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Original Article

Associations of circulating c-reactive protein levels with central Alzheimer's disease biomarkers

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ABSTRACT

Background: C-reactive protein (CRP) is well-known marker of inflammation and immune response. Its potential role in Alzheimer's disease (AD) pathophysiology remains unclear, particularly in relation to central AD biomarkers, including beta-amyloid (Aβ), tau, and neurodegeneration.

Objectives: To investigate the associations between circulating CRP levels and central AD biomarkers-including Aβ deposition, tau, and AD-signature neurodegeneration-in nondemented older adults.

Design, Setting, Participants: This cross-sectional observational study analyzed data from a Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer Disease conducted from 2014 to 2020. A total of 417 nondemented older adults underwent comprehensive evaluations, including blood sampling and multimodal neuroimaging for measuring of Aβ and AD-signature neurodegeneration. A subset of participants ($N = 123$) also underwent tau positron emission tomography (PET) scan.

Measurements: The primary outcomes were A/T/N biomarkers of AD, including brain Aβ and tau deposition measured via amyloid and tau PET, as well as AD-signature neurodegeneration measured by fluorodeoxyglucose (FDG)-PET. Associations between CRP levels and these biomarkers were analyzed while adjusting for CRP-decreasing allele scores, as well as other confounders, including age, sex, vascular risk score, body mass index, nonsteroidal anti-inflammatory drug (NSAID) usage, smoking status, and *APOE* ε4 carrier status.

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Results: The mean (SD) age of participants was 70.57 (8.00) years, with 179 (42.9 %) females. Circulating CRP levels showed non-linear associations with A/T/N biomarkers of AD, showing a U-shaped relationship with Aβ and tau deposition and an inverted U-shaped association with neurodegeneration. Threshold effect analyses revealed that CRP was inversely associated with Aβ deposition (B = -0.081; 95 % CI, -0.153 to -0.007; p = 0.031) below 0.63 mg/L, after adjusting for all confounding variables. In contrast, higher CRP levels were associated with lower cerebral glucose metabolism in AD-signature regions, indicative of greater AD-related neurodegeneration, when above 2.15 mg/L (B = -0.056; 95 % CI, -0.112 to -0.001; p = 0.042).
Conclusions: Our study revealed differential associations between circulating CRP levels and central AD biomarkers that varied according to the CRP concentration. Further studies are necessary to elucidate the mechanisms underlying the inverse relationship between circulating CRP and brain Aβ within the clinically normal range, as well as potential aggravating effects of elevated CRP on Aβ-independent neurodegeneration.

1. Introduction

C-reactive protein (CRP) is a widely recognized marker of inflammation and immune response, commonly used in clinical practice and research due to its high sensitivity and convenience [1]. CRP plays a crucial role in innate immunity by activating complement and promoting opsonization, thereby activating adaptive immune responses [2,3]. Given that mechanisms involving inflammatory and immune-mediated responses are deeply involved in the pathogenesis of Alzheimer's disease (AD) [4,5], elucidating the relationship between CRP and neuropathological changes using AD biomarkers could provide insights into the AD pathogenesis within this context.

Several epidemiological studies on the relationship between circulating CRP levels and AD dementia reported mixed results. Some previous studies have reported that individuals with clinically diagnosed AD dementia have significantly higher CRP levels than healthy controls, and that elevated CRP levels were associated with an increased risk of conversion to AD dementia [6–8]. However, other previous studies have reported that circulating CRP levels have no significant association or a negative association with the risk of AD dementia, as well as greater cognitive and functional decline [9–11]. Since these studies relied on clinical diagnoses, it is necessary to examine the association between CRP levels and *in vivo* AD biomarkers, including beta-amyloid (Aβ), tau, and neurodegeneration, to elucidate heterogeneities among previous studies. Additionally, several single nucleotide polymorphisms (SNPs) in the CRP gene are known to decrease blood CRP levels [12]. Thus, considering individual genetic differences will be needed to minimize potential confounding factors.

To date, only a small number of studies have attempted to investigate the association between CRP level and *in vivo* AD pathologies to explore the association between CRP and AD-related brain changes occurring in the early stage of the disease. One previous study has reported a positive association between baseline CRP level and an increase of global Aβ deposition during follow-up of 64 Aβ-positive, nondemented older adults [13]. In contrast, another study has reported a negative association between CRP level and cortical Aβ deposition in 259 nondemented elderly individuals [14]. On the other hand, one study with a relatively small sample size (N = 78) has reported no significant association between CRP level and Aβ deposition [15]. Thus far, the nature of the relationship between CRP levels and AD biomarkers remains unclear.

Hence, we investigated associations between circulating CRP levels in peripheral blood and central A/T/N biomarkers for AD in nondemented older adults by estimating the pattern of association between CRP level and each AD biomarker according to CRP levels. Additionally, we examined these associations after controlling for possible confounders, including individual genetic differences influencing CRP levels.

2. Methods

2.1. Participants

For this study, nondemented older adults, consisting of cognitively normal (CN) and mild cognitive impairment (MCI) groups, were recruited from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's disease (KBASE), launched in 2014 in Seoul, Republic of Korea. Detailed information on the study design and participant recruitment for the KBASE cohort has been previously described [16]. Inclusion and exclusion criteria are also provided in Supplementary Materials (eMethod1). Briefly, the CN group consisted of individuals with a global Clinical Dementia Rating (CDR) score of 0 and no diagnosis of MCI or dementia. The MCI group included individuals who met the core clinical feature for MCI diagnosis as outlined in the guidelines from the National Institute on Aging – Alzheimer's Association (NIA-AA) [17], with a global CDR score of 0.5. The study protocol received approval from the Institutional Review Boards of Seoul National University Hospital (C-1401–027–547) and Seoul Metropolitan Government-Seoul National University Boramae Medical Center (26–2015–60) in Seoul, Republic of Korea. Informed written consent was obtained from all participants. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.2. Clinical assessment

All participants underwent a comprehensive clinical assessment, which included standardized clinical evaluation integrating the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease assessment packet (CERAD-K) [16,18], conducted by trained psychiatrists. Systematic interviews with participants and their informants by trained nurses were also conducted to assess vascular risk factors (VRFs), including included hypertension, diabetes mellitus, dyslipidemia, stroke, transient ischemic attack, and coronary heart disease. The VRF score (VRS) was computed based on the number of VRFs identified [19]. In addition, information regarding concomitant medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), and smoking status were also collected by same manner. Body mass index (BMI) was calculated by dividing each participant's weight in kilograms by the square of their height in meters.

2.3. Central A/T/N biomarkers of AD

All participants underwent [^{11}C]-Pittsburgh compound B (PiB)-positron emission tomography (PET) for Aβ deposition, and [^{18}F] Fluorodeoxyglucose (FDG)-PET for neurodegeneration. In addition, a subset of participants (N = 123) underwent [^{18}F] AV-1451 PET for tau deposition. Detailed methodology on image acquisition and preprocessing is provided in our previous studies and Supplementary Material (eMethod2). Briefly, for measurement of cerebral Aβ deposition, global PiB deposition was measured in ROIs consisting of the frontal,

posterior cingulate cortex (PCC)-precuneus, lateral parietal, and lateral temporal cortices [20]. For tau deposition, AV-1451 standardized uptake value ratio (SUVR) in AD-signature regions, including the fusiform, parahippocampal, amygdala, entorhinal, middle temporal, and inferior temporal cortices were measured [21]. For neurodegeneration biomarker of AD, cerebral glucose metabolism measured by FDG-PET in AD-signature regions (AD-CM), including the PCC, angular gyri, and inferior temporal gyri, was used in this study [20].

2.4. Circulating CRP levels, CRP-decreasing allele score, and apolipoprotein E (APOE) genotyping

Blood samples were collected in the morning via venipuncture after an overnight fast. Serum samples were stored in a −80 °C deep freezer, then thawed to measure of serum high-sensitivity CRP (hs-CRP) levels using an immunoturbidimetric assay method with a Cobas c702 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) following manufacturer protocols [22]. The hs-CRP assay is highly sensitive and capable of detecting even low levels of CRP [23]. Individuals with hs-CRP levels > 10 mg/L, indicative of acute infection and inflammation, were excluded from all analyses to lessen confounding factors related to serious medical comorbidities [24].

DNA was extracted, and *APOE* genotyping was performed according to a previous study [25]. *APOE4* carrier was defined as a participant with at least one ε4 allele. Additionally, to minimize variations in CRP levels due to genetic contribution [12], CRP-decreasing allele score was calculated as the total number of CRP decreasing alleles in each individual, based on previous studies [26–28]. A genome-wide association study (GWAS) genotyping was performed for all participants using the Illumina Global Genotyping Platform enriched for Asian variants. Four SNPs within the *CRP* gene that have been shown to be associated with blood CRP levels - rs1205, rs1130864, rs1800947, and rs3093077 [29,30] - were extracted from TOPMed-based imputed GWAS genotyping data in KBASE (Supplementary Material: eTable 1). For each SNP, the presence or absence of the allele associated with decreased CRP levels was coded as 1 or 0, and these values were summed to generate CRP-decreasing score for each individual, ranging 0 to 8 by its definition.

Table 1
Demographic and clinical characteristics of participants.

	Total (n = 417)
Age	70.57 ± 8.00
Female	179 (42.9)
Educational years	11.35 ± 4.78
Clinical diagnosis	
Cognitively normal	273 (65.5)
Mild cognitive impairment	144 (34.5)
ApoE ε4 carrier	106 (25.4)
Vascular risk score	1.1 ± 0.98
BMI	24.38±2.98
Smoking status	
Never	283 (67.9)
Quit	113 (27.1)
Currently smoking	21 (5.0)
NSAIDs usage	14 (3.4)
CRP (mg/L)	1.10 ± 1.41
CRP-decreasing allele score	4.86 ± 1.23
Central A/T/N biomarker	
Global Aβ deposition (SUVR)	1.31 ± 0.35
AD-signature tau deposition[a] (SUVR)	1.66 ± 0.81
AD-CM (SUVR)	1.38 ± 0.14

Note. Data are presented in mean ± SD or N (%).
Abbreviations: APOE4, apolipoprotein E ε4; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; CRP, C-reactive protein; Aβ, beta-amyloid; SUVR, standardized uptake value ratio; AD, Alzheimer's disease; AD-CM, AD-signature cerebral glucose metabolism.
[a] Data were available for N = 123.

2.5. Statistical analysis

Due to the positive skew of serum hs-CRP levels, log transformation was applied for normal distribution. Log-transformed CRP levels that deviated more than three standard deviations from the mean were excluded as outliers. Measures for central A/T/N biomarkers of AD were also log-transformed due to the positive skewed distribution. To explore nonlinearity between serum hs-CRP and A/T/N biomarkers, natural cubic spline curves were utilized [31]. The p value for non-linearity was calculated by performing a likelihood ratio test comparing the spline model against the linear regression model. If non-linear relationships were identified, a threshold effect analysis was performed using piecewise regression models to elucidate how associations differed around the breakpoint [32]. All analyses included confounders known to affect circulating CRP levels, such as smoking status, BMI, and NSAID usage [33,34], as well as demographic variables, *APOE* ε4 carrier status, and VRS (model 1A). Global Aβ retention (SUVR) was additively controlled in analysis regarding tau and neurodegeneration biomarkers (model 1B). We then performed the same piecewise linear regression analyses, including CRP-decreasing allele score along with other covariates (model 2A; model 2B: model 2A + global Aβ deposition). To interpret the regression coefficients (unstandardized B) derived from each model, we calculated and reported the percentage change in Y corresponding to the percentage change in X based on the log–log regression model, while holding other covariates constant, as both CRP (X) and the A/T/N biomarkers (Y) were log-transformed. All statistical analyses were conducted using the R version 4.3.2 (The R Foundation for Statistical Computing) software.

3. Results

3.1. Participant characteristics

A total of 417 participants were analyzed. Demographic and clinical characteristics of subjects are presented in Table 1. The mean (SD) age of participants was 70.57 (8.00) years, with 179 (42.93 %) females. The mean (SD) concentration of CRP was 1.10 (1.41) mg/L. Among them, 273 (65.47 %) were in the CN group and 144 (34.53 %) were in the MCI group. A total of 106 participants (25.42 %) were *APOE4* carriers. The mean (SD) of CRP-decreasing allele scores was 4.86 (1.23) (Table 1).

3.2. Nonlinear relationships between circulating CRP levels and A/T/N biomarkers

Using natural cubic spline analyses, we identified significant nonlinearities in the associations between circulating CRP levels and all three A/T/N biomarkers after adjusting for covariates (age, sex, VRS, *APOE4* status, BMI, smoking status and NSAIDs usage) (Fig. 1). Circulating CRP levels exhibited a nonlinear, U-shaped association with Aβ (p = 0.029; Fig. 1A) and tau deposition (p = 0.037; Fig. 1B), whereas a nonlinear, inverted U-shaped association was observed with AD-CM (p = 0.023; Fig. 1C).

3.3. Threshold effect analyses of the association between circulating CRP levels and A/T/N biomarkers using piecewise linear regression

Given the nonlinear associations between circulating CRP levels and each A/T/N biomarkers, we conducted threshold effect analyses using piecewise linear regression. For the Aβ biomarker, after adjusting for covariates (Model 1A), the breakpoint identified in the association between CRP level and global Aβ deposition was 0.63 mg/L (Fig. 2A). Below this threshold, CRP was inversely associated with global Aβ deposition (B = −0.082; 95 % CI, −0.154 to −0.007; p = 0.028), such that lower CRP levels were associated with greater global Aβ deposition: a 2-fold decrease corresponded to an estimated 5.85 % increase in global Aβ deposition, and a 4-fold decrease corresponded to a 12.04 % increase.

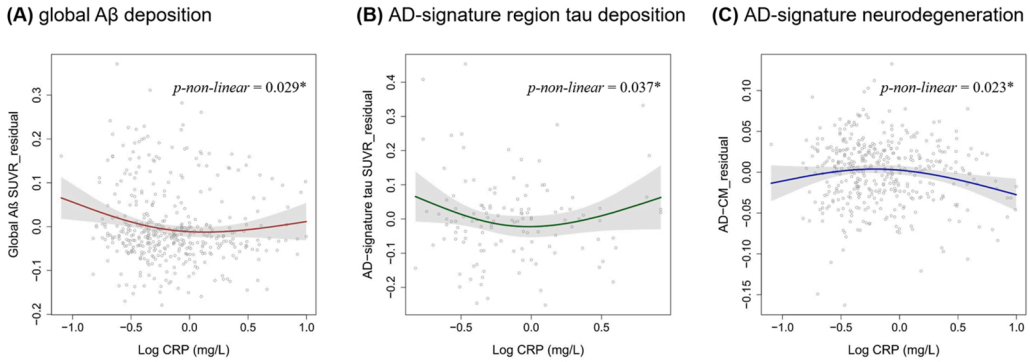

Fig. 1. Natural cubic spline of associations between serum CRP levels and A/T/N biomarkers of AD: (A) global Aβ deposition, (B) AD-signature region tau deposition, and (C) AD-signature neurodegeneration.
*adjusted $p < 0.05$. Note. Data for 417,123, and 417 individuals were available for A/T/N biomarkers of AD. For analysis of Aβ biomarker, age, sex, VRS, *APOE4* carrier status, BMI, and NSAIDs usage were adjusted as covariates. For analysis of tau and neurodegeneration biomarker, global Aβ deposition were also included as covariates. Abbreviations: CRP, C-reactive protein; A/T/N, Amyloid, tau, and neurodegeneration; AD, Alzheimer's disease; Aβ, beta-amyloid; VRS, vascular risk score; *APOE4*, apolipoprotein E ε4; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs

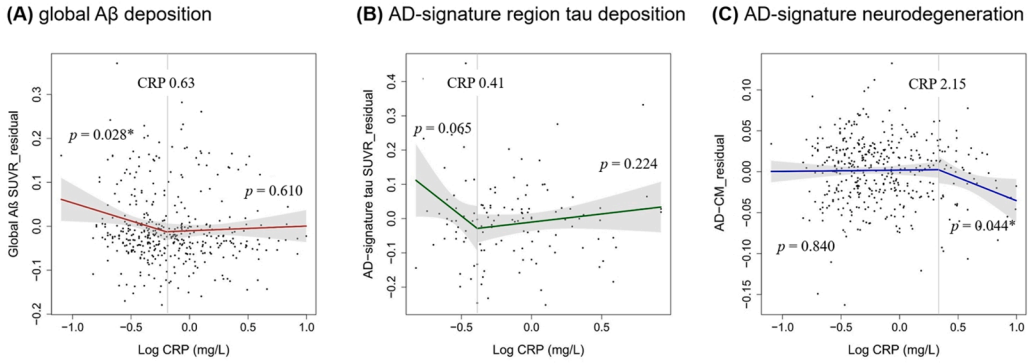

Fig. 2. Piecewise linear regression analyses on associations between serum CRP levels and A/T/N biomarkers of AD: (A) global Aβ deposition, (B) AD-signature region tau deposition, and (C) AD-signature neurodegeneration.
*adjusted $p < 0.05$. Note. Data for 417,123, and 417 individuals were available for A/T/N biomarkers of AD. For analysis of Aβ biomarker, age, sex, VRS, *APOE4* carrier status, BMI, and NSAIDs usage were adjusted as covariates. For analysis of tau and neurodegeneration biomarker, global Aβ deposition were also included as covariates. Abbreviations: CRP, C-reactive protein; A/T/N, Amyloid, tau, and neurodegeneration; AD, Alzheimer's disease; Aβ, beta-amyloid; VRS, vascular risk score; *APOE4*, apolipoprotein E ε4; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs

However, no significant association was found above 0.630 mg/L (B = 0.010; 95 % CI, −0.031 to 0.052; p = 0.610).

When we performed the same analysis for tau deposition, after adjusting for covariates including global Aβ deposition (Model 1B), the breakpoint was 0.41 mg/L (Fig. 2B). A trend toward a negative association between CRP levels and tau deposition in AD-signature region was observed below this level (B = −0.331; 95 % CI, −0.675 to 0.019; p = 0.065), but no significant association was found above 0.410 mg/L.

For the neurodegeneration biomarker of AD, the breakpoint identified in the association between CRP level and AD-CM was 2.15 mg/L (Fig. 2C), after adjusting for covariates including Aβ (Model 1B). Above this threshold, circulating CRP level was inversely associated with AD-CM (B = −0.023; 95 % CI, −0.112 to −0.001; p = 0.044), indicating that higher CRP levels were associated with lower AD-CM: a 2-fold increase corresponded to an estimated 1.58 % decrease, and a 4-fold increase corresponded to an estimated 3.14 % decrease. No significant association was observed below 2.15 mg/L.

3.4. Associations between circulating CRP levels and A/T/N biomarkers, after controlling the effect of CRP-decreasing allele score

To minimize the influence of individual genetic variations in CRP levels, we calculated the CRP-decreasing allele score for all participants. This score was inversely associated with circulating CRP levels (B = −0.122; 95 % CI, −0.216 to −0.026; p = 0.013), and the association remained significant after adjusting for covariates in Model 1A (B = −0.119; 95 % CI, −0.212 to −0.023; p = 0.014; eFig. 1). When we repeated the threshold effect analyses using piecewise linear regression, additionally controlling for the effect of the CRP-decreasing allele score along with other covariates, the overall results remained consistent (Table 2 and Fig. 3).

Specifically, the breakpoints for association between circulating CRP levels and each A/T/N biomarkers did not change after adjusting covariates including CRP-decreasing allele score (Model 2A). In addition, an inverse association was observed between circulating CRP levels and *in vivo* brain Aβ below 0.63 mg/L (B = −0.081; 95 % CI, −0.152 to −0.005; p = 0.031), indicating that lower CRP levels were associated with greater global Aβ deposition: a 2-fold decrease corresponded to an estimated 5.78 % increase, and a 4-fold decrease to an estimated 11.89 % increase. An inverse association between circulating CRP levels and AD-CM above 2.15 mg/L still remained significant (B = −0.056; 95 % CI, −0.112 to −0.002; p = 0.042), demonstrating that higher CRP levels were associated with lower AD-CM: a 2-fold increase corresponded to an estimated 3.81 % decrease, and a 4-fold increase to an estimated 7.47 % decrease.

Table 2
Threshold effect analysis of the relationship between serum CRP levels and central A/T/N biomarkers using piecewise linear regression.

	Breakpoint (mg/L)	CRP range (mg/L)	N	B	Standard error	p-value
Aβ[a]	0.630	0.08–0.62	217	−0.081	0.037	**0.031***
		0.63–9.93	200	0.011	0.021	0.616
Tau[b]	0.410	0.15–0.41	37	−0.302	0.173	0.082
		0.43–8.36	86	0.049	0.039	0.211
AD-CM[b]	2.150	0.08–2.11	363	0.001	0.008	0.827
		2.15–9.93	54	−0.056	0.028	**0.042***

*adjusted $p < 0.05$.
[a] Model 2A: adjusted for age, sex, vascular risk score, APOE4 carrier status, smoking status, BMI, NSAIDs usage, and CRP-decreasing allele score.
[b] Model 2B: adjusted for covariates included in Model 2A and global Aβ deposition.

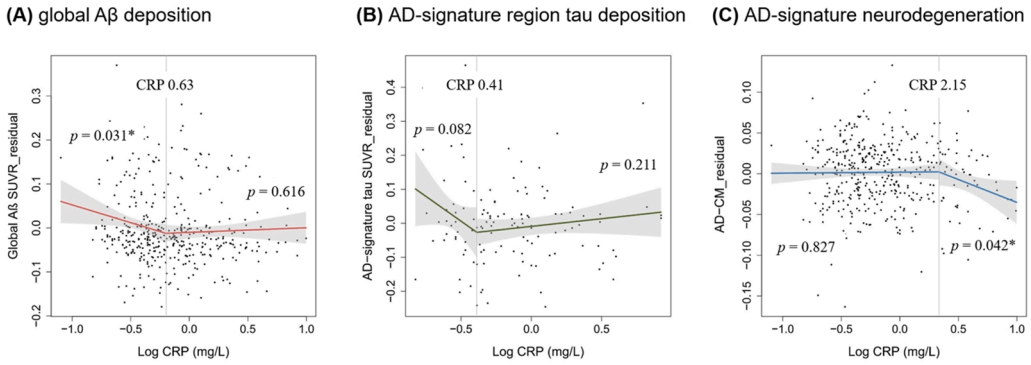

Fig. 3. Piecewise linear regression analyses on associations between serum CRP level and each A/T/N biomarkers of AD after controlling CRP-decreasing allele score: (A) global Aβ deposition, (B) AD-signature region tau deposition, and (C) AD-signature neurodegeneration.
*adjusted $p < 0.05$. Note. Data for 417,123, and 417 individuals were available for A/T/N biomarkers of AD. For analysis of Aβ biomarker, age, sex, VRS, *APOE4* carrier status, BMI, NSAIDs usage and CRP-decreasing allele score were adjusted as covariates. For analysis of tau and neurodegeneration biomarker, global Aβ deposition were also included as covariates. Abbreviations: CRP, C-reactive protein; A/T/N, Amyloid, tau, and neurodegeneration; AD, Alzheimer's disease; Aβ, beta-amyloid; VRS, vascular risk score; *APOE4*, apolipoprotein E ε4; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs

4. Discussion

We identified non-linear associations between circulating CRP levels and each A/T/N biomarkers of AD using natural cubic spline in non-demented older adults. Specifically, circulating CRP levels exhibited U-shaped associations with amyloid *in vivo* brain Aβ (A) and tau (T) deposition, and inverted U-shaped association with AD-CM (N). In threshold effect analyses, CRP was inversely associated with global Aβ when below 0.630mg/L, after adjusting for potential confounders. A similar trend was observed for tau, while an inverse association with AD-CM emerged when CRP was above 2.15mg/L. These findings remained consistent even after adjusting for genetic variation using the CRP-decreasing allele score.

In this study, lower circulating CRP level was associated with greater cerebral Aβ deposition below 0.630mg/L, a level close to the clinically normal range of CRP, even after adjusting for genetic factors influencing circulating CRP levels. Our findings align with previous epidemiological studies that have reported an association between lower CRP levels and a higher risk of AD and all-cause dementia, as well as greater cognitive and functional deterioration in patients with AD and more rapid progression to AD dementia in individuals with MCI [9,10,26]. Additionally, our results are consistent with a prior study that found a negative association between CRP levels and cortical Aβ deposition in non-demented elderly individuals [14]. However, a previous study reported a positive association between baseline CRP level and an increase in global Aβ deposition during follow-up in Aβ-positive nondemented older adults [13], while another study has reported no significant association [15]. Considering that our piecewise linear regression analysis revealed that associations between circulating CRP levels and central AD biomarkers may vary depending on CRP levels, inconsistencies among previous studies could be partly attributed to differences in sample characteristics, including the range of CRP levels, definition of abnormal CRP levels, and relatively small sample sizes compared to our study.

The inverse association between circulating CRP levels and *in vivo* Aβ pathologies —specifically within the context of clinically normative peripheral CRP concentrations—in our study indicates that biological pathway related to maintain baseline concentration of circulating CRP levels might be related to cerebral Aβ accumulation in nondemented individuals. It is known that plasma and cerebrospinal fluid (CSF) CRP levels are strongly correlated, suggesting that circulating CRP may serve as an indicator of both peripheral and central immune activity [35,36]. Although CRP is known to rapidly increase in response to external stimuli such as acute infection [37], baseline CRP is constitutively expressed at low levels [38,39]. CRP plays a crucial role in innate immunity by mediating the phagocytosis of sensitized erythrocytes and activating the classical complement cascade [2,3,40]. Several studies have underscored the significant role of the complement system in the pathophysiology of AD. Prior studies have suggested that reduced CRP levels may lead to diminished opsonization, cell lysis and phagocytosis of Aβ by microglia, along with reduced activation of the complement system, ultimately resulting in less effective clearance of Aβ and subsequent neurotoxic effects [41,42]. Moreover, CRP is also known to prevent development of autoimmunity in mice models; for instance, administration of a single injection of human CRP prior to disease onset significantly delayed the development of lymphadenopathy and proteinuria in NZB/NZW mice, a widely used animal model of human systemic lupus erythematosus [43–45]. Taken together, these findings suggest that in the absence of clinically elevated CRP levels, a relative CRP deficiency may contribute to cerebral Aβ accumulation through its immunomodulatory role. Similarly, based on our findings on a marginal association between circulating CRP levels and tau deposition, a comparable mechanism related to deficient CRP levels might be implicated

in tau pathologies. However, further studies are warranted to elucidate the precise mechanisms underlying the associations between circulating CRP levels and *in vivo* AD pathologies,

In addition, after adjusting for all covariates, including global Aβ deposition, we observed an inverse association between circulating CRP levels and AD-related neurodegeneration (AD-CM) when CRP levels exceeded 2.15 mg/L, indicating that higher CRP levels were associated with lower cerebral glucose metabolism in AD-signature regions, that is, greater AD-related neurodegeneration. This finding suggests that circulating CRP levels above this threshold may be linked to a distinct mechanism that exacerbates AD-type neurodegeneration, independent of Aβ. Our results are consistent with several previous studies reporting an association between elevated CRP levels and progression of neurodegeneration, including decreased gray matter and hippocampal volume [15,46,47]. It is conceivable that persistent systemic inflammation may contribute to neurodegenerative processes through mechanisms such as neuronal apoptosis and alterations in synaptic plasticity [48,49]. Based on findings of our study, circulating CRP levels may be associated with distinct AD pathophysiological mechanisms. Specifically, lower circulating CRP concentrations within normal range (*i.e.*, < 1.0mg/L) appear to be linked to an Aβ-dependent pathway, whereas elevated CRP levels above certain cutoff (*i.e.*, >2.15mg/L) may be related to Aβ-independent neurodegeneration process.

To the best of our knowledge, this study is the first to demonstrate a non-linear association between circulating CRP level and each A/T/N biomarker of AD, as well as to identify the threshold at which the direction of association between CRP and central AD biomarker changes in a large cohort of nondemented older adults. Since the KBASE is one of the large-sized, and well-characterized cohort with deep phenotyping data, including clinical assessments, multi-modal neuroimaging for A/T/N biomarkers, blood samples and genetic data, it was possible to explore relationships of circulating CRP levels with multiple AD biomarkers, along with GWAS genotyping data simultaneously. Our study has strength in that we controlled for effects of genetic variants that could decrease CRP levels by using genetic data. CRP level is a complex trait influenced by both clinical and genetic factors [50–52]. Family and twin studies have found that approximately 27–40 % of the variability in CRP levels can be attributed to genetic components [53,54]. Our analyses, after controlling for the CRP-decreasing allele score as well as multiple other confounding factors as covariates, enhances the robustness of our findings.

Nevertheless, our study had several limitations. First, due to a cross-sectional design, it was difficult to infer causal relationships. Thus, further longitudinal studies are needed. Second, the relatively modest sample size for [^{18}F] AV-1451 PET scans ($N = 123$) might have compromised the statistical power of our analyses, potentially limiting our ability to detect subtle associations. In addition, further studies examining other potentially relevant inflammatory markers—such as Interluekin-1 (IL-1), IL-6, tumor necrosis factor- α, or interferon-γ, in conjunction with circulating CRP—may provide a more comprehensive understanding of the inflammatory and immune-mediated pathways involved in AD.

5. Conclusions

In this study, circulating CRP levels exhibited non-linear relationships (*i.e.*, U-shaped or inverted U-shaped associations) with central AD biomarkers in non-demented older adults. These findings suggest that circulating CRP levels may be linked to distinct AD pathophysiological mechanisms—encompassing both Aβ-mediated and Aβ-independent neurodegeneration process—depending on their concentration. Further investigations are warranted to elucidate the mechanisms underlying the inverse relationship between circulating CRP and brain Aβ within the clinically normal range, as well as the pathway by which elevated CRP may exacerbate AD-type neurodegeneration.

Data availability

The datasets generated and analyzed during the present study are not publicly available, owing to ethics considerations and privacy restrictions. However, data may be made available upon reasonable request and approval by the Institutional Review Board of Seoul National University Hospital, South Korea, through the corresponding author.

CRediT authorship contribution statement

Hye Ji Choi: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Min Soo Byun:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Dahyun Yi:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation. **Hyejin Ahn:** Writing – review & editing, Investigation, Data curation. **Gijung Jung:** Writing – review & editing, Investigation, Data curation. **Sangyong Park:** Writing – review & editing, Visualization, Methodology, Investigation. **Joon Hyung Jung:** Writing – review & editing, Investigation, Data curation. **Musung Keum:** Writing – review & editing, Investigation, Data curation. **Bo Kyung Sohn:** Writing – review & editing, Investigation, Data curation. **Yu Kyeong Kim:** Writing – review & editing, Methodology, Investigation, Data curation. **Hongyoon Choi:** Writing – review & editing, Methodology, Investigation, Data curation. **Yun-Sang Lee:** Writing – review & editing, Methodology, Investigation, Data curation. **Jun-Young Lee:** Writing – review & editing, Investigation, Data curation. **Koung Mi Kang:** Writing – review & editing, Methodology, Investigation, Data curation. **Chul-Ho Sohn:** Writing – review & editing, Methodology, Investigation, Data curation. **Yen-Ning Huang:** Writing – review & editing, Methodology, Investigation, Data curation. **Andrew J. Saykin:** Writing – review & editing, Investigation, Funding acquisition, Data curation. **Kwangsik Nho:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation. **Dong Young Lee:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrew J Saykin reports financial support was provided by Avid Radiopharmaceuticals Inc. Andrew J Saykin reports a relationship with Scientific Advisory Boards (Bayer Oncology, Eisai, Novo Nordisk, and Siemens Medical Solutions USA, Inc), NIA External Advisory Committees that includes: board membership. If there are other authors, they 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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100368.

References

[1 Pay JB, Shaw AM. Towards salivary C-reactive protein as a viable biomarker of systemic inflammation. Clin Biochem 2019;68:1–8.
[2 Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 2005;117(2):104–11.
[3 Du Clos TW. Function of C-reactive protein. Ann Med 2000;32(4):274–8.
[4 Chen X, Holtzman DM. Emerging roles of innate and adaptive immunity in Alzheimer's disease. Immunity 2022;55(12):2236–54.
[5 Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21(3):383–421.
[6 Long S, Chen Y, Meng Y, et al. Peripheral high levels of CRP predict progression from normal cognition to dementia: a systematic review and meta-analysis. J Clin Neurosci 2023;107:54–63.
[7 O'Bryant SE, Waring SC, Hobson V, et al. Decreased C-reactive protein levels in Alzheimer disease. J Geriatr Psychiatry Neurol 2010;23(1):49–53.
[8 Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 2002;52(2):168–74.
[9 Locascio JJ, Fukumoto H, Yap L, et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch Neurol 2008;65(6):776–85.
[10 Fernandes A, Tábuas-Pereira M, Duro D, et al. C-reactive protein as a predictor of mild cognitive impairment conversion into Alzheimer's disease dementia. Exp Gerontol 2020;138:111004.
[11 Tao Q, Ang TFA, DeCarli C, et al. Association of chronic low-grade inflammation with risk of Alzheimer disease in APOE4 carriers. JAMA Netw Open 2018;1(6):e183597.
[12 Danik JS, Ridker PM. Genetic determinants of C-reactive protein. Curr Atheroscler Rep 2007;9(3):195–203.
[13 Oberlin LE, Erickson KI, Mackey R, et al. Peripheral inflammatory biomarkers predict the deposition and progression of amyloid-β in cognitively unimpaired older adults. Brain Behav Immun 2021;95:178–89.
[14 Hooper C, De Souto Barreto P, Cantet C, et al. Chronically raised C-reactive protein is inversely associated with cortical β-amyloid in older adults with subjective memory complaints. Exp Gerontol 2018;108:226–30.
[15 Wang Y, Grydeland H, Roe JM, et al. Associations of circulating C-reactive proteins, APOE ε4, and brain markers for Alzheimer's disease in healthy samples across the lifespan. Brain Behav Immun 2022;100:243–53.
[16 Byun MS, Yi D, Lee JH, et al. Korean Brain aging study for the early diagnosis and prediction of Alzheimer's Disease: methodology and baseline sample characteristics. Psychiatry Investig 2017;14(6):851–63.
[17 Petersen RC, Aisen P, Boeve BF, et al. Mild cognitive impairment due to Alzheimer disease in the community. Ann Neurol 2013;74(2):199–208.
[18 Lee JH, Lee KU, Lee DY, et al. Development of the Korean version of the consortium to establish a registry for Alzheimer's Disease assessment packet (CERAD-K): clinical and neuropsychological assessment batteries. J Gerontol: B 2002;57(1):P47–53.
[19] DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. Neurology 2004;63(2):220–7.
[20] Jack Jr CR, Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. Lancet Neurol 2014;13(10):997–1005.
[21] Jack Jr CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement 2017;13(3):205–16.
[22] Otsuji S, Shibata H, Umeda M. Turbidimetric immunoassay of serum C-reactive protein. Clin Chem 1982;28(10):2121–4.
[23] Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004;29(8):439–93.
[24] Nehring SM, Goyal A, Patel BC. C reactive protein, in statpearls. Treasure Island (FL): StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC; 2024.
[25] Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. Lancet 1991;337(8750):1158–9.
[26] Hegazy SH, Thomassen JQ, Rasmussen IJ, Nordestgaard BG, Tybjaerg-Hansen A, Frikke-Schmidt R. C-reactive protein levels and risk of dementia-observational and genetic studies of 111,242 individuals from the general population. Alzheimers Dement 2022;18(11):2262–71.
[27] Burgess S, Thompson SG. Use of allele scores as instrumental variables for mendelian randomization. Int J Epidemiol 2013;42(4):1134–44.
[28] Haase CL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. HDL cholesterol and risk of type 2 diabetes: a mendelian randomization study. Diabetes 2015;64(9):3328–33.
[29] Kathiresan S, Larson MG, Vasan RS, et al. Contribution of clinical correlates and 13 C-reactive protein gene polymorphisms to interindividual variability in serum C-reactive protein level. Circulation 2006;113(11):1415–23.
[30] Fransén K, Pettersson C, Hurtig-Wennlöf A. CRP levels are significantly associated with CRP genotype and estrogen use in the Lifestyle, Biomarker and Atherosclerosis (LBA) study. BMC Cardiovasc Disord 2022;22(1):170.
[31] Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Bone Marrow Transpl 2020;55(4):675–80.
[32] Muggeo VM. Estimating regression models with unknown break-points. Stat Med 2003;22(19):3055–71.
[33] Prasad K. C-reactive protein (CRP)-lowering agents. Cardiovasc Drug Rev 2006;24(1):33–50.
[34] Xie S, Galimberti F, Olmastroni E, et al. Effect of lipid-lowering therapies on C-reactive protein levels: a comprehensive meta-analysis of randomized controlled trials. Cardiovasc, Res 2024;120(4):333–44.
[35] Coccaro EF, Lee R, Coussons-Read M. Cerebrospinal fluid and plasma C-reactive protein and aggression in personality-disordered subjects: a pilot study. J Neural Transm (Vienna) 2015;122(2):321–6.
[36] Felger JC, Haroon E, Patel TA, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry 2020;25(6):1301–11.
[37] Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999;7(2):169–77.
[38] Gould JM, Weiser JN. Expression of C-reactive protein in the human respiratory tract. Infect Immun 2001;69(3):1747–54.
[39] Claus DR, Osmand AP, Gewurz H. Radioimmunoassay of human C-reactive protein and levels in normal sera. J Lab Clin Med 1976;87(1):120–8.
[40] Peisajovich A, Marnell L, Mold C, Du Clos TW. C-reactive protein at the interface between innate immunity and inflammation. Expert Rev Clin Immunol 2008;4(3):379–90.
[41] Bodman-Smith KB, Melendez AJ, Campbell I, Harrison PT, Allen JM, Raynes JG. C-reactive protein-mediated phagocytosis and phospholipase D signalling through the high-affinity receptor for immunoglobulin G (FcgammaRI). Immunology 2002;107(2):252–60.
[42] Gershov D, Kim S, Brot N, Elkon KB. C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. J Exp Med 2000;192(9):1353–64.
[43] Rodriguez W, Mold C, Kataranovski M, Hutt J, Marnell LL, Du Clos TW. Reversal of ongoing proteinuria in autoimmune mice by treatment with C-reactive protein. Arthritis Rheum 2005;52(2):642–50.
[44] Russell AI, Cunninghame Graham DS, Shepherd C, et al. Polymorphism at the C-reactive protein locus influences gene expression and predisposes to systemic lupus erythematosus. Hum Mol Genet 2004;13(1):137–47.
[45] Szalai AJ. C-reactive protein (CRP) and autoimmune disease: facts and conjectures. Clin Dev Immunol 2004;11(3–4):221–6.
[46] Hilal S, Ikram MA, Verbeek MM, et al. C-reactive protein, plasma amyloid-β levels, and their interaction with magnetic resonance imaging markers. Stroke 2018;49(11):2692–8.
[47] Taki Y, Thyreau B, Kinomura S, et al. Correlation between high-sensitivity C-reactive protein and brain gray matter volume in healthy elderly subjects. Hum Brain Mapp 2013;34(10):2418–24.
[48] Semmler A, Okulla T, Sastre M, Dumitrescu-Ozimek L, Heneka MT. Systemic inflammation induces apoptosis with variable vulnerability of different brain regions. J Chem Neuroanat 2005;30(2–3):144–57.
[49] Tancredi V, D'Antuono M, Cafè C, et al. The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK. J Neurochem 2000;75(2):634–43.
[50] Sas AA, Vaez A, Jamshidi Y, et al. Genetic and environmental influences on stability and change in baseline levels of C-reactive protein: a longitudinal twin study. Atherosclerosis 2017;265:172–8.
[51] Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. Clin Chem 2003;49(8):1258–71.
[52] Shen J, Ordovas JM. Impact of genetic and environmental factors on hsCRP concentrations and response to therapeutic agents. Clin Chem 2009;55(2):256–64.
[53] Pankow JS, Folsom AR, Cushman M, et al. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis 2001;154(3):681–9.
[54] Wessel J, Moratorio G, Rao F, et al. C-reactive protein, an 'intermediate phenotype' for inflammation: human twin studies reveal heritability, association with blood pressure and the metabolic syndrome, and the influence of common polymorphism at catecholaminergic/beta-adrenergic pathway loci. J Hypertens 2007;25(2):329–43.