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RESEARCH ARTICLE

Biomarkers of chronic inflammation and cognitive decline: A prospective observational study

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Abstract

We sought to determine whether the biomarkers of chronic inflammation predict cognitive decline in a prospective observational study. We measured baseline serum soluble urokinase plasminogen activator receptor (suPAR) and high sensitivity C-reactive protein (hs-CRP) levels in 282 participants of the University of Michigan Memory and Aging Project. Cognitive function was measured using the Montreal Cognitive Assessment (MoCA) and the Clinical Dementia Rating (CDR) scale for up to five time points. SuPAR and hs-CRP levels were not significantly higher in participants with mild cognitive impairment ($n = 97$) or dementia ($n = 59$), compared to those with normal cognitive function ($n = 126$). Overall, 14% of participants experienced significant cognitive decline over the study period. The change in MoCA or CDR scores over time did not differ significantly according to baseline suPAR or hs-CRP levels. Chronic systemic inflammation, as measured by serum suPAR or hs-CRP levels, is unlikely to contribute significantly to cognitive decline.

KEYWORDS
Alzheimer's disease, cognition, dementia, hs-CRP, suPAR

Bhavna A. Guduguntla and Alexi Vasbinder contributed equally to this manuscript.

1 | INTRODUCTION

Chronic inflammation is thought to be a significant contributor to the pathogenesis and progression of dementias.[1,2] Alzheimer's disease (AD) is the most prevalent form of dementia in adults, accounting for approximately 60% of all dementia cases.[3,4] Retrospective observational studies have suggested long-term use of anti-inflammatory medications (e.g., non-steroidal anti-inflammatory drugs) is associated with a lower risk of developing AD.[5] However, these findings have not been corroborated by large-scale clinical trials.[2,5] Characterizing the inflammatory burden of patients with dementias, including AD, may allow for selection of those who would benefit best from anti-inflammatory therapies. Several blood-based biomarkers such as C-reactive protein (CRP),[6–10] and interleukin-6,[11–15] have been explored as surrogates of inflammation in dementias, with conflicting findings, likely due to differences in study population, the retrospective nature of many studies and the nature of these biomarkers as acute phase reactants with highly variable levels.[11,16,17]

Soluble urokinase plasminogen activator receptor (suPAR) is a circulating glycoprotein produced by immune cells.[18] Elevated levels of suPAR, which reflect chronic inflammation, have been linked to well-established contributing factors to AD, such as aging, smoking, and other inflammatory diseases, such as diabetes, atherosclerosis, sepsis, HIV, chronic kidney disease and cardiovascular diseases.[18–21] Unlike other markers of inflammation, suPAR is not an acute phase reactant, with levels shown to be stable even after highly inflammatory events such as myocardial infarction or surgery.[22,23] The urokinase receptor system has recently been shown to play an important role in brain development and pathology, with high levels of brain suPAR expression associated with over-production of amyloid-β and central nervous system diseases such as epilepsy, autism, AD, AIDS dementia and others.[24–28] Whether blood suPAR levels could be a more useful biomarker of inflammation for predicting progression of dementias is unknown.

Education level, race, and other social and demographic factors contribute to disparities in cognitive function with age through multiple biologicals.[29,30] Specifically, adversities that come with disadvantaged social positions increase the risk for inflammatory-based diseases.[31] Accounting for social and demographic factors, we sought to determine whether systemic chronic inflammation as measured by serum suPAR and high-sensitivity CRP (hs-CRP) levels were related to baseline cognitive screening measures and whether these indicators predict cognitive decline in a prospective cohort study of participants with and without dementia who underwent serial evaluation of cognition as part of the University of Michigan Memory and Aging Project (UM-MAP).

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed of published original research and review articles. Several retrospective studies has examined the role of biomarkers of chronic inflammation in the relationship with cognitive decline with conflicting findings. No study has examined the role of soluble urokinase plasminogen activator receptor (suPAR), a highly stable biomarker of chronic inflammation.
2. **Interpretation**: This study found that biomarkers of chronic inflammation were not elevated in participants with dementia compared to those without, and levels at baseline were not predictive of cognitive decline. These findings support the absence of a strong relationship between systemic inflammation and non-vascular dementias. Our study provides important evidence informing the debate on the role of systemic inflammation in the progression of dementia.
3. **Future directions**: Future, large-scale prospective longitudinal studies are needed to confirm the association between chronic inflammatory biomarkers and cognitive decline in patients with dementia.

2 | METHODS

2.1 | Study design

UM-MAP is a prospective observational study in the National Institute on Aging P30 Michigan Alzheimer's Disease Research Center (MADRC). The study's main purpose is to investigate longitudinal changes in cognitive function. Enrollees in UM-MAP are adults over 55 years of age including healthy (cognitively intact) volunteers and participants with cognitive and functional impairment arising from etiologies such as mild cognitive impairment (MCI), AD dementia, frontotemporal dementia, Lewy body dementia, and mixed dementia. All participants completed baseline and annual standardized neurological and neuropsychological assessments, along with a physical exam, blood draw, and a history and symptom survey. The diagnoses were established by consensus of at least three MADRC clinicians (neurologists/neuropsychologists) after review of all material at annual visit, including Clinical Dementia Rating scale (CDR), Montreal Cognitive Assessment (MoCA), and the neuropsychological battery. Study participants were recruited from the University of Michigan Health System, University of Michigan (U-M) – Detroit Center, and the Minority Satellite Diagnostic and Treatment Center (MSDTC) at the Ypsilanti Family Practice Center. The U-M Detroit Center allows recruitment from an urban environment and the MSDTC serves a large Black-American and Hispanic community. Both recruitment sites help ensure that the UM-MAP has a diverse study population. Additional volunteers were found through MADRC Outreach, Recruitment, and Engagement Core community talks and recruitment events. In line with the mission of other national Alzheimer's Disease Research Centers through the National Alzheimer's Coordinating Center (NACC), the MADRC contributes data from these annual standardized assessments to a uniform dataset (UDS) housed at the NACC.[32] All diagnoses adhere to NACC guidelines and are made during a consensus conference that

includes neurologists, neuropsychologists, social workers, nurses, and other professionals (as appropriate).

We measured baseline suPAR and hs-CRP levels in all UM-MAP participants with available blood samples (n = 282 of 315, 90% of the UM-MAP patient population), compared levels between participants with dementia (of any etiology), MCI, and those with intact cognition, and assessed whether baseline levels predicted cognitive decline at follow-up as measured by the MoCA total score and the Clinical Dementia Rating scores, accounting for key social and demographic indicators. The study was approved by the University of Michigan Institutional Review Board, and all patients provided informed consent for enrollment in UM-MAP. This study was performed in accordance with all relevant guidelines and regulations.

2.2 | Measurements of cognitive function

The MoCA is a screening tool for cognitive impairment that assesses various aspects of cognitive functioning including visuospatial abilities, executive function, short-term memory, language, and orientation to time and place. Higher scores indicate better cognitive functioning. The MoCA test is relatively non-specific and is not typically used for gold-standard diagnoses of MCI or dementia, but rather to identify persons who may have non-specific, overall cognitive impairment.[33,34] The MoCA test was performed by trained and certified staff.

The CDR uses informant report to evaluate six aspects of cognitive and behavioral functioning (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) to determine the severity of MCI or dementia, which results in two subscores, the CDR – Sum of Boxes (CDR-SB) score (six domains summed to create a 0-18 score) and the CDR – Global Score (CDR-GS, ranked 0-3). Lower scores indicate better cognitive functioning.[35,36] Compared to the CDR-GS score, the CDR-SB score provides more information and is better able to assess dementia in subtler presentations.[37]

The MoCA and CDR were assessed at baseline and yearly up to five years. Values for the MoCA total score, CDR-SB, and CDR-GS at enrollment along with participant diagnoses and all subsequent values and measurements were obtained through the NACC UDS (version 3.0).

2.3 | Sample collection and measurement of suPAR and hs-CRP

Blood samples from the UM-MAP participants (via two 10-mL ethylenediaminetetraacetic acid [EDTA] tubes) were obtained from the baseline visit. Serum, plasma, buffy coat, and packed red cells were then processed and stored in −80°C. Serum levels of suPAR were measured with the suPARnostic kit (ViroGates, Copenhagen, Denmark) by experienced technicians blinded to the clinical data. The assay has a lower limit of detection of 100 pg/mL, an intra-assay variation of 2.75% and an inter-assay variation of 9.17%, according to the manufacturer. Serum hs-CRP were measured using the OriGene solid phase sandwich enzyme-linked immunosorbent assay (ELISA) colorimetric assay kit (OriGene, MD) with a minimum detectable limit of 0.1 mg/L and an upper limit of detection of 10 mg/L, with a sensitivity of 0.1 mg/L. The assay has an intra-assay coefficient of variation of 4.1%, and inter-assay CV% of less than 7.5%. Samples outside of the standard curve were further diluted and re-assayed.

2.4 | Statistical analysis

We present continuous variables as both means (SD) and medians (with interquartile ranges) for normally and non-normally distributed data, respectively, and present categorical variables counts and percentages. Participant characteristics are reported stratified by neurocognitive diagnosis, suPAR tertiles, and CRP tertiles, and compared using analysis of variance (ANOVA) or Kruskal–Wallis tests for continuous variables, and chi-squared tests for categorical variables. The MoCA total score and CDR-SB were examined as continuous variables. The CDR-GS was examined as an ordinal variable (0 indicates normal, 0.5 MCI/very mild dementia, 1 mild, 2 moderate and 3 severe).

SuPAR and hs-CRP levels were log-transformed (natural log) due to their skewed distribution. We used Spearman Rank correlation to examine associations between suPAR and hs-CRP levels and cognitive function (MoCA total scores and CDR-SB) at enrollment. Multivariable linear regression was used to examine the baseline factors associated with total MoCA and CDR-SB scores at enrollment. Confounders were selected a priori based on biological and scientific rationale. Each outcome was examined in separate models adjusted for age, sex, race, education, body mass index, hs-CRP, and suPAR. We plotted measures of both total MoCA and CDR-SB scores across visits stratified by cognitive impairment (no impairment, MCI, and dementia), suPAR tertiles, and hs-CRP tertiles to visualize differences in cognitive decline between groups.

We used linear mixed modeling, with a random intercept and slope, to assess the association between biomarkers measured at enrollment (independent variable) and change in cognitive functioning scores during follow-up (dependent variable)—in separate models for each biomarker (suPAR or hs-CRP) and each score (MoCA total score and CDR-SB). Biomarkers were log-transformed (natural log). Model 1 includes the biomarker alone and corresponding baseline cognitive function score. Model 2 adds age, sex, race, and education. Model 3 incorporates the aforementioned variables in addition to baseline body mass index and history of hypertension, diabetes mellitus, myocardial infarction, and cancer. Last, model 4 additionally includes baseline cognitive function (normal cognition vs. MCI vs. dementia) to model 3. In each model, we assessed the interaction between the baseline biomarker and follow-up time in years. To assess for potential differences in the association between biomarkers of inflammation and cognitive decline between relevant subpopulations, we performed sensitivity analyses including interaction terms between each baseline biomarkers and age (continuous), sex (male vs. female), race (Black vs. White individuals), education (Master's or Doctorate degree vs. Bachelor's or GED) in separate models. All analyses were performed using R Version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Demographic and clinical characteristics of study participants stratified by dementia diagnosis.

Parameter	Normal cognition (*N* = 126)	Mild cognitive impairment (*N* = 97)	Dementia (*N* = 59)	*P*-Value
Age (years), mean ± SD	70.5 ± 7.0	73.5 ± 8.8	72.3 ± 8.9	**0.023**
Sex – no. (%)				
Male	37 (29.4)	37 (38.1)	29 (49.2)	**0.031**
Female	89 (70.6)	60 (61.9)	30 (50.8)	
Race – no. (%)				
White	90 (71.4)	49 (50.5)	53 (89.8)	<**0.001**
Black	36 (28.6)	48 (49.5)	6 (10.2)	
Education Level – no. (%)				
High School or GED	12 (9.5)	17 (17.5)	17 (29.3)	**0.004**
Bachelor's degree	48 (36.1)	50 (51.5)	22 (37.9)	
Master's degree	50 (39.7)	22 (22.7)	15 (25.9)	
Doctorate degree	16 (12.7)	8 (8.2)	4 (6.9)	
Body mass index (kg/m^2), mean ± SD	28.6 ± 6.2	27.7 ± 7.4	25.0 ± 6.3	**0.002**
Clinical characteristics – no. (%)				
Tobacco use	41 (32.5)	27 (27.8)	19 (32.2)	0.73
Hypertension	57 (45.2)	60 (61.9)	28 (47.5)	**0.038**
Type 2 diabetes mellitus	17 (13.5)	12 (12.4)	5 (8.5)	0.62
Hypercholesterolemia	61 (48.4)	51 (52.6)	37 (62.7)	019
Prior myocardial infarction	4 (3.2)	4 (4.1)	3 (5.1)	0.81
Cancer	38 (30.2)	32 (33.0)	11 (18.6)	0.14
MoCA total score, mean ± SD	27.9 ± 8.0	23.2 ± 3.2	20.5 ± 19.4	<**0.001**
CDR – SB, mean ± SD	0.42 ± 0.25	0.93 ± 0.13	4.36 ± 3.07	<**0.001**
CDR – GS ≥ 1 (at least mild), no. (%)	0 (0%)	0 (0%)	26 (44.1)	<**0.001**
Hs-CRP (mg/L), median (IQR)	1.39 (0.78-2.73)	1.42 (0.59-2.92)	0.84 (0.48-1.92)	**0.022**
SuPAR (ng/mL), median (IQR)	2.61 (2.23-3.34)	2.84 (1.41-4.27)	2.92 (2.26-3.64)	0.38

Abbreviations: CDR-GS, Clinical Dementia Rating scale – Global Score; CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; Hs-CRP, high sensitivity C-reactive protein; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; SD, standard deviation; suPAR, soluble urokinase plasminogen activator receptor.

Note: *P*-Values were found using Kruskal-Wallis Tests (continuous variables) or chi-squared tests (categorical variables).

Bolded values indicate statistical significance with P<0.05.

3 | RESULTS

3.1 | Clinical characteristics of the UM-MAP cohort

The study comprised 282 participants (mean age 71.8 years, 63.5% women, 31.9% Blacks) enrolled in UM-MAP from 2017 to 2019, after excluding 24 without blood samples (Table 1). At baseline, there were 126 participants (44.7%) with normal cognition, 97 (34.4%) with MCI, and 59 (20.9%) with a clinical diagnosis of dementia, of whom 39 had a diagnosis of AD, 9 with frontotemporal dementia, 4 with Lewy body dementia, 4 with mixed dementia, and 3 were classified as other dementia. Higher baseline CDR scores and lower MoCA scores were noted in participants with a diagnosis of dementia compared to participants without impairment or MCI (Table 1). Among patients with a diagnosis of dementia, baseline MoCA (mean 21.3 vs. 18.9, $P = 0.65$) and CDR-SB (mean 4.37 vs. 4.55, $P = 0.85$) scores did not differ according to dementia diagnosis (AD vs. non-AD, respectively). Compared to participants with no cognitive impairment, those with dementia were older (72.3 vs. 70.5 years), more likely to be men (49.2% vs. 29.4%), of white race (89.8% vs. 71.4%), and less likely to have a post-secondary education degree (70.7% vs. 88.5%). We found no major differences in cardiovascular risk factors between participants with and without cognitive impairment (Table 1). Baseline CRP levels differed by cognitive impairment ($P = 0.022$). Participants with dementia had a lower median hs-CRP levels compared to those with normal cognition or MCI (0.84 mg/L vs 1.39 and 1.42 mg/L, respectively). SuPAR levels did not differ between participants with normal cognition (median of 2.61 ng/mL, [IQR 1.50-3.71 ng/mL]), MCI (median of 2.84 ng/mL, [IQR 1.41–4.27 ng/mL]), or dementia (median 2.92 ng/mL [IQR 1.54–4.30 ng/mL] ($P = 0.38$) (Table 1).

TABLE 2 Determinants of baseline MoCA and CDR-SB scores.

	MoCA		CDR-SB	
Parameter	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-Value**
Age, per 1 year	0.18 (−0.14, 0.18)	0.83	**0.03 (0.00, 0.06)**	**0.032**
Male sex versus Female	0.96 (−1.69, 3.60),	0.48	**−0.57 (−1.07, −0.08)**	**0.023**
Black race versus White	−1.89 (−4.68, 0.90)	0.18	**−0.79 (−1.31, −0.27)**	**0.003**
Masters or Doctorate Degree versus Bachelor's Degree or GED	2.99 (−0.38, 6.37)	0.08	**−0.69 (−1.32, −0.06)**	**0.033**
Body Mass Index, per 1 kg/m^2	0.14 (−0.11, 0.40)	0.27	−0.01 (−0.06, 0.04)	0.75
Hs-CRP, per 100% increase	0.97 (−0.18, 2.13)	0.09	−0.10 (−0.32, 0.11)	0.35
SuPAR, per 100% increase	−0.77 (−3.81, 2.70)	0.62	−0.25 (−0.32, 0.82)	0.39

Abbreviations: CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; CI, confidence interval; Hs-CRP, high sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment; suPAR, soluble urokinase plasminogen activator receptor.
Bolded values indicate statistical significance with P<0.05

3.2 | Determinants of SuPAR and hs-CRP levels

Characteristics of participants stratified by baseline suPAR and hs-CRP tertiles are provided in Supplementary Tables 1 and 2. Age, and history of hypertension and malignancy differed according to suPAR tertiles. Participants in the third tertile had the highest age and prevalence of hypertension compared to participants in the first and second tertiles (Supplementary Table 1). BMI and history of hypertension were associated with hs-CRP tertiles. Participants in the highest hs-CRP tertile had the highest BMI and prevalence of hypertension (Supplementary Table 2). SuPAR levels did not correlate with CDR-SB ($\rho = 0.100$, $P = 0.09$) or MoCA ($\rho = -0.079$, $P = 0.19$) scores. We found hs-CRP levels were negatively correlated with CDR-SB ($\rho = 0.200$, $P < 0.001$), and weakly correlated with MoCA ($\rho = 0.100$, $P = 0.065$) scores. In multivariable analysis, neither baseline suPAR levels or hs-CRP were independently associated with baseline CDR-SB or MoCA scores (Table 2).

3.3 | SuPAR, hs-CRP, and cognitive decline

Of the 282 participants enrolled, the median number of visits per participant was three over a median (IQR) follow-up of 2.0 (1.0, 2.6) years. Overall, 14% of participants experienced significant cognitive decline over the study period defined as a change in CDR-GS of 0.5 or greater. Participants with a diagnosis of dementia demonstrated significant worsening in cognitive function by visit three (31.3% decline in MoCA scores; 155% increase in CDR-SB scores; $P < 0.001$) compared to patients with MCI or normal cognition (Figure 1). Among patients with a diagnosis of dementia, changes in MoCA ($P = 0.08$) or CDR-SB ($P = 0.18$) scores did not differ when comparing patients with AD versus non- AD.

When stratified by suPAR or hs-CRP tertiles, we found no difference in changes in MoCA total score or CDR-SB between groups (Figure 2). Linear mixed models showed no association between baseline suPAR or hs-CRP and changes in MoCA or CDR-SB scores in unadjusted or adjusted models (Table 3). In sensitivity analyses, the association between suPAR or hs-CRP levels and cognitive decline did not differ according to age, sex, race, or education level (Supplementary Table 3).

4 | DISCUSSION

In this prospective study of 282 participants with a wide range of cognitive and functional abilities who completed serial evaluations, we found that the biomarkers of chronic inflammation suPAR and hs-CRP were not independently associated with dementia or cognitive decline at a median follow-up of 2 years. Cognition was assessed longitudinally using two well-established measures, the MoCA and CDR, in a participant population with a wide range of cognitive function and dementias of predominantly non-vascular etiology, of whom 14% exhibited a significant decline in cognition in the time frame of the study. In addition to hs-CRP, we sought to explore suPAR's association with dementia and cognitive decline given that it is not an acute phase reactant, has stable levels, and reflects inflammatory pathways that differ from hs-CRP. Neither suPAR or hs-CRP levels were associated with cross-sectional or longitudinal differences in cognition. Overall, our analyses suggest that systemic chronic inflammation is unlikely to be a major contributor to non-vascular dementias and informs the debate on the role of systemic inflammation in non-vascular dementia.

Studies evaluating the association between inflammation and cognitive dysfunction have reported conflicting results in the past, which may be related to the populations studied.[16,17,38] A prospective study of 5,257 participants from the general population in England reported that while hs-CRP levels did not correlate with different aspects of cognitive function at baseline, it was associated with a decline in cognitive scores at follow-up. The study assessed cognition in a largely healthy population, used a cognitive assessment tool devised by the researchers and that relies on recall, and only found a numerically minor difference in the rate of cognitive decline between hs-CRP quartiles.[38] Another population-based cohort study found that the highest tertile of hs-CRP (examined only as a categorical

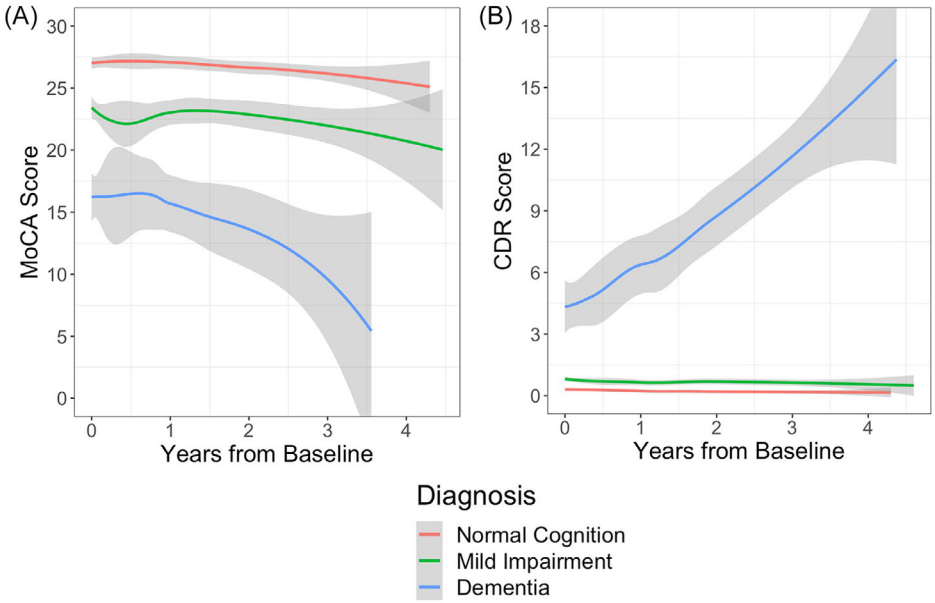

FIGURE 1 Longitudinal MoCA and CDR-SB scores stratified by baseline cognitive function. Plot of the average (A) MoCA score and (B) CDR-SB score over follow-up time stratified by baseline cognitive function: normal cognition (red), mild cognitive impairment (green), and dementia (blue). The gray area represents the 95% confidence interval. Abbreviations: CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; MoCA, Montreal Cognitive Assessment.

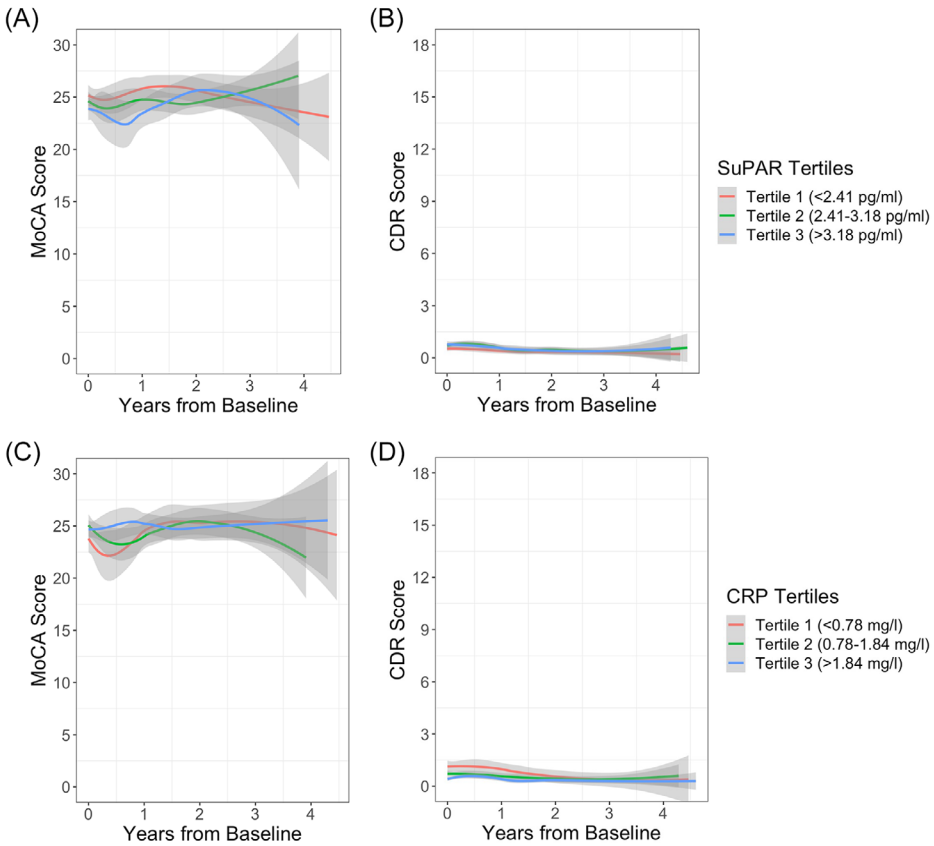

FIGURE 2 Longitudinal MoCA and CDR-SB Scores Stratified by SuPAR and Hs-CRP Tertiles. Plot of the average MoCA score and CDR-SB score over follow-up time stratified by baseline suPAR and hs-CRP tertiles. (A) MoCA and suPAR tertiles, (B) CDR and suPAR tertiles, (C) MoCA and hs-CRP tertiles, and (D) CDR and hs-CRP tertiles. In each biomarker, first tertile (red), second tertile (green), and third tertile (blue). The gray area represents the 95% confidence interval. Abbreviations: CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; hs-CRP, high sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment; suPAR, soluble urokinase plasminogen activator receptor.

TABLE 3 Multivariable analysis of the association between biomarkers of inflammation and cognitive decline.

	MoCA		CDR-SB	
Parameter	B (95% CI)	*P*-value	B (95% CI)	*P*-Value
SuPAR				
Model 1	−0.51 (−2.08, 1.07)	0.52	0.05 (−0.36, 0.45)	0.82
Model 2	−0.42 (−1.98, 1.20)	0.60	−0.01 (−0.41, 0.39)	0.96
Model 3	−1.26 (−4.01, 1.48)	0.39	0.19 (−0.31, 0.68)	0.47
Model 4	−1.29 (−4.05, 1.48)	0.38	0.05 (−0.40, 0.50)	0.83
Hs-CRP				
Model 1	0.02 (−0.46, 0.50)	0.92	−0.07 (−0.20, 0.06)	0.30
Model 2	0.04 (−0.44, 0.52)	0.87	−0.07 (−0.20, 0.05)	0.27
Model 3	0.18 (−0.62, 0.98)	0.67	0.02 (−0.13, 0.16)	0.76
Model 4	0.20 (−0.60, 1.00)	0.64	0.01 (−0.12, 0.14)	0.85

Note: SuPAR and CRP are log-transformed; coefficient presented is the interaction between years*biomarker.
Model 1: Biomarker alone.
Model 2: Biomarker, age, race, education.
Model 3: Model 2 + body mass index, hypertension, diabetes mellitus, myocardial infarction, cancer.
Abbreviations: CDR-SB, Clinical Dementia Rating scale – Sum of Boxes; Hs-CRP, high sensitivity C-reactive protein; MoCA, Montreal Cognitive Assessment; suPAR, soluble urokinase plasminogen activator receptor.

variable) was associated with all-cause dementia at 8 years follow-up.[39] The relationship was only significant in the subgroup of participants age < 65 years old.[39] This difference related to age was reported in another study specifically looking a diagnosis of AD (n = 52).[40] There was however no association between hs-CRP and AD in the overall group, and no cognitive testing was performed as part of the study.[40] These data suggest age may be a moderator of the association between hs-CRP and dementia. We did find in our study an inverse correlation between hs-CRP and a diagnosis of dementia which was not significant after adjustment for socio-demographic (or list them) covariates. The clinical significance of such an inverse association is unclear, as hs-CRP typically increases with age while dementia worsens. Our findings are in line with a recent published study which used large-scale proteomics quantifying 1,160 plasma proteins in AD patients and controls, and found that proteins involved in the inflammatory response were downregulated in AD.[41]

We measured suPAR levels as a biomarker of inflammation with high stability over time (<5% variation in intra-individual levels over 5 years) to account for the variation in findings surrounding the link between inflammation and AD, attributed at least partially to the highly variable levels of most conventionally measured biomarkers (hs-CRP, interleukins and others). SuPAR levels show no circadian variation, and remain stable during episodes of acute stress such as cardiac surgery, or myocardial infarction.[42–44] SuPAR outperforms conventional biomarkers of inflammation in predicting outcomes in various patient populations.[45–55] Despite these characteristics, findings surrounding suPAR and dementia or cognitive decline are consistent with that of hs-CRP and support the absence of a strong relationship between systemic inflammation and non-vascular dementias. These observations did not differ according to sex, race, educational status, or clinical characteristics.

We cannot completely exclude the existence of a link between inflammation and non-vascular dementias based on hs-CRP and suPAR alone. Biomarkers of inflammation, regardless of the pathway involved, tend to correlate at least modestly. Should systemic inflammation have a major contributing role to the progression of AD, a consistent relationship should be observed. One study reported that higher levels of peripheral CRP, monocyte chemoattraction protein (MCP)-1, MCP-2, interleukin (IL)-2, IL-6, IL-8, IL-18, IL-1ß, and IP-10 were associated with AD.[16] Another study reported that higher levels of peripheral cytokines IL-6, IL-12, IL-18, IL-1β, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, along with higher levels of cerebrospinal TGF-β, were associated with AD.[11] However, the clinical significance of these associations remains unclear. The only overlapping biomarkers of significance between these studies were IL-6, IL-8, and IL-1β. As biomarkers of acute inflammation, these increased levels do not provide sufficient evidence to draw a definitive, novel connection to the pathogenesis of AD in patients.[22,23]

4.1 | Strengths and limitations

Our study has several strengths, including its prospective nature, the use of well-established and validated tools to measure general cognitive function over time, and a diverse participant population with a wide range of cognitive function at baseline. This is the first study to our knowledge that examined the association between suPAR, a highly stable inflammatory biomarker, and cognitive dysfunction.[18] We acknowledge several limitations. First, given that we measured select biomarkers, we cannot extrapolate findings to all biomarkers of inflammation. Second, the sample size of the study is not powered to detect

small differences in levels of inflammation biomarkers between participants. However, the clinical significance of small differences in levels would be debatable. Third, the follow-up time was relatively short, and a difference may be detectable in a longer time frame, although the clinical significance of the findings would also be debatable given the median age of the population was 70 years. The diagnoses of dementia were made based on a consensus clinical assessment following the NACC guidelines but did not include the use of AD biomarkers.[32] Last, biomarkers were measured peripherally. It is plausible that cerebrospinal fluid (CSF) measurements of inflammatory biomarkers could provide more insight, particularly in the context of central nervous system diseases and cognitive impairment. There is evidence that suggests CSF suPAR dynamics may differ from serum and could potentially provide additional insights into disease progression and prognosis.[56–58] may differ from serum and could potentially provide additional insights into disease progression and prognosis. Further research directly comparing CSF and serum suPAR levels in various CNS diseases and cognitive impairment is warranted to better understand the potential of CSF suPAR as a biomarker in these contexts.

5 | CONCLUSION

In conclusion, suPAR and hs-CRP levels were not associated with a diagnosis of MCI or dementia at enrollment nor were they predictive of changes in cognitive functioning scores at follow-up. These findings suggest that it is unlikely that systemic inflammation, as measured by suPAR and hs-CRP, are major contributors to AD and cognitive decline.

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CONFLICT OF INTEREST STATEMENT

SSH is a member of the scientific advisory board of Walden Biosciences. Other authors do not have a conflict of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was approved by the University of Michigan Institutional Review Board, and all patients provided informed consent for enrollment in UM-MAP. This study was performed in accordance with all relevant guidelines and regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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