RESEARCH ARTICLE

Impact of C-Reactive Protein on Cognition and Alzheimer Disease Biomarkers in Homozygous *APOE* ε4 Carriers

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Abstract

Background and Objectives

Previous research has shown that elevated blood C-reactive protein (CRP) is associated with increased Alzheimer disease (AD) risk only in *APOE* ε4 allele carriers; the objective of this study was to examine the interactive effects of plasma CRP and *APOE* genotype on cognition and AD biomarkers.

Methods

Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study were analyzed, including *APOE* genotype; plasma CRP concentrations; diagnostic status (i.e., mild cognitive impairment and dementia due to AD); Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Dementia Staging Instrument scores; CSF concentrations of β-amyloid peptide ($A\beta_{42}$), total tau (t-Tau) and phosphorylated tau (p-Tau); and amyloid (AV45) PET imaging. Multivariable regression analyses tested the associations between plasma CRP and *APOE* on cognitive and biomarker outcomes.

Results

Among 566 ADNI participants, 274 (48.4%) had no, 222 (39.2%) had 1, and 70 (12.4%) had 2 *APOE* ε4 alleles. Among only participants who had 2 *APOE* ε4 alleles, elevated CRP was associated with lower MMSE score at baseline (β [95% confidence interval] −0.52 [−1.01, −0.12]) and 12-month follow-up (β −1.09 [−1.88, −0.17]) after adjustment for sex, age, and education. The interaction of 2 *APOE* ε4 alleles and elevated plasma CRP was associated with increased CSF levels of t-Tau (β = 11.21, SE 3.37, $p < 0.001$) and p-Tau (β = +2.74, SE 1.14, $p < 0.01$). Among those who had no *APOE* ε4 alleles, elevated CRP was associated with decreased CSF t-Tau and p-Tau. These effects were stronger at the 12-month follow-up.

Discussion

CRP released during peripheral inflammation could be a mediator in *APOE* ε4–related AD neurodegeneration and serve as a drug target for AD.

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at links.lww.com/WNL/B469.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

Aβ = β-amyloid peptide; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CDR** = Clinical Dementia Rating Scale; **CDR-SB** = CDR Sum of Boxes; **CI** = confidence interval; **CN** = cognitively normal; **CRP** = C-reactive protein; **FHS** = Framingham Heart Study; **MCI** = mild cognitive impairment; **mCRP** = monomeric CRP; **MMSE** = Mini-Mental State Examination; **NfL** = neurofilament light chain; **p-Tau** = phosphorylated tau protein; **pCRP** = native CRP; **SUVR** = standardized uptake value ratio; **t-Tau** = total tau protein.

APOE ε4 allele is a major genetic risk factor for late-onset Alzheimer disease (AD).[1] However, even among *APOE* ε4 carriers who are >90 years of age,[2] not all *APOE* ε4 carriers develop dementia. One potential mediator may be C-reactive protein (CRP). Elevated blood CRP has been linked to increased AD risk only in *APOE* ε4 allele carriers, suggesting that CRP might modify *APOE* ε4 effects leading to AD-related neurodegeneration.[3] Still, the interactions between *APOE* ε4 and CRP on cognitive decline and AD pathology are unknown.

CRP is a protein involved in immune response to toxins or injuries in systemic inflammation,[4] and CRP levels increase with age.[4] There are 2 types of CRP: native CRP (pCRP) is a pentameric oligoprotein and acute-phase reactant that is produced during active inflammatory reaction,[5] and monomeric CRP (mCRP), or free subunits of pCRP, is produced during and after the acute phase by the irreversible dissociation of pCRP, which has much lower aqueous solubility and damaged tissues.[6] CRP has been implicated in the pathogenesis of chronic diseases associated with aging, including cardiovascular disease,[7] age-related macular degeneration,[8] and poststroke inflammation.[9]

The objective of this study was to investigate the independent and interactive effects of *APOE* ε4 status (0, 1, and 2 *APOE* ε4 alleles) and peripheral CRP on cognition and in vivo AD biomarkers, including CSF β-amyloid peptide 42 ($A\beta_{42}$), total tau (t-Tau), and phosphorylated tau (p-Tau), in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.[10]

Methods

ADNI Study

Data were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael W. Weiner, MD. The overall objective of ADNI is to develop and validate in vivo biomarkers for AD. Detailed methodology and description of ADNI can been found on the ADNI website. There are 4 phases of the ADNI study: ADNI1, ADNIGO, ADNI2, and ADNI3. Only the ADNI1 dataset has plasma CRP data. Therefore, this study included only participants from the ADNI1 database.

Standard Protocol Approvals, Registrations, and Patient Consents

The ADNI study has 63 sites (including Boston University) across the United States and Canada. The protocol was approved by the Institutional Review Board from each institute/site for the experiments using human participants described in this study. This study obtained the deidentified data for data analyses.

Participants

This study included 566 ADNI1 participants who had *APOE* genotype data, baseline plasma CRP measurements, a research diagnosis of cognitively normal (CN), mild cognitive impairment (MCI), or AD dementia, as well as 2-year follow-up measurements of the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Scale (CDR). We also obtained data for participants who had PET AV45 data; CSF $A\beta_{42}$, t-Tau and p-Tau; CSF neurogranin; plasma and CSF neurofilament light chain (NfL); and plasma APOE protein.

Plasma CRP

All participants in this study analysis had data on plasma CRP. A subset of the ADNI1 cohort had overnight fasting plasma samples and were analyzed with a 190-analyte multiplex immunoassay panel, which included CRP measures. Next to other proteins, plasma CRP was measured by using targeted multiplex proteomic strategies implemented in the Biomarkers Consortium Project of the ADNI study.[11] The Luminex xMAP technology (Luminex Corp, Austin, TX) with a low-based laser apparatus was used.

Cognitive Diagnoses and MMSE and CDR Scores

For ADNI, diagnoses of CN, MCI, and AD dementia are based on established research diagnostic criteria.[12] MMSE scores served as a measure for global cognitive status.[13] The MMSE is a brief cognitive screening measure with scores ranging from 0 to 30 that is commonly used to detect and monitor dementia severity. The CDR Sum of Boxes (CDR-SB)[14] was also used to assess overall severity of clinical impairment. MMSE and CDR-SB scores were measured at baseline and 12 and 24 months after the CRP measurements.

Fluid Biomarkers

Aliquots of CSF samples, which had never been thawed, were measured and analyzed by electrochemiluminescence immunoassays (lot for each analyte: P09 for $A\beta_{1\text{-}42}$ and P02 for t-tau and p-tau181). The Roche Elecsys β-Amyloid (1–42) CSF, Elecsys Total-Tau CSF, and Elecsys Phospho-Tau (181P) CSF immunoassays (Elecsys Corp, Lenexa, KS) were used following the Roche Study Protocol at the University of Pennsylvania/ADNI Biomarker Laboratory and in accord with the preliminary kit manufacturer's instructions.[15] We

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Table 1 Demographic, Cognitive Diagnoses, and Tau AD Biomarkers Based on *APOE* Genotypes in ADNI Study

Characteristics	Total (n = 566)	*APOE* ε4 Carrier			
		0 *APOE* ε4 Alleles (n = 274)	1 *APOE* ε4 Allele (n = 222)	2 *APOE* ε4 Alleles (n = 70)	*p* Value
Age, y	74.8 ± 7.4	75.7 ± 7.8	74.9 ± 6.7	70.9 ± 6.4	<0.001
Female, n (%)	215 (38.0)	105 (38.3)	81 (36.5)	29 (41.4)	0.749
Education, y	15.5 ± 3.0	15.7 ± 3	15.4 ± 3.2	15.5 ± 2.6	0.391
MMSE scores	26.5 ± 2.4	27.0 ± 2.2	26.2 ± 2.4	25.7 ± 2.4	<0.001
CDR-SB scores	2.0 ± 1.6	1.6 ± 1.4	2.3 ± 1.6	2.6 ± 1.9	<0.001
Diagnosis, n (%)					
CN	58 (10.2)	53 (19.3)	5 (2.3)	0 (0)	0.001
MCI	396 (70.0)	185 (67.5)	164 (73.9)	47 (67.1)	
AD	112 (19.8)	36 (13.1)	53 (23.9)	23 (32.9)	
Plasma biomarkers					
logCRP, mg/L	0.29 ± 1.23	0.64 ± 1.15	0.02 ± 1.21	−0.21 ± 1.20	<0.001
logAPOE, mg/L	3.9 ± 0.4	4.1 ± 0.4	3.8 ± 0.4	3.5 ± 0.5	<0.001
logNfL, pg/mL[a]	3.6 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	3.6 ± 0.4	0.625
Brain PET imaging, n	129	79	40	10	
AV45	1.20 ± 0.20	1.10 ± 0.20	1.32 ± 0.20	1.49 ± 0.23	<0.001
CSF markers					
No.	358	176	138	44	
$A\beta_{42}$, pg/mL	171.7 ± 57.8	203.8 ± 57.6	147.7 ± 38.8	118.6 ± 21.5	<0.001
t-Tau, pg/mL	101.4 ± 57.3	86.1 ± 50.9	115.5 ± 62.7	117.8 ± 48	<0.001
p-Tau, pg/mL	35.4 ± 19.3	29.7 ± 17.5	40 ± 19.6	43.7 ± 19	<0.001
No.	344	170	131	43	
logNfL, pg/mL	7.2 ± 0.5	7.2 ± 0.5	7.2 ± 0.4	7.1 ± 0.3	0.482
logNg, pg/mL	5.7 ± 1.4	5.6 ± 1.4	5.8 ± 1.5	6.2 ± 1.1	0.005

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CN = cognitively normal; CRP = C-reactive protein; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NfL = neurofilament light chain; Ng = neurogranin.
ADNI participants were stratified into 3 groups based on the presence of 0 vs 1 vs 2 *APOE* ε4 alleles. Brain AV45 PET scan shows the summary data (standardized uptake value ratio) of PET with ^{18}F-AV45 (florbetapir). The concentrations of CRP, APOE, NfL and Ng were log-transformed. Mean ± SD values were reported for continuous variables; number (percent) for binary variables. The *p* values for the comparisons of 3 *APOE* groups are shown.
[a] Plasma NfL was measured for a subset of participants (n = 361): 181 with 0 *APOE* ε4 alleles, 137 with 1 *APOE* ε4 allele, and 43 with 2 *APOE* ε4 alleles.

also obtained the data on plasma APOE protein, CSF neurogranin, and plasma and CSF NfL from the ADNI database.

^{18}F-AV45 PET

Summary data (standardized uptake value ratio [SUVR]) of ^{18}F-AV45 (florbetapir) PET, obtained 2 years after baseline CRP measurements, were used. The techniques, methods, and results related to amyloid imaging in ADNI have been reported elsewhere.[16] The AV45 summary data were calculated from the cortical sum of regions of interest divided by the whole cerebellum reference region. In this study, we used the AV45 variable from the R ADNIMERGE package as the florbetapir mean of whole cerebellum (reference region) in regions defined by FreeSurfer. The AV45 studies were conducted after 3 to 10 years after plasma CRP was measured.

Statistical Analysis

Statistical analysis was performed with R (version 3.60; R Foundation for Statistical Computing) statistical software. The concentrations of CRP, APOE protein, NfL, and neurogranin were log-transformed due to skewed distributions. One-way analysis of variance was used to compare means when there were >2 groups, and χ^2 tests were used for binary variables in Table 1. Multivariable linear regression models were implemented to investigate the interaction effects between CRP and *APOE* ε4 (CRP × *APOE* ε4) on MMSE

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Table 2 Bootstrap Regression Analyses of the Interaction Effect Between 2 *APOE* ε4 Alleles and CRP on MMSE Scores

MMSE Scores	Model 1 *β* (95% CI)	Model 2 *β* (95% CI)	Model 3 *β* (95% CI)
Baseline (n = 566)			
Plasma logCRP, mg/L	−0.03 (−0.22, 0.14)	−0.10 (−0.29, 0.07)	0.12 (−0.13, 0.33)
***APOE* ε4 × CRP interaction**	—	—	−0.34 (−0.57, −0.11)[a]
At 12 mo (n = 510)			
Plasma logCRP, mg/L	0.10 (−0.19, 0.37)	−0.08 (−0.38, 0.20)	0.30 (−0.12, 0.69)
***APOE* ε4 × CRP interaction**	—	—	−0.60 (−1.01, −0.15)[a]
At 24 mo (n = 441)			
Plasma logCRP, mg/L	0.33 (−0.10, 0.76)	0.00 (−0.44, 0.41)	0.23 (−0.35, 0.77)
***APOE* ε4 × CRP interaction**	—	—	−0.36 (−0.96, 0.29)

Abbreviations: CI = confidence interval; CRP = C-reactive protein; MMSE = Mini-Mental State Examination.
The bias-corrected and accelerated bootstrap interval from bootstrap analysis (based on 10,000 bootstrap replicates) was used to test the association between log-transformed plasma CRP and its interaction with 2 *APOE* ε4 alleles and MMSE scores at baseline and 12- and 24-month follow-up. Model 1: unadjusted association. Model 2: adjusted for age, sex, education, and 2 *APOE* ε4 alleles. Model 3: model 2 plus adjustment for the interaction between CRP and 2 *APOE* ε4 alleles.
[a] $p < 0.01$.

scores, CDR-SB scores, AD fluid, and PET biomarkers. By using a forward selection procedure, we included different sets of variables in 3 models: model 1 was unadjusted; model 2 was adjusted for age, sex, education, and *APOE* genotype; and model 3 added the CRP × *APOE* ε4 interaction variable. Due to the skewed distribution of MMSE and CDR-SB scores, we generated a bootstrapped 95% confidence interval (CI) for the regression coefficients (β). The bootstrapped CI is based on 10,000 replications, and we reported the bias-corrected and accelerated bootstrap interval. Follow-up Pearson correlations and scatterplots were conducted to depict the cross-sectional and longitudinal relationships between plasma CRP and MMSE scores, CDR-SB scores, AV45 PET scan, and CSF AD biomarkers. These analyses were conducted with the whole sample and stratified by *APOE* genotypes status. All tests were 2 sided, and statistical significance was defined by a value of $p < 0.05$.

Data Availability

Supplement Tables and Figures are available from the Dryad Digital Repository: doi.org/10.5061/dryad.08kprr52f.

Results

Sample Characteristics

The sample included 566 ADNI participants who had complete *APOE* genotype data and baseline plasma CRP measurements. The average age of the sample was 74.8 ± 7.4 years (mean ± SD), and 215 (38%) participants were female. Participants were stratified into 3 *APOE* genotype groups: (1) no *APOE* ε4 allele (ε4 noncarriers, n = 274), (2) 1 *APOE* ε4 allele (n = 222), and (3) 2 *APOE* ε4 alleles (genotype ε4/4, n = 70) (Table 1). There were no statistically significant differences between the groups in sex or education.

The dataset included 58 individuals with CN (10.2%), 396 participants with MCI (70.0%), and 112 participants with AD dementia (19.8%). The group with 2 *APOE* ε4 alleles had the highest rate of AD dementia, the lowest average MMSE scores, and the highest CDR-SB scores (Table 1). The group with 2 *APOE* ε4 alleles had lower levels of CRP (mean ± SD −0.21 ± 1.20 mg/L vs 0.02 ± 1.21 mg/L vs 0.64 ± 1.15 mg/L, $p < 0.001$) and plasma APOE protein ($p < 0.001$) than those with 1 *APOE* ε4 allele, followed by those who had no *APOE* ε4 allele. Greater number of *APOE* ε4 alleles corresponded to higher levels of CSF t-Tau, p-Tau, and neurogranin, as well as lower CSF $A\beta_{42}$ (Table 1). This finding remained significant after CN participants were excluded (eTable 1 [doi.org/10.5061/dryad.08kprr52f]). Among the 3 *APOE* allele groups, there were no differences in NfL in either CSF or plasma.

Negative Association Between Plasma CRP and Cognitive Scores in the Presence of 2 *APOE* ε4 Alleles

First, we used bootstrap regression analyses to study the association between plasma CRP and baseline MMSE and CDR-SB scores. Unadjusted and adjusted regressions were performed for age, sex, education, and *APOE* ε4 alleles (Table 2). Although plasma CRP as an independent variable was not associated with MMSE scores in unadjusted or adjusted models, the interaction of *APOE* ε4 and CRP was negatively associated with MMSE scores at baseline (β [95% CI] = −0.34 [−0.57, −0.11], $p < 0.01$) and at 12-month follow-up (β [95% CI] = −0.60 [−1.01, −0.15], $p < 0.01$) (model 3). There was no statistical significance at the 24-month follow-up. After

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Table 3 Stratified Analysis of the CRP Association With MMSE, and CSF t-Tau and p-Tau Among Different *APOE* Genotype Groups

Outcomes at baseline and follow-ups	*APOE* ε4 = 0	*APOE* ε4 = 1	*APOE* ε4 = 2
MMSE score[a]			
At baseline	0.09 (−0.17, 0.33)	−0.18 (−0.48, 0.11)	−0.52 (−1.01, −0.12)[c]
At 12 mo	0.17 (−0.25, 0.65)	−0.14 (−0.16, 0.26)	−1.09 (−1.88, −0.17)[c]
At 24 mo	0.01 (−0.62, 0.59)	0.14 (−0.55, 0.85)	−0.76 (−2.02, 0.55)
CSF t-Tau			
Baseline	−7.19 ± 3.38[c]	3.03 ± 4.35	11.2 ± 4.96[c]
At 12 mo	−10.72 ± 4.02[b]	1.64 ± 4.48	20.8 ± 8.37[c]
At 24 mo	−11.04 ± 5.05[c]	2.47 ± 10.61	42.73 ± 20.42
CSF p-Tau			
Baseline	−1.37 ± 1.18	1.02 ± 1.39	3.03 ± 2.09
At 12 mo	−3.93 ± 1.63[c]	0.98 ± 1.81	1.31 ± 3.68
At 24 mo	−1.83 ± 1.69	−3.08 ± 3.52	−1.29 ± 7.49

Abbreviations: CI = confidence interval; CRP = C-reactive protein; MMSE = Mini-Mental State Examination; p-Tau = phosphorylated tau; t-Tau = total tau. Alzheimer's Disease Neuroimaging Initiative participants were stratified into 3 groups based on 0 *APOE* ε4 alleles (*APOE* ε4 = 0), 1 *APOE* ε4 allele (*APOE* ε4 = 1), and 2 *APOE* ε4 alleles (*APOE* ε4 = 2).
[a] Bootstrapping regression, β (95% confidence interval), was used to study the relationships between baseline log-transformed plasma C-reactive protein (CRP) as the determining factor and MMSE scores as outcomes, adjusted for age, sex, and education. The bias-corrected and accelerated bootstrap intervals from bootstrap analysis (based on 10,000 bootstrap replicates) were reported. The linear models, $\beta \pm$ SE, were used to study the relationships between baseline log-transformed plasma CRP as the determining factor and CSF markers t-Tau and p-Tau as outcomes, adjusted for age and sex, respectively. Outcomes at different time points, including baseline and 12- and 24-month follow-ups, were used in the models.
[b] $p < 0.01$.
[c] $p < 0.05$.

stratification by *APOE* genotypes, the negative association patterns were observed in the group of participants who had 2 *APOE* ε4 alleles but not in any of the other *APOE* genotype groups (Table 3, MMSE score section). The interaction between CRP and *APOE* ε4 alleles on CDR-SB scores showed similar relationships in the bootstrap regression models (eTable 2 [doi.org/10.5061/dryad.08kprr52f]).

Next, we used Pearson correlation analyses to test the relationship between baseline plasma CRP concentrations and cognition in those with 0, 1, and 2 *APOE* ε4 alleles. Because of imbalanced numbers of individuals with CN in each *APOE* group in Table 1, we excluded those with CN to conduct scatterplots. Plasma CRP levels were negatively correlated with MMSE scores at baseline among those who had 2 *APOE* ε4 alleles ($r = -0.29$, $p = 0.015$); this effect remained statistically significant at the 12-month follow-up ($r = -0.26$, $p = 0.025$) but not at the 24-month follow-up (Figure 1A). Among participants with MCI, there was no statistically significant association between baseline plasma CRP and MMSE score. However, there was a statistically significant effect at the 12-month follow-up ($r = -0.42$, $p = 0.0045$) in the 2 *APOE* ε4 allele group (eFigure 2A [doi.org/10.5061/dryad.08kprr52f]).

Among those who had 1 *APOE* ε4 allele, plasma CRP levels were slightly correlated with MMSE scores at baseline ($r = -0.17$, $p = 0.015$) but not at follow-ups. Among those who had no *APOE* ε4 allele, plasma CRP levels were not associated with MMSE score (Figure 1A).

Plasma CRP levels also positively correlated with CDR-SB score only in participants with 2 *APOE* ε4 alleles at baseline ($r = 0.34$, $p = 0.0045$). Results for CDR-SB score at follow-ups were similar (Figure 1B). Among those with MCI, this association was observed only at the 12-month follow-up, not at baseline or the 24-month follow-up (eFigure 2 [doi.org/10.5061/dryad.08kprr52f]). There was no association between plasma CRP and CDR-SB score among those with 0 or 1 *APOE* ε4 allele.

Positive Correlation Between Plasma CRP and Brain Aβ in the Total Sample but Not Among *APOE* Genotype Groups

The association between plasma CRP and CSF levels of $A\beta_{42}$ was tested. eFigure 1A (doi.org/10.5061/dryad.08kprr52f]) shows that plasma CRP measurements were positively associated with CSF $A\beta_{42}$ levels in the entire sample ($r = 0.12$, $p = 0.043$). However, this relationship was due to collinearity because both plasma CRP and CSF $A\beta_{42}$ from the highest to the lowest followed the pattern of no *APOE* ε4 >1 *APOE* ε4 >2 *APOE* ε4 (Table 1). In each *APOE* genotype group, there was no association between plasma CRP and CSF Aβ42 (eFigure 1C

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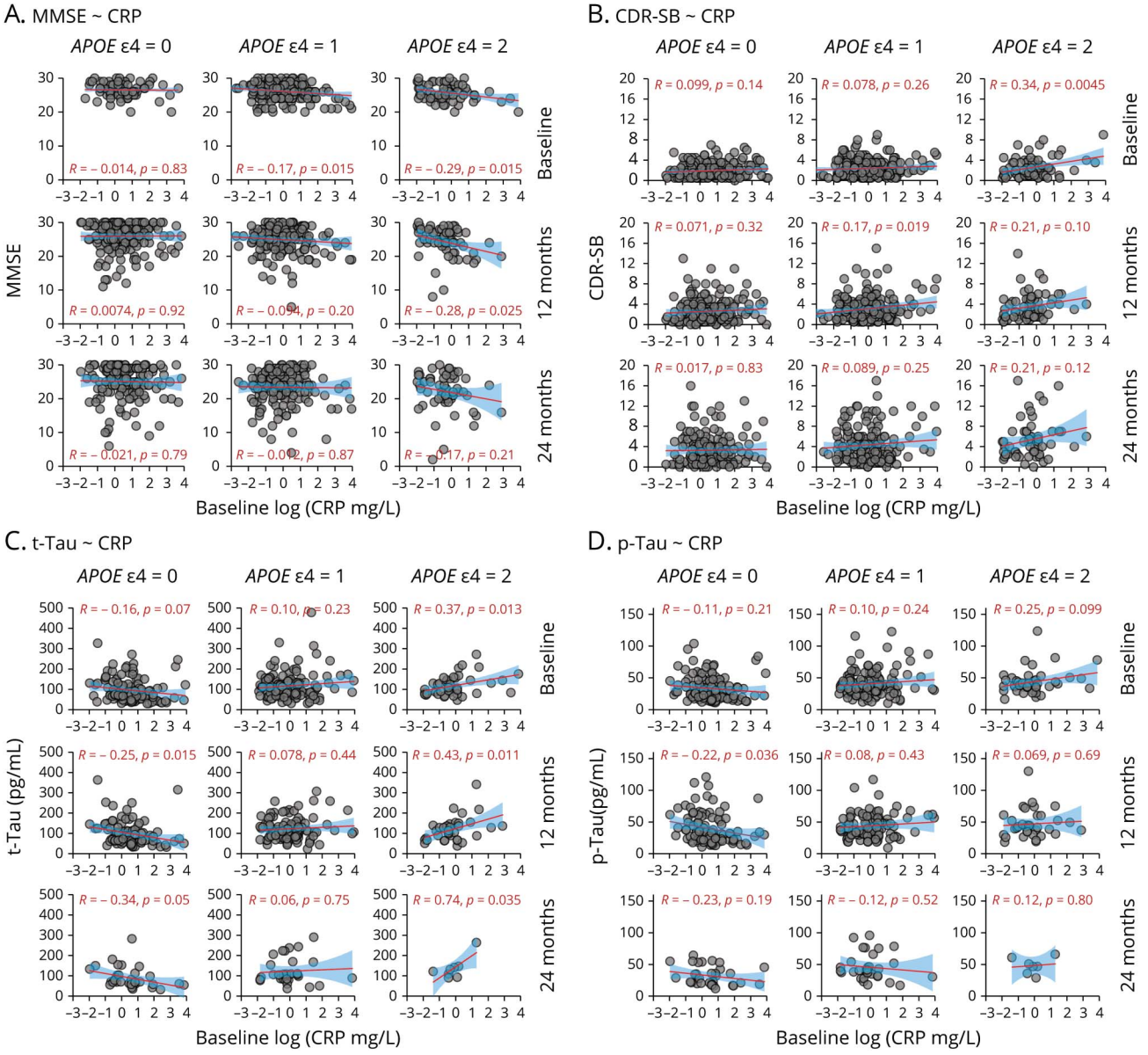
Figure 1 Association Between Baseline Plasma CRP and MMSE and CDR-SB Scores and CSF Biomarkers (t-Tau and p-Tau) Among Participants With MCI and AD Dementia Across 3 *APOE* Genotypes



Because of imbalanced numbers of cognitive normal (CN) controls in each *APOE* group in Table 1, we excluded CN from the scatterplots. Participants with mild cognitive impairment (MCI) (n = 396) or Alzheimer Disease (AD) dementia (n = 112) were divided into 3 groups based on *APOE* genotypes: 0 *APOE* ε4 alleles (*APOE* ε4 = 0), 1 *APOE* ε4 allele (*APOE* ε4 = 1), and 2 *APOE* ε4 alleles (*APOE* ε4 = 2). Relationships between baseline plasma C-reactive protein (CRP) and trajectory cognitive tests or CSF AD biomarkers at baseline, 12 months, and 24 months were examined. Associations between baseline CRP and Mini-Mental State Examination (MMSE) scores (A), Clinical Dementia Rating Sum of Boxes (CDR-SB) score (B), CFS total tau (t-Tau) (C), and CFS phosphorylated tau (p-Tau) (D) are shown by using scatterplots with a linear regression line with 95% confidence bands (shaded area), the Pearson coefficient of correlation, and its *p* value.

[doi.org/10.5061/dryad.08kprr52f]). In multivariable regression analyses across the total sample, neither plasma CRP alone nor the *APOE* ε4 × CRP interaction term was associated with CSF $A\beta_{42}$, suggesting collinearity of *APOE* genotype and CRP (eTable 3 [doi.org/10.5061/dryad.08kprr52f]).

Plasma CRP was negatively associated with AV45 PET SUVR values ($r = -0.23$, $p = 0.023$) in the entire sample (eTable 1 and eFigure 1B [doi.org/10.5061/dryad.08kprr52f]). However, there was no association between plasma CRP and AV45 PET SUVR in multivariable regression analysis (data not shown). Again, there was no statistically significant relationship between CRP and AV45 PET SUVR in each *APOE* genotype group (eFigure 1D [doi.org/10.5061/dryad.08kprr52f]).

Positive Correlation Between Plasma CRP and CSF t-Tau Only in the Presence of 2 *APOE* ε4 Alleles

Using unadjusted and multivariable linear regression models, Table 4 shows that plasma CRP was not associated with CSF

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Table 4 General Linear Regression Analyses of the Interaction Effect Between 2 *APOE* ε4 Alleles and CRP on CSF t-Tau Level

CSF t-Tau	Model 1 $\beta \pm$ SE	Model 2 $\beta \pm$ SE	Model 3 $\beta \pm$ SE
Baseline (n = 358)			
Plasma logCRP, mg/L	2.19 ± 2.48	0.12 ± 2.5	−8.36 ± 3.39[c]
***APOE* ε4 × CRP interaction**	—	—	11.21 ± 3.37[a]
At 12 mo (n = 277)			
Plasma logCRP, mg/L	−4.33 ± 2.88	−1.86 ± 2.92	−12.62 ± 3.82[b]
***APOE* ε4 × CRP interaction**	—	—	16.20 ± 4.10[a]
At 24 mo (n = 88)			
Plasma logCRP, mg/L	−6.62 ± 5.32	−2.99 ± 5.37	−12.52 ± 6.12[c]
***APOE* ε4 × CRP interaction**	—	—	22.47 ± 8.41[b]

Abbreviations: CRP = C-reactive protein; t-Tau = total tau.
General linear regression was used to test the relationship between log-transformed plasma CRP, its interaction with 2 *APOE* ε4 alleles, and the level of CSF t-Tau. Model 1: unadjusted association. Model 2: adjusted for age, sex, education, and 2 *APOE* ε4 alleles. Model 3: model 2 plus adjustment for the interaction between CRP and 2 *APOE* ε4 alleles.
[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$.

t-Tau levels (models 1 and 2). However, the interaction with 2 *APOE* ε4 alleles and plasma CRP on CSF t-Tau levels (model 3) was significant at baseline (β = 11.21, SE = 3.37, $p < 0.001$), 12 months (β = +16.20, SE = 4.10, $p < 0.001$), and 24 months (β = 22.47, SE 8.41, $p < 0.01$). After stratification by *APOE* ε4 group, there was a positive association between baseline plasma CRP and CSF t-Tau levels at baseline and the 12-month and 24-month follow-up in the group of participants who had 2 *APOE* ε4 alleles (Table 3). However, there were negative associations in the group with no *APOE* ε4 alleles and no association in the group of 1 *APOE* ε4 allele.

Due to the small sample sizes of participants with CN who had brain biomarkers in the *APOE* ε4 groups with 1 (n = 5) and 2 (n = 0) alleles (Table 1), we excluded those with CN and conducted Pearson correlation analyses to test the association between plasma CRP and CSF tau biomarkers. Figure 1C shows that baseline plasma CRP levels were positively correlated with baseline ($r = 0.37$, $p = 0.013$) and 12-month ($r = 0.43$, $p = 0.011$) and 24-month ($r = 0.74$, $p = 0.035$) CSF t-Tau levels in the 2 *APOE* ε4 allele group. In contrast, in the group without an *APOE* ε4 allele, baseline plasma CRP was negatively correlated with baseline ($r = −0.16$, $p = 0.07$) and 12-month ($r = −0.25$, $p = 0.015$) and 24-month ($r = −0.34$, $p = 0.05$) CSF t-Tau levels. Among those who had 1 *APOE* ε4 allele, there was no positive or negative relationship between plasma CRP and CSF t-Tau. Sensitivity analyses examined this relationship in participants with MCI only (eFigure 2C [doi.org/10.5061/dryad.08kprr52f]). Among only participants with MCI who had no *APOE* ε4 allele, there was an effect between baseline plasma CRP and 24-month CSF t-Tau levels ($r = −0.46$, $p = 0.012$).

Positive Correlation Between Plasma CRP and CSF p-Tau Only in the Presence of 2 *APOE* ε4 Alleles

Plasma CRP was not associated with CSF p-Tau (models 1 and 2) (Table 5). However, the interaction between 2 *APOE* ε4 alleles and plasma CRP (model 3) was positively associated with CSF p-Tau at baseline (β = 2.74, SE 1.14, $p < 0.05$) and at the 12-month follow-up (β = 3.54, SE 1.66, $p < 0.05$). There was no statistical significance at the 24-month follow-up (Table 5). When stratified by *APOE* ε4 allele group, similar trends of the relationship were observed but did not reach statistical significance at most time points (Table 3).

Figure 1D shows positive correlations between baseline plasma CRP levels and CSF p-Tau levels in the 2 *APOE* ε4 allele group, although this association did not reach statistical significance. In participants without the *APOE* ε4 allele, baseline plasma CRP negatively correlated with CSF p-Tau at the 24-month follow-up ($r = −0.22$, $p = 0.036$). Among participants with MCI, similar trends were observed (eFigure 2D [doi.org/10.5061/dryad.08kprr52f]).

Discussion

This study extends our previous research[3] by investigating the interaction between *APOE* ε4 and CRP levels on cognitive decline and in vivo biomarkers of amyloid and tau using longitudinal data from the ADNI study. Results showed that higher baseline plasma CRP levels predicted accelerated global cognitive decline at a 1-year follow-up among individuals who had 2 *APOE* ε4 alleles. No such effect was observed among participants who had 1 or 0 *APOE* ε4 alleles. We additionally observed a positive association between baseline plasma CRP and trajectory levels of CSF t-Tau and p-Tau biomarkers among those who had 2 *APOE* ε4 alleles. This effect was reversed among those without an *APOE* ε4 allele. Our results suggest that participants with homozygous *APOE* ε4 alleles might be more susceptible to the effects of peripheral inflammatory factors on AD risk compared with those with 1 or 0 *APOE* ε4 allele. Thus, CRP may play an important mediator role in the *APOE* ε4–related pathway for AD risk. Treatment of chronic low-grade inflammation to reduce CRP levels, especially in 2 *APOE* ε4 allele carriers, may delay AD onset.

Baseline CRP was negatively associated with global cognitive function in the group of participants who had 2 *APOE* ε4 alleles, both cross-sectionally and longitudinally (Figure 1). CRP is involved in the immune response to toxins or injuries in systemic inflammation[4] and is elevated in age-related diseases (e.g., cardiovascular diseases,[7] age-

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Table 5 General Linear Regression Analyses of the Interaction Effect Between 2 *APOE* ε4 Alleles and CRP on CSF p-Tau Level

CSF p-Tau	Model 1 $\beta \pm$ SE	Model 2 $\beta \pm$ SE	Model 3 $\beta \pm$ SE
Baseline (n = 358)			
Plasma logCRP, mg/L	−0.77 ± 0.84	0.25 ± 0.83	−1.71 ± 1.15
***APOE* ε4 × CRP interaction**	—	—	2.74 ± 1.14[a]
At 12 mo (n = 277)			
Plasma logCRP, mg/L	−2.24 ± 1.13[a]	−1.27 ± 1.15	−3.64 ± 1.55[a]
***APOE* ε4 × CRP interaction**	—	—	3.54 ± 1.66[a]
At 24 mo (n = 87)			
Plasma logCRP, mg/L	−3.40 ± 1.71	−1.99 ± 1.68	−2.36 ± 2.06
***APOE* ε4 × CRP interaction**	—	—	1.04 ± 2.84

Abbreviations: CRP = C-reactive protein; p-Tau = phosphorylated tau.
General linear regression was used to test the relationship between log-transformed plasma CRP, its interaction with 2 *APOE* ε4 alleles, and the level of CSF p-Tau. Model 1: unadjusted association. Model 2: adjusted for age, sex, education, 2 *APOE* ε4 alleles, and plasma CRP. Model 3: model 2 plus adjustment for the interaction between CRP and 2 *APOE* ε4 alleles.
[a] $p < 0.05$.

related macular degeneration,[8] and poststroke inflammation[9]). Infections of the respiratory, gastrointestinal, and urinary tract systems are common in older adults and can trigger chronic low-grade inflammation (i.e., high CRP levels).[3] Such inflammatory response may increase susceptibility to AD, especially among those already at risk (i.e., *APOE* ε4 carriers).

Higher plasma CRP was also associated with higher CSF t-Tau and p-Tau levels only in those with 2 *APOE* ε4 alleles. Although peripheral CRP modestly correlated with fluid and PET biomarkers of amyloidosis, the CRP-Aβ relationships might be due to collinearity with *APOE* genotype. Compared with Aβ, tau biomarkers are more strongly associated with cognitive function.[17] The amyloid cascade hypothesis is the most common proposed mechanism of AD pathogenesis whereby Aβ triggers the development of p-Tau, resulting in neurodegeneration.[21] CRP may represent one causal pathway by which Aβ leads to tau phosphorylation, especially when it comes to *APOE* ε4–associated pathways to AD. However, the mechanisms by which *APOE* ε4 and CRP levels lead to tauopathy and cognitive decline are still unknown. One hypothesis is that *APOE* ε4 may make blood-facing endothelia in the brain more vulnerable to increased plasma CRP. Supporting this idea, a preclinical AD study found that mCRP exacerbates the severity of tauopathy in the brain of mice with transgenic genes of amyloid precursor protein and tau.[22]

Baseline plasma CRP had a consistent effect on tauopathy biomarkers and MMSE and CDR-SB scores at the 12-month, but not 24-month, follow-up in the 2 *APOE* ε4 alleles group. CSF AD biomarkers are shown to be elevated 10 to 20 years before the onset of clinical symptoms.[23] Our findings suggest that CRP might enhance disease progression at an earlier rather than later stage of the long neurodegenerative process. Although genetic risk factors such as *APOE* ε4 are present across the lifespan, disease onset does not occur until later in life.[2] *APOE* ε4 is the major genetic risk factor for AD,[24] and delaying onset by 5 years can reduce AD risk by nearly 50%.[25] Early detection and treatment of inflammation may be an important therapeutic target to prevent chronic inflammation and subsequent AD risk in *APOE* ε4 carriers.

Finally, plasma CRP was negatively associated with CSF biomarkers of tau at follow-up time points among those who were *APOE* ε4 noncarriers, as opposed to those who were 2 *APOE* ε4 allele carriers. *APOE* ε4 noncarriers had higher CRP levels compared with *APOE* ε4 carriers (Table 1). One possible explanation may be that *APOE* ε2 vs *APOE* ε4 brains are differentially affected by molecular pathways from chronic inflammation such as CRP and mCRP. *APOE* ε2 carriers may be more efficient at clearing t-Tau, p-Tau, and other brain AD pathologic proteins, so that *APOE* ε2 brains may be more resilient to chronic low-grade inflammation and AD risk. Whereas peripheral chronic low-grade inflammation may facilitate a clearance mechanism for tauopathy in those with *APOE* ε2 allele, inhibiting the inflammatory reaction in *APOE* ε2 carriers may not delay AD pathogenesis. Previous prevention trials of anti-inflammatory drugs for AD have failed,[26] potentially because of differences in *APOE* status. *APOE* ε4 carriers may be a more appropriate population for future clinical trials of anti-inflammatory drugs.

This study has several limitations. The main limitation of this study is the lack of CN individuals in the group of 2 *APOE* ε4 alleles in the ADNI1 dataset (Table 1). Thus, we were limited to investigating the relationship between plasma CRP and AD biomarkers in normal cognition and at an earlier preclinical stage than MCI. In addition, the methods used to measure plasma CRP levels in the ADNI1 study are different from those used in clinical practice and other studies. Most studies such as the Framingham Heart Study (FHS) and clinical practice use enzymatic immunoassays (ELISAs) to measure serum CRP.[27] ELISA specifically targets CRP. In contrast, the ADNI1 study used a targeted multiplex proteomic technique to measure CRP, along with 189 other proteins. The specificity of this approach is inferior to that of ELISA. Future research should examine the effect of CRP levels on cognitive decline using a more comprehensive neuropsychological test battery instead of assessing only MMSE scores. Nevertheless, based on 3 studies—the findings reported here, the results from our published FHS study on CRP and AD,[3] and the preclinical result of CRP on AD[5]—it is likely that CRP, specifically mCRP, plays a meaningful role in *APOE* ε4–related pathways to AD.

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Our findings suggest that CRP may represent an explanatory factor of the *APOE* ε4 vs ε2 risk pathway toward AD. Our results further suggest that *APOE* ε2 brains may be more resilient to peripheral inflammatory attacks. Because systemic infections are common among older adults, recovery of the immune system to normal CRP levels (<1 mg/L) could be critical for certain genotypes such as *APOE* ε4 in mitigating AD risk. Targeting *APOE* ε4 carriers may be an important consideration for future anti-inflammatory clinical trials.

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Disclosure

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Ting Fang Alvin Ang, MD MPH	Boston University School of Medicine, MA	Acquired and interpreted the data; revised the manuscript for intellectual content
Samia C. Akhter-Khan, MS	Humboldt University of Berlin, Germany; King's College London, UK	Interpreted the data and revised the manuscript for intellectual content
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Wei Qiao Qiu, MD, PhD	Boston University School of Medicine, MA; Boston University School of Public Health, MA	Designed and conceptualized the study; interpreted the data; and drafted, revised, and reviewed the manuscript for intellectual content

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