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Elevated c-reactive protein levels are associated with prevalent dementia in the oldest-old

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Abstract

Background—C-reactive protein (CRP) is a nonspecific marker of inflammation that is increased in the brain and serum of patients with Alzheimer's disease (AD) and has been associated with increased risk of developing dementia. Inflammation increases with age and the number of people reaching the age of 90 and older is growing, making the association between inflammation and dementia increasingly relevant. Using a cross-sectional design, we examined if high levels of serum CRP are associated with increased odds of prevalent dementia in the oldest-old.

Methods—Serum CRP levels of 305 participants (mean age 94.3 ± 2.9 years) from ***The 90+ Study***, a longitudinal cohort study of people 90 and older, were evaluated with respect to all-cause dementia (DSM-IV criteria). CRP levels were divided into three categories: undetectable (< 0.5 mg/dL), detectable (0.5 – 0.7 mg/dL) and elevated (≥0.8 mg/dL). Odds ratios (OR) were calculated using logistic regression and adjusted for covariates.

Results—Relative to participants with undetectable CRP levels, participants with detectable or elevated CRP levels had increased odds of all-cause dementia (detectable: OR 3.0, 95% CI 1.2 – 7.3; elevated: OR 5.0, 95% CI 1.9 – 12.9). When participants were subdivided by gender, significantly increased odds ratios were seen only in women.

Conclusions—In the oldest-old, high CRP levels are associated with increased odds of all-cause dementia, particularly in women. Prospective studies are necessary to confirm if increased CRP levels are associated with increased risk of developing dementia in this age group.

Keywords

C-reactive protein; dementia; nonagenarian; serum; inflammation

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1. Introduction

Inflammation has been implicated in the development of Alzheimer's disease (AD)[1] and c-reactive protein (CRP) is a nonspecific marker of inflammation [2]. Levels of CRP are elevated in the brain of AD patients [3,4] and the serum of patients with AD or vascular dementia (VD) [5,6] or all-cause dementia [7]. Studies of incident dementia have suggested that high levels of CRP may be a risk factor for the development of all-cause dementia, AD, and VD [8,9, 10].

Aging is associated with increases in inflammation, and levels of CRP are increased in elderly participants [11]. The oldest-old are the fastest growing segment of the United States population [12] and are at high risk for developing dementia, yet the association between inflammation and dementia has rarely been examined in this age group. In centenarians, elevated blood levels of another inflammatory marker, tumor necrosis factor alpha (TNFα), and a polymorphism in the TNFα gene were both associated with dementia [13,14], suggesting that increased levels of inflammatory markers may be associated with prevalent dementia in the oldest-old. The purpose of this study was to test the hypothesis that high levels of CRP would be associated with increased odds of having all-cause dementia in subjects aged 90 years and older.

2. Methods

2.1. Participants

Participants were from ***The 90+ Study***, a population-based, longitudinal cohort study of people aged 90 years and older [15]. Community-dwelling and institutionalized participants from ***The 90+ Study*** who are examined in-person receive a neurological exam, a neuropsychological battery, blood draw, and a medical history questionnaire, among other procedures. As part of the neurological exam, a neurologist or nurse practitioner assigns a cognitive diagnosis. Participants were assigned a cognitive diagnosis of Dementia if they met Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for dementia [16]. Participants with no cognitive or functional loss were assigned a diagnosis of Normal and participants with some cognitive or functional loss who did not meet criteria for dementia were assigned a diagnosis of Cognitive Impairment Not Demented (CIND). In participants with a diagnosis of Dementia, the suspected dementia etiology was also assigned (AD, VD, AD + VD, etc.). Scores on the Mini-Mental State Exam (MMSE)[17], a measure of global cognitive function, and the Clinical Dementia Rating (CDR) scale [18], a staging tool for dementia severity, were also obtained. All participants provided informed consent and this research was approved by the Institutional Review Board of the University of California, Irvine.

The inclusion criteria for this study were: 1) cognitive diagnosis from an in-person exam; and 2) serum CRP measurement from that exam. Of the 550 who had received a cognitive diagnosis from an in-person examination, 305 had a serum CRP measurement (measurement of serum CRP requires a blood sample and some participants chose not to provide a blood sample). The 245 participants who did not provide blood samples were significantly older (95.4 years versus 94.3 years; $p < 0.01$) and had significantly lower MMSE scores (21.2 points versus 23.9 points; $p < 0.01$) than participants who did provide blood samples.

2.2. CRP measurement

Non-fasting serum CRP was measured using an immunoturbidimetric assay (Beckman Synchron LX System, Kit number 465131). Reference material was traceable to BCR CRM 470 and the coefficient of variation was < 5% for the range of CRP values reported in this study. This was not a high-sensitivity assay: the lower detection limit of the assay was 0.5 mg/

dL (5 mg/L) and CRP values of 0.8 mg/dL (8 mg/L) or higher were considered elevated using this assay. The CRP cutoffs used in this study were dictated by the assay.

2.3. Covariates

To determine the covariates to be used in the main analysis, the following variables were analyzed for an association with CRP: age, gender, residential status (living at home alone or with another person, assisted living or board and care facility, or nursing home), education (less than high school, high school to some college, or college graduate to post-graduate education), presence of one or more apolipoprotein e4 (APOE4) alleles, smoking or alcohol use (current versus no or past use), current level of physical activity (participants who reported performing vigorous physical activity a few times per week or daily versus those reporting less or no physical activity), current use of estrogen, statins, aspirin or non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) (prescription and over-the-counter use; any use versus no use), medical history of hypertension, coronary artery disease (CAD), myocardial infarction, atrial fibrillation or arrythmias, heart valve disease, congestive heart failure (CHF), stroke, transient ischemic attack (TIA), high cholesterol, diabetes, cancer (other than skin), rheumatoid arthritis, or osteoarthritis (any history versus no history). Smoking, alcohol use, physical activity, and medical history were reported by participants or their informants as part of the in-person interview.

2.4. Data analysis

The association between CRP and potential covariates was analyzed using nonparametric tests, specifically Mann-Whitney (MW) or Kruskal-Wallis (KW) for comparisons of CRP levels between groups and Spearman's rho (ρ) for correlations between levels of CRP and continuous variables. CRP was then converted into a categorical variable with three groups for the remainder of the analyses: 1) undetectable levels (< 0.5 mg/dL); 2) detectable levels below the value considered elevated in this assay (0.5 – 0.7 mg/dL); and 3) elevated levels (≥ 0.8 mg/dL). Comparisons between the 3 CRP groups were done using an analysis of variance (ANOVA) with a Bonferroni post-hoc test for comparisons of means and a Chi-square for comparisons of frequency. Logistic regression was used to compute odds ratios (OR) for the outcome of all-cause dementia. Subjects with a cognitive diagnosis of Normal or CIND were grouped together as non-demented and used as the reference group. To further categorize the non-demented group, multinomial logistic regression was used to compute odds ratios for the separate outcomes of CIND and all-cause dementia, as compared with normal cognition. Results were considered significant at $p < 0.05$.

3. Results

CRP values were not normally distributed. Of the 305 CRP values, 92 were below the detection limit of the assay. Detectable CRP values in all subjects ranged from 0.5 to 5.6 mg/dL with a median of 0.6 mg/dL (men: median CRP 0.6 mg/dL, range 0.5 – 1.9 mg/dL; women: median CRP 0.6 mg/dL, range 0.5 – 5.6 mg/dL). Participants ranged in age from 90 to 105 years (94.3 ± 2.9 years), 205 (67%) were women, and 73 (24%) were diagnosed with dementia.

3.1. CRP by covariates

CRP levels were positively correlated with age when undetectable levels were imputed as zeroes ($\rho = 0.14$, $p = 0.02$) or when undetectable levels were excluded ($\rho = 0.15$, $p = 0.03$). CRP levels did not differ by gender (MW, $p = 0.51$) and 30% of men and 31% of women had elevated CRP levels. CRP levels were higher in those reporting a history of TIA (MW, $p = 0.008$) or a history of CHF (MW, $p = 0.04$). There was a trend towards increased CRP in women reporting current estrogen use (MW, $p = 0.08$). CRP levels did not differ by aspirin use (current use versus not currently using; MW, $p = 0.199$) or by NSAID use (current use versus not

currently using; MW, p = 0.440). CRP did not differ with the presence of one or more APOE4 alleles in all participants (MW, p = 0.12) or demented participants (MW, p = 0.49), although there was a trend towards decreased CRP in nondemented APOE4 carriers (MW, p = 0.06). CRP levels did not differ by any other covariate examined (p > 0.10).

Covariates were also compared by CRP group (Table 1). There was no difference between CRP groups in age, gender, APOE4, residential status, education, smoking, alcohol use, physical activity, estrogen use, statin use, or NSAID use. History of CAD was lowest in the elevated CRP group (Chi-square, p = 0.01), while history of TIA and aspirin use was highest in the elevated CRP group (Chi-square, p = 0.05 and p = 0.06, respectively).

In addition to age, gender, education, and APOE4 status, any covariate that was associated with CRP levels (p < 0.10) or differed among the CRP groups in frequency (p < 0.10) was included in the logistic regression, therefore, history of TIA, CHF, CAD, current estrogen use (in women) and current aspirin use were included in the fully adjusted model.

3.2. Cognitive variables by CRP group

Table 2 shows a comparison of cognitive variables by CRP group. The mean MMSE score differed between the groups (ANOVA, p = 0.01), with a higher mean MMSE score in the undetectable CRP group compared to the elevated CRP group (Bonferroni, p = 0.01). A greater percentage of subjects with elevated CRP had MMSE score < 13 or CDR score = 3.0 when compared to those with undetectable or detectable CRP levels, meaning that a higher proportion of subjects with elevated CRP were severely impaired. While subjects with elevated CRP were also more likely to have a cognitive diagnosis of dementia, the etiology of the dementia did not differ between the CRP groups.

3.3. Odds ratios for dementia

Table 3 shows the age-adjusted and fully-adjusted odds ratios for all-cause dementia. After adjustment for age, gender, education, APOE4 status, history of TIA, CHF, CAD, and aspirin use, participants with detectable or elevated CRP levels had significantly higher odds of having all-cause dementia than participants with undetectable CRP levels (detectable: OR 3.0, 95% CI 1.2 – 7.3; elevated: OR 5.0, 95% CI 1.9 – 12.9). When analyses were done separately for men and women, detectable and elevated CRP levels were associated with significantly higher odds ratios of dementia in women only. In a multinomial logistic regression, the fully-adjusted odds ratio for CIND was 1.0 (95% CI 0.5 – 1.8) for detectable CRP levels and 0.8 (95% CI 0.4 – 1.6) for elevated CRP levels compared to undetectable CRP levels. The fully-adjusted odds ratio for all-cause dementia in the multinomial logistic regression was 2.9 (95% CI 1.1 – 7.5) for detectable CRP levels and 4.5 (95% CI 1.7 – 12.3) for elevated CRP levels compared to undetectable CRP levels.

Fifty-two of the 73 participants with dementia had a suspected etiology of AD, and the fully adjusted odds ratios for the outcome of AD were similar to those for all-cause dementia (detectable: OR 2.8, 95% CI 1.01 – 7.7; elevated: OR 4.4, 95% CI 1.5 – 13.0). Odds ratios could not be calculated for the outcome of VD only because there were no cases of VD in the undetectable CRP group (reference group).

Eleven participants (3.6%) were not included in the logistic regression analysis because they were missing covariates from the adjusted model. Excluded participants were evenly distributed across CRP groups. These participants were, however, included in the covariate analyses to provide a more complete investigation of the relationship between CRP and covariates.

4. Discussion

In this cross-sectional study of the oldest-old, CRP was positively correlated with age, demonstrating that CRP continues to increase with age even in the very elderly. In addition, detectable or elevated levels of CRP were associated with increased odds ratios of prevalent all-cause dementia. When men and women were analyzed separately, this association was significant only in women.

In general, CRP levels are higher in women than in men [11], but previous studies of CRP and incident dementia either control for gender [9,10] or include a single gender [8]. The impact of risk factors for dementia can differ for men and women [19], and high CRP levels could be a more potent risk factor in women. However, there were fewer cases of dementia in the men, resulting in estimates with wide confidence intervals that overlapped with those of the women, and this result may reflect a lack of power in the men only analysis rather than a true difference between the genders. It is also possible that the difference between men and women is the result of using prevalent dementia cases. Prevalent cases reflect both disease incidence and duration, and perhaps CRP is associated with longer disease duration in women, rather than increased incidence in women.

Previous studies have suggested that the association between CRP and dementia may be stronger for VD than for AD [8,9,10]. The majority of the dementia cases in this study had an etiology of AD, and an analysis for AD only yielded similar odds ratios to all-cause dementia. While there were an insufficient number of VD cases to investigate the hypothesis that elevated CRP levels are associated with higher odds of VD, it is notable that there were no cases of VD or mixed dementia (AD + VD) in those participants with undetectable CRP levels. It can be difficult to diagnosis dementia type in this age group and it is possible that some subjects with a diagnosis of AD had a vascular contribution, and vice versa, making all-cause dementia a more reliable outcome than dementia type.

CRP may be both a marker and a risk factor for disease. CRP is found in association with plaque and tangle pathology in AD brain [3,4] and concentrations of CRP similar to those detected in the serum of AD patients are neurotoxic *in vitro* [20]. CRP may also contribute to atherosclerotic processes [21] and can increase the expression of adhesion molecules such as vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1) in vascular endothelial cells [21,22], including endothelial cells in human brain [23]. Although inflammation is typically thought of as a risk factor for AD [1], the relationship between CRP and atherosclerotic processes which can underlie VD [24] may account for the relationship between this inflammatory marker and VD.

There are limitations to this study. The CRP assay used here had low sensitivity and did not permit differentiation of CRP levels below the 0.5 mg/dL detection limit. Use of a high sensitivity assay would not have changed the results because elevated CRP levels would be detected by both assays, however, a high-sensitivity assay would have allowed for additional analysis using lower cut-off points such as the 3.0 mg/L cut-point used for cardiovascular disease risk studies [25]. Participants who did not provide blood samples tended to be older and more cognitively impaired than the participants who were included in this study. However, because CRP increased with increasing age and decreasing MMSE score, exclusion of participants who could not provide blood samples would bias the results towards the null hypothesis. Other covariates, such as high body mass index (BMI), urinary tract infections, periodontal disease and chronic obstructive pulmonary disease (COPD) that may be related to high CRP levels could not be analyzed because this data was either not collected as part of the study or was missing for a high number of subjects. Additionally, because members of ***The 90***

+ ***Study*** are generally white and highly educated, these results may not be applicable to all nonagenarians.

The strengths to this study include the large sample size. The majority of CRP studies have very few participants over the age of 90, an age when both CRP and risk of developing dementia are high. Also, the ability to analyze CRP by numerous covariates allowed us to include many relevant covariates in the adjusted model.

Because this is a cross-sectional study, it is not possible to determine if elevated CRP levels occur prior to the development of dementia or are a consequence of the disease. The next step would be to determine if high levels of CRP are associated with incident dementia in the oldest-old. If CRP levels are found to be associated with incident dementia in the oldest-old, this would be the first step in evaluating whether treatment of elevated CRP may be used to reduce the risk of dementia in this age group.

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Abbreviations

CRP
: C-reactive protein

AD
: Alzheimer’s disease

VD
: vascular dementia

OR
: odds ratio

CI
: confidence interval

TNFα
: tumor necrosis factor alpha

DSM-IV
: Diagnostic and Statistical Manual of Mental Disorders IV

CIND
: Cognitive Impairment Not Demented

CDR
: Clinical Dementia Rating scale

APOE4
: apolipoprotein e4

NSAIDs
: non-steroidal anti-inflammatory drugs

CAD

coronary artery disease

CHF
congestive heart failure

TIA
transient ischemic attack

COX
cyclooxygenase

MW
Mann-Whitney

KW
Kruskal-Wallis

ANOVA
analysis of variance

BMI
body mass index

COPD
chronic obstructive pulmonary disease

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Table 1

Comparison of covariates by CRP group

Variable	CRP Groups			p-value
	Undetectable < 0.5 mg/dL	Detectable 0.5 – 0.7 mg/dL	Elevated ≥0.8 mg/dL	
N	92	119	94	
Demographics				
Age (years ± SD)	94.0 ± 2.7	94.2 ± 2.9	94.7 ± 3.1	0.19
Male/Female (% Male)	33/59 (36)	37/82 (31)	30/64 (32)	0.75
N (%) with APOE4	22 (24)	30 (25)	14 (15)	0.17
Residential Status, N (%)				
At home (alone or with someone)	76 (83)	93 (78)	69 (73)	0.43
Assisted Living or Board & Care	15 (16)	22 (19)	20 (22)	
Nursing Home	1 (1)	4 (3)	5 (5)	
Education Level, N (%)				
Less than HS	5 (5)	12 (10)	7 (7)	0.17
HS grad to some college	42 (46)	61 (51)	55 (60)	
College grad to post-grad	45 (49)	46 (39)	30 (33)	
Current smoking and alcohol use, N (%)				
Smoke	2 (2)	1 (1)	1 (1)	0.67
Alcohol	57 (66)	70 (63)	51 (60)	0.70
Current physical activity, N (%)				
Vigorous exercise (few times/week or more)	40 (53)	34 (40)	23 (41)	0.19
Current medication use in all subjects, N (%)				
Statins	14 (15)	18 (15)	12 (13)	0.63
Aspirin	33 (36)	40 (34)	46 (49)	0.06
Non-aspirin NSAIDs	21 (23)	18 (15)	17 (18)	0.28
Estrogen (in women)	2 (2)	8 (7)	8 (9)	0.17
Medical history, N (%)				
Hypertension	40 (44)	64 (54)	46 (52)	0.32
Coronary Artery Disease	14 (15)	26 (22)	7 (7)	0.01*
Myocardial Infaction	11 (13)	13 (11)	12 (13)	0.90
Atrial fibrillation/arrythmias	18 (20)	36 (32)	27 (30)	0.17
Heart Valve Disease	6 (7)	10 (9)	6 (7)	0.84
Congestive Heart Failure	5 (6)	14 (12)	13 (14)	0.16
Stroke	8 (9)	10 (8)	8 (9)	0.99
Transient Ischemic Attack	10 (11)	21 (18)	23 (25)	0.05
High Cholesterol	19 (22)	36 (31)	20 (23)	0.27
Diabetes	4 (4)	6 (5)	4 (4)	0.97
Cancer (other than skin)	27 (31)	23 (20)	32 (35)	0.32
Rheumatoid Arthritis	10 (12)	10 (9)	9 (10)	0.76
Osteoarthritis	35 (42)	49 (43)	37 (42)	0.97

* $p < 0.05$

CRP = C-reactive protein; SD = standard deviation; APOE = apolipoprotein E; HS = High School; VS = Vocational School; NSAID = nonsteroidal anti-inflammatory drug

Table 2

CRP group and cognitive outcomes

Variable	CRP Groups			p-value
	Undetectable < 0.5 mg/dL	Detectable 0.5 – 0.7 mg/dL	Elevated ≥0.8 mg/dL	
MMSE score (mean ± SD)	25.1 ± 4.9	24.0 ± 5.2	22.5 ± 7.5	0.01*
Distribution of MMSE scores, N (%)				
Score 28 – 30	35 (38)	28 (23)	28 (30)	0.09
Score 25 – 27	27 (30)	43 (36)	23 (24)	
Score 14 – 24	25 (27)	41 (35)	30 (32)	
Score < 13	4 (4)	7 (6)	11 (12)	
Missing data†	1 (1)	0 (0)	2 (2)	
Distribution of CDR scores, N (%)				
Score = 0	50 (54)	56 (47)	39 (42)	0.02*
Score = 0.5	34 (38)	40 (34)	30 (33)	
Score = 1	2 (2)	13 (11)	6 (6)	
Score = 2	4 (4)	6 (5)	9 (10)	
Score = 3	1 (1)	3 (2)	8 (9)	
Missing data†	1 (1)	1 (1)	2 (2)	
Frequency of cognitive diagnosis, N (%)				
Nondemented	44 (48)	50 (42)	36 (38)	0.004*
CIND	38 (41)	39 (33)	25 (27)	
Demented	10 (11)	30 (25)	33 (35)	
Dementia etiology, N (%)				
AD	9 (90)	21 (70)	22 (67)	0.41
VD or AD + VD	0 (0)	8 (27)	9 (27)	
Other	1 (10)	1 (3)	2 (6)	

*$p < 0.05$

†not included in Chi-square analysis

CRP = C-reactive protein; SD = standard deviation; MMSE = Mini-Mental Status Exam; CDR = Clinical Dementia Rating; CIND = Cognitive Impairment Not Demented; AD = Alzheimer's Disease; VD = Vascular Dementia

Table 3

Odds ratios* for all-cause dementia by CRP group

	All Subjects		Men		Women	
Total N	294		96		198	
N with all-cause dementia	66		10		56	
Age-Adjusted Model	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Undetectable (< 0.5 mg/dL)	1.00	--	1.00	--	1.00	--
Detectable (0.5 – 0.7 mg/dL)	3.4 (1.4 – 7.9)	0.005	2.1 (0.36 – 12.4)	0.41	4.1 (1.5 – 11.3)	0.006
Elevated (≥ 0.8 mg/dL)	4.5 (1.9 – 10.6)	0.001	2.7 (0.45 – 16.1)	0.28	5.5 (2.0 – 15.1)	0.001
Fully-Adjusted Model†	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Undetectable (< 0.5 mg/dL)	1.00	--	1.00	--	1.00	--
Detectable (0.5 – 0.7 mg/dL)	3.0 (1.2 – 7.3)	0.02	1.9 (0.27 – 13.2)	0.52	4.6 (1.4 – 14.9)	0.01
Elevated (≥ 0.8 mg/dL)	5.0 (1.9 – 12.9)	0.001	3.3 (0.46 – 24.3)	0.23	8.1 (2.4 – 27.3)	0.001

*Odds ratios (OR), 95% confidence intervals (CI), and p-values were computed using logistic regression. Covariates included in the adjusted model were age, gender, education, APOE4 status, aspirin use, history of transient ischemic attack (TIA), congestive heart failure, or coronary artery disease. Odds ratios for women were also adjusted for current estrogen use.

†In all subjects, age and gender were significant covariates in the adjusted model. In men, the only significant covariate was age, whereas in women, age, APOE4 status, or a history of TIA were associated with significantly increased odds of all-cause dementia.