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Unveiling the link between systemic inflammation markers and cognitive performance among older adults in the US: A population-based study using NHANES 2011–2014 data

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A B S T R A C T

Purpose: This study aimed to evaluate the association between systemic inflammation markers and cognitive performance among older US adults.
Methods: This cross-sectional study assessed 3,632 older participants from the 2011–2014 National Health and Nutrition Examination Survey (NHANES). The main analysis included participants aged over 60 years. Systemic inflammation markers were quantified by calculating the composite inflammation indicators from the blood routine count, and cognitive performance was assessed using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test, Animal Fluency test (AFT), and Digit Symbol Substitution test (DSST).
Results: There were 2,743 individuals enrolled in the current analysis. The overall mean age was 64.9 years and 48.7 % were males. The levels of SIRI and PIV were significant negative associated with scores of CERAD, CERAD delayed recall, and DSST in the unadjusted models. Moreover, SII were significant negative associated with scores of CERAD and CERAD delayed recall. After adjusting the covariates of demographics, lifestyle factors, history of chronic diseases and BMI, significant negative association were observed between systematic inflammation markers and cognitive performance. Additionally, a progressive and significant decrease in the score of cognitive performance assessments with the increased levels of SIRI, SII, and PIV were respectively observed. Finally, the correlation between systemic inflammation markers and cognitive performance were evidenced in the sensitive analysis.
Conclusion: Findings support a strong inverse correlation between systemic inflammation markers and cognitive performance, suggesting that addressing inflammation could be a promising avenue for enhancing cognitive health and mitigating age-related cognitive decline.

1. Introduction

Dementia, in which Alzheimer disease (AD) is the main type, is one of the syndromes most strongly associated with ageing, characterized as encompassing widespread cognitive function decline, particularly in memory, to an extent that hampers social and occupational capacities [1]. Considering the rapidly increasing proportion of the ageing population, dementia imposes a substantial burden on both personal and public health [2].

Due to imperceptibility and the vary clinical presentation of early stage of dementia, distinguishing among age-related cognitive decline, mild cognitive impairment and Alzheimer disease may be challenging. Of many clinical batteries and rating scales for dementia, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning test, Animal Fluency test, and the Digit Symbol Substitution test (DSST) have withstood the test of time and enjoyed extensive and varied use, not only for diagnostic of dementia but evaluation of cognitive function by intuitive scores [3].

According to previous studies, cognitive decline may be triggered by a combination of various factors, including physical, psychological,

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social, and environmental variables, as well as health-related factors that interact with both inherited and external influences. The search for modifiable risk factors and early biomarkers for cognitive decline has intensified in recent years to develop targeted interventions to mitigate cognitive impairment [4]. Chronic systemic inflammation has been implicated in the pathogenesis of AD [5,6]. Especially in the old individuals, their bodies tend less functional and more susceptible to inflammation [7] There is growing evidence that elevated blood inflammatory indicators are closely related to disease progression. For example, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR), have been employed to predict the prognosis in melanoma [8]; lymphocyte count and neutrophil count are associated with risk of cardiovascular disease (CVD) [9] and platelet count was significantly associated with stroke events [10]. This suggests that inflammation might play a crucial role in the complex interplay between ageing and cognitive functions. The association between common markers of inflammation, including CRP, WBC, IL-6, IL-1β, TNF-α, and cognitive performance have been proven in previous studies [11–13].

As more comprehensive peripheral blood inflammatory markers are now understood, the system inflammation response index (SIRI), systemic immune inflammation index (SII) and pan-immune-inflammation value (PIV), three novel composite indices integrating three independent white blood cell subsets and platelets, are reminiscent of the interaction of thrombocytosis, inflammation, and immunity [14]. Accumulating evidence has proven the associations of increased SIRI, SII, and PIV levels with the increased risks of chronic disease such as CVD [14], hyperlipidemia [15] and hepatic steatosis [16]. However, there is little comprehensive evidence to clarify the relationships between SIRI, SII, PIV and cognitive performance. Therefore, we extracted data from the National Health and Nutrition Examination Survey (NHANES) (2011–2012 and 2013–2014) conducting a population-based cross-sectional study to investigate the relationship between SIRI, SII, PIV and cognitive performance and advance our understanding of the potential role of inflammation in cognitive aging which could have important implications for the development of preventive strategies and targeted interventions to promote cognitive health and reduce the burden of cognitive impairment in older adults.

2. Methods

2.1. Study population

This was a cross-sectional analysis included participants ≥ 60 years old from 2011 to 12 and 2013–14 cycles of National Health and Nutrition Examination Survey (NHANES) sample. All protocols were approved by the National Center for Health Statistics Ethics Review Board, and participants provided written informed consent [17]. Participants were excluded from this study if they met at least one of the following conditions: (i) age < 60 years; (ii) missing data on complete blood routine count and cognitive assessment; (iii) missing data on demographics; (iv) missing data on lifestyle factors; (v) missing data on BMI, and chronic diseases. A total of 3,632 participants ≥ 60 years old were assessed in the two NHANES cycles included in this analysis. Among them, 2,743 individuals underwent both complete blood routine count, and cognitive assessment were enrolled for the analysis (Fig. 1).

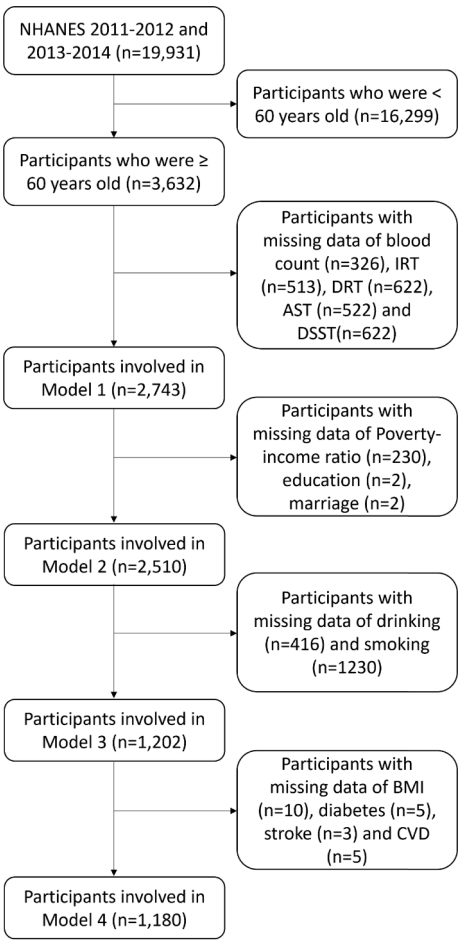

Fig. 1. Flowchart of the study design.

2.2. Definition of systematic inflammation markers and classification into groups

The absolute peripheral counts of lymphocyte, monocyte, neutrophil, and platelet counts were measured by complete blood count using automated hematology analyzing devices (Coulter® HMX analyzer in 2011-2012wave; Coulter®DxH 800 analyzerin 2013–2014 wave) and presented as $\times 10^3$ cells/ml. Three systemic inflammation markers were calculated: SIRI [18], SII [19] and PIV [19]. Calculations were as follows:

SIRI = neutrophil * monocyte / lymphocyte,

SII = neutrophils * platelets/lymphocytes, and

PIV = neutrophil * platelets * monocytes / lymphocytes.

The values of SIRI, SII and PIV and were analyzed as continuous variables. However, based on previous reports, there is no established standard for grouping SIRI, SII and PIV. Therefore, in the sensitivity analysis, participants were divided into four groups based on quartiles of SIRI, SII and PIV, respectively.

2.3. Cognitive assessment

Cognitive performance assessment was performed at a mobile examination center. A series of tests were performed by a highly trained medical team from National Center for Health Statistics (NCHS), which is a federal agency that gathers health data for the United States, to evaluate participants' working memory, delayed recall, and verbal fluency. Participants consented to audio-record the testing throughout the assessment for quality purposes, and the score was approved by all participants (https://www.cdc.gov/nchs/nhanes/index.htm).

The wave of 2011–2012 and 2013–2014 of NHANES used the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning test, the Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST) to assess different cognitive domains. Specially, the CERAD is specifically designed to evaluate immediate and delayed learning of new verbal information within the memory domain [20] here are two parts of the CERAD Word Learning test (1) three consecutive learning trials, where the participant is requested to recall a list of ten unrelated words immediately after their presentation. Each word

corresponds to one point, and the result is presented as a total score across the three trials; and (2) a delayed word recall test, performed after AFT and DSST. The AFT focuses on categorical verbal fluency, an aspect of executive function. This test helps differentiate between individuals with normal cognitive function and those with varying degrees of cognitive impairment, ranging from mild to more severe [21]. Participants are given one minute to generate as many animal names as possible. The DSST assesses several cognitive domains, including executive function, processing speed, attention, spatial perception, and visual scanning (https://wwwn.cdc.gov/Nchs/Nhanes/2013–2014/CFQ_H.htm (accessed on March 2017)). During this test, participants are allotted two minutes to match symbols to corresponding numbers. For all the tests, higher scores represent better cognitive function. Unfortunately, cutoffs for cognitive tests that can be used as a gold standard remain unavailable. Based on the historical literature, the quartile of the scores is widely applied as the cutoff value [22].

2.4. Covariates

Demographics (age, gender, ethnicity, education, marriage, and poverty–income ratio), lifestyle factors (drinking and smoking status), and health history (CVD, diabetes and depression) were obtained from the questionnaires. In the NHANES, age (years) was used as a continuous variable. Sex was classified as female or male. The race/ethnicity categories were classified as Mexican American, non-Hispanic Black, non-Hispanic White, other/multiracial. Education attainment was categorized as incomplete high school, high school graduate, incomplete college, and college graduate or above. Marital status was classified as married/cohabiting, widowed/divorced/separated, and never married. Poverty–income ratio, a measure that considers the ratio of household income to the poverty threshold after accounting for inflation and family size, was categorized into < 1.30 (poorer) or ≥ 1.30 (richer). Smoking status was categorized as smoker or non-smoker at the time of testing. Participants who had at least 12 alcoholic drinks in any one year or more than 2 drinking alcohol frequency in the past 12 months were considered alcohol drinkers. Body mass index (BMI) calculated as weight divided by height squared ($<$18.5, 18.5–24.9, 25.0–29.9 and $\geq$ 30.0 kg/m^2). Participants were considered to have CVD if they had been diagnosed with congestive heart failure, coronary heart disease, angina, or heart attack in the clinic. History of diabetes, hypertension, and stroke was identified if the participant self-reported being previously diagnosed with diabetes by a physician. Depression symptoms were measured with the 9-item Patient Health Questionnaire (PHQ-9). Analyses examined clinically significant depression symptoms defined using the standard cut point of PHQ-9 scores of 10 or greater [23].

2.5. Statistical analysis

Mean and standard deviation (SD) were used for descriptive analysis of continuous variables and differences among groups were analyzed by the one-way analysis of variance (ANOVA). Absolute frequencies and percentages were used to report categorical variables differences among groups were analyzed by Chi-Square test. The association between systematic inflammation makers and cognitive performance was evaluated by multivariate linear regression. Further to unadjusted models (Model 1), three adjusted models were tested: (1) Model 2: adjusted for demographics (age, gender, ethnicity, education, marriage, and poverty–income ratio); (2) Model 3: demographics and lifestyle factors (smoking and drinking status); (3) Model 4: demographics, lifestyle factors, BMI, and chronic diseases (history of CVD, diabetes, depression, hypertension, and stroke).

To examine the robustness of our results, we performed a sensitivity analysis to compare the relations between different quartiles group. Cognitive assessment scores were compared across quartiles of systematic inflammation makers (i.e., SIRI, SII and PIV) using generalized linear regression models. Tests of linear trend were carried out by treating quartiles as a continuous ordinal variable. We used the restricted cubic spline function to visualize the dose–response relationship of systematic inflammation markers (i.e., SIRI, SII and PIV) with cognitive performance.

All analyses were completed using R software, version 4.3.1 (R Foundation). Statistical significance was defined as a two-tailed $P < 0.05$.

3. Results

3.1. Characteristics of the study population

Of 2,743 participants, who met the inclusion criteria and were included in the current study, 1,336 (48.7 %) were males; the mean (SD) age was 69.4 years (Table 1). The detailed selection process was presented in flowchart (Fig. 1). The overall average of SIRI, SII and PIV in the study was 1.39 (1.17), 20.36 (13.52), 11.71 (9.71), respectively. In addition, the study population was divided into 4 groups in the sensitive analysis based on the quartile of SIRI, SII, and PIV, respectively. The first quartile group [Q1, (SIRI $\leq$ 0.76, n = 706), (SII $\leq$ 318.12, n = 686), (PIV $\leq$ 151.74, n = 686)], the second quartile group [Q2, (0.76 $<$ SIRI $\leq$ 1.12, n = 676), (318.12 $<$ SII $\leq$ 451.43, n = 686), (151.74 $<$ PIV $\leq$ 240.56, n = 686)], the third quartile group [Q3, (1.12 $<$ SIRI $\leq$ 1.70, n = 675), (451.43 $<$ SII $\leq$ 657.04, n = 685), (240.56 $<$ PIV $\leq$ 385.06, n = 685)], and the fourth quartile group [Q4, (1.70 $<$ SIRI, n = 686), (657.04 $<$ SII, n = 686), (385.06 $<$ PIV, n = 686)] (Table S1-3). A progressive and significant decrease in the score of cognitive performance assessments (i.e., CERAD, CERAD delayed recall, Animal fluency, and DSST) with the increased levels of SIRI, SII, and PIV were respectively observed in Table S1-3.

3.2. SIRI, SIII, and PIV values in cognitive performance

To investigate the relationship between systemic inflammation markers (i.e., SIRI, SII, and PIV) and cognitive performance mass we performed multivariate linear regression models. The potential confounding factors which were adjusted in each model were presented in the method section. We observed that all inflammation markers (i.e., SIRI, SII, and PIV) were significant negative associated with scores of cognitive assessments of CERAD, CERAD delayed recall, and DSST from crude models (Table 2). In fully adjusted models, three systemic inflammation markers associated with at least one score.

Restricted cubic spline plots were performed to demonstrate the dose–response graphical relationship between the levels of SIRI, SII and PIV and the cognitive test scores, and revealed an inverted U-shape association of SII and Animal fluency, SII and DSST, PIV and Animal fluency, PIV and DSST (Figs. 2-4). Thus, the sensitive analysis was carried out to assess the association between SIRI, SIII, and PIV values in cognitive performance using quartiles of SIRI, SII and PIV. Table S4-6 showed that significant associations were observed between systemic inflammation markers and the cognitive assessment results in both unadjusted and adjusted models. Specially, after full adjustments, compared to individuals in the lowest group of SIRI, those in the highest group had a significantly decreased in scores of all cognitive assessments of CERAD, CERAD delayed recall, and DSST. Moreover, individuals in the highest group of SII and PIV had significantly decreased in scores of CERAD delayed recall when compared to the lowest group, respectively.

4. Discussion

Aging is accompanied by an increase in chronic, low-grade inflammation, known as inflammaging, which is a risk factor for chronic disease [24]. Since SIRI, SII and PIV are indices integrated inflammatory information from lymphocyte, monocyte, neutrophil, and platelet counts, it driven the hypothesis that SIRI, SII and PIV could be associated with cognitive performance in elderly population. Therefore, in this

Table 1
Basic characteristics of the study population.

	Overall (n = 2,743)
Age, years	69.4 (6.8)
Sex, n (%)	
Male	1,336 (48.7)
Female	1,407 (51.3)
Race/ethnicity, n (%)	
Mexican American	241 (8.8)
Non-Hispanic White	541 (19.7)
Non-Hispanic Black	1,337 (48.7)
Other/multiracial	624 (22.7)
Education, n (%)	
Incomplete high school	679 (24.8)
High school or equivalent	656 (23.9)
Incomplete college	770 (28.1)
College or above	636 (23.2)
Marital status, n (%)	
Married/cohabiting	1,597 (58.3)
Widowed/divorced/separated	985 (35.9)
Never married	159 (5.8)
Poverty-income ratio, n (%)	
< 1.30	739 (29.4)
≥ 1.30	1,774 (70.6)
BMI, n (%)	
Underweight (<18.5 kg/m2)	57 (2.1)
Normal weight (18.5–24.9 kg/m2)	795 (29.3)
Overweight (25–29.9 kg/m2)	993 (36.6)
Obese (≥30 kg/m2)	871 (32.1)
Tobacco smoking, n (%)	
Yes	1,041 (74.8)
No	351 (25.2)
Alcohol drinker, n (%)	
Yes	1,986 (87.2)
No	292 (12.8)
Diabetes, n (%)	
Yes	544 (19.9)
No	2,188 (80.1)
Hypertension, n (%)	
Yes	1,034 (37.8)
No	1,705 (62.2)
Stroke, n (%)	
Yes	190 (6.9)
No	2,548 (93.1)
CVD, n (%)	
Yes	477 (17.5)
No	2,252 (82.5)
Depression, n (%)	
Yes	255 (9.4)
No	2,450 (90.6)
CERAD, mean (SD)	19.2 (4.4)
CERAD delayed recall, mean (SD)	6.1 (2.1)
AFT, mean (SD)	16.7 (5.4)
DSST, mean (SD)	46.2 (17.1)
SIRI	1.39 (1.17)
SII	540.74 (405.89)
PIV	315.21 (294.12)

n: number; SD: standard deviation; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; AFT: Animal Fluency test; DSST: Digit Symbol Substitution test; SIRI: Systemic Inflammation Response Index; SII: Systemic Immune-Inflammation Index; PIV: Pan-Immune-Inflammation Value.

large population-based study, we investigated the association between systematic inflammation marker (including SII, SIRI, and PINI) and cognitive performance in senior individuals participating in NHANES from 2011 to 2014. The results determined that systematic inflammation markers (including SII, SIRI, and PINI), as signs of inflammatory response, were significantly negative associated with cognitive performance.

Our findings have unveiled a gradual and noteworthy decline in cognitive performance scores, encompassing CERAD, CERAD delayed recall, Animal fluency, and DSST, in direct correlation with the escalation of SIRI, SII, and PIV levels. This evidence lends strong support to the notion that heightened systemic inflammation levels are linked to diminished cognitive performance in older adults. Previous population-based studies reported controversial results of the associations of dementia with various inflammation markers. In earlier instances within the Rotterdam Study with middle-aged and older individuals, overarching indicators of systemic inflammation, such as granulocyte, lymphocyte, and platelet cell counts, demonstrated an association with heightened dementia risk [25]. However, using serum immunoglobulins (Igs) as the markers of systemic inflammation based on the same community-dwelling cohort, the serum Igs were not associated with prevalent or incident dementia [26]. Numerous investigations into cytokine levels concerning mild cognitive impairment or Alzheimer's disease have yielded contentious or inconclusive results. This is particularly true for studies examining well-studied cytokines such as tumor necrosis factor alpha (TNF-α) or interleukin-6 (IL-6) [27–30]. These inconsistent results may be attribute to the limited sample size of these previous studies. A recent study with large sample size, based on UK Biobank cohort, used white blood (leucocyte) cell count and C-Reactive Protein to build an inflammatory biomarker score and identified inflammation is associated with cognitive performance and future dementia diagnosis [31], which obtained consistent results with our study.

A thought-provoking hypothesis emerges from the observation that aging organisms commonly manifest a pro-inflammatory state, marked by elevated levels of pro-inflammatory markers in cells and tissues [24]. This phenomenon is often referred to as inflammageing, a term initially introduced in the year 2000 [32]. Chronic inflammation has been implicated in neuroinflammatory processes, leading to neuronal damage and cognitive decline [5,33,34]. Using cognitive performance measured by CERAD-WLT, AFT, and DSST, our results align with the existing evidence linking systematic inflammation to cognitive impairment and neurodegenerative diseases, including Alzheimer's disease, thoroughly determining the relationship between inflammation and MCI and its advanced stage, dementia.

Mild cognitive impairment (MCI) denotes the intermediate phase between the normal cognitive changes associated with ageing and the more severe decline observed in dementia [35]. Age is therefore the closely risk factors for both MCI and dementia. In addition, there are a great number of risk factors that are associated with cognitive impairment, such as smoking and drinking status, BMI, and chronic diseases (history of CVD, diabetes, depression, hypertension, and stroke). To clarify the role of age within this relationship, we conducted multivariate linear regression models, adjusting for potential inflammageing-related confounding factors including age, smoking and drinking status, BMI, and chronic diseases (history of CVD, diabetes, depression, hypertension, and stroke). Our analyses demonstrated significant negative associations between all inflammation markers (SIRI, SII, and PIV) and cognitive assessments, such as CERAD, CERAD delayed recall, and DSST, in both crude and adjusted models. The dose–response relationships of systemic inflammation markers with cognitive assessment scores were further examined using restricted cubic spline plots. The plots revealed a consistent downward trend, indicating that as systemic inflammation marker levels increase, cognitive performance tends to decline. These dose–response relationships strengthen the evidence for an association between systemic inflammation and cognitive function in older individuals. In addition, there are a mass of evidence to support that high levels of SIRI, SII, and PIV are risk factors for chronic disease and neurological disorders. For example, Wang et al and Zhang et al found that ischemic stroke patients with higher SII and SIRI were more likely to have poor outcomes [18]; moreover, Zhu et al evidenced SII could be applied as a biological indictor of depressive disorders [36]. And Wu et al discovered that elevated PIV was associated with increased all-cause mortality and cardiovascular mortality in hypertensive patients. Thus, our findings are consistent with previous studies, and it further supports the reliability of our results.

While our findings provide valuable insights into the association between systemic inflammation markers and cognitive performance in older adults, several limitations should be considered. Firstly, the cross-

Table 2
Association between systemic inflammation markers and cognitive performance in adults ≥ 60 years old from NHANES 2011–2014 (n = 2,713).

		Model 1		Model 2		Model 3		Model 4	
		β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
SIRI	CERAD	−0.373	<0.001	−0.147	0.036	−0.152	0.074	−0.138	0.108
	CERAD delayed recall	−0.265	<0.001	−0.148	<0.001	−0.143	<0.001	−0.130	**0.002**
	AFT	−0.106	0.231	−0.013	0.880	−0.026	0.811	0.006	0.953
	DSST	−1.006	<0.001	−0.171	0.474	−0.351	0.225	−0.116	0.686
SII	CERAD	-6.367×10^{-4} (2.063×10^{-4})	0.002	-4.330×10^{-4} (1.927×10^{-4})	0.025	5.271×10^{-4} (2.639×10^{-4})	0.046	3.114×10^{-4} (1.871×10^{-4})	0.096
	CERAD delayed recall	-4.364×10^{-4} (1.003×10^{-4})	<0.001	-3.076×10^{-4} (9.467×10^{-5})	0.001	3.686×10^{-4} (8.573×10^{-4})	0.045	-3.337×10^{-4} (1.303×10^{-4})	**0.011**
	AFT	-2.889×10^{-4} (2.556×10^{-4})	0.259	-1.640×10^{-4} (2.451×10^{-4})	0.503	-2.803×10^{-4} (3.409×10^{-4})	0.411	-2.027×10^{-4} (3.404×10^{-4})	0.552
	DSST	-9.270×10^{-4} (8.063×10^{-4})	0.250	-3.479×10^{-4} (6.591×10^{-4})	0.598	-4.751×10^{-4} (8.962×10^{-4})	0.596	-2.451×10^{-5} (8.804×10^{-4})	0.978
PIV	CERAD	9.825×10^{-4} (2.846×10^{-4})	<0.001	-3.601×10^{-4} (2.693×10^{-4})	0.181	-4.344×10^{-4} (3.336×10^{-4})	0.193	-3.508×10^{-4} (3.353×10^{-4})	0.296
	CERAD delayed recall	-7.967×10^{-4} (1.380×10^{-4})	<0.001	-4.676×10^{-4} (1.321×10^{-4})	<0.001	-4.953×10^{-4} (1.634×10^{-4})	0.002	-4.456×10^{-4} (1.644×10^{-4})	**0.007**
	AFT	-4.457×10^{-4} (3.528×10^{-4})	0.207	-6.051×10^{-5} (3.423×10^{-4})	0.860	6.503×10^{-5} (4.306×10^{-4})	0.880	1.937×10^{-4} (4.297×10^{-4})	0.652
	DSST	-3.078×10^{-3} (1.111×10^{-3})	0.006	-6.705×10^{-4} (9.203×10^{-4})	0.466	-9.242×10^{-4} (1.132×10^{-3})	0.414	-1.317×10^{-4} (1.111×10^{-3})	0.906

Model 1: unadjusted.
Model 2: demographics (age, gender, ethnicity, education, marriage and poverty–income ratio).
Model 3: demographics, lifestyle factors (drinking and smoking status).
Model 4: demographics, lifestyle factor, BMI, and chronic diseases (history of CVD, diabetes, depression, and stroke).
SE: standard error; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; AFT: Animal Fluency test; DSST: Digit Symbol Substitution test; SIRI: Systemic Inflammation Response Index; SII: Systemic Immune-Inflammation Index; PIV: Pan-Immune-Inflammation Value.

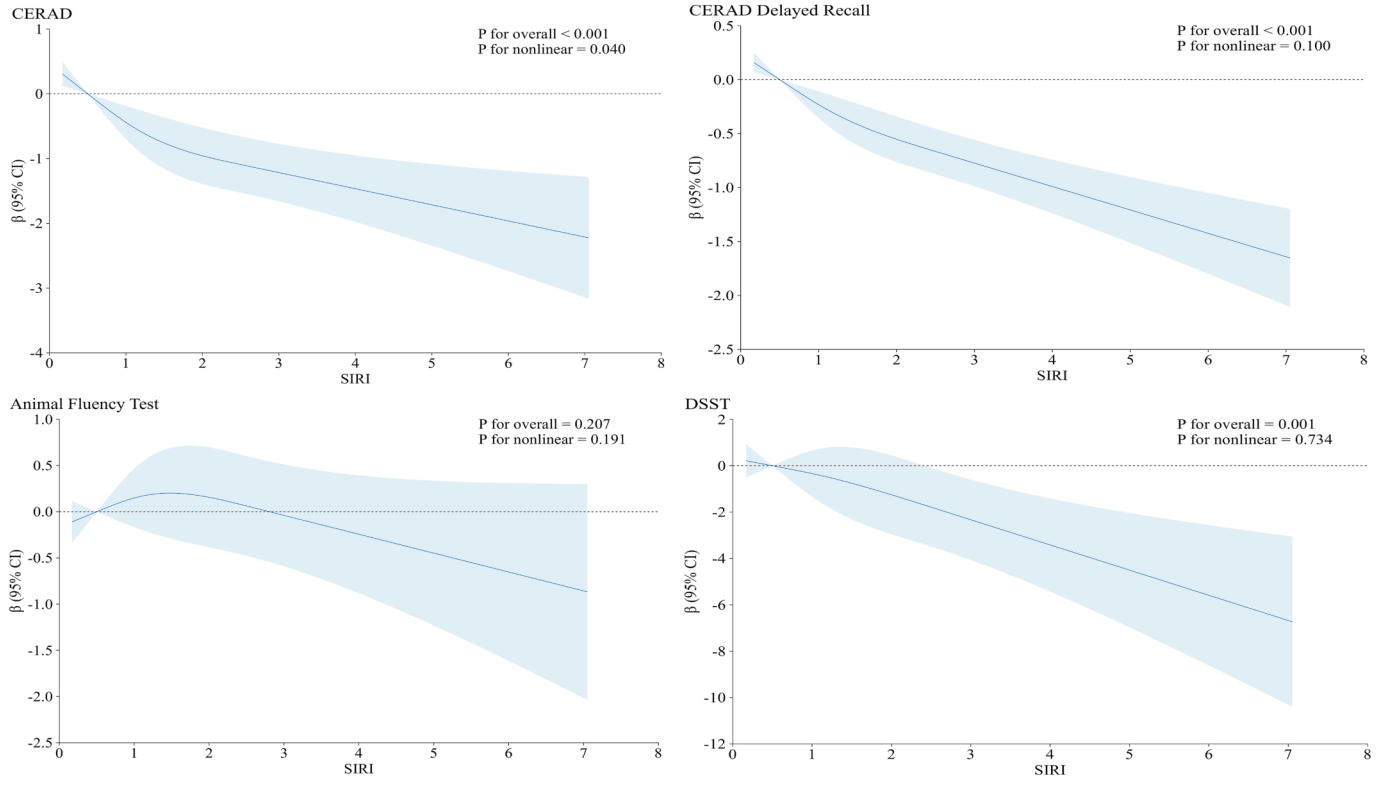

Fig. 2. The relationship between SIRI and cognitive test scores (i.e., CERAD, CERAD Delayed Recall, Animal Fluency, and DSST).

sectional design prevents us from establishing causality between inflammation and cognitive decline. Longitudinal studies would be necessary to infer the causal relationship between these factors; moreover, reverse causality should also be kept into consideration since the pathological changes in cognitive impairment might manifest as increase in systemic inflammatory markers. Secondly, our study's reliance on cognitive assessments from NHANES limits the scope of cognitive domains assessed, and there is lack of other cognitive assessments, such

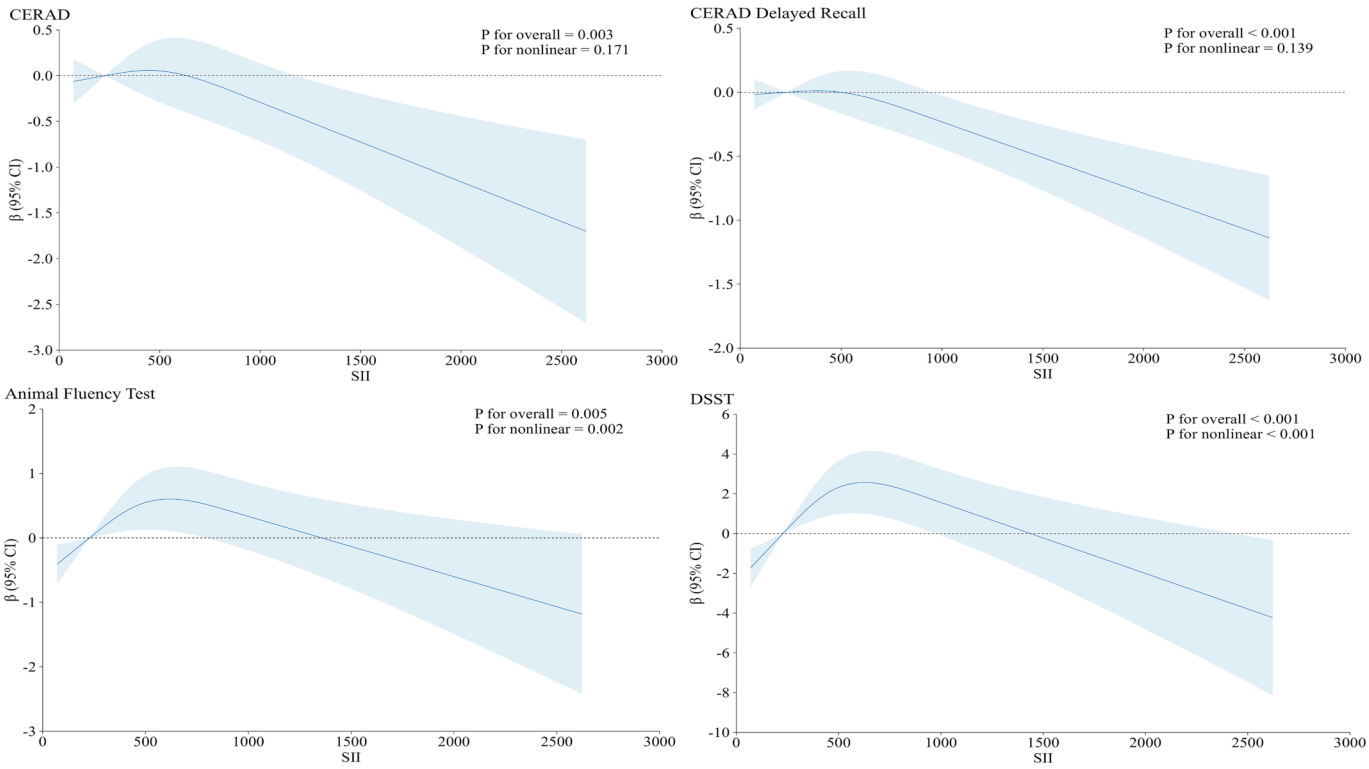

Fig. 3. The relationship between SII and cognitive test scores (i.e., CERAD, CERAD Delayed Recall, Animal Fluency, and DSST).

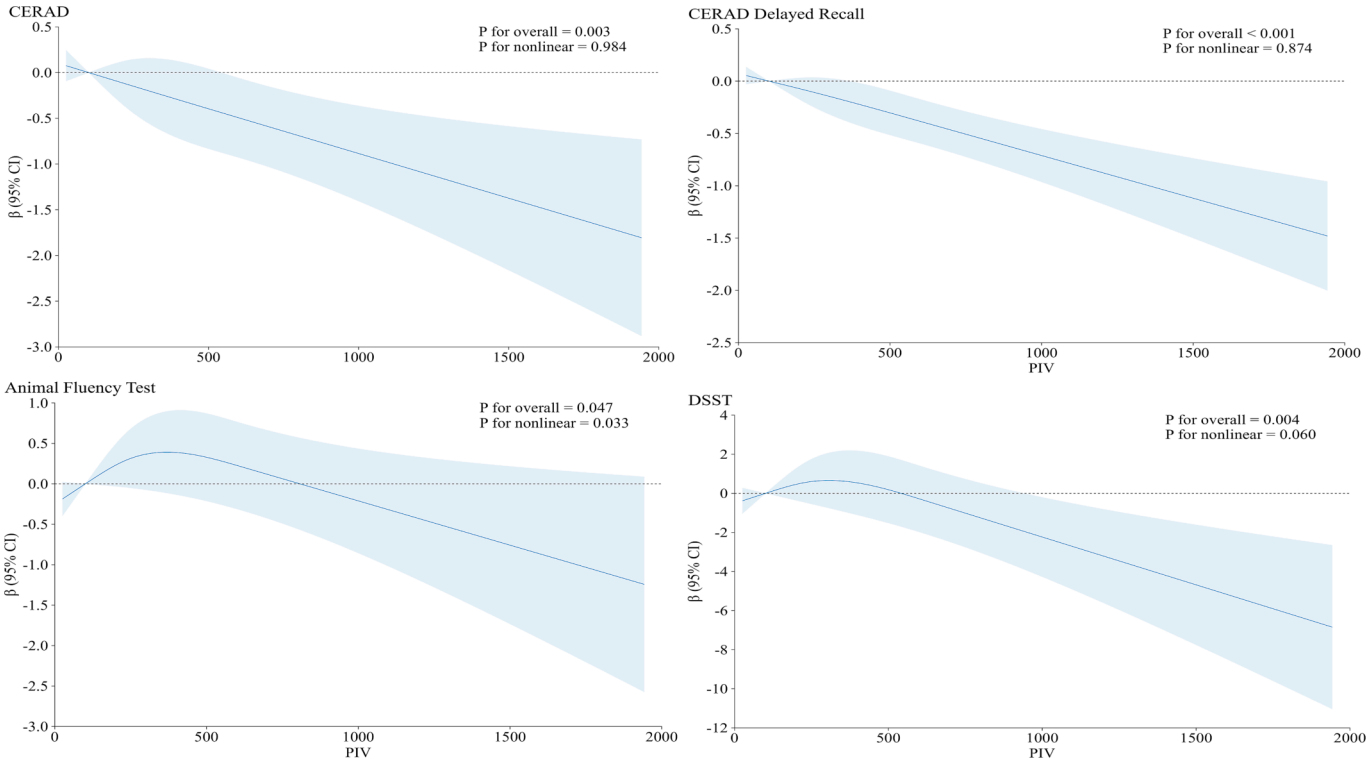

Fig. 4. The relationship between PIV and cognitive test scores (i.e., CERAD, CERAD Delayed Recall, Animal Fluency, and DSST).

as Mini-Mental State Examination (MMSE), Wechsler Adult Intelligence Scale (WAIS), Frontal Assessment Battery (FAB) widely used around the world. Future research using comprehensive neuropsychological batteries could provide a more comprehensive understanding of the association between inflammation and cognitive function. Despite these limitations, our study contributes to the growing body of evidence supporting the role of systemic inflammation in cognitive aging with the large sample size and database. These findings have potential implications for public health, as they suggest that targeting systemic inflammation may be a potential strategy to promote cognitive health in older

adults. Interventions aimed at reducing inflammation, such as lifestyle modifications and pharmacological approaches, could be explored to mitigate cognitive decline and improve the quality of life for older individuals.

5. Conclusion and future prospect

Our cross-sectional analysis of older Americans from the NHANES 2011–2014 highlights a significant negative association between systemic inflammation markers (SIRI, SII, and PIV) and cognitive performance. Higher levels of these inflammation markers were consistently linked to lower cognitive function across various cognitive assessments. These findings emphasize the potential role of systemic inflammation in cognitive aging and underscore the need for further research to understand the underlying mechanisms. Targeting inflammation may hold promise as a strategy to promote cognitive health in older individuals and reduce the burden of cognitive decline.

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7. Ethics approval

The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. All participants granted written informed consent before participating NHANES.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2023.11.004.

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