from MCI to normal cognition may continue to be at higher risk for future cognitive impairment.[10]

Incidence and Prevalence

Estimates of the prevalence of MCI vary significantly. A 2012 review of population-based studies published on MCI prevalence reported estimates between 3% and 42%, with a median estimate of 26.4%; however, when including other synonymous terms, the prevalence estimates ranged from 0.5% to 42%.[2] Estimates of incidence rates for MCI are similarly broad, ranging from 21.5 to 71.3 per 1,000 person-years among individuals 65 years of age and older.[2] In the US, the most recent estimate for all-cause MCI prevalence was 22.7% (95% CI: 22.3%, 23.2%).[11] Prevalence of MCI differed by race; prevalence among non-Hispanic Blacks was estimated to be 32.0%, prevalence among Hispanics was estimated to be 25.9%, while prevalence among non-Hispanic Whites was estimated to be 21.1%.[11] The prevalence of MCI in the US is expected to increase over the next 40 years by 76.2%, with larger increases seen among Hispanics (333.8%) and non-Hispanic Blacks (141.8%) than in non-Hispanic Whites (25.9%); however, other studies have found that the incidence of MCI is not increasing or is even

decreasing.[11, 12] Studies have suggested that these trends could be explained by changes in diagnosis over time, as well as changes in risk factors such as education.[13, 14]

Risk Factors

A variety of risk factors are associated with MCI. The most well-established of these is age, which is associated with MCI through a variety of potential mechanisms. An analysis of data from the Italian Longitudinal Study of Aging found that those over 75 had 5.93 (95% CI: 3.17, 11.10) times the risk of MCI compared to those between 65 and 74.[15] A meta-analysis of 41 studies found that the prevalence of MCI increased from 9.5% (95% CI: 7.4%, 12.1%) among those between 60 and 69, to 14.6% (95% CI: 12.4%, 17.1%) among those between 70 and 79, to 23.6% (95% CI: 20.4%, 27.4%) among those 80 years and older.[16] As the US population is aging, the populations most at risk of MCI are rapidly increasing.[17]

While evidence has been mixed, studies suggest that sex may be associated with MCI. Multiple studies suggest that male sex is associated with higher risk of MCI.[18-20] However, other studies suggest that female sex is associated with higher risk of MCI, or support no association between MCI and sex.[21-23] Similarly, evidence also suggests race may be associated with MCI, although studies have had mixed results, with some studies showing that Black and Hispanic individuals have higher MCI risk, and other studies showing no association.[24-26] A proposed explanation for this variability in results is that sociodemographic factors – such as education, socioeconomic status, and access to care – are associated with race and may be responsible for any observed association of race with MCI.[26]

Educational attainment is well-established as a protective factor for MCI. Odds ratios estimating the effect of education on MCI range from 0.8 (95% CI: 0.61, 0.99) to 0.04 (95% CI:

0.02, 0.07).[15, 24] Additionally, higher educational level was associated with slower cognitive decline over a 12 month period, as assessed by several cognitive tests.[27]

Strong evidence suggests that a variety of cardiovascular diseases (CVD) and risk factors are risk factors for MCI. Risk factors for CVD include hypertension, diabetes mellitus, and dyslipidemia.[28] Studies of these CVD risk factors have indicated that they may be associated with MCI. Several longitudinal studies have found that higher blood pressure at baseline was associated with lower cognitive function at follow-up.[29-32] A systematic review presenting results of 54 studies found that several studies found significant associations between Type 2 diabetes with mild cognitive impairment.[33] Additionally, a meta-analysis found that the odds of progression from MCI to dementia was 1.53 (95% CI: 1.20, 1.97) higher in those with diabetes and 2.95 (95% CI: 1.23, 7.05) times higher in those with metabolic syndrome.[34] There may also be a genetic component to the relationship between diabetes and cognition, as a SNP associated with higher susceptibility to type 2 diabetes has also been linked to progression from MCI to AD.[35] Although there is comparatively less evidence for an association between dyslipidemia and cognitive impairment, some studies have shown that dyslipidemia is associated with cognitive dysfunction.[36, 37] Lifestyle risk factors for CVD may also play a role in MCI; studies have shown associations between MCI and factors such as smoking and diet.[38-40] Additionally, CVD conditions, such as heart failure and coronary artery disease, are associated with MCI. In a meta-analysis of four case-control studies, the odds ratio for cognitive impairment among those with heart failure was 1.67 (95% CI: 1.15, 2.42).[41] Another meta-analysis of 15 studies found that the odds of MCI or dementia were 1.32 (95% CI: 1.17, 1.48) times higher among those with coronary artery disease; additionally, analysis of six longitudinal studies reported a hazard ratio

for incident MCI or dementia of 1.51 (95% CI: 1.24, 1.85) among those with coronary artery disease.[42]

Inflammation and MCI

Several biological mechanisms are implicated in MCI, such as oxidative stress and amyloid beta accumulation.[43-45] Previous literature has established that inflammation is also involved in MCI.[46-49] Inflammation is an immune response that consists of many pathways involved in processes such as wound-healing and defense against foreign bodies.[50, 51] Features of the inflammatory response include increased vasodilation and endothelial permeability, infiltration of leukocytes into tissue, and increased circulation of proinflammatory cytokines, growth factors, and enzymes.[51, 52] While acute inflammation commonly occurs in response to immediate threats such as trauma or infection, chronic inflammation is an inflammatory state that persists for long periods and can be due to a variety of causes.[51] Several leading causes of global morbidity and mortality are mediated by chronic inflammation, including diabetes, cardiovascular disease, arthritis, chronic obstructive pulmonary disease, and cognitive decline and dementia.[52]

The link between inflammation and cognition has been well-established. A meta-analysis of seven studies found that increased C-reactive protein (CRP) was associated with 45% (95% CI: 10%, 91%) higher risk of all-cause dementia, while increased IL-6 was associated with a 32% (95% CI: 6%, 64%) higher risk of all-cause dementia.[53] Another meta-analysis of 40 studies investigating cytokine levels found that peripheral levels of several proinflammatory cytokines, including IL-6, TNF-α, IL-1β, TGF-β, IL-12 and IL-18, were significantly associated with AD.[54] Additionally, several risk factors for cognitive decline, including age, diet, and smoking, are associated with chronic low-level inflammation.[52] However, the association between

inflammation with MCI is less clear. A meta-analysis of 44 studies found no association between MCI and any of 14 inflammatory markers assessed, while a different meta-analysis of 31 studies yielded significant associations between four inflammatory markers and MCI. [55, 56] Differences in these estimates may be explained by use of different definitions or diagnostic criteria to assess MCI.

A variety of inflammatory markers have been investigated in relation to cognition. While investigation of individual cognitive markers provides support for the association between inflammation and cognition, inflammation is a complex process involving many biological molecules. Composite measures of inflammation could provide a more comprehensive evaluation of the inflammatory state associated with cognitive impairment. Two previous studies that have used composite measures of inflammatory biomarkers have found that these measures are associated with cognitive decline.[57, 58] Various methods for calculating inflammation scores have been described.[57-61] In this analysis, we used an inflammation score calculated using quantiles of four inflammatory markers to investigate association with cognitive outcomes. We aimed to assess whether this inflammation score was associated with cognition at the time of measurement as well as after two- and ten- years of follow-up in a prospective cohort study of 4,228 participants.

Introduction

Mild cognitive impairment (MCI) refers to a loss of cognitive function among older individuals beyond what is expected for their age, that does not diminish the ability to carry out day-to-day tasks.[1, 2] MCI is a disease of aging and is expected to increase significantly in prevalence in the future as the US elderly population grows.[17] Current estimates place the prevalence of MCI in the US at 22.7% (95% CI: 22.3%, 23.2%), with a projected prevalence of 76.2% by 2060.[11] MCI can be considered a transitional state between normal cognition and more severe impairment, such as Alzheimer's disease (AD).[3] Previous literature suggests that the average annual conversion rate of MCI to AD is 10.25% (95% CI: 6.9%, 11.9%).[8]

Many mechanisms are associated with cognitive impairment and loss of cognitive function, including chronic inflammation. Studies have shown that higher inflammation is associated with cognitive impairment, though evidence for association with MCI specifically is inconsistent. Several studies have assessed the association of inflammatory markers, such as C-reactive protein (CRP), ferritin, fibrinogen, and white blood cell (WBC) count, with cognitive function. Though most studies thus far have focused on single markers of inflammation, composite measures of multiple inflammatory markers may better reflect the inflammatory state.

To better understand the relationship of composite measures of inflammation with cognition, we sought to assess the association of cognitive function both cross-sectionally and longitudinally with an inflammation score incorporating four inflammatory markers in a sample of 4,228 participants. We hypothesized that the inflammation score would be inversely associated with cognitive function in both cross-sectional and longitudinal analyses.

Methods

Participants

Details on the design of the English Longitudinal Study of Aging (ELSA) have been published.[62] Briefly, ELSA is a nationally representative prospective cohort of adults over 50 years of age living in England. Waves 4, 5, and 9 of ELSA received approval from the National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint Research Ethics Committee, the Berkshire Research Ethics Committee, and the South Central - Berkshire Research Ethics Committee, respectively, and all participants provided informed consent upon enrollment. Participants were recruited from respondents to the Health Survey for England (HSE), an annual cross-sectional study, and were eligible if they or a member of their household had participated in the 1998, 1999, or 2001 HSE and agreed to follow-up, were born before 1 March 1952, and were living in a private household in England at the time of data collection. The initial cohort consisted of 11,391 core participants and the individual response rate was 67%. Refreshment samples were added at waves 3, 4, 6, 7, and 9. Eligibility criteria remained the same except for birth year requirements.

Data collection for the ELSA occurs in two-year "waves" and consist of in-home computer-assisted personal interviews conducted by an interviewer, and self-completion questionnaires. Data collected encompass demographic information, physical and mental health status, and social, behavioral, and psychological factors. Additionally, participants were asked to participate in nurse home visits to collect data on various physical measures and samples for biomarker assessment at waves 2, 4, 6, 8, and 9.

Data for this report were obtained at waves 4, 5, and 9. There were 9,896 core participants in wave 4, of whom 6,879 participated in the cognitive assessments and had complete cognitive and covariate data. Of the core participants who had complete data, 4,282

participated in the nurse visit and had complete data on inflammatory markers. After excluding participants with prevalent dementia, senility, serious memory impairment, Parkinson's disease, and AD, 4,228 participants were included in the analysis. For the longitudinal analyses, data from waves 5 and 9 were used. The analytic sample for the longitudinal analyses consisted of the 3,670 and 2,604 participants who had complete cognitive data at waves 5 and 9, respectively.

Measures

Inflammatory Markers

Data on inflammatory markers were collected during the wave 4 nurse visit. Blood samples were taken from consenting participants who did not have a clotting or bleeding disorder, had never had seizures, and were not taking anticoagulant medications. Fasting blood samples, defined as those drawn when the participant had not consumed food or drink besides water for at least five hours prior to blood collection, were taken when possible. Respondents who were over 80 years old, who were diabetic and on treatment, who had clotting or bleeding disorder, had a history of seizures, who were taking anticoagulant medications, who seemed frail, or whose health the nurse was concerned about were not asked to fast prior to sample collection.

Inflammatory markers measured at wave 4 were C-reactive protein (CRP), ferritin, fibrinogen, and white blood cell (WBC) count. Details on measurement of blood analytes are described in the Heath Survey for England technical report, as the same methods were used for analysis of ELSA samples.[63] High-sensitivity serum CRP was measured using the NLatex CRP mono Immunoassay on the Behring Nephelometer II Analyzer. Analysis of ferritin was conducted using the Abbott Microparticle Enzyme Immunoassay (MEIA)/IMX ferritin assay method. Fibrinogen was measured using the Organon Teknika MDA 180 analyzer, using a

modified Clauss thrombin clotting method. WBC count was measured using the Abbott Diagnostics Cell-Dyn 4000 hematology-automated analyzer. All blood sample analysis was performed at the Royal Victoria Infirmary Laboratory in Newcastle-upon-Tyne, UK.

Inflammation Score

To calculate the inflammation score, values of each inflammatory marker were divided into quintiles and assigned a value from 0 (lowest quintile) to 4 (highest quintile). The inflammation scores for each subject were calculated by summing these values across inflammatory markers. The first inflammation score (IS1) included CRP, ferritin, and fibrinogen, with possible values between 0 and 12. The second inflammation score (IS2) included CRP, ferritin, fibrinogen, and WBC count, with possible values between 0 and 16. Additionally, the two inflammation scores were calculated using values of the inflammatory markers divided into sex-specific quintiles to yield sex-specific inflammation scores. Similar methods to calculate inflammation scores have been used in other analyses.[59, 61]

Cognitive Function

Three measures of cognitive function were used from waves 4 and 5, and two measures of cognitive function were used from wave 9. All cognitive tests used have been used extensively in other studies of cognition. To assess memory, a word span task was used. A list of 10 words were read aloud at the speed of one word every two seconds. One of four possible word lists was randomly assigned to each participant. Participants were asked to recall as many words as possible immediately after the list was read; the immediate recall score was the number of words remembered. Participants were also asked to recall as many words as possible after completing other cognitive tests; the number of words remembered after the delay was the delayed recall score. The total sum of words remembered in both the immediate and delayed recall trials was

used to assess memory. Cancellation tests have been studied as measures of processing speed.[64] A double letter cancellation test was administered, in which participants were asked to cross out as many Ps and Ws as possible in one minute from a page filled with random letters. At the end of the minute, participants were asked to underline the last letter searched. The total number of letters searched was used to assess processing speed in waves 4 and 5; in wave 9, the cancellation test was not conducted. Executive function was assessed using the Semantic Verbal Fluency test, in which participants were asked to name as many animals as possible within one minute.[65] The number of animals names was used to measure executive function. A measure of aggregate cognition was calculated by normalizing the results of each test and averaging the normalized results of each test together. Similar methods to assess cognition in analysis of ELSA data have been reported.[66]

Confounders

Confounders were selected based on prior literature. Demographic variables include age, modelled continuously, and sex, modelled as a binary variable. Ethnicity was considered as a confounder; however, as no non-white participants were included in the analytic sample, ethnicity was not included. Education was assessed as five categories based on highest achieved qualification, incorporating both technical and academic qualifications. Loosely, the categories correspond to: college degree; some college; completion of secondary school; some secondary school; no qualifications. Marital status was assessed as a binary variable, with married status incorporating participants currently married or in civil partnerships. Occupation was used to model socioeconomic status. Occupations were classified into three categories (higher managerial, administrative, and professional occupations; intermediate occupations; routine and

manual occupations) based on the English National Statistics Socio-economic Classification (NS-SEC).

Cardiovascular disease (CVD) and related risk factors were also included in the analysis, as CVD is associated with cognitive dysfunction.[67] Prevalent CVD was modelled as binary variable based on self-reported physician diagnosis of any of the following conditions: angina, coronary artery disease, heart failure, or other ischemic heart disease. Prevalent high cholesterol, prevalent hypertension, and prevalent stroke were all modelled as binary variables based on self-reported physician diagnosis of high cholesterol, hypertension, and stroke, respectively. Smoking was modelled as a binary variable based on whether participants had ever smoked.

Statistical Analysis

All statistical analysis was conducted using SAS 9.4. Concentrations of CRP and ferritin were log-transformed to reduce skewness. The association of inflammatory markers with covariates was assessed by calculating the Pearson correlation coefficient for continuous covariates, and two-sample t-tests or one-way analysis of variance as appropriate for categorical covariates. Normalized individual cognitive outcome data were averaged to create an aggregate measure of cognition. Ordinary least squares regression was performed for each cognitive outcome and for the aggregate measure of cognition. Robust standard errors were reported due to heteroscedasticity. Three models were used for the cross-sectional analysis. Model 1 was a crude model, with no covariate adjustment. Model 2 included adjustment for demographic and socioeconomic factors, including age, sex, marital status, education, and occupation. Model 3 included adjustment for all model 2 factors, and additionally adjusted for CVD, associated risk factors, and smoking. The longitudinal analyses were conducted similarly to the cross-sectional analysis; however, outcome data from waves 5 and 9 were used for the 2-year and 10-year

follow-up, respectively. In addition to the three models used in the cross-sectional analysis, model 4 adjusted for baseline cognitive outcome data. Additionally, as the cognitive function data collected in wave 9 did not use the letter cancellation task, processing speed was not used as an outcome or in calculating the aggregate measure of cognition in the longitudinal 10-year analysis.

Results

Sample Characteristics

Sample characteristics are summarized in Table 1. Of the 4,228 participants included in the cross-sectional analysis, 2001 (47.33%) were male and (52.67%) were female, with an average participant age of 65 years at baseline. Demographics of participants included in the longitudinal analyses were similar to those in the cross-sectional analysis, with an average participant age of 65 years in both samples and 47.98% and 47.24% male participants included in the two- and ten-year analyses, respectively. Participants across each analysis were also distributed similarly in terms of educational attainment, occupation, cognition at baseline and follow-up, inflammatory marker levels, IS1, IS2, and health and smoking status. For participants in the longitudinal analysis, average cognition for any of the outcomes did not change significantly from baseline to follow up in either group.

Concentrations of at least one inflammatory marker correlated with each of the covariates ($p = 0.03$ to <0.0001) included in the model. Additionally, all inflammatory markers were correlated with each other, except for ferritin and fibrinogen. Higher concentrations of inflammatory markers were associated with greater age, lower occupational status, lower educational achievement, being unmarried, prevalent CVD, hypertension, high cholesterol,

history of stroke, and smoking. IS1 and IS2 were both approximately normally distributed. Both IS1 and IS2 were correlated with all covariates except prevalent CVD and history of stroke among the participants included in the cross-sectional analysis, all covariates except prevalent CVD, history of stroke, and marital status among participants in the two-year longitudinal analysis, and all covariates except prevalent CVD, history of stroke, marital status, and high cholesterol among participants in the ten-year longitudinal analysis.

Cross-Sectional Analysis

Results of the cross-sectional analysis are summarized in Table 2. Inflammatory marker concentrations were significantly associated with multiple domains of cognition in the unadjusted model. FOR EXAMPLE, However, upon adjustment for socioeconomic and demographic factors, most associations were no longer significant, and only two associations remained significant after adjustment for CVD and associated risk factors. Higher concentrations of ferritin were associated with better memory, and higher WBC count was associated with slower processing speed. IS1 and IS2 were significantly associated with all cognitive outcomes in the unadjusted model; however, no significant associations persisted after adjustment for sociodemographic factors.

Longitudinal Analyses

Results of the longitudinal analysis are presented in Table 3 (two-year follow-up) and Table 4 (ten-year follow-up). After two years of follow-up, CRP and fibrinogen were significantly associated with executive function, processing speed, and aggregate cognition in the unadjusted model. After adjustment for demographic factors, the only significant associations were between CRP and executive function, fibrinogen and processing speed, and fibrinogen and aggregate cognition. No significant associations were observed in models 3 or 4. IS1 and IS2

were both significantly associated with executive function, processing speed, and aggregate cognition in the unadjusted model; only the association between processing speed and IS2 persisted in model 2, and no associations were observed in model 3. At ten years of follow-up, the only significant association observed was between WBC count and memory in the unadjusted model. After adjustment, no significant associations were observed. No significant associations were observed between IS1 and IS2 and any cognitive outcome in any of the models.

Discussion

The aim of this study was to examine cross-sectional associations and longitudinal associations between cognitive function and inflammation, using both individual markers of inflammation and composite measures incorporating multiple inflammatory markers. In a large, nationally representative sample, we observed cross-sectional associations between ferritin and memory as well as WBC count and processing speed after adjustment for sociodemographic and health related variables; no other significant relationships were observed in the fully adjusted model. In the longitudinal analyses, no significant associations were observed in the fully adjusted model at either two or ten years of follow-up. Additionally, no significant associations were observed with the inflammation scores and cognition after adjustment, either cross-sectionally or longitudinally.

The observation that inflammatory markers were not associated with cognitive function was inconsistent with previous work. Previous studies have demonstrated cross-sectional associations between cognition and markers of low-grade inflammation. In an analysis of data from the Rotterdam Study investigating 3,874 individuals, CRP and IL-6 were significantly

associated with worse overall cognition and executive function.[68] Another analysis of 1,965 participants found significant associations between decreased cognitive function and several inflammatory biomarkers, including soluble tumor necrosis factor receptors 1 and 2, CRP, and interleukin-6 (IL-6).[69] Other studies have shown similar cross-sectional associations between inflammatory markers and cognitive function.[70-73] However, a previous analysis of ELSA data investigating CRP and cognitive function also found no cross-sectional association between cognition and CRP at baseline, after adjustment for CVD and related risk factors.[74]

Similarly, studies have shown longitudinal associations between inflammation and cognitive function. A study of ELSA wave 2 data found that higher CRP predicted poorer memory, executive function, and global cognition at follow-up.[74] Several other studies have found similar results in different cohorts.[75-77] However, a prospective population-based cohort study found that participants with higher CRP had lower risk of cognitive impairment compared to those with low CRP (HR: 0.46, 95% CI: 0.26, 0.80), and that baseline inflammation was not associated with risk of cognitive impairment, while high IL-6 levels were association with cognitive impairment.[78] The authors of this study posited that medications usage, survival effects, or other confounding factors could be responsible for this observation. Some of these factors, particularly medication usage, which was not controlled for in this analysis, could explain the results of our analysis.

The observation that increased ferritin levels are cross-sectionally associated with better memory is consistent with research that suggests that iron deficiency is linked to poorer memory. Though most research on anemia and cognitive function is in infants and children, three studies have found significant cross-sectional associations between anemia and cognitive function.[79-81]

As an iron storage protein, ferritin levels are affected by iron levels in the blood and as such, the observed association most likely reflects processes related to anemia rather than inflammation.[82]

Other studies have used composite measures of inflammation in assessing cognition. In a study using data from the Atherosclerosis Risk in Communities cohort study, four inflammatory markers (fibrinogen, WBC count, von Willebrand factor, and factor VIII) were converted to z-scores and then averaged to create an inflammation score that was significantly associated cognition at 20 years follow-up.[58] Another study used a similar method to calculate inflammation scores based on ten biomarkers (pentraxin 3, serum amyloid P, endothelin-1, adiponectin, resistin, plasminogen activating inhibitor-1, receptor for advanced glycation end products, interleukin-6, interleukin-2, and interleukin-10) and found significant cross-sectional and longitudinal associations with cognition.[57] The methods and biomarkers used to calculate the inflammation scores in both studies is different than in our analysis, and as such may partially explain the null findings in our investigation of the association of inflammation scores with cognitive function.

Observational and clinical studies of the role of NSAIDs in cognitive impairment have had mixed results, suggesting that the role of inflammation in cognitive impairment may not be causal but rather reflective of other processes that affect cognition. In a case-control study of approximately 50,000 cases and 200,000 controls, NSAIDs were found to significantly decrease the odds of AD with five or more years of use.[83] However, some observational studies have found that the protective effect of NSAIDs on cognitive function is related to *APOE* genotype, while others show no association or even a positive association between NSAID use and cognitive decline or dementia.[84-87] Several clinical trials in AD patients or in elderly populations have also shown no effect of NSAIDs on slowing cognitive decline or preventing AD.[88-90] As

such, further research is needed before drawing conclusions about the role of inflammation in cognitive function.

Strengths and Limitations

While this study had a large, nationally representative set of participants with extensive data on a variety of sociodemographic and health-related variables, this study did have several limitations. As ELSA is an observational study, it is not possible to draw causal inferences from this analysis. Additionally, participants were predominantly white, possibly limiting the generalizability of findings. Measures of both cognition and inflammatory markers were limited; analysis of more comprehensive cognitive testing or incorporation of more inflammatory biomarkers into the inflammation scores may have yielded different results. In the longitudinal analyses, there may also have been bias due to attrition. Based on the results of this analysis, inflammation does not appear to be associated with cognitive function cross-sectionally or longitudinally in the population studied.

Public Health Significance

Inflammation scores have been used in investigation of other health conditions as well as in other studies of cognition. The value of inflammation scores is in the ability to represent the comprehensive inflammatory state more finely as compared to single measures of inflammation, which could have value in predicting disease course. However, results of this analysis suggest that there is no significant association between inflammation and cognition, either cross-sectionally or longitudinally. While further research is required to reconcile inconsistencies with other studies that have found longitudinal associations between inflammation and cognition, the results of this analysis suggest inflammation may not be the best target for interventions to improve cognitive function or slow cognitive decline. As such, future research into risk factors or possible therapies for cognitive decline should consider other mechanisms that could affect cognitive impairment.

Tables

Table 1. Participant Characteristics

Variable	Cross-Sectional (*n = 4228*) *n* (%) or Mean ±SD	Longitudinal – Two Year (*n = 3670*) *n* (%) or Mean ±SD	Longitudinal – Ten Year (*n = 2604*) *n* (%) or Mean ±SD
Age (years)	65.55 ± 9.07	65.40 ± 9.01	64.93 ± 8.90
Sex			
Male	2001 (47.33%)	1761 (47.98%)	1230 (47.24%)
Female	2227 (52.67%)	1909 (52.02%)	1374 (52.76%)
Marital status			
Single	1331 (31.48%)	1135 (30.93%)	1331 (31.48%)
Married or civil partnership	2897 (68.52%)	2535 (69.07%)	2897 (68.52%)
Education			
No qualifications	1315 (31.10%)	1144 (31.17%)	747 (28.69%)
Some secondary school	909 (21.50%)	792 (21.58%)	582 (22.35%)
Completion of secondary school	398 (9.41%)	348 (9.48%)	266 (10.22%)
Some college	734 (17.36%)	633 (17.25%)	450 (17.28%)
College degree	827 (20.62%)	753 (20.52%)	559 (21.47%)
Occupation			
Higher managerial, administrative, and professional	1541 (36.45%)	1345 (36.65%)	979 (37.60%)
Intermediate	1065 (25.19%)	921 (25.10%)	668 (25.65%)
Routine or manual	1622 (38.36%)	1404 (38.26%)	957 (36.76%)
Cognition at baseline			
Memory (total words recalled)	10.78 ± 3.39	10.84 ± 3.40	10.97 ± 3.35
Executive function (animals mentioned in one minute)	21.45 ± 6.53	21.56 ± 6.52	21.77 ± 6.58
Processing speed (letters searched)	300.84 ± 82.96	300.75 ± 82.24	-
Aggregate cognition (mean of normalized individual cognitive measures)	0.00 ± 0.71	0.01 ± 0.71	0.05 ± 0.84
Cognition at follow-up			
Memory (total words recalled)	-	10.97 ± 3.30	10.63 ± 3.63

Executive function (animals mentioned in one minute)	-	21.99 ± 6.49	22.80 ± 7.27
Processing speed (letters searched)	-	300.15 ± 79.81	-
Aggregate cognition (mean of normalized individual cognitive measures)	-	0.00 ± 0.71	0.00 ± 0.86
Inflammatory markers			
CRP (log)	0.65 ± 1.13	0.64 ± 1.13	0.61 ± 0.59
Ferritin (log)	4.49 ± 0.85	4.48 ± 0.85	4.49 ± 0.84
Fibrinogen (g/L)	3.37 ± 0.56	3.37 ± 0.56	3.35 ± 0.55
WBC count (x 10^9 cells/L)	6.44 ± 1.92	6.42 ± 1.52	6.37 ± 1.84
Inflammation scores			
Inflammation Score 1	6.17 ± 2.83	6.13 ± 2.83	6.09 ± 2.84
Inflammation Score 2	8.22 ± 3.49	8.16 ± 3.49	8.10 ± 3.52
CVD risk factors			
Prevalent ischemic heart disease	383 (9.06%)	322 (8.77%)	211 (8.10%)
History of stroke	127 (3.00%)	112 (3.05%)	82 (3.15%)
Prevalent hypertension	1583 (37.44%)	1359 (37.03%)	931 (35.75%)
Prevalent high cholesterol	1482 (35.05%)	1283 (34.96%)	925 (35.52%)
Smoking			
Current smoker	604 (14.29%)	505 (13.76%)	362 (13.90%)
Former or non-smoker	3624 (85.71%)	3165 (86.24%)	2242 (86.10%)

Table 2. Cross-Sectional Associations

Variable	Model 1 B (S.E.)	Model 2 B (S.E.)	Model 3 B (S.E.)
CRP			
Memory	-0.34 (0.05)*	-0.10 (0.04)*	-0.08 (0.04)
Executive function	-0.44 (0.09)*	-0.01 (0.08)	0.03 (0.09)
Processing speed	-2.83 (1.16)*	-0.93 (1.15)	-0.03 (1.16)
Aggregate cognition	-0.07 (0.01)*	0.01 (0.01)	-0.01 (0.01)
Ferritin			
Memory	0.11 (0.06)	0.12 (0.06)*	0.11 (0.06)*
Executive function	0.32 (0.12)*	0.06 (0.11)	0.06 (0.11)
Processing speed	-3.92 (1.50)*	-0.13 (1.53)	-0.15 (1.53)
Aggregate cognition	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
Fibrinogen			
Memory	-0.55 (0.09)*	-0.08 (0.08)	-0.02 (0.08)
Executive function	-0.70 (0.17)*	0.17 (0.17)	0.29 (0.17)
Processing speed	-4.55 (2.27)*	-1.57 (2.20)	-0.10 (2.25)
Aggregate cognition	-0.11 (0.02)*	-0.01 (0.02)	0.01 (0.02)
WBC Count			
Memory	-0.13 (0.03)*	-0.05 (0.02)*	-0.04 (0.02)
Executive function	-0.13 (0.05)*	-0.02 (0.05)	0.03 (0.05)
Processing speed	-2.84 (0.66)*	-1.90 (0.63)*	-1.35 (0.65)*
Aggregate cognition	-0.03 (0.01)*	-0.01 (0.01)*	-0.01 (0.01)
Inflammation Score 1			
Memory	-0.1 (0.02)*	-0.01 (0.02)	0.00 (0.02)
Executive function	-0.09 (0.04)*	0.04 (0.03)	0.05 (0.03)
Processing speed	-1.38 (0.45)*	-0.17 (0.43)	0.07 (0.44)
Aggregate cognition	-0.02 (0.00)*	0.00 (0.00)	0.00 (0.00)
Inflammation Score 2			
Memory	-0.09 (0.01)*	-0.02 (0.01)	-0.01 (0.01)
Executive function	-0.08 (0.03)*	0.02 (0.03)	0.05 (0.03)
Processing speed	-1.59 (0.36)*	-0.55 (0.35)	-0.27 (0.37)
Aggregate cognition	-0.02 (0.00)*	0.00 (0.00)	0.00 (0.00)

B reflects unstandardized coefficient for cognitive outcome
S.E. presented are robust standard error estimates
* $p < 0.05$
Model 1: unadjusted
Model 2: adjusted for age, sex, marital status, education, and occupation
Model 3: adjusted for model 2 covariates and prevalent ischemic heart disease, prevalent hypertension, prevalent high cholesterol, history of stroke, and current smoking

Table 3. Longitudinal Associations at Two Years Follow Up

Variable	Model 1 B (S.E.)	Model 2 B (S.E.)	Model 3 B (S.E.)	Model 4 B (S.E.)
CRP				
Memory	-0.08 (0.05)	-0.01 (0.05)	-0.01 (0.05)	0.00 (0.05)
Executive function	-0.32 (0.10)*	-0.19 (0.10)*	-0.16 (0.10)	-0.17 (0.10)
Processing speed	-2.88 (1.14)*	-2.04 (1.16)	-1.54 (1.18)	-1.47 (1.15)
Aggregate cognition	-0.04 (0.01)*	-0.02 (0.01)	-0.02 (0.01)	-0.01 (0.01)
Ferritin				
Memory	-0.01 (0.07)	0.02 (0.07)	0.01 (0.07)	-0.01 (0.07)
Executive function	-0.12 (0.13)	-0.16 (0.14)	-0.17 (0.14)	-0.18 (0.13)
Processing speed	-1.66 (1.57)	-0.21 (1.63)	-0.32 (1.63)	-0.24 (1.62)
Aggregate cognition	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)
Fibrinogen				
Memory	-0.14 (0.10)	-0.03 (0.10)	-0.01 (0.10)	0.00 (0.10)
Executive function	-0.55 (0.19)*	-0.30 (0.20)	-0.23 (0.20)	-0.30 (0.20)
Processing speed	-6.64 (2.38)*	-5.61 (2.43)*	-3.96 (2.49)	-3.78 (2.44)
Aggregate cognition	-0.07 (0.02)*	-0.04 (0.02)*	-0.03 (0.02)	-0.03 (0.02)
WBC Count				
Memory	-0.03 (0.03)	-0.01 (0.03)	-0.01 (0.03)	0.00 (0.03)
Executive function	-0.06 (0.06)	-0.03 (0.06)	0.00 (0.06)	0.00 (0.06)
Processing speed	-1.31 (0.74)	-0.86 (0.73)	-0.15 (0.76)	0.09 (0.75)
Aggregate cognition	-0.01 (0.01)	-0.01 (0.01)	0.00 (0.01)	0.00 (0.00)
Inflammation Score 1				
Memory	-0.01 (0.02)	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)
Executive function	-0.10 (0.04)*	-0.06 (0.04)	-0.04 (0.04)	-0.05 (0.05)
Processing speed	-1.37 (0.46)*	-0.88 (0.46)	-0.66 (0.47)	-0.65 (0.46)
Aggregate cognition	-0.01 (0.00)*	-0.01 (0.00)	0.00 (0.00)	0.00 (0.00)
Inflammation Score 2				
Memory	-0.01 (0.02)	0.01 (0.02)	0.01 (0.02)	0.01 (0.02)
Executive function	-0.07 (0.03)*	-0.03 (0.03)	-0.02 (0.03)	-0.03 (0.03)
Processing speed	-1.24 (0.37)*	-0.82 (0.38)*	-0.55 (0.39)	-0.48 (0.39)
Aggregate cognition	-0.01 (0.00)*	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

B reflects unstandardized coefficient for cognitive outcome
S.E. presented are robust standard error estimates
* $p < 0.05$
Model 1: unadjusted
Model 2: adjusted for age, sex, marital status, education, and occupation
Model 3: adjusted for model 2 covariates and prevalent ischemic heart disease, prevalent hypertension, prevalent high cholesterol, history of stroke, and current smoking
Model 4: adjusted for model 3 covariates and cognitive measure at baseline

Table 4. Longitudinal Associations at Ten Years Follow Up

Variable	Model 1 B (S.E.)	Model 2 B (S.E.)	Model 3 B (S.E.)	Model 4 B (S.E.)
CRP				
Memory	-0.09 (0.06)	0.00 (0.06)	0.00 (0.06)	0.01 (0.06)
Executive function	-0.12 (0.12)	0.03 (0.12)	0.07 (0.12)	0.06 (0.12)
Aggregate cognition	-0.02 (0.01)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)
Ferritin				
Memory	0.01 (0.09)	0.04 (0.09)	0.03 (0.09)	0.01 (0.09)
Executive function	-0.07 (0.17)	-0.14 (0.18)	-0.13 (0.18)	-0.15 (0.18)
Aggregate cognition	0.00 (0.02)	0.00 (0.02)	-0.01 (0.02)	-0.01 (0.02)
Fibrinogen				
Memory	-0.16 (0.13)	0.01 (0.13)	0.00 (0.14)	0.01 (0.14)
Executive function	-0.17 (0.26)	0.16 (0.27)	0.24 (0.27)	0.17 (0.27)
Aggregate cognition	-0.03 (0.03)	-0.01 (0.03)	0.02 (0.03)	0.01 (0.03)
WBC Count				
Memory	-0.08 (0.04)*	-0.06 (0.04)	-0.07 (0.04)	-0.06 (0.04)
Executive function	-0.07 (0.08)	-0.05 (0.08)	-0.03 (0.08)	-0.02 (0.08)
Aggregate cognition	-0.02 (0.01)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)
Inflammation Score 1				
Memory	-0.02 (0.02)	0.02 (0.02)	0.01 (0.02)	0.01 (0.02)
Executive function	-0.06 (0.05)	-0.01 (0.05)	0.00 (0.05)	-0.01 (0.05)
Aggregate cognition	-0.01 (0.01)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)
Inflammation Score 2				
Memory	-0.03 (0.02)	0.01 (0.02)	0.00 (0.02)	0.00 (0.02)
Executive function	-0.05 (0.04)	-0.01 (0.04)	0.01 (0.04)	0.00 (0.04)
Aggregate cognition	-0.01 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)

B reflects unstandardized coefficient for cognitive outcome
S.E. presented are robust standard error estimates
* $p < 0.05$
Model 1: unadjusted
Model 2: adjusted for age, sex, marital status, education, and occupation
Model 3: adjusted for model 2 covariates and prevalent ischemic heart disease, prevalent hypertension, prevalent high cholesterol, history of stroke, and current smoking
Model 4: adjusted for model 3 covariates and cognitive measure at baseline

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References

1. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. The Lancet. 2006; 367:1262-70.
2. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: Disparity of incidence and prevalence estimates. Alzheimer's & Dementia. 2012; 8:14-21.
3. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild Cognitive Impairment: Clinical Characterization and Outcome. Archives of Neurology. 1999; 56:303-8.
4. Langa KM, Levine DA. The Diagnosis and Management of Mild Cognitive Impairment: A Clinical Review. JAMA. 2014; 312:2551-61.
5. Breton A, Casey D, Arnaoutoglou NA. Cognitive tests for the detection of mild cognitive impairment (MCI), the prodromal stage of dementia: Meta-analysis of diagnostic accuracy studies. International Journal of Geriatric Psychiatry. 2019; 34:233-42.
6. Nordlund A, Rolstad S, Hellström P, Sjögren M, Hansen S, Wallin A. The Goteborg MCI study: mild cognitive impairment is a heterogeneous condition. Journal of Neurology, Neurosurgery & Psychiatry. 2005; 76:1485-90.
7. Ribeiro F, de Mendonça A, Guerreiro M. Mild Cognitive Impairment: Deficits in Cognitive Domains Other than Memory. Dementia and Geriatric Cognitive Disorders. 2006; 21:284-90.
8. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. International Psychogeriatrics. 2004; 16:129-40.
9. Malek-Ahmadi M. Reversion From Mild Cognitive Impairment to Normal Cognition: A Meta-Analysis. Alzheimer Dis Assoc Disord. 2016; 30:324-30.
10. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. Neurology. 2012; 79:1591-8.
11. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). Alzheimer's & Dementia. 2021; 17:1966-75.
12. Rajan KB, Weuve J, Wilson RS, Barnes LL, McAninch EA, Evans DA. Temporal changes in the likelihood of dementia and MCI over 18 years in a population sample. Neurology. 2020; 94:e292-e8.
13. Akushevich I, Yashkin AP, Kravchenko J, Ukraintseva S, Stallard E, Yashin AI. Time Trends in the Prevalence of Neurocognitive Disorders and Cognitive Impairment in the United States: The Effects of Disease Severity and Improved Ascertainment. Journal of Alzheimer's Disease. 2018; 64:137-48.
14. Hale JM, Schneider DC, Gampe J, Mehta NK, Myrskylä M. Trends in the Risk of Cognitive Impairment in the United States, 1996-2014. Epidemiology. 2020; 31:745-54.
15. Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology. 2004; 63:1882-91.
16. Lu Y, Liu C, Yu D, Fawkes S, Ma J, Zhang M, et al. Prevalence of mild cognitive impairment in community-dwelling Chinese populations aged over 55 years: a meta-analysis and systematic review. BMC Geriatrics. 2021; 21:10.

17. Anderson LA, Goodman RA, Holtzman D, Posner SF, Northridge ME. Aging in the United States: Opportunities and Challenges for Public Health. American Journal of Public Health. 2012; 102:393-5.
18. Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology. 2010; 75:889-97.
19. Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. Neurology. 2012; 78:342-51.
20. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med. 2008; 148:427-34.
21. Au B, Dale-McGrath S, Tierney MC. Sex differences in the prevalence and incidence of mild cognitive impairment: A meta-analysis. Ageing Res Rev. 2017; 35:176-99.
22. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. Arch Neurol. 2003; 60:1385-9.
23. Luck T, Riedel-Heller SG, Kaduszkiewicz H, Bickel H, Jessen F, Pentzek M, et al. Mild cognitive impairment in general practice: age-specific prevalence and correlate results from the German study on ageing, cognition and dementia in primary care patients (AgeCoDe). Dement Geriatr Cogn Disord. 2007; 24:307-16.
24. Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A, et al. Risk Factors for Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study: Part 2. Archives of Neurology. 2003; 60:1394-9.
25. Wright CB, DeRosa JT, Moon MP, Strobino K, DeCarli C, Cheung YK, et al. Race/Ethnic Disparities in Mild Cognitive Impairment and Dementia: The Northern Manhattan Study. Journal of Alzheimer's Disease. 2021; 80:1129-38.
26. Ysea-Hill O, Gomez C, Shah A, Hammel I, Rodriguez-Suarez M, Ruiz JG. Race-Based Differences in MCI And Dementia: A Propensity Score Matching Study. The American Journal of Geriatric Psychiatry. 2021; 29:S48-S9.
27. Vadikolias K, Tsiakiri-Vatamidis A, Tripsianis G, Tsivgoulis G, Ioannidis P, Serdari A, et al. Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. Brain and Behavior. 2012; 2:620-7.
28. Nash DT, Fillit H. Cardiovascular Disease Risk Factors and Cognitive Impairment. The American Journal of Cardiology. 2006; 97:1262-5.
29. Skoog I, Nilsson L, Persson G, Lernfelt B, Landahl S, Palmertz B, et al. 15-year longitudinal study of blood pressure and dementia. The Lancet. 1996; 347:1141-5.
30. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. American journal of epidemiology. 1993; 138:353-64.
31. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension. 1998; 31:780-6.
32. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function: the Honolulu-Asia Aging Study. Jama. 1995; 274:1846-51.

33. Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. Diabetic Medicine. 1999; 16:93-112.
34. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001; 56:42-8.
35. Girard H, Potvin O, Nugent S, Dallaire-Théroux C, Cunnane S, Duchesne S. Faster progression from MCI to probable AD for carriers of a single-nucleotide polymorphism associated with type 2 diabetes. Neurobiology of Aging. 2018; 64:157.e11-.e17.
36. Vintimilla R, Balasubramanian K, Hall J, Johnson L, O'Bryant S. Cardiovascular Risk Factors, Cognitive Dysfunction, and Mild Cognitive Impairment. Dementia and Geriatric Cognitive Disorders Extra. 2020; 10:154-62.
37. Zou Y, Zhu Q, Deng Y, Duan J, Pan L, Tu Q, et al. Vascular Risk Factors and Mild Cognitive Impairment in the Elderly Population in Southwest China. American Journal of Alzheimer's Disease & Other Dementias®. 2014; 29:242-7.
38. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a Risk Factor for Dementia and Cognitive Decline: A Meta-Analysis of Prospective Studies. American Journal of Epidemiology. 2007; 166:367-78.
39. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. Alzheimer's & Dementia. 2015; 11:1015-22.
40. Etgen T, Sander D, Bickel H, Förstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int. 2011; 108:743-50.
41. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, et al. Cognitive Impairment and Heart Failure: Systematic Review and Meta-Analysis. J Card Fail. 2017; 23:464-75.
42. Xia C, Vonder M, Sidorenkov G, Oudkerk M, de Groot JC, van der Harst P, et al. The Relationship of Coronary Artery Calcium and Clinical Coronary Artery Disease with Cognitive Function: A Systematic Review and Meta-Analysis. J Atheroscler Thromb. 2020; 27:934-58.
43. Mufson EJ, Binder L, Counts SE, DeKosky ST, de Toledo-Morrell L, Ginsberg SD, et al. Mild cognitive impairment: pathology and mechanisms. Acta Neuropathol. 2012; 123:13-30.
44. Parfenov VA, Ostroumova OD, Ostroumova TM, Kochetkov AI, Fateeva VV, Khacheva KK, et al. Vascular cognitive impairment: pathophysiological mechanisms, insights into structural basis, and perspectives in specific treatments. Neuropsychiatric disease and treatment. 2019; 15:1381.
45. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab. 2016; 36:172-86.
46. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. Archives of neurology. 2009; 66:300-5.
47. Gorelick PB. Can we save the brain from the ravages of midlife cardiovascular risk factors? : AAN Enterprises; 1999. p. 1114-.
48. Gorelick PB, Erkinjuntti T, Hofman A, Rocca WA, Skoog I, Winblad B. Prevention of vascular dementia. Alzheimer disease and associated disorders. 1999; 13:S131-9.
49. Launer LJ. Nonsteroidal anti-inflammatory drugs and Alzheimer disease: what's next? Jama. 2003; 289:2865-7.
50. Ahmed AU. An overview of inflammation: mechanism and consequences. Frontiers in Biology. 2011; 6:274.
51. Ward PA. Acute and chronic inflammation. Fundamentals of inflammation. 2010:1-16.

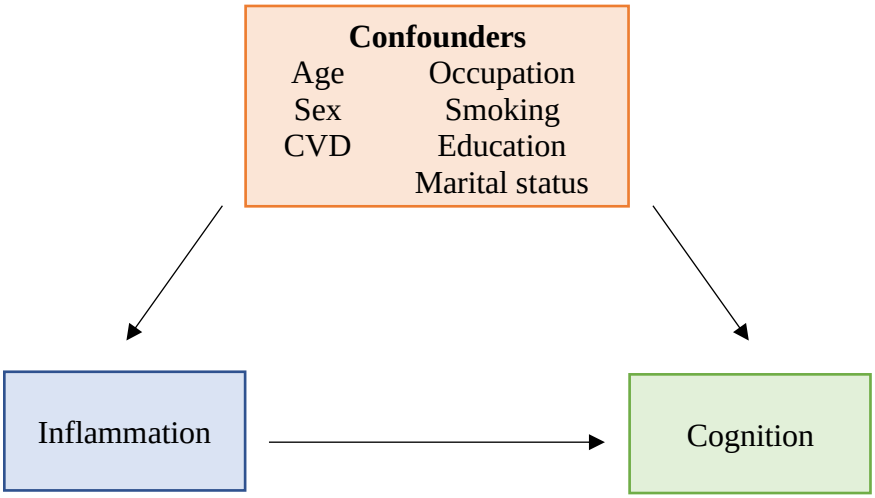
52. Pahwa R, Goyal A, Bansal P, Jialal I. Chronic Inflammation: StatPearls Publishing, Treasure Island (FL); 2021.
53. Koyama A, O'Brien J, Weuve J, Blacker D, Metti AL, Yaffe K. The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis. J Gerontol A Biol Sci Med Sci. 2013; 68:433-40.
54. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A Meta-Analysis of Cytokines in Alzheimer's Disease. Biological Psychiatry. 2010; 68:930-41.
55. Shen X-N, Niu L-D, Wang Y-J, Cao X-P, Liu Q, Tan L, et al. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. Journal of Neurology, Neurosurgery & Psychiatry. 2019; 90:590-8.
56. Saleem M, Herrmann N, Swardfager W, Eisen R, Lanctôt KL. Inflammatory Markers in Mild Cognitive Impairment: A Meta-Analysis. Journal of Alzheimer's Disease. 2015; 47:669-79.
57. Chi GC, Fitzpatrick AL, Sharma M, Jenny NS, Lopez OL, DeKosky ST. Inflammatory Biomarkers Predict Domain-Specific Cognitive Decline in Older Adults. The Journals of Gerontology: Series A. 2016; 72:796-803.
58. Walker KA, Gottesman RF, Wu A, Knopman DS, Gross AL, Mosley TH, Jr., et al. Systemic inflammation during midlife and cognitive change over 20 years: The ARIC Study. Neurology. 2019; 92:e1256-e67.
59. Bonaccio M, Di Castelnuovo A, Pounis G, De Curtis A, Costanzo S, Persichillo M, et al. A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study. Haematologica. 2016; 101:1434-41.
60. Bugada D, Allegri M, Lavand'homme P, De Kock M, Fanelli G. Inflammation-Based Scores: A New Method for Patient-Targeted Strategies and Improved Perioperative Outcome in Cancer Patients. BioMed Research International. 2014; 2014:142425.
61. Faria AP, Ritter AMV, Gasparetti CS, Corrêa NB, Brunelli V, Almeida A, et al. A Proposed Inflammatory Score of Circulating Cytokines/Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters. Arq Bras Cardiol. 2019; 112:383-9.
62. Zaninotto P, Steptoe A. English Longitudinal Study of Ageing. In: Gu D, Dupre ME, editors. Encyclopedia of Gerontology and Population Aging. Cham: Springer International Publishing; 2019. p. 1-7.
63. Sproston K, Mindell J. Health Survey for England 2004: Methodology and Documentation: Information Centre; 2006.
64. McCrea SM, Robinson TP. Visual Puzzles, Figure Weights, and Cancellation: Some Preliminary Hypotheses on the Functional and Neural Substrates of These Three New WAIS-IV Subtests. ISRN Neurol. 2011; 2011:123173.
65. Whiteside DM, Kealey T, Semla M, Luu H, Rice L, Basso MR, et al. Verbal Fluency: Language or Executive Function Measure? Appl Neuropsychol Adult. 2016; 23:29-34.
66. Elpers A-L, Steptoe A. Associations between dehydroepiandrosterone sulphate (DHEAS) and cognitive function in 5,061 older men and women in the English Longitudinal Study of Ageing. Psychoneuroendocrinology. 2020; 117:104702.
67. Leritz EC, McGlinchey RE, Kellison I, Rudolph JL, Milberg WP. Cardiovascular Disease Risk Factors and Cognition in the Elderly. Curr Cardiovasc Risk Rep. 2011; 5:407-12.
68. Schram MT, Euser SM, De Craen AJM, Witteman JC, Frölich M, Hofman A, et al. Systemic Markers of Inflammation and Cognitive Decline in Old Age. Journal of the American Geriatrics Society. 2007; 55:708-16.

69. Windham BG, Simpson BN, Lirette S, Bridges J, Bielak L, Peyser PA, et al. Associations Between Inflammation and Cognitive Function in African Americans and European Americans. Journal of the American Geriatrics Society. 2014; 62:2303-10.
70. Hu P, Lee J, Beaumaster S, Kim JK, Dey S, Weir D, et al. Cognitive Function and Cardiometabolic-Inflammatory Risk Factors Among Older Indians and Americans. Journal of the American Geriatrics Society. 2020; 68:S36-S44.
71. Pedersen A, Stanne TM, Redfors P, Viken J, Samuelsson H, Nilsson S, et al. Fibrinogen concentrations predict long-term cognitive outcome in young ischemic stroke patients. Research and Practice in Thrombosis and Haemostasis. 2018; 2:339-46.
72. Wersching H, Duning T, Lohmann H, Mohammadi S, Stehling C, Fobker M, et al. Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology. 2010; 74:1022-9.
73. Xu G, Zhang H, Zhang S, Fan X, Liu X. Plasma fibrinogen is associated with cognitive decline and risk for dementia in patients with mild cognitive impairment. International Journal of Clinical Practice. 2008; 62:1070-5.
74. Zheng F, Xie W. High-sensitivity C-reactive protein and cognitive decline: the English Longitudinal Study of Ageing. Psychol Med. 2018; 48:1381-9.
75. Komulainen P, Lakka TA, Kivipelto M, Hassinen M, Penttilä IM, Helkala E-L, et al. Serum high sensitivity C-reactive protein and cognitive function in elderly women. Age and Ageing. 2007; 36:443-8.
76. Laurin D, David Curb J, Masaki KH, White LR, Launer LJ. Midlife C-reactive protein and risk of cognitive decline: A 31-year follow-up. Neurobiology of Aging. 2009; 30:1724-7.
77. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003; 61:76-80.
78. Wichmann MA, Cruickshanks KJ, Carlsson CM, Chappell R, Fischer ME, Klein BEK, et al. Long-Term Systemic Inflammation and Cognitive Impairment in a Population-Based Cohort. Journal of the American Geriatrics Society. 2014; 62:1683-91.
79. Fretham SJ, Carlson ES, Georgieff MK. The role of iron in learning and memory. Adv Nutr. 2011; 2:112-21.
80. Qin T, Yan M, Fu Z, Song Y, Lu W, Fu Ad, et al. Association between anemia and cognitive decline among Chinese middle-aged and elderly: evidence from the China health and retirement longitudinal study. BMC Geriatrics. 2019; 19:305.
81. Schneider ALC, Jonassaint C, Sharrett AR, Mosley TH, Astor BC, Selvin E, et al. Hemoglobin, Anemia, and Cognitive Function: The Atherosclerosis Risk in Communities Study. The Journals of Gerontology: Series A. 2015; 71:772-9.
82. Worwood M. Ferritin. Blood Reviews. 1990; 4:259-69.
83. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. Neurology. 2008; 70:1672-7.
84. Arvanitakis Z, Grodstein F, Bienias JL, Schneider JA, Wilson RS, Kelly JF, et al. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology. 2008; 70:2219-25.
85. Breitner JC, Haneuse SJ, Walker R, Dublin S, Crane PK, Gray SL, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology. 2009; 72:1899-905.

86. Hayden KM, Zandi PP, Khachaturian AS, Szekely CA, Fotuhi M, Norton MC, et al. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology. 2007; 69:275-82.
87. Szekely CA, Breitner JCS, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, et al. NSAID use and dementia risk in the Cardiovascular Health Study*. Neurology. 2008; 70:17.
88. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. Jama. 2003; 289:2819-26.
89. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. Low dose aspirin and cognitive function in the women's health study cognitive cohort. Bmj. 2007; 334:987.
90. Price JF, Stewart MC, Deary IJ, Murray GD, Sandercock P, Butcher I, et al. Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial. Bmj. 2008; 337.
91. Banks, J., Batty, G.D., Breedvelt, J.J.F., Coughlin, K., Crawford, R., Marmot, M., Nazroo, J., Oldfield, Z., Steel, N., Steptoe, A., Wood, Martin., Zaninotto, P. (2021) English Longitudinal Study of Ageing: Waves 0-9, 1998-2019 [data collection]. 36th Edition. UK Data Service. SN: 5050, http://doi.org/10.5255/UKDA-SN-5050-23

Appendices

Appendix 1: Directed Acyclic Graph



Appendix 2: IRB Determination of Non-Human Subjects Research Form

NON-HUMAN SUBJECTS RESEARCH DETERMINATION FORM

Emory does not require IRB review of studies that do not meet the definitions of "human subjects research" (DHHS) or "clinical investigation" (FDA). This tool is to help you define your project and to ensure proper review and regulatory requirements are met.

If the tool results in an outcome of "no IRB review required," this form will serve as your documentation of that determination. Please keep the completed copy in your records.

AUDIT: The IRB will periodically audit completed forms and your written proposal to ensure that the tool is providing accurate results.

NOTE: this tool should only be used for projects completed by Emory/EHC affiliates doing work for Emory purposes. When answering the questions in this determination tool, consider only the project activities performed by Emory/EHC affiliates in the current proposed project (e.g. if your study is a secondary data analysis, do not include the primary data collection activities when considering your responses.) Emory/EHC affiliates who are completing a project for academic credit at a different institution should seek a determination from that institution's IRB.

1

Project Title *

Investigating Inflammation as a Mediator of the Association Between Stress and Cognitive Impairme

2

PROJECT LEADER (not necessarily the person filling in this form) *

Ambar Kulshreshtha

3

FUNDING *

Will these activities be supported by a DHHS award (e.g., NIH, NSF, DoE, DoD) through a grant, contract, subaward/subcontract, or cooperative agreement?

NOTE: If Emory is the prime recipient of a DHHS award and the funding application indicates that human subjects will be involved, IRB submission is required.

Also, if Emory is the prime recipient of a DHHS award, but contracting with another site to carry out all non-exempt human subjects research activities for that award, please contact the Emory IRB for guidance instead of using this form.
If Emory is the subrecipient, only the activities done by Emory should be considered for this form, even if other sites are performing human subjects research.

- ○ Yes
- ◉ No

4

SHARING DATA OUTSIDE OF EMORY *

Will you be sharing data (identified or de-identified) outside of Emory? If yes, you need to contact OTT (ott.emory.edu) to determine if a Data Use Agreement is needed.

- ○ Yes
- ◉ No

5

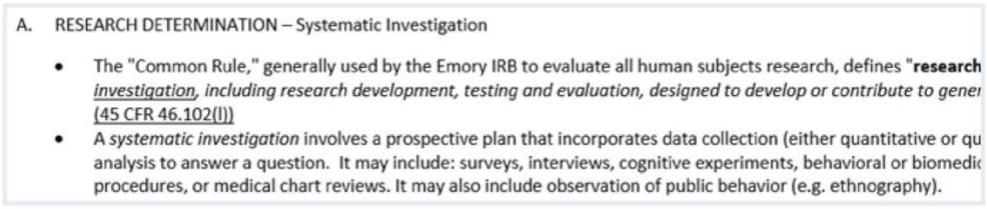
Does the project involve Veterans Affairs?
(e.g. study site, data source, researcher's affiliation) *

- ( ) Yes
- (•) No

6

RESEARCH DETERMINATION- Systematic Investigation *

Is the proposed project a "systematic investigation?" For example: are you conducting online or in-person surveys, focus group discussions, or data analysis?



A. RESEARCH DETERMINATION – Systematic Investigation

- The "Common Rule," generally used by the Emory IRB to evaluate all human subjects research, defines "**research** *investigation, including research development, testing and evaluation, designed to develop or contribute to gener* (45 CFR 46.102(l))
- A *systematic investigation* involves a prospective plan that incorporates data collection (either quantitative or qu analysis to answer a question. It may include: surveys, interviews, cognitive experiments, behavioral or biomedic procedures, or medical chart reviews. It may also include observation of public behavior (e.g. ethnography).

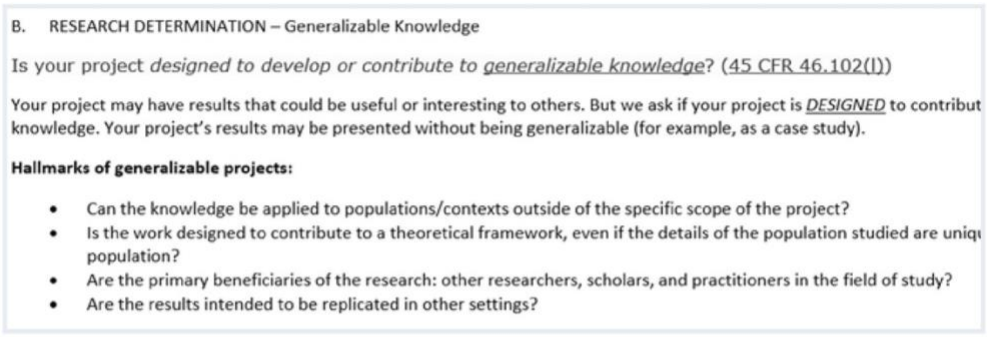
- ( ) No
- (•) Yes

7

RESEARCH DETERMINATION- Generalizable Knowledge
Is the proposed project "designed to develop or contribute to generalizable knowledge?" *

Review these links if your project falls into one of the following categories:
Case Studies/Series (http://irb.emory.edu/forms/review/casestudy.html)
Classroom Activities (http://irb.emory.edu/forms/review/classroom.html)
Public Health Practice (http://irb.emory.edu/forms/review/PH.html)
Program Evaluations (http://irb.emory.edu/forms/review/programeval.html)
Quality Improvement (http://irb.emory.edu/forms/review/QI.html)
Sociobehavioral research: Oral History/Journalism and Ethnography/Anthropology (http://irb.emory.edu/forms/socio.html)

If you still have questions, you can call our office for clarification at (404) 712-0720.



B. RESEARCH DETERMINATION – Generalizable Knowledge

Is your project *designed to develop or contribute to generalizable knowledge*? (45 CFR 46.102(l))

Your project may have results that could be useful or interesting to others. But we ask if your project is *DESIGNED* to contribut knowledge. Your project's results may be presented without being generalizable (for example, as a case study).

Hallmarks of generalizable projects:

- Can the knowledge be applied to populations/contexts outside of the specific scope of the project?
- Is the work designed to contribute to a theoretical framework, even if the details of the population studied are uniq population?
- Are the primary beneficiaries of the research: other researchers, scholars, and practitioners in the field of study?
- Are the results intended to be replicated in other settings?

- ◉ Yes
- ○ No

8

HUMAN SUBJECTS DETERMINATION *

Does this study involve obtaining information about living individuals? Answer "yes" if you're obtaining de-identified data or anonymous survey results if the results contain information about living people.

- ◉ Yes
- ○ No

9

If yes, does the study involve intervention or interaction with the individuals (e.g., online or in-person surveys [even if generating anonymous results], prospective collection of specimens, scans, etc.)?

- ○ Yes
- ◉ No

10

Do the activities involve accessing or generating individually identifiable and private information about living individuals?

Please review the list of identifiers for more information (http://www.irb.emory.edu/documents/phi_identifiers.pdf)

- ○ Yes
- ◉ No

11

Does the study involve analysis of existing data/specimens, where ALL data and/or specimens already exist prior to the start of the study? (Important: all parts of this question must apply if answering Yes.)

- ◉ Yes
- ○ No

12

If yes, would ANY member of the research team be able to reidentify the data/specimens, either directly, or via a code and key?
* If anyone on the newly-proposed study team took part in the original collection of the existing specimens or data, your should answer Yes.
* If there are codes on the data, but no one on the study team has access to a link: you may answer "No" to this question only if you have a documented agreement with the data/specimen providers that prohibits your team from having access to the link.

- ○ Yes
- ◉ No

13

HUMAN SUBJECTS RESEARCH DETERMINATION - FDA

Will any individual be a recipient of any test article (i.e., drug, medical device) or be used as a control?

FDA 21 CFR 56.102 (23c&e)

Human Subject- an individual who is or becomes a participant in research, either as a recipient of the test article or Clinical Investigation- any experiment that involves a test article and one or more human subjects.

- ○ Yes
- ◉ No

14

Will any device be tested (including software, apps, in-vitro assays) using any individual's specimens or data, even if completely deidentified?

- ○ Yes
- ◉ No

15

This project does not require IRB review because it is not research with "human subjects", nor is it a "clinical investigation" as defined in the federal regulations. Please use the Microsoft Print to PDF or Microsoft XPS Document Writer option to save a copy of your responses to this form. *

- ◉ There is no eIRB submission necessary. I will protect the confidentiality of information accessed or obtained in this project. I will keep a copy of my responses to this form for my records.