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RESEARCH ARTICLE

Prospective associations of interleukin-6 and *APOE* allele with cognitive decline in biracial community-dwelling older adults: The Chicago Health and Aging Project (CHAP)

Ted K. S. Ng[1] | **Todd Beck**[1] | **Pankaja Desai**[1] | **Klodian Dhana**[1] | **Robert S. Wilson**[2] | **Denis A. Evans**[1] | **Kumar B. Rajan**[1,2]

[1]Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA

[2]Rush Alzheimer's Disease Research Center, Rush University Medical Center, Chicago, Illinois, USA

Correspondence
Ted K. S. Ng, Rush Institute for Healthy Aging, Department of Internal Medicine, Rush University Medical Center, 1700 W Van Buren St., Suite 245, Chicago, IL 60612, USA.
Email: kheng_s_ng@rush.edu

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Abstract

INTRODUCTION: It is unclear whether inflammation, that is, high interleukin-6 (IL-6) levels, and genetic risk, that is, apolipoprotein E (*APOE*) ε4 allele, have a compounding effect on cognitive decline (CD).

METHODS: We analyzed a subset of participants from the longitudinal cohort study, Chicago Health and Aging Project, comprising 1120 biracial community-dwelling older adults (60% Black and 62% women), and mean follow-up = 6.4 years. We ran adjusted mixed-effects models on2 longitudinal CD.

RESULTS: In *APOE* ε4 carriers, higher serum IL-6 was not associated with the rate of CD ($\beta = -0.0091$ [standard deviation (SD) = 0.0165, $p = 0.5800$]). Conversely, in non-ε4 carriers, compared to the lower tertile, those with the upper tertile of serum IL-6 levels experienced significantly accelerated CD ($\beta = -0.0257$ [SD = 0.0084, $p = 0.0023$]).

DISCUSSION: Even without the largest genetic risk factor for late-onset Alzheimer's disease/Alzheimer's disease and related dementias (AD/ADRD), elevated serum IL-6 still accelerate the rate of CD in non-*APOE* ε4 carriers. Hence, interventions ameliorating inflammation may prevent AD/ADRD.

KEYWORDS
Alzheimer's disease, cognition, dementia, epidemiology, health disparity, inflammation, moderating effect, race

Highlights

- Interleukin-6 (IL-6) and the apolipoprotein E (*APOE*) ε4 allele have been separately associated with an increased risk for cognitive decline, but their interaction remains unclear.
- In ε4 carriers, IL-6 was not associated with cognitive decline. However, even without the biggest genetic risk factor for Alzheimer's disease (AD), that is, *APOE* ε4, elevated serum IL-6 still could confer accelerated rate of cognitive decline, with a detrimental effect half of that imposed by *APOE* ε4 alone.

- We found no racial differences in these associations.
- These findings contribute complementary evidence on non–*APOE* ε4-dependent and non-AD biological pathways through which cognitive decline can still be accelerated in non-*APOE* ε4 carriers and highlight a specific subgroup of older adults who are at a higher risk of AD and thus may benefit from anti-inflammatory interventions.

1 | BACKGROUND

Alzheimer's disease (AD) is a complex and multi-etiological disease, conferred by risk factors including genetics and inflammation. Apart from the canonical neuropathological hallmarks of the accumulation of amyloid beta (Aβ) plaques and tau protein tangles evidenced in the brain of patients with AD, neuroinflammation has gained traction in recent years as an understudied hallmark of AD.

Misfolded and aggregated proteins can trigger innate immune responses aimed at clearing plaques and tangles, leading to the release of inflammatory mediators, such as interleukin-6 (IL-6).[1,2] Among the triggering factors and aggravators, IL-6 is a pleiotropic cytokine produced in response to stressors and stimuli, including social–environmental stressors,[3,4] and Aβ plaques in the brain. [1,2] IL-6 can trigger a cascade of molecular events that lead to the production of more inflammatory cytokines and further the activation of microglia and astrocytes. Hence, apart from its roles in acute responses to stressors, IL-6 also controls chronic inflammatory responses.[5] Furthermore, chronic low-grade inflammation can lead to dysregulations in the intricate molecular control mechanisms, contributing to neuronal inflammation and eventual neuronal cell death. Hence, chronic low-grade inflammation caused by IL-6 predisposes cognitively normal older adults to hasten cognitive decline and in the long term developing AD.[6]

The apolipoprotein E (*APOE*) ε4 allele is the single largest genetic risk factor for late-onset AD/AD and related dementias (ADRD), with *APOE* ε4 carriers having an increased risk of developing late-onset AD/ADRD. Notably, a recent study showed that compared to *APOE* ε3 homozygotes, almost all *APOE* ε4 homozygotes had significantly higher levels of AD biomarkers.[7] Among several mechanisms, *APOE* ε4 has been postulated to contribute to AD pathogenesis via eliciting and aggravating neuroinflammation.[8] Specifically, in the central nervous system, the glial cells, predominantly astrocytes, express the apoE protein. The apoE protein can exacerbate the inflammatory response to stressors, leading to even greater neuroinflammation and neuronal cell death. This hypothesis is substantiated by animal studies showing that humanized *APOE* ε4 mice had increased IL-6 levels. [9,10]

Both IL-6 and the *APOE* ε4 allele, independently, have been implicated in cognitive decline (CD) in humans. However, there is a scarcity of studies examining both IL-6 and *APOE* ε4 *concurrently* as risk factors for CD in humans, particularly investigating how *APOE* ε4 influences the effects of IL-6 on CD. The combined detrimental effects of IL-6 and *APOE* ε4 on CD could indicate an even greater neurodegenerative burden and neuronal damage than their independent effects. Therefore, further investigation is critical to disentangle the complex relationship among *APOE* ε4, IL-6, and CD.

African Americans, that is, Blacks, have a higher risk for and steeper increase in incident AD/ADRD in the United States in the next 40 years,[11–13] which could be in part attributed to Blacks having a higher frequency of the *APOE* ε4 allele (due to genetic inheritance/ancestry)[14] and higher IL-6 levels, due to social–environmental stressors, including experiencing systemic racism.[15] However, extant studies on the longitudinal associations between either the *APOE* ε4 allele or IL-6 and CD have predominantly focused on White Americans,[16,17] hindering generalizability to minorities, including Blacks. Furthermore, many blood-based biomarker studies recruited human subjects mostly from clinical settings, which have been demonstrated to exhibit distinct demographics and thus differential risk than community-dwelling older adults.

It is thus imperative to investigate potential interactions between the *APOE* ε4 allele and IL-6 in a more racially diverse and community-dwelling population. In this paper, analyzing our biracial cohort comprising solely community-dwelling older adults, we first tested whether the genetic predisposition of AD, through the presence of the *APOE* ε4 allele, increases the rate of CD in people with chronic, low-grade inflammation, as indicated by blood-based IL-6 levels. Due to established racial differences in the exposure variables and the potential differences in the associations, we additionally performed a priori exploratory race-stratified analyses.

2 | METHODS

2.1 | Study design, setting, and population

The Chicago Health and Aging Project (CHAP) is a prospective population-based cohort study designed to assess bio-psycho-social and structural risk factors for age-related chronic conditions in older adults, with a specific focus on AD/ADRD.[18] Briefly, we started recruitment in 1993, enrolling participants based on four geographically defined Chicago neighborhoods that had substantial proportions of non-Hispanic Black and White residents. The only two inclusion criteria for the cohort were living in the study catchment area and having a minimum age of 65 years at enrollment.

During in-home assessments, research assistants administered questionnaires and neurocognitive tests every 3 years and up to six times throughout the study period. Blood specimen collection and processing have previously been described in detail.[19] In brief, over the

course of the study, oversampling for Black participants, approximately one third of CHAP participants were selected for a clinical assessment for AD when they also provided blood samples. Upon laboratory processing, we stored the samples in −80°C freezers within 3 hours of collection. There were 1327 participants with serum samples assayed. For this paper, we analyzed data from 1120 participants with baseline levels of IL-6 assayed and *APOE* ε4 allele genotyped and at least two follow-up cognitive testings.

2.2 | *APOE* carrier status

The *APOE* ε4 carrier status was ascertained with two single nucleotide polymorphisms (SNPs): rs7412 and rs429358.[20] The genotyping was performed at the Broad Institute Center for Genotyping using the hME Sequenom MassARRAY platform. Genotyping call rates were 100% for SNP rs7412 and 99.8% for SNP rs429358. Both SNPs were in Hardy–Weinberg equilibrium with *p* values of 0.0833 and 0.7925, respectively. Based on these two SNPs, we created an indicator variable for participants with and without the *APOE* ε4 allele.[21] *APOE* ε4 carriers were participants with at least one copy of the *APOE* ε4 allele, that is, ε2/ε4, ε3/ε4, and two copies of the *APOE* ε4 allele, that is, ε4/ε4. The second group, the non-*APOE* ε4 carriers, were those without any copy of the *APOE* ε4 allele, that is, ε2/ε2, ε2/ε3, and ε3/ε3 genotypes.

2.3 | Quantification of serum IL-6 levels

At the end of the in-home assessments, research assistants transported the blood samples on dry ice to a Rush biorepository. After centrifugation, the serum was extracted, aliquoted and bio-banked in −80°C freezers. Previously unthawed samples were transported in dry ice for biomarker detection at Quanterix. The serum IL-6 levels were measured using CorPlex Human Cytokine 10-plex panel 1 assay (CPX). SIMOA and HD-X were used for IL-6 quantification. IL-6 has a lower limit of detection of 0.037 pg/mL (range 0.008–0.067 pg/mL) and coefficient of variation of 11%.[22]

2.4 | Global and domain-specific tests of cognition

The four tests included two tests of episodic memory, one test of executive function, and the Mini-Mental State Examination. The rationale for selecting these four tests was due to the simplicity and feasibility of administration during in-home assessments for a population-wide epidemiological study. After centering and scaling each test to the cohort's baseline means and standard deviations (SDs), we derived standardized scores for both a global measure of cognitive function and domain-specific cognitive tests. Individual domain-specific cognitive tests were based on two tests for memory and one executive function–based speed test. The global measure of cognitive function was calculated by averaging the four cognitive tests, which we described in detail in our previous publication.[21,23,24]

RESEARCH IN CONTEXT

1. **Systematic review**: Interleukin-6 (IL-6) and the apolipoprotein E (*APOE*) ε4 allele, separately, have been associated with an increased risk for cognitive decline in humans. Animal studies have shown that mice with the *APOE* ε4 allele have higher IL-6 levels. However, it remains unclear whether the increased risk for cognitive decline is accelerated in *APOE* ε4 carriers, and whether these associations differ by race. Hence, we attempted to address, for the first time, these four important AD risk factors, namely *APOE* ε4 status (i.e., carriers vs. non-carriers), serum IL-6 levels, race, and cognitive decline, within a single longitudinal human cohort study.
2. **Interpretations**: In *APOE* ε4 carriers, surprisingly, IL-6 was not associated with cognitive decline. However, even without the biggest genetic risk factor for Alzheimer's disease (AD), that is, *APOE* ε4, elevated serum IL-6 still could confer accelerated rate of cognitive decline, with a detrimental effect half of that imposed by *APOE* ε4 alone. On the contrary, non-*APOE* ε4 carriers without elevated serum IL-6 levels had the slowest decline and thus the lowest risk of cognitive decline in the long term. We found no racial differences in these associations.
3. **Future directions**: These findings may implicate precision medicine, highlighting a specific subgroup of older adults who are at a higher risk of cognitive decline and AD, and thus may benefit from anti-inflammatory interventions. Specifically, even without the *APOE* ε4 allele, which constitutes most of the population, heightened systemic inflammation still accelerate cognitive decline. In light of recent findings showing overwhelming biological penetrance of the *APOE* ε4 allele on canonical AD biomarkers and pathologies, our finding is significant in contributing complementary evidence on non–*APOE* ε4-dependent and non-AD biological pathways through which cognitive decline can still be accelerated in non-*APOE* ε4 carriers. Replications of our findings presented here, especially in cohorts including more diverse racial groups, for example, Hispanics, is needed.

2.5 | Covariates

Pertinent covariates collected during the baseline assessment were controlled for. They included the age at first blood sample collection (centered at 75 years), biological sex (males or females), race (non-Hispanic Black and non-Hispanic White), education (measured in the number of years of schooling completed, centered at 12 years), body mass index (BMI), and chronic health conditions (i.e., hypertension,

diabetes, stroke, heart condition, cancer, and hip fracture). The centering for age and education was decided using their approximate means.

2.6 | Statistical analyses

Serum IL-6 levels were positively skewed and above zero. Hence, we made a $\log_{10}$ transformation with geometric mean and its 95% confidence interval. Descriptive comparisons between non-*APOE* ε4 carriers and *APOE* ε4 carriers were based on *t* tests for untransformed characteristics, chi-square test for frequencies, and Wilcoxon rank test for serum IL-6 levels. All regression models were adjusted for age at first blood assay (centered at 75 years), education (centered at 12 years), male sex, non-Hispanic Black race/ethnicity, BMI, and common chronic health conditions.

We used a linear mixed effects regression model to examine the association of baseline serum IL-6 levels with longitudinal change in cognitive function. These mixed models included random intercepts and slopes and allow us to measure both within- and across-participant variability. Time since baseline blood assessment was measured in years, capturing the annual rate of change in cognitive function over time. We operationalized serum IL-6 levels in two different ways. First, we used log-transformed continuous biomarker levels. Second, we divided serum IL-6 levels into tertiles, to examine the association of higher tertiles of IL-6 levels with CD.

We also performed two sets of analyses; we first added an interaction term in a three-way interaction model (i.e., $\log_{10}$ transformed continuous IL-6 levels/tertiles x *APOE* ε4 x time). Upon detecting a significant three-way interaction effect, we then performed stratifications of the total sample by the *APOE* ε4 allele and examined two-way interaction models (i.e., $\log_{10}$ transformed continuous IL-6 levels/ tertiles x time).

Due to established racial differences in the exposure variables and thus, the potential differences in associations, we additionally performed exploratory race-based stratified analyses repeated for all statistical models, while considering the sample size and power limitations.

All regression models were performed using SAS 9.4, and graphical representations were performed with the R program.[25] A *P* value of 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline demographics

Of the total 1120 participants (*APOE* ε4 carriers = 378 and non-*APOE* ε4 carriers = 742), most baseline characteristics (see Table 1) did not show a significant difference between the carriers and non-carriers, except for race (higher Black for *APOE* ε4 carriers; *n* = 247, 65% vs. lower Black in non-*APOE* ε4 carriers; *n* = 424, 57%), global cognitive function (mean [SD] = 0.29 [0.62] in non-*APOE* ε4 carriers and 0.17 [0.64] in *APOE* ε4 carriers), and time in study (mean [SD] = 6.7 [3.8] in non-*APOE* ε4 carriers and in 5.9 [3.4] in *APOE* ε4 carriers).

Supplementary text and Table S1a in supporting information show group differences (and lack thereof) in demographics in the tertile subgroups.

3.2 | 2-way interaction models

Tables S2a&b in supporting information show significant two-way interaction between $\log_{10}$ IL-6 levels and time, with beta estimate (SD, *p* value) = −0.0211 (0.0092, 0.0223), and between IL-6 tertiles and time −0.0167 (0.0077, 0.0302).

3.3 | 3-way interaction models

3.3.1 | Continuous $\log_{10}$-transformed IL-6 levels

There was no statistically significant three-way interaction among $\log_{10}$ IL-6 levels, *APOE* ε4 carrier status, and time, with 0.0316 (0.0209, 0.1307; Table 2A).

3.3.2 | IL-6 tertiles

There was no statistically significant three-way interaction among the middle tertile of IL-6 levels, *APOE* ε4 carrier status, and time, with 0.0117 (0.0162, 0.4699) compared to those in the lower tertile (Table 2B).

There was a statistically significant three-way interaction among the upper tertile IL-6 levels, *APOE* ε4 carrier status, and time, with 0.0331 (0.0166, 0.0457) compared to the lower tertile.

3.4 | Models stratified by *APOE* ε4 carrier status

3.4.1 | Log_{10}-transformed IL-6 levels

Regardless of *APOE* ε4 carrier status, we detected no significant association of baseline serum IL-6 levels with baseline level of global cognition. *APOE* ε4 carriers = −0.0955 (0.0878, 0.2775); non-*APOE* ε4 carriers = −0.0147 (0.0593, 0.8045; Table 3A).

Longitudinally, compared to non-*APOE* ε4 carriers, *APOE* ε4 carriers had a significantly accelerated average annual rate of CD, with −0.0155 (0.0081, 0.0565) and −0.0974 (0.0176, 0.0000), respectively.

For examining longitudinal associations and making within-group comparisons, for every one unit increase in $\log_{10}$-transformed IL-6 levels, non-*APOE* ε4 carriers with elevated IL-6 had almost triple the rate of CD, with an additional −0.0275 (0.0097, 0.0047). In contrast, log IL-6 levels did not accelerate the rate of CD in *APOE* ε4 carriers, 0.0044 (0.0211, 0.8368).

Comparing groups, the magnitude of accelerated CD is noteworthy: The average rate of CD was approximately half that of *APOE* ε4 carriers.

TABLE 1 Baseline demographics by *APOE* ε4 carrier status.

Variable	Total sample *N* = 1120[a]	Non-*APOE* ε4 carriers *N* = 742	*APOE* ε4 carriers *N* = 378	*p* value[b]
Age (years), mean (SD)	77.2 (6.0)	77.5 (6.1)	76.8 (5.6)	0.061
Education (years), mean (SD)	12.6 (3.5)	12.7 (3.5)	12.5 (3.4)	0.46
Female, *n* (%)	699 (62)	466 (63)	233 (62)	0.75
Black, *n* (%)	671 (60)	424 (57)	247 (65)	**0.010***
Chronic conditions, mean (SD)	1.3 (1.0)	1.3 (1.0)	1.3 (1.0)	0.57
BMI (kg/m^2), mean (SD)	27.6 (5.5)	27.7 (5.6)	27.4 (5.3)	0.34
Global cognitive function, mean (SD)	0.25 (0.63)	0.29 (0.62)	0.17 (0.64)	**0.006****
Time in study (years), mean (SD)	6.4 (3.7)	6.7 (3.8)	5.9 (3.4)	**<0.001*****
IL-6 (pg/mL), median (IQR)	2.6 (1.7–4.4)	2.6 (1.7–4.4)	2.5 (1.6–4.3)	0.44
IL-6 tertile, *n* (%)				0.21
1	379 (34)	239 (32)	140 (37)	
2	382 (34)	264 (36)	118 (31)	
3	359 (32)	239 (32)	120 (32)	

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation.
[a]Mean (SD); *n* (%); median (IQR).
[b]Welch two sample *t* test; Pearson chi-squared test; Wilcoxon rank sum test.
*and bold text indicates < 0.05.
**and bold text indicates < 0.01.
***and bold text indicates < 0.0001.

TABLE 2A Total sample: three-way interaction model with the interaction term "Log_{10} transformed IL-6 levels x *APOE* ε4 x time" and association with 12-year cognitive decline.

	Total sample estimate (SD, *p* value) *N* = 1120
Log_{10} IL-6, pg/mL	−0.0168 (0.0598, 0.7784)
APOE ε4	−0.0526 (0.0576, 0.3611)
Time	−0.0219 (0.0084, **0.0087***)
Log_{10} IL-6 x time	−0.0297 (0.0108, **0.0062****)
Log_{10} IL-6 x *APOE* ε4	−0.0693 (0.1032, 0.5020)
APOE ε4 x time	−0.0572 (0.0110, **< 0.0001***)
Log_{10} IL-6 x *APOE* ε4 x time	0.0316 (0.0209, 0.1307)

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

TABLE 2B Total sample: three-way interaction model with the interaction term "IL-6 tertiles x *APOE* ε4 x time" and association with 12-year cognitive decline.

	Total sample estimate (SD, *p* value) *N* = 1120
IL-6 tertile 1	Reference
IL-6 tertile 2	−0.0333 (0.0491, 0.4975)
IL-6 tertile 3	−0.0387 (0.0505, 0.4438)
APOE ε4	−0.0810 (0.0584, 0.1658)
Time	−0.0247 (0.0087, **0.0047***)
IL-6 tertile 1 x time	Reference
IL-6 tertile 2 x time	−0.0040 (0.0090, 0.6594)
IL-6 tertile 3 x time	−0.0270 (0.0094, **0.0040****)
IL-6 tertile 1 x *APOE* ε4	Reference
IL-6 tertile 2 x *APOE* ε4	0.0245 (0.0845, 0.7722)
IL-6 tertile 3 x *APOE* ε4	−0.0373 (0.0848, 0.6599)
APOE ε4 x time	−0.0571 (0.0110, **< 0.0001***)
IL-6 tertile 1 x *APOE* ε4 x time	Reference
IL-6 tertile 2 x *APOE* ε4 x time	0.0117 (0.0162, 0.4699)
IL-6 tertile 3 x *APOE* ε4 x time	0.0331 (0.0166, **0.0457***)

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001

3.4.2 | IL-6 tertiles

In non-*APOE* ε4 carriers with the lowest tertile of IL-6 level, the rate of CD was −0.0177 (0.0084, 0.0363; Table 3B). Compared to the reference group, non-*APOE* ε4 carriers with elevated IL-6, that is, those having the upper tertile of IL-6, had an additional rate of decline of

TABLE 3A Stratified samples: two-way interaction model with the interaction term "Log_{10}-transformed IL-6 levels x time" and association with 12-year cognitive decline, stratified by *APOE* ε4 carrier status.

	APOE ε4 carriers estimate (SD, *p* value) *N* = 378	Non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 742
Log_{10} IL-6, pg/mL	−0.0955 (0.0878, 0.2775)	−0.0147 (0.0593, 0.8045)
Time	−0.0974 (0.0176, < **0.0001*****)	−0.0155 (0.0081, 0.0565)
Log_{10} IL-6 x time	0.0044 (0.0211, 0.8368)	−0.0275 (0.0097, **0.0047****)

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

TABLE 3B Stratified samples: two-way interaction model with the interaction term "IL-6 tertile x time" and association with 12-year cognitive decline, stratified by *APOE* ε4 carrier status.

	APOE ε4 carriers estimate (SD, *p* value) *N* = 378	Non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 742
IL-6 tertile 1	Reference	Reference
IL-6 tertile 2	−0.0219 (0.0719, 0.7604)	−0.0246 (0.0487, 0.6130)
IL-6 tertile 3	−0.0930 (0.0712, 0.1923)	−0.0343 (0.0502, 0.4951)
Time	−0.1005 (0.0173, < **0.0001**[a])	−0.0177 (0.0084, **0.0363**[c])
IL-6 tertile 1 x time	Reference	Reference
IL-6 tertile 2 x time	0.0078 (0.0163, 0.6323)	−0.0036 (0.0081, 0.6533)
IL-6 tertile 3 x time	0.0091 (0.0165, 0.5800)	−0.0257 (0.0084, **0.0023**[b])

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
[a]and bold text Indicates < 0.0001.
[b]and bold text Indicates < 0.01.
[c]and bold text Indicates < 0.05.

−0.0257 (0.0084, 0.0023). Interestingly, non-*APOE* ε4 carriers with moderate IL-6 at the middle tertile, −0.0036 (0.0081, 0.6533), did not experience accelerated CD. Neither the middle nor the upper tertiles were significant in the *APOE* ε4 carriers.

Comparing the groups, similar to our findings using the operationalization of IL-6 levels on a continuous log_{10}-transformed scale, the accelerated rate of CD in non-*APOE* ε4 carriers with upper IL-6 tertile was almost half that of *APOE* ε4 carriers (Figure 1).

3.4.3 | Exploratory race-stratified analyses

See supplementary text and Tables 4A, 4B, 4C, and 4D.

4 | DISCUSSION

Our study presented several notable findings. First, in *APOE* ε4 carriers, serum IL-6 was not associated with CD. However, it is worth noting that in the non-*APOE* ε4 carriers, compared to those having lower serum IL-6 levels, those having elevated serum IL-6 levels experienced significantly accelerated CD. Specifically, compared to non-*APOE* ε4 carriers with the lower tertile of IL-6 levels, non-*APOE* ε4 carriers who had the upper tertile of IL-6 levels (but not those in the middle IL-6 tertile) had significantly accelerated rate of CD, to the extent of approximately half the rate of decline of that of *APOE* ε4 carriers. These results did not differ by race. Hence, without the largest genetic risk factor for AD, that is, *APOE* ε4, elevated serum IL-6 still could confer accelerated rate of CD, with a similar detrimental effect half of that imposed by *APOE* ε4 alone. The slowest CD was observed in non-carriers who had the lowest levels/tertiles of serum IL-6 levels. Hence, non-*APOE* ε4 carriers without elevated serum IL-6 levels, that is, those without a genetic predisposition and late-life stressors, have the lowest risk of CD and possibly the lowest risk of AD/ADRD.

We initially hypothesized that the ε4 allele may exert its detrimental effects via inflammatory mechanisms and thus the presence of the ε4 allele will compound the rate of CD conferred by high IL-6 levels. However, contrary to our hypothesis, in the presence of genetic effects imposed by the *APOE* ε4 allele, serum IL-6 levels did not seem to exert an additional impact in affecting CD. It is plausible that *APOE* ε4 elicits its detrimental effects via alternative pathways instead, with

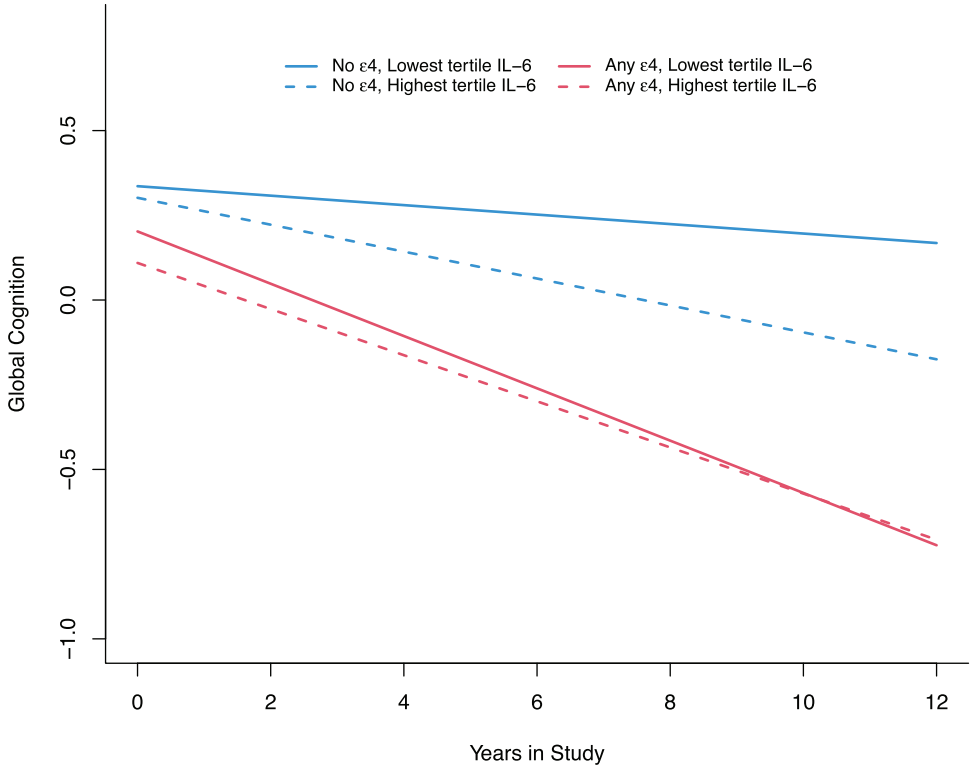

FIGURE 1 Twelve-year global cognitive decline by *APOE* ε4 status and IL-6 tertiles. The accelerated rate of CD in non-*APOE* ε4 carriers with upper IL-6 tertile was approximately half that of *APOE* ε4 carriers. APOE, apolipoprotein E; CD, cognitive decline; IL-6, interleukin-6.

potential candidates including lipid and cholesterol dysregulations, as one of the main functions of apoE protein include clearing cholesterol and lipids.[10] There are also other candidates; apoE protein may instead interact with amyloid, tau, and/or neurodegeneration markers, including elevated glial fibrillary acidic protein, total tau, and neurofilament light chain. A study showed that by age 65, nearly all *APOE* ε4 homozygote participants show abnormal levels of canonical AD biomarkers, evidenced by abnormal cerebrospinal fluid Aβ1-42 levels and 75% had positive amyloid scans.[7] On the contrary, serum IL-6 is a non-canonical and non-specific AD biomarker indicative of systemic inflammatory processes that originate both from the periphery and the brain. Taken together these complementary findings, our findings suggest that instead of a systemic marker indicative of both peripheral and central nervous system inflammation, that is, IL-6, the *APOE* ε4 allele may interact with neurodegeneration and neuroinflammation more specific to the brain.

In non-*APOE* ε4 carriers, elevated serum IL-6 accelerated CD. It is noteworthy that there seemed to be a threshold effect of IL-6 with CD. The findings were not significant when serum IL-6 levels were operationalized as continuous $\log_{10}$ IL-6 nor in the middle tertile, but were significant in only the upper tertile. Taken together, our findings suggested that to affect CD in the absence of *APOE* ε4 allele, serum IL-6 levels may need to be above a certain threshold level to exert its detrimental effects on CD. Hence, cognitive effects of serum IL-6 levels depend not only on *APOE* ε4 allele, but also how high IL-6 levels are. These findings highlight a specific subgroup of older adults who are more at risk and who could potentially benefit from anti-inflammatory interventions. Given the findings on almost full penetrance of *APOE* ε4 homozygotes on canonical AD biomarkers,[7] our findings provide complementary yet important evidence on non-*APOE* ε4 and non-canonical AD-dependent processes that accelerate cognitive decline.

One of the possible sources of heterogeneity in previous literature could be race-based differences in both the *APOE* ε4 allele frequency and serum IL-6 levels. Due to genetic ancestry, compared to Whites, Blacks have a higher *APOE* ε4 allele frequency. Systemic issues faced by Blacks in their daily lives, including discrimination, systemic racism, and access to health care, could contribute to elevated serum IL-6 levels.[15,26] Hence, some studies[27–30] suggest that these differences potentially contribute differently to the pathophysiology of dementia. Here, we showed that despite the lack of a significant difference in IL-6 levels, given significant difference in *APOE* ε4 carriers in Blacks versus Whites, all the associations in Blacks versus Whites did not seem to differ. Conversely, two previous cross-sectional studies showed that blood-based IL-6 was significantly associated with CD in Blacks but not Whites.[30–32] Furthermore, two other longitudinal studies showed no racial differences on the effect of inflammation on CD.[33,34] However, it is worth noting that these previous studies did not examine the interaction effects of blood-based IL-6 with *APOE* ε4 allele, let alone in a sample comprising a substantial percentage of Blacks. Owing to these mixed results of previous studies, our cohort offers a unique opportunity to interrogate this issue, showing for the first time no racial differences in the interaction effects. In all, there is a need for repli-

TABLE 4A Total and stratified samples: three-way and two-way interaction models with the interaction term "IL-6 tertiles x *APOE* ε4 x time" and association with 12-year cognitive decline, stratified a priori by race—Black subgroup.

	Total Black sample estimate (SD, *p* value) *N* = 671	Black *APOE* ε4 carriers estimate (SD, *p* value) *N* = 247	Black non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 424
IL-6 lower tertile	Reference	Reference	Reference
IL-6 middle tertile	−0.0689 (0.0638, 0.2807)	−0.0753 (0.0836, 0.3688)	−0.0632 (0.0651, 0.3317)
IL-6 upper tertile	−0.0188 (0.0684, 0.7837)	−0.1205 (0.0821, 0.1434)	−0.0144 (0.0699, 0.8369)
APOE ε4	−0.0316 (0.0748, 0.6730)	–	–
Time	−0.0208 (0.0115, 0.0700)	−0.0612 (0.0192, **0.0015****)	−0.0242 (0.0102, **0.0174***)
IL-6 lower tertile x time	Reference	Reference	Reference
IL-6 middle tertile x time	−0.0042 (0.0118, 0.7236)	0.0078 (0.0213,0.7147)	−0.0033 (0.0096, 0.7289)
IL-6 upper tertile x time	−0.0243 (0.0129, 0.0592)	−0.0041 (0.0213,0.8475)	−0.0228 (0.0107, **0.0333***)
IL-6 lower tertile x *APOE* ε4	Reference	Reference	Reference
IL-6 middle tertile x *APOE* ε4	−0.0029 (0.1058, 0.9784)	–	–
IL-6 upper tertile x *APOE* ε4	−0.0970 (0.1077, 0.3678)	–	–
APOE ε4 x time	−0.0505 (0.0143, **0.0004****)	–	–
IL-6 lower tertile x *APOE* ε4 x time	Reference	Reference	Reference
IL-6 middle tertile x *APOE* ε4 x time	0.0160 (0.0201, 0.4274)	–	–
IL-6 upper tertile x *APOE* ε4 x time	0.0199 (0.0209, 0.3411)	–	–

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

cation of these findings in other cohorts with a more diverse racial representation.

A few potential issues may have limited our interpretations. Due to sample availabilities, we examined serum IL-6 at a single timepoint and lacked other inflammatory marker levels. Future analyses of additional cytokines across timepoints are needed. Additionally, there might have been a potential statistical power issue with our a priori race stratifications, which might have rendered reduced power to detect statistical significance and a complicated four-way interaction model infeasible. Conversely, interpreting a four-way interaction model is inherently challenging and may not be feasible. Although it would have been useful to perform sensitivity analyses on *APOE* ε4 homozygotes, the requirement of a larger sample size for interaction and stratification analyses deter us from performing such analyses. Our study lacked other genetic characterization, such as *TREM2*, which impacts neuroinflammation. Recent studies have suggested that both *APOE* and *TREM2* are required for microglia to cluster around the Aβ plaque and clear apoptotic neurons.[35] Similarly, we also did not have IL-6 genotyping; several studies have shown that the G/G IL-6 genotype, predominantly found in Blacks,[36,37] could result in elevated IL-6 production. Future studies should build on our findings here and examine the roles of/control for these other genotypes.

Our study has several notable strengths. In stark contrast to previous studies, our cohort comprised solely community-dwelling older adults who were relatively healthy. Participants had an average of one chronic condition and were relatively free of cardiovascular and cardiometabolic diseases. These are two critical factors that have been shown to influence inflammatory markers[26,30] and thus could have potentially confounded findings of previous studies. For example, a previous study analyzed a cohort comprising ≈ 50% of participants who had hypertension and/or cardiovascular conditions.[30] Despite controlling for the confounding effects of chronic conditions on IL-6 levels in the statistical model, residual confounding effect may remain, as the chronic conditions were inherent to the participants and thus likely have affected other variables. Second, this study addressed the issue of scarcity of studies examining inflammation and cognitive function in cohorts with substantial Black participants, thus enhancing the generalizability of findings. Third, in previous studies, even when minorities, such as Blacks, were included, race was frequently operationalized as a covariate and not as a core variable, thus impeding a direct comparison of racial differences in the associations. In this study, with 60% of Black population, we conducted both total and subgroup analyses to examine racial differences in the associations.

TABLE 4B Total and stratified samples: three-way and two-way interaction models with the interaction term "IL-6 tertiles x *APOE* ε4 x time" and association with 12-year cognitive decline, stratified a priori by race—White subgroup.

	Total White sample estimate (SD, *p* value) *N* = 449	White *APOE* ε4 carriers estimate (SD, *p* value) *N* = 131	White non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 318
IL-6 lower tertile	Reference	Reference	Reference
IL-6 middle tertile	0.0227 (0.0771, 0.7690)	0.0692 (0.1364, 0.6125)	0.0322 (0.0724, 0.6568)
IL-6 upper tertile	−0.0617 (0.0753, 0.4130)	−0.0506 (0.1382, 0.7152)	−0.0534 (0.0709, 0.4520)
APOE ε4	−0.1709 (0.0939, 0.0693)	–	–
Time	−0.0303 (0.0128, **0.0178***)	−0.1435 (0.0239, **< 0.0001***)	−0.0159 (0.0132, 0.2295)
IL-6 lower tertile x time	Reference	Reference	Reference
IL-6 middle tertile x time	0.0002 (0.0146, 0.9882)	0.0090 (0.0271, 0.7410)	0.0007 (0.0140, 0.9588)
IL-6 upper tertile x time	−0.0299 (0.0143, **0.0370***)	0.0271 (0.0277, 0.3280)	−0.0286 (0.0137, **0.0374***)
IL-6 lower tertile x *APOE* ε4	Reference	Reference	Reference
IL-6 middle tertile x *APOE* ε4	0.0679 (0.1408, 0.6299)	–	–
IL-6 upper tertile x *APOE* ε4	0.0441 (0.1390, 0.7510)	–	–
APOE ε4 x time	−0.0700 (0.0178, **0.0001****)	–	–
IL-6 lower tertile x *APOE* ε4 x time	Reference	Reference	Reference
IL-6 middle tertile x *APOE* ε4 x time	0.0015 (0.0280, 0.9565)		
IL-6 upper tertile x *APOE* ε4 x time	0.0597 (0.0281, **0.0339***)		

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

TABLE 4C Total and stratified samples: three-way and two-way interaction models with the interaction term "Log_{10}-transformed IL-6 levels x *APOE* ε4 x time" and association with 12-year cognitive decline, stratified a priori by race—Black subgroup.

	Total Black sample estimate (SD, *p* value) *N* = 671	Black *APOE* ε4 carriers estimate (SD, *p* value) *N* = 247	Black non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 424
Log_{10} IL-6, pg/mL	0.0211 (0.0787, 0.7888)	−0.1192 (0.1003, 0.2360)	0.0198 (0.0804, 0.8053)
APOE ε4	0.0119 (0.0720, 0.8690)	–	–
Time	−0.0175 (0.0106, 0.0997)	−0.0594 (0.0201, **0.0032****)	−0.0210 (0.0095, **0.0271***)
Log10 IL-6 x time	−0.0278 (0.0147, 0.0577)	−0.0032 (0.0280, 0.9094)	−0.0246 (0.0121, **0.0425***)
Log10 IL-6 x *APOE* ε4	−0.1582 (0.1292, 0.2211)	–	–
APOE ε4 x time	−0.0528 (0.0140, **0.0002****)	–	–
Log10 IL-6 x *APOE* ε4 x time	0.0297 (0.0266, 0.2640)	–	–

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

TABLE 4D Total and stratified samples: three-way and two-way interaction models with the interaction term "Log_{10}-transformed IL-6 levels x *APOE* ε4 x time" and association with 12-year cognitive decline, stratified a priori by race—White subgroup.

	Total White sample estimate (SD, *p* value) *N* = 449	White *APOE* ε4 carriers estimate (SD, *p* value) *N* = 131	White non-*APOE* ε4 carriers estimate (SD, *p* value) *N* = 318
Log_{10} IL-6, pg/mL	−0.0594 (0.0925, 0.5209)	−0.0470 (0.1732, 0.7867)	−0.0476 (0.0873, 0.5856)
APOE ε4	−0.1568 (0.0963, 0.1043)	–	–
Time	−0.0274 (0.0121, **0.0244**[c])	−0.1380 (0.0237, < **0.0001**[a])	−0.0130 (0.0126, 0.3022)
Log_{10} IL-6 x time	−0.0320 (0.0170, 0.0593)	0.0075 (0.0342, 0.8265)	−0.0288 (0.0162, 0.0764)
Log_{10} IL-6 x *APOE* ε4	0.0471 (0.1729, 0.7853)	–	–
APOE ε4 x time	−0.0694 (0.0182, **0.0001**[b])	–	–
Log_{10} IL-6 x *APOE* ε4 x time	0.0414 (0.0345, 0.2293)	–	–

Note: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, Black race/ethnicity, BMI, hypertension, and diabetes, and included the interaction of these characteristics with time since baseline.
Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index; IL-6, interleukin-6; SD, standard deviation.
*and bold text Indicates < 0.05.
**and bold text Indicates < 0.01.
***and bold text Indicates < 0.0001.

In all, our data showed that the detrimental effects of serum IL-6 levels were contingent upon *APOE* ε4 carrier status. Specifically, in the presence of the *APOE* ε4 allele, regardless of IL-6 levels, *APOE* ε4 carriers experienced accelerated CD at a similar rate. However, even without any *APOE* ε4 allele, which constitutes most of the population, heightened systemic inflammation still accelerate cognitive decline. In light of recent findings showing overwhelming biological penetrance of the *APOE* ε4 allele on canonical AD biomarkers and pathologies,[7] our finding is significant in contributing complementary evidence on non–*APOE* ε4-dependent and non-AD biological pathways through which cognitive decline can still be accelerated in at-risk non-*APOE* ε4 carriers. Though the main effect of *APOE* ε4 in different races was validated, race-stratified exploratory analyses did not show race-based differential interaction effects with serum IL-6 levels. This study thus highlights the complexity of the inter-relationships among race, *APOE* ε4 allele, serum IL-6 levels, and CD, while for the first time attempting to address myriad important AD risk factors within a single study. Consequently, this study has pertinent implications. Despite the *APOE* ε4 allele being a non-modifiable risk factor for AD/ADRD, serum IL-6, an indicator of chronic low-grade inflammation, is a modifiable risk factor that could be ameliorated by modulating stressors. Hence, strategies aimed at mitigating IL-6 levels may have therapeutic potential. Indeed, several existing non-pharmacological interventions have previously been conducted, demonstrating potential to improve IL-6 levels, including diet combined with resistance training,[38] mindfulness practices,[39] and horticultural therapy.[40] In all, this study not only furthered our understanding of the neurodegenerative disease processes, but it also identified a high-risk subgroup of vulnerable older adults. Hence, findings may inform the development of more targeted therapies and interventions, which is a step forward in precision medicine in AD/ADRD.

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CONSENT STATEMENT

The institutional review board of the Rush University Medical Center approved the CHAP study protocols, and all participants provided written consent for population interviews, blood collection, and clinical evaluations.

DATA AVAILABILITY STATEMENT

The institutional review board of the Rush University Medical Center approved the study protocols, and all participants provided written consent for blood and DNA collection, population interviews, and clinical evaluations. Data that support study findings are available through data request and a data use agreement from our research resource data portal, https://riha.rush.edu/dataportal.html.

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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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