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Trajectories of inflammatory markers and cognitive decline over 10 years

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Abstract

We aimed to examine trajectories of inflammatory markers and cognitive decline over 10 years. Cox proportional hazards models were used to examine the association between interleukin-6 (IL-6) and C-reactive protein (CRP) trajectory components (slope, variability, and baseline level) and cognitive decline among 1,323 adults, age 70 to 79 years in the Health, Aging and Body Composition Study. We tested for interactions by sex and apolipoprotein E (APOE) genotype. In

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models adjusted for multiple covariates and comorbidities, extreme CRP variability was significantly associated with cognitive decline (HR 1.6, 95% CI: 1.1-2.3). This association was modified by sex and APOE e4 ($p<0.001$ for both), such that the association remained among women (HR=1.8; 95% CI: 1.1, 3.0) and among those with no APOE e4 allele (HR=1.6; 95% CI: 1.1, 2.5). There were no significant associations between slope or baseline level of CRP and cognitive decline, nor between IL-6 and cognitive decline. We believe CRP variability likely reflects poor control of or greater changes in vascular or metabolic disease over time, which in turn is associated with cognitive decline.

Keywords

Inflammatory markers; cognitive decline; C-reactive protein; Interleukin-6

1. Introduction

The relationship between inflammation and dementia or Alzheimer's disease (AD) has been widely investigated for several reasons. First, inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been found in the amyloid plaques and neurofibrillary tangles that develop in AD.(Neuroinflammation Working Group, et al., 2000) It has also been proposed that inflammatory markers contribute to the etiologic progression of dementia via several pathways, including vascular disease and overall neurodegeneration. (Brunello, et al., 2000; Eagan, et al., 2012; Ridker, Rifai, Rose, Buring, & Cook, 2002) While many studies have found a significant association between elevated CRP and IL-6 measured from one time point, and risk of AD or cognitive decline (Kravitz, Corrada, & Kawas, 2009; Schmidt, et al., 2002; Yaffe, et al., 2003), several studies have not supported such associations.(Gallacher, et al., 2010; Sundelof, et al., 2009; Tan, et al., 2007; van Oijen, Witteman, Hofman, Koudstaal, & Breteler, 2005) While inflammatory markers are variable in nature, it has recently been suggested that levels of inflammation over time have considerable intra-individual variability, and that this fluctuation in levels of inflammatory markers over time is greater than originally expected.(deGoma, et al., 2012) Specifically, CRP has been shown to have considerable intra-individual variability over time, with a minimum of three CRP measurements suggested to accurately determine the association with cardiovascular outcomes.(Koenig, et al., 2003) Thus, previous studies are greatly limited by having inflammation measured at only one point in time, often many years prior to the measurement of the outcome. By trying to characterize highly variable inflammatory markers with only one measurement, valueable information about how these markers change over time is missing, and such information may provide further insight as to how inflammatory markers are contributing to the process of cognitive decline. More studies are needed to investigate the association between inflammatory markers measured at multiple time points, and cognitive function.

The objectives of this study were to examine the association between IL-6 and CRP trajectory patterns and incident cognitive decline and impairment over 10 years. We hypothesized that the slope and variability of IL-6 and CRP trajectories over time would be stronger predictors of cognitive function than individual levels of either marker, due to intra-

individual variability over time. A second objective was to determine if these associations were modified by sex or apolipoprotein E (APOE) genotype. As previous studies have found stronger associations among non-APOE e4 carriers and women, we hypothesized that our results would be similar.(Eriksson, et al., 2011; Kravitz, et al., 2009)

2. Methods

2.1 Study population

Community-dwelling white and black older adults were enrolled in the ongoing Health Aging and Body Composition (Health ABC) study. This prospective cohort study began in 1997 and included adults ranging in age from 70 to 79 years at enrollment who lived in Memphis, TN or Pittsburgh, PA. Participants were recruited from a random sample of Medicare eligible adults living within designated zip codes, and were eligible if they reported no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. They also had to be free of life-threatening cancers, and plan to remain within the study area for at least three years. Our analytic cohort consisted of 1,323 participants who had CRP and IL-6 measured at a minimum of three time points (baseline, plus at least two other time points). All participants included in this analytic cohort were also free of cognitive impairment at baseline; consistent with previous literature, cognitive impairment was defined as a Modified Mini-Mental Status Exam (3MS) score <80.(Slinin, et al., 2010) This study was approved by the institutional review boards of the University of Pittsburgh and the University of Tennessee, Memphis, and that of the Coordinating Center, the University of California San Francisco. All participants signed a written informed consent.

2.2 Cognitive function

Cognitive function was assessed with the Modified Mini-Mental Status Exam (3MS) at baseline (Year 1), and study Years 3, 5, 8 and 10. The 3MS is an assessment of global cognitive function with components for orientation, concentration, language, praxis, and immediate and delayed memory with scores ranging from 0 to 100 (higher scores indicating higher function).(Teng & Chui, 1987) Consistent with previous studies, we examined two potential outcomes: incident cognitive decline defined as the first decline of 5 points or more from baseline, which is equivalent to 1 SD of baseline 3MS scores, and incident cognitive impairment defined as the first occurrence of a score ≤80 on the 3MS.(Lin, et al., 2013; Stweart, et al., 2013) We chose to examine both incident cognitive decline and incident cognitive impairment a priori because we believe both outcomes represent clinically important entities; cognitive decline showing a gradual worsening of cognitive function perhaps similar to a diagnosis of mild cognitive impairment, and cognitive impairment indicating a more significant loss in cognitive abilities, perhaps similar to a more severe clinical diagnosis.

2.3 Inflammatory markers

Measures of high sensitivity CRP and IL-6 were obtained from frozen serum collected five times throughout the study, at baseline (Year 1), and Years 2, 4, 6 and 8, between 7 am and 9 am, after an overnight fast. Samples were frozen at -70°C and were shipped to the Core

Laboratory at the University of Vermont.(Yaffe, et al., 2003) At baseline, serum CRP was measured by ELISA on the basis of purified protein and polyclonal anti-CRP antibodies, and assays were standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/ml.(Kalogeropoulos, et al., 2010) In Years 2, 4, and 6, serum CRP was measured using an automated chemoluminescent immunoassay system from Diagnostics Products Corporation (Los Angeles, CA) at Wake Forest University. The inter-assay coefficients of variation for this assay were 12%, 10%, and 15% for low, medium and high ranges, respectively. In Year 8, plasma CRP was measured at Wake Forest University from citrated plasma using commercially available high sensitivity assays from R&D systems (Minneapolis, MN). Due to the different measurement techniques over the years, a calibration based on pilot studies was conducted at Wake Forest University to convert the baseline values and the Year 8 values to values comparable to those measured in the other 3 years, and allow for longitudinal analyses. Baseline serum IL-6 was measured by ELISA kits from the R&D Systems (Minneapolis, MN).(Yaffe, et al., 2003) In Years 2, 4, and 6, serum IL-6 was measured at Wake Forest University using the high sensitivity Quantikine calorimetric immunoassay kit from R&D systems (Minneapolis, MN). The inter-assay coefficients of variation for this assay were 14%, 11%, and 13% for low, medium and high ranges, respectively. In Year 8, IL-6 was measured at Wake Forest University from citrated plasma using the same kit from R&D systems as in previous years (Minneapolis, MN). Similar to the method used for CRP, and due to the different measurement techniques over the years, a calibration based on pilot studies was conducted at Wake Forest University to convert the baseline values and the Year 8 values to values comparable to those measured in the other 3 years, and allow for longitudinal analyses.

2.4 Covariates

At baseline, demographic data including self-reported participant age, race, sex and education were recorded. Prevalent disease algorithms based on both self-report and physician diagnoses, recorded medications and laboratory data were used to create comorbidity variables indicating presence of diabetes mellitus, hypertension, stroke or transient ischemic attack (TIA), and myocardial infarction (MI). Body mass index (BMI) (kg/m^2) was calculated from direct height and weight measurements at baseline. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms with a score ≥16 consistent with possible depression.(Radloff, 1977) APOE genotype was determined using standard Single Nucleotide Polymorphism (SNP) genotyping techniques and dichotomized into having one or more APOE e4 alleles versus no allele.(Hixson & Vernier, 1990) Creatinine and cystatin-C were obtained from frozen serum collected at baseline after an overnight fast. Samples were frozen at -70°C and were shipped to the Core Laboratory at the University of Vermont. An inventory of prescription and over-the-counter medications was recorded at baseline by examining participants' medication bottle(s). Consistent with a previous study using anti-inflammatory medication use as a covariate, we coded medications according to the Iowa Drug Information System (IDIS) code.(Pahor, et al., 1994; Yaffe, et al., 2003) With use of the IDIS, the daily use of anti-inflammatory drugs (IDIS code 2808), statins (IDIS code 2406), and oral estrogens (with or without progestins) (IDIS code 6816) was compiled.(Pahor, et al., 1994; Yaffe, et al., 2003)

2.5 Statistical analysis

Pearson's chi-square or analysis of variance tests (ANOVAs) were used to determine the association between baseline characteristics and baseline levels of IL-6 and CRP dichotomized at the median. Because a minimum of three measurements are required to define variability, all 1,323 participants in the analytic cohort had CRP and IL-6 available at three to five time points for analysis of trajectories; 569 (43.0%) had 5 time points, 548 (41.4%) had 4 time points, and 206 (15.6%) had only 3 time points. To allow for interpretation on a relative scale, and to account for skewed distributions, CRP and IL-6 levels were log transformed (natural log). We used linear regression to model each inflammatory marker over time for each person, and determine trajectory slope and variability around the trajectory of IL-6 and CRP. The slope on the log scale can be interpreted as the annual relative change in the original non-transformed scale. The variability around the trajectory was calculated by determining the root mean square error (RMSE) in a model with a linear trajectory. These analytic techniques were based on a previous study examining trajectories of another biological marker (Dehydroepiandrosterone Sulfate) with an outcome of mortality.(Cappola, et al., 2009)

Cox proportional hazards models were performed to estimate the relative hazard of incident cognitive decline and incident cognitive impairment with predictors of baseline level of IL-6 or CRP, trajectory slope, and variability around the trajectory entered into models individually, and then in combination. Slope and variability of both IL-6 and CRP were modeled as time-varying covariates; at each measurement of either marker, slope and variability were recalculated using all measures through that date and carried forward until the next measurement of the marker. By updating the slope and variability at each measurement, the hazard ratios (HRs) were estimated with respect to current, not future, exposure status. Relative hazards of incident cognitive decline by standard deviation of baseline ln(IL-6) or ln(CRP) level, and decile of slope and variability were estimated. After examination of hazards ratios by decile histograms for dose response groupings, deciles for slope and variability were defined.(Cappola, et al., 2009) For slope, decile 10 was defined as steep slope, and deciles 1 through 9 were defined as non-steep slope; for variability, deciles 1-7 were defined as minimal variability, deciles 8-9 were moderate variability, and decile 10 was defined extreme variability. All models were then adjusted for demographic variables that were selected as covariates a priori, including age, race, education and sex, as well as variables that differed by inflammatory marker at baseline, including BMI, diabetes, APOE e4 allele, and cystatin-C. We also adjusted all models by anti-inflammatory drug use due to the possible impact on inflammation levels. Finally, all IL-6 models were adjusted for baseline ln(CRP), and all CRP models were adjusted for baseline ln(IL-6). Interactions of baseline IL-6 and CRP level, slope, and variability with sex, race and APOE e4 were assessed using likelihood ratio test. All analyses were conducted with SAS, version 9.3 (SAS Institute Inc., Cary, NC).

3.0 Results

Participants had a baseline mean age of 73.4 (±2.81) years, 697 (52.7%) were female, and 771 (58.3%) were black. At baseline, those with a higher CRP level (>median), compared to

those with a lower CRP level (≤median), were more likely to be black (69.5% vs 49.0%, p<0.001), to be female (59.4% vs. 47.1%, p<0.001), and to have diabetes (25.2% vs. 16.9%, p<0.001), and were less likely to have an APOE e4 allele (24.0% vs. 29.1%, p=0.02) (Table 1). Those with a higher CRP level also had a higher BMI (27.8±4.9 vs. 26.4±4.1, p<0.001), higher baseline ln(IL-6) (0.9±0.7 vs. 0.5±0.6, p<0.001), and higher Cystatin-C (1.0 mg/L ±0.3 vs. 1.0 mg/L±0.2), indicating poorer kidney function(Table 1). Patterns of baseline characteristics by IL-6 levels were similar to those for CRP (data not shown). The correlation coefficient of ln(IL-6) and ln(CRP) at baseline was 0.4 (p<0.001), and at Year 8 was 0.4 (p<0.001). The correlation coefficient of ln(CRP) at baseline with ln(CRP) at Year 8 was 0.3 (p<0.001); the correlation coefficient of ln(IL-6) at baseline with ln(IL-6) at Year 8 was 0.4 (p<0.001). In this cohort, 145 (11.0%) had a steep CRP slope versus 1,178 (89.0%) without a steep slope; 134 (10.2%) had extreme CRP variability, 264 (19.9%) had moderate variability, and 925 (69.9%) had minimal variability. Steep CRP slope and extreme CRP variability were signifcantly correlated, (r=0.3, p<0.001). The distributions for IL-6 slope and variability were similar to what was seen for CRP. There was no systematic increase or decrease of IL-6 or CRP over time.

In Cox proportional hazards models, there were no significant associations between baseline ln(IL-6) level, slope or variability and cognitive decline (Table 2). There were also no significant associations between baseline ln(CRP) level or slope and cognitive decline (Table 2). However, those with extreme variability of CRP compared to those with minimal variability had an increased risk of cognitive decline in 3 models: a model with variability only (HR=1.5; 95% CI: 1.1, 2.1); a model with slope and variability (HR=1.5; 95% CI: 1.1, 2.1); and a model with baseline ln(CRP), slope, and variability (HR=1.5; 95% CI: 1.1, 2.2). These associations remained significant after adjustment for age, race, sex, education, BMI, diabetes, APOE e4, cystatin-C, anti-inflammatory drug use and baseline ln(IL-6) (Table 2). There were no significant associations between any component of IL-6 or CRP with incident cognitive impairment.

There was a significant interaction of baseline ln(CRP) level, slope and variability with APOE (χ^2=372.9, 2 degrees of freedom, p<0.001), and with sex (χ^2=52.3, 2 degrees of freedom, p<0.001), but not with race. The relationship between the variability about the CRP trajectory remained significant among women, and among those with no APOE e4 allele. In a model with baseline ln(CRP), slope and variability, women with extreme variability compared to those with minimal variability had an increased risk of cognitive decline (HR=1.8; 95% CI: 1.1, 3.0), but the same was not true for men (HR=1.3; 95% CI: 0.8, 2.2). This remained true after adjustment for age, race, education, BMI, diabetes, APOE e4, cystatin-C, anti-inflammatory drug use and baseline ln(IL-6) (Table 3). Similarly, in a model with baseline ln(CRP), slope and variability, those with no APOE e4 allele and extreme CRP variability had an increased risk of cognitive decline (HR=1.6; 95% CI: 1.1, 2.5), but the same was not true for those with ≥1 APOE e4 allele (HR=1.4; 95% CI: 0.6, 3.0). This remained true after adjustment for age, race, sex, education, BMI, diabetes, Cystatin-C, anti-inflammatory drug use and baseline ln(IL-6) (Table 3).

4.0 Discussion

To our knowledge, this is the first prospective cohort study to examine the association between trajectories of inflammation including three to five time points and cognitive decline. Those with extreme variability in CRP over time, who were women or who had no APOE e4 allele, had an increased risk of incident cognitive decline over the same period of time. This association remained significant even after adjustment for age, race, education, BMI, diabetes, cystatin-C, anti-inflammatory drug use, and baseline IL-6. There was no significant association between baseline CRP level or CRP slope and incident cognitive decline, and there was no association between any CRP trajectory component and incident cognitive impairment. We also found no significant associations between any trajectory patterns of IL-6 and incident cognitive decline or incident cognitive impairment.

Our results complement previous studies reporting a significant association between elevated CRP measured from one time point, and AD or cognitive decline.(Kravitz, et al., 2009; Schmidt, et al., 2002; Yaffe, et al., 2003) Similarly, one study which had CRP measured at 2 time points found that doubling of CRP was significantly associated with greater decline in the 3MS over 9 years.(Jenny, et al., 2012) However, it has recently been found that there may be high intra-individual variability in CRP levels over time, so our interpretation of the results from these previous studies is limited.(deGoma, et al., 2012; Koenig, et al., 2003) Thus, our study contributes to the literature by not only looking at elevated levels of CRP at baseline, but by examining individuals' slope and variability of CRP trajectories over time. Our finding that variability of CRP over time was significantly associated with cognitive decline points to the need to have inflammation and cognitive function measured at multiple time points when assessing such an association, and supports previous literature finding similar results with cardiovascular outcomes.(deGoma, et al., 2012; Koenig, et al., 2003)

We believe CRP variability may be associated with increased cognitive decline over time due to greater overall morbidity, especially in terms of vascular and metabolic disease. Vascular disease, risk factors such as diabetes, and metabolic syndrome components have all been associated with increased risk for cognitive decline.(Kivipelto, et al., 2001; Shah, et al., 2012; Yaffe, et al., 2004; Yaffe, Weston, Blackwell, & Krueger, 2009) Similarly, elevated levels of CRP have been associated with a variety of vascular and metabolic disease states, including obesity, cardiovascular disease, atherosclerosis and diabetes.(deGoma, et al., 2012; Ferri, et al., 2007; Wang, et al., 2013) Other evidence supporting such an underlying pathway is evidence that CRP is more stable, and lacks intra-individual variability in the absence of disease.(Kluft & de Maat, 2001) Thus, what we may be measuring with variability in CRP is greater morbidity over time, and perhaps conditions that are more poorly controlled by medication and behavioral interventions. However, in post-hoc analyses when we investigated factors related to extreme CRP variability, the only medical condition associated with extreme CRP variability was a history of diabetes (24.6% among those with extreme variability vs. 17.7% with minimal variability, p=0.05). There were no significant associations with CRP variability and hypertension, or history of MI or stroke. Future studies should examine whether variability is related to subclinical measures of vascular disease rather than end-stage clinical outcomes.

One interesting finding is that we found an association between extreme CRP variability and cognitive decline, but no association between moderate CRP variability and cognitive decline. This could be due to a threshold effect, where only the most extreme levels of variability are associated with subsequent decline. We also found the association between CRP variability and increased risk for cognitive decline was restricted to women and those with no APOE e4 allele. Being female and having no APOE e4 allele are typically associated with better health in older adults. Thus, a potential explanation for these results could be the etiology of the cognitive decline. It is widely known that those with at least one APOE e4 allele are at an increased risk for AD(Ingelsson, et al., 2003), so perhaps we are measuring cognitive decline related to vascular changes rather than changes in cognitive function consistent with AD pathology. Furthermore, while men are known to have a greater burden of vascular disease earlier on in life, this gap decreases with age, and once over the age of 80 years, women actually have a greater burden of cardiovascular disease.(Roger, et al., 2012) Perhaps, given the age of these participants (approximately 73 years at baseline and 83 years when cognitive function was last assessed), the finding may reflect greater vascular disease burden among women.(Roger, et al., 2012)

This study had several strengths, including the measurement of inflammatory markers at 3 to 5 time points. Furthermore, we had a relatively large sample size providing ample analytical power for this study. Measurement of numerous comorbidities and demographic data also allowed us to investigate a large number potential covariates and confounders. There are also several weakness that should be taken into consideration when interpreting these results. These adults were all well-functioning and community-dwelling at baseline, and represented persons who survived a minimum of three years post-baseline, and on average much longer, so results may not be generalizable to all older adults – for example, nursing home populations. We were also limited to examining only CRP and IL-6, but other inflammatory markers have previously been related to cognitive function, and may provide more information. We adjusted for anti-inflammatory drugs that were taken on a daily basis, but had no information on intermittent use. Finally, different laboratory techniques were used to measure samples in three different ways over the course of the study, and could have contributed to variability. While we hope calibration of these different measurement techniques accounted for these differences, future studies using the same techniques at all time points will be useful. Finally, inflammatory markers and cognitive function were measured in largely the same time period, with only one cognitive assessment occurring after the inflammatory markers were measured. Thus, we cannot state that trajectories of inflammatory markers are predictive of cognitive decline, but rather associated with decline in cognitive function over the same time period. Future studies should investigate how trajectories of inflammatory markers predict subsequent cognitive function.

We found that high CRP variability was significantly associated with increased cognitive decline over 10 years among women and among those with no APOE e4 allele, and that variability measured from 3 to 5 time points was a stronger predictor than individual levels of CRP or the slope of CRP over time. We believe CRP variability may reflect a greater burden of vascular and metabolic disease, and perhaps signify conditions that are more poorly controlled. Future studies should investigate if CRP variability is related to AD- and vascular dementia-specific pathologies, such as amyloid deposition in the brain and white

matter hyperintensities to allow a better understanding of how CRP variability may be influencing cognitive function.

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Highlights

- We used a prospective to examine the association between trajectories of inflammatory markers, CRP and IL-6, and cognitive decline.
- Extreme variability in CRP over time was associated with an increased risk of incident cognitive decline.
- This association was stronger among women, and among those who had no APOE e4 allele. There was no significant association between baseline CRP level or CRP slope and incident cognitive decline.
- There were no significant associations between any trajectory patterns of IL-6 and incident cognitive decline.

Table 1

Association between baseline characteristics and baseline CRP level.

Baseline Characteristic Mean (SD) or N (%)	≤ Median[a] CRP (N=724)	>Median[a] CRP (N=599)	p-value
Age	73.5 (2.8)	73.3 (2.9)	0.23
Black Race	355 (49.0%)	416 (69.5%)	<0.0001
Education (≤High School)	321 (44.3%)	300 (50.1%)	0.11
Female Sex	341 (47.1%)	356 (59.4%)	<0.0001
Body Mass Index (kg/m^2)	26.4 (4.1)	27.8 (4.9)	<0.0001
Diabetes	122 (16.9%)	151 (25.2%)	0.0002
Hypertension	511 (70.6%)	436 (72.8%)	0.38
Stroke/TIA	58 (8.0%)	44 (7.4%)	0.65
Myocardial Infarction	70 (9.7%)	53 (8.9%)	0.61
Baseline 3MS Score	93.9 (3.9)	93.7 (3.7)	0.44
APOE e4 Allele	211 (29.1%)	144 (24.0%)	0.02
Serum Creatinine (mg/dL)	1.0 (0.2)	1.0 (0.2)	0.21
Cystatin-C (mg/L)	1.0 (0.2)	1.0 (0.3)	0.01
Anti-Inflammatory Drug Use	409 (56.5%)	322 (53.8%)	0.34
CES-D Score	4.5 (5.3)	4.4 (4.7)	0.71
Baseline IL-6	0.5 (0.6)	0.9 (0.7)	<0.001

[a] Median ln(CRP) level = 1.0 μg/mL

Table 2

Adjusted associations between IL-6 and CRP with cognitive decline over 10 years.

IL-6 Adjusted[a] Model	Measure	HR (95% CI)
Baseline only	Baseline	1.1 (0.9, 1.2)
Slope only	Slope	1.0 (0.7, 1.4)
Variability only	Minimal Variability	Reference
	Moderate Variability	1.1 (0.9, 1.5)
	Extreme Variability	0.9 (0.6, 1.3)
Slope + Variability	Slope	1.0 (0.7, 1.5)
	Minimal Variability	Reference
	Moderate Variability	1.1 (0.9, 1.5)
	Extreme Variability	0.9 (0.6, 1.3)
Baseline + Slope + Variability	Baseline	1.1 (0.9, 1.3)
	Slope	0.9 (0.6, 1.4)
	Minimal Variability	Reference
	Moderate Variability	1.1 (0.8, 1.4)
	Extreme Variability	0.8 (0.6, 1.3)
CRP Adjusted[a] Model	**Measure**	**HR (95% CI)**
Baseline only	Baseline	1.0 (0.9, 1.1)
Slope only	Slope	1.2 (0.9, 1.7)
Variability only	Minimal Variability	Reference
	Moderate Variability	1.0 (0.8, 1.3)
	Extreme Variability	1.5 (1.1, 2.1)
Slope + Variability	Slope	1.0 (0.6, 1.4)
	Minimal Variability	Reference
	Moderate Variability	1.0 (0.8, 1.4)
	Extreme Variability	1.5 (1.4, 2.2)
Baseline + Slope + Variability	Baseline	1.0 (0.9, 1.1)
	Slope	0.9 (0.6, 1.3)
	Minimal Variability	Reference
	Moderate Variability	1.0 (0.8, 1.4)
	Extreme Variability	1.6 (1.1, 2.3)

[a] Adjusted for age, race, sex, education, BMI, diabetes, APOE e4, Cystatin-C, anti-inflammatory drug use and baseline ln(CRP).

Table 3

Association between CRP and cognitive decline over 10 years by sex and by APOE e4.

		HR (95% CI)	
Adjusted[a] Model	**Measure**	**Male HR**	**Female HR**
Baseline only	Baseline	1.0 (0.9, 1.3)	0.9 (0.8, 1.1)
Slope only	Slope	1.4 (0.9, 2.2)	1.1 (0.7, 1.7)
Variability only	Minimal Variability	Reference	Reference
	Moderate Variability	1.0 (0.7, 1.4)	1.1 (0.7, 1.6)
	Extreme Variability	1.5 (0.9, 2.3)	1.5 (0.9, 2.3)
Slope + Variability	Slope	1.4 (0.8, 2.4)	0.7 (0.4, 1.2)
	Minimal Variability	Reference	Reference
	Moderate Variability	0.9 (0.6, 1.4)	1.2 (0.8, 1.7)
	Extreme Variability	1.3 (0.7, 2.2)	1.8 (1.1, 3.0)
Baseline + Slope + Variability	Baseline	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)
	Slope	1.4 (0.8, 2.5)	0.5 (0.3, 1.0)
	Minimal Variability	Reference	Reference
	Moderate Variability	0.9 (0.6, 1.4)	1.2 (0.8, 1.7)
	Extreme Variability	1.3 (0.7, 2.2)	2.0 (1.2, 3.3)
Adjusted[b] Model	**Measure**	**≥1 APOE e4 allele**	**No APOE e4 allele**
Baseline only	Baseline	0.9 (0.7, 1.1)	1.0 (0.9, 1.2)
Slope only	Slope	1.4 (0.7, 2.6)	1.2 (0.8, 1.7)
Variability only	Minimal Variability	Reference	Reference
	Moderate Variability	1.1 (0.7, 1.8)	1.0 (0.7, 1.4)
	Extreme Variability	1.3 (0.7, 2.8)	1.6 (1.1, 2.3)
Slope + Variability	Slope	1.2 (0.5, 2.6)	0.9 (0.6, 1.4)
	Minimal Variability	Reference	Reference
	Moderate Variability	1.1 (0.6, 1.8)	1.0 (0.7, 1.4)
	Extreme Variability	1.2 (0.5, 2.7)	1.7 (1.1, 2.5)
Baseline + Slope + Variability	Baseline	0.9 (0.7, 1.1)	1.0 (0.9, 1.2)
	Slope	1.0 (0.5, 2.4)	0.8 (0.5, 1.3)
	Minimal Variability	Reference	Reference
	Moderate Variability	1.1 (0.6, 1.8)	1.0 (0.7, 1.4)
	Extreme Variability	1.4 (0.6, 3.1)	1.7 (1.1, 2.6)

[a] Adjusted for age, race, education, BMI, diabetes, APOE e4, Cystatin-C, anti-inflammatory drug use and baseline ln(IL-6).

[b] Adjusted for age, race, sex, education, BMI, diabetes, Cystatin-C, anti-inflammatory drug use and baseline ln(IL-6).