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Elevated C-Reactive Protein Is Related to Cognitive Decline in Older Adults with Cardiovascular Disease

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Abstract

Objectives—To prospectively relate C-reactive protein (CRP), a systemic marker of inflammation, to cognitive change over a 1-year follow-up period.

Design—Prospective 1-year follow-up.

Setting—Outpatient university medical setting.

Participants—Seventy-eight adults (aged 56–84; 39% female) with cardiovascular disease.

Measurements—CRP levels were measured using a high-sensitivity assay, and participants completed a neuropsychological battery at study entry. Neuropsychological assessment was repeated 1 year later.

Results—The association between CRP and change in cognition over the 1-year follow-up was examined using hierarchical linear regression modeling for five cognitive domains (global cognition, language, memory, visuospatial abilities, and attention-executive-psychomotor). High CRP levels were associated with subtle declines in attention-executive-psychomotor performance (CRP β =

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−0.22, $P = .04$) after adjusting for the effects of age and cognitive performance at study entry. CRP was not significantly associated with change in language, memory, or visuospatial performance.

Conclusion—These data provide preliminary evidence that inflammation, potentially contributing to atherosclerotic processes, may underlie the association between high CRP and changes in attention-executive-psychomotor performance.

Keywords

C-reactive protein; cognition; inflammation; cardiovascular disease

Inflammation is associated with the initiation and progression of small-vessel disease and atherosclerosis.[1] One of the most extensively studied systemic markers of inflammation is serum C-reactive protein (CRP), a protein that hepatocytes produce under the influence of cytokines such as interleukin-6 and tumor necrosis factor-alpha.[2] High serum CRP concentration is associated with atherosclerosis, and CRP is a predictor of future cardiovascular[3] and cerebrovascular[4] disease. These observations have generated significant interest in characterizing the deleterious systemic effects of CRP and in examining CRP as a potentially modifiable cardiovascular risk factor for use in clinical practice.[5–7]

Adding to the potential importance of CRP as a marker of cardiovascular and cerebrovascular disease is evidence that high CRP is associated with cognitive impairment in people with dementia and those who are cognitively normal. Although the results from previous studies have been mixed,[8] several population-based studies have reported associations between CRP and cognitive decline.[9] High serum levels of CRP preceded the onset of Alzheimer's disease and vascular dementia by several decades in the Honolulu-Asia Aging Study.[10] More recently, a population-based study demonstrated that high CRP was associated with risk for vascular dementia.[11]

Inflammation may be one mechanism that accelerates the progression from subtle vascular cognitive impairment to dementia. Understanding the link between inflammatory processes and cognition in patients with cardiovascular disease (CVD) may contribute to early intervention and prevention. These patients often have cognitive impairments that do not meet criteria for dementia, yet they are at risk for functional impairment and early mortality.[12] Nevertheless, few studies have examined the association between CRP levels and cognition in elderly individuals without dementia with CVD. It has been reported that high CRP levels are associated with low cognitive performance in a cross-sectional analysis of outpatients with stable CVD.[13] These data suggest that CRP may be an important risk factor for cognitive decline in the absence of an acute vascular event.

The aim of the current study was to examine CRP in relation to cognitive changes over a 1-year follow-up period in a cohort of outpatients with stable CVD. Participants completed a comprehensive neuropsychological battery at study entry and 1 year later. Given previous evidence that cognitive skills mediated by frontal-subcortical pathways (i.e., attention, executive function, and psychomotor speed) are particularly susceptible to impairment in the presence of atherosclerosis and coronary artery disease,[14] it was hypothesized that high levels of CRP would be associated with declines in the attention-executive-psychomotor cognitive domain but not in language, memory, or visual-spatial skills.

Methods

Institutional review board approval was received, and all participants provided written informed consent before enrollment.

Study Sample

All participants were enrolled in a prospective study investigating cognitive functioning in older adults with CVD. To be enrolled in the study, individuals had to be aged 55 to 85 and have a documented history of CVD including at least one of the following: myocardial infarction, cardiac surgery, heart failure, coronary artery disease, and hypertension. Participants were recruited from cardiac rehabilitation programs and cardiology practices and through advertisements. Exclusion criteria were current signs of dementia as defined by a score lower than 24 on the Mini-Mental State Examination (MMSE); history of a major neurological disorder such as dementia, Parkinson's disease, seizures, large-vessel stroke, or clinically significant traumatic brain injury; and history of major psychiatric disorder requiring hospitalization, such as schizophrenia, bipolar illness, or substance abuse.

The sample included all participants who had blood drawn at study entry and completed the cognitive assessment at study entry and 1 year later. CRP was measured for 126 participants at the study entry visit.[13] One year later, 115 were contacted for follow-up, with 81 completing the follow-up examination (70% retention rate). Participants who withdrew (n = 34) were an average of 4 years younger (mean age 66.8 vs 70.6; $t = 52.6$, degrees of freedom (df) = 113, $P < .05$) and less educated (mean 13.3 vs 14.6 years; $t = 2.3$, $df = 109$, $P < .05$) than participants returning for follow-up (n = 81). Participants who withdrew were comparable with those who returned for the follow-up examination on MMSE performance and CRP levels. Three of the 81 follow-up participants had missing data for at least one of the key variables; thus, the primary analysis is based on a final sample of 78 participants with data from study entry and 1-year follow-up.

Descriptive statistics regarding the sample demographic and medical characteristics are presented in Table 1. Briefly, participants had an average age of 70.6 ± 7.4 (range 56–84). Approximately 39% of the sample was female. The sample was approximately 98% Caucasian and 2% African American.

Procedure

During the study entry visit, participants had blood drawn to obtain CRP levels and completed a comprehensive neuropsychological battery on the same day. A detailed medical history interview was completed with a focus on CVD. Cardiovascular risk factors such as hypertension, hypercholesterolemia, smoking, and diabetes mellitus and cardiovascular events, including myocardial infarctions, percutaneous coronary intervention, coronary artery bypass graft (CABG), and valve surgery, were coded as present or absent according to participants' self-report and were validated through medical records when available. Neuropsychological assessment was repeated during a follow-up visit approximately 1 year later.

CRP Measurement

CRP levels were obtained using a high-sensitivity assay. To minimize the risk of hypoglycemia confounding cognitive performance, nonfasting laboratory measures were employed. CRP was determined on a Beckman CX4 autoanalyzer using reagents obtained from Pointe Scientific (Lincoln Park, MI). The interassay coefficient of variation was 2.0%. Laboratory values for the sample are shown in Table 1. As expected, CRP values were positively skewed. Thus, rank-order transformation was used to normalize CRP values for entry into the regression analyses.

Neuropsychological Assessment

All participants completed an extensive neuropsychological assessment including measures of global cognition, language, memory, attention, executive functioning, psychomotor speed, and

visual-spatial ability (Table 2). A trained research assistant administered all tests using standard procedures under the supervision of a licensed psychologist (RAC).

Cognitive measures were grouped into five cognitive domains: language, visual-spatial abilities, memory, attention-executive-psychomotor functions, and global cognition (Table 2). Tests of skills presumably mediated by frontal-subcortical pathways (attention, executive function, and psychomotor speed) were combined in a single composite based on previous evidence that this domain is particularly susceptible to changes in patients with systemic CVD.[14] Participants' raw test scores were converted to z-scores using the study sample mean and standard deviation. Five composite cognitive domain z-scores were calculated for each participant by averaging the z-scores of all tests within that domain.

Data Analysis

A series of paired *t*-tests was calculated to compare differences in the average neuropsychological test performance of the entire sample at study entry and follow-up. Given the multiple comparisons in this series of preliminary, descriptive analyses, the alpha level was adjusted to reduce the risk of Type I error using a Bonferroni correction (i.e., $P<.002$).

The primary analyses examining the association between CRP and longitudinal neuropsychological test performance were conducted for each of the five cognitive domains using hierarchical linear regression modeling with the change in the composite domain z-score over the follow-up period entered as the dependent variable. The potential effects of education and sex were examined, and it was determined that they were not associated with change in cognition; thus, education and sex were not included in the primary regression models. In the first step of each regression analysis, the association between CRP and change in cognition was adjusted for the effects of baseline age and cognitive performance in the cognitive domain being examined. Finally, to examine the association between CRP level and change in cognition over the 1-year follow-up, rank-ordered CRP was entered in the second and final step.

To explore the pattern of association between CRP and change in the attention-executive-psychomotor speed domain, individuals were dichotomized according to CRP level into high-risk (≥3.0 mg/L; n = 15) and low- to moderate-risk (<3.0 mg/L; n = 63) groups. This cutoff is based on the 2003 Consensus Statement from the Centers for Disease Control and Prevention and the American Heart Association, which concluded that CRP values greater than 3.0 mg/L suggest high risk for future cardiovascular events in patients with known CVD.[15] The change in cognition between high and low to moderate CRP risk groups was compared using *t*-tests.

Secondary analyses were also conducted to explore the potential effect of history of CVD and current medication use on change in cognition for those domains that were significantly associated with CRP (attention-executive-psychomotor). The effects of cardiovascular history variables (history of hypertension, hypercholesterolemia, diabetes mellitus, smoking, atrial fibrillation, heart failure, myocardial infarction, valve surgery, CABG, percutaneous coronary intervention) and medication class (antihypertensives, lipid-lowering agents, aspirin, antiplatelets, vitamins, nonsteroidal antiinflammatory drugs (NSAIDs), psychoactive medications, and hypoglycemics) on change in the attention-executive-psychomotor domain were examined using chi-square analyses, with a cutoff of $P = .10$. Finally, initial CRP values for participants who were taking lipid-lowering agents and NSAIDS were compared with those of participants who were not using *t*-tests to clarify potential medication effects on CRP. Data were analyzed using SPSS 11.0 statistical software (SPSS Inc., Chicago, IL). An alpha level of 0.05 was used as the a priori criterion for statistical significance for all primary analyses.

Results

Raw neuropsychological test performances at study entry and follow-up are presented in Table 2. Paired *t*-tests comparing difference in raw mean neuropsychological test performance for the sample revealed statistically significant mean group decline on Complex Figure Test Copy ($t = 4.66$, $P = .001$), increase on California Verbal Learning Test immediate recall ($t = -3.32$, $P = .001$), and increase in the Trail Making Test Part A ($t = 3.51$, $P = .001$).

Hierarchical linear regression revealed that higher CRP values at study entry were associated with change in performance in the attention-executive-psychomotor speed domain (CRP $\beta = -0.22$, $P = .04$) after adjusting for baseline age and baseline cognitive performance (Table 3). When the sample was dichotomized according to CRP level (i.e., high risk, n = 15 and low to moderate risk, n = 63), participants with high-risk CRP levels demonstrated a decline in the attention-executive-psychomotor domain (mean z-score change = −0.1), whereas individuals in the moderate-risk group demonstrated an increase in the domain score (mean *z* score change +0.1; $t = 2.0$, $df = 76$, $P = .048$).

The potential effect of CVD history and current medication use were examined in follow-up analysis. None of the cardiovascular history variables or medication classes were found to have a significant effect on change in neuropsychological test performance. Furthermore, there were no significant differences between initial CRP levels of patients who were taking lipid-lowering agents and levels of those who were not or between levels of patients who were taking NSAIDs and those who were not. Thus, the primary analysis was not repeated with cardiovascular history variables or medication class as a covariate.

To examine potential differences between subjects with mean attention-executive-psychomotor increases and those whose performance remained stable or declined over the follow-up period, a series of *t*-tests and chi-square analyses were conducted. *T*-tests comparing the groups in terms of age, education, and systolic and diastolic blood pressure were conducted, and no significant differences were found. Chi-square analyses comparing the groups in terms of the presence or absence of atrial fibrillation, stent insertion, CABG, heart failure, heart valve surgery, and myocardial infarction were conducted, and no significant differences were found.

Discussion

Preliminary evidence was found that circulating CRP levels are associated with changes in attention-executive-psychomotor functioning speed over a 1-year follow-up period in older adults without dementia with stable CVD. Specifically, higher CRP levels at study entry were associated with greater decline in cognitive performance in the attention-executive-psychomotor domain over the subsequent year, after adjusting for age and cognitive performance at study entry. When the data were examined dichotomously in secondary analyses, individuals with higher CRP levels (≥3.0 mg/L, high-risk group) were more likely to show a decline in their cognitive performance in the attention-executive-psychomotor domain than individuals with low to moderate CRP levels (<3.0 mg/L). The group with low-to-moderate CRP levels showed a modest improvement in cognitive scores, which may reflect practice effects from previous exposure to the cognitive measures. In contrast, despite potential underlying practice effects, the high-risk group's cognitive performance declined over the 1-year follow-up.

Secondary analyses were conducted to ensure that past or present CVD variables were not driving the relationship between CRP and change in cognitive functioning. Results of these analyses revealed that none of the CVD history variables (history of hypertension, hypercholesterolemia, diabetes mellitus, smoking, atrial fibrillation, heart failure, myocardial infarction, valve surgery, CABG, percutaneous coronary intervention) or use of current

medications (antihypertensives, lipid-lowering agents, aspirin, antiplatelets, vitamins, NSAIDs, psychoactive medications, hypoglycemics) were independently associated with change in attention-executive-psychomotor performance. It is possible that the lack of effects for individual history variables is because the participants were treated, stable outpatients and that the CRP measurement was not obtained after an acute event or surgery. There was a wide range of heterogeneity with respect to the specific cardiovascular risk factors and interventions that each participant had experienced. It is likely that underlying CVD severity affected CRP in part but that determining only the presence or absence of past disease and events did not capture this relationship. Moreover, CRP may be a marker of systemic inflammation that the cumulative effects of CVD and a range other health status variables influence.

The observation that CRP is associated with subsequent change in cognitive performance is consistent with prospective studies linking high CRP levels with risk for dementia in population-based cohorts.[9] Furthermore, the current finding builds upon a previous report that CRP levels are related to cognition on cross-sectional examination[13] by demonstrating that high CRP levels are associated with declines in executive functioning, attention, and psychomotor speed over time in patients with CVD. Understanding novel vascular risk factors for cognitive decline, such as CRP, is an important research endeavor, because early identification and intervention for “at risk” individuals could contribute to prevention of dementia.

The underlying mechanism by which CRP affects the vasculature is currently an area of considerable research attention. Inflammation, as measured according to CRP, has been associated with all stages of the atherosclerotic process,[1] including proinflammatory, proatherosclerotic, and prothromotic effects.[6] CRP may negatively affect the vasculature by altering vascular homeostasis (i.e., endothelial cell and smooth muscle function in blood vessels) and by promoting coagulation.[6] Consistent with this observation, interventions that reduce risk of coronary events, such as statin agents, lower CRP levels,[3] but whether CRP acts as a causal agent or as a downstream marker of inflammatory activation and severity of CVD continues to be controversial.[7]

Regarding the interpretation of the current findings, the global cognitive performance of the participants fell largely within normal limits. As may be expected in a sample of individuals with stable CVD, the average cognitive performance of the sample as a whole remained consistent over the 1-year follow-up period, although there was variability in cognitive change across individuals in the sample. The observed association between CRP and cognition reflected subtle declines in the attention-executive-psychomotor speed domain. These changes, although modest, may have clinical significance because attention and executive deficits are associated with functional changes in patients with CVD[16] and are a hallmark feature of vascular dementia.[14] The changes that were observed may represent a precursor to more functionally compromising cognitive problems in the future, but given the subtle effects and the short 1-year follow-up period, the current findings should be considered preliminary, and longitudinal data examining conversion to dementia will be necessary before definitive conclusions can be drawn about the long-term clinical effect of high CRP.

Strengths of the current study include the prospective design, the focus on individuals at risk for cognitive decline by virtue of having CVD, and the examination of CRP in relation to changes in multiple cognitive domains, unlike some prior studies that used brief cognitive assessments. The more-comprehensive neuropsychological test protocol permitted an examination of different cognitive domains, focusing on attention, executive functioning, and psychomotor speed. The fact that CRP was uniquely associated with change in the attention-executive-psychomotor domain (but not the other cognitive domains assessed, including language, visual-spatial, memory, and global cognition) was consistent with the hypothesis

that executive functioning, attention, and psychomotor skills are most susceptible to vascular risk factors and CVD.

Prospective studies are essential to establish the causal relations that observation of an association between CRP and cognition suggests. The current study is among the first to examine CRP and change in cognition over time in a group of patients with stable CVD. The primary observation that CRP level at study entry was associated with changes in attention, executive function, and psychomotor speed suggests that chronic inflammation may confer a risk for cognitive impairment in elderly patients with CVD. Previous research has documented associations between CRP and other inflammatory biomarkers and the severity and progression of cerebral small-vessel disease (white matter lesions and lacunar infarctions[4]) and brain atrophy,[17] supporting the idea that vascular inflammation maybe one of the mechanistic links between CVD, cerebrovascular disease, and progression of cognitive deficits in elderly people. Given the current preliminary finding that CRP is associated with changes in attention-executive-psychomotor performance, future studies in other cohorts should include comprehensive measures of cognitive functioning to determine whether the relationship between CRP and attention-executive-psychomotor speed can be replicated. Future studies including cognitive measures and neuroimaging will also be an important area for follow-up potentially linking vascular inflammation, cerebrovascular changes, and cognition.

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Table 1

Demographic and Clinical Characteristics of Sample

Characteristic	Value
Demographic	
Age, mean ± SD	70.6 ± 7.4
Female, %	38.5
Education, years, mean ± SD	14.6 ± 2.7
Clinical measures, mean ± SD	
Systolic blood pressure, mmHg	129.5 ± 20.1
Diastolic blood pressure, mmHg	66.1 ± 9.4
C-reactive protein, mg/L	1.8 ± 1.5
Medical history, %	
Hypertension	71.8
Hypercholesterolemia	55.1
Type 2 diabetes mellitus	21.8
Cigarette smoking	35.9
Atrial fibrillation	13.2
Heart failure	19.1
Myocardial infarction	43.6
Percutaneous coronary intervention	26.1
Coronary artery bypass graft	34.6
Valve surgery	11.4
Medications, %	
Antihypertensive medication	87.2
Lipid-lowering agents	79.5
Aspirin/antiplatelet agents	37.2
Vitamins	37.2
Nonsteroidal antiinflammatory agents	20.5
Psychoactive medications	20.5
Hypoglycemics	17.9

SD = standard deviation.

Table 2

Neuropsychological Test Scores by Cognitive Domain

Measures by Domain	Raw Score Mean ± Standard Deviation		*T*	*P*-Value
	Study Entry	Follow-Up		
Global cognitive functioning				
Mini-Mental State Examination[18]	28.6 ± 1.5	28.7 ± 1.5	−0.68	.50
Dementia Rating Scale[19]	137.8 ± 4.7	138.7 ± 4.9	−1.71	.09
Language				
Boston Naming Test[20]	55.3 ± 4.6	55.5 ± 5.2	−1.69	.10
Category Fluency for Animals[21]	19.4 ± 5.6	19.7 ± 5.1	−0.49	.63
Visual-spatial				
Hooper Visual Organization Test[22]	24.2 ± 3.0	24.2 ± 3.3	0.21	.84
Complex Figure Test—Copy[23]	31.8 ± 4.3	28.7 ± 5.3	4.66	.001
WAIS III Block Design Subtest[24]	33.5 ± 10.7	34.2 ± 9.3	−1.69	.24
Memory				
California Verbal Learning Test[25]				
Immediate Recall	9.1 ± 3.2	10.0 ± 3.3	−3.32	.001
Delayed Recall	9.5 ± 3.3	10.2 ± 3.6	−2.19	.03
Recognition Discrimination	91.7 ± 6.1	91.2 ± 11.3	0.38	.70
Complex Figure Test[23]				
Immediate Recall	16.4 ± 7.5	16.1 ± 6.9	0.49	.62
Delayed Recall	16.1 ± 7.1	15.5 ± 6.9	0.40	.69
Recognition Discrimination	19.6 ± 2.6	19.8 ± 2.5	−0.49	.63
Brief Visual Memory Test—Revised[26]				
Delayed Recall	7.4 ± 3.1	7.9 ± 3.0	−1.18	.24
Recognition Discrimination	5.2 ± 1.0	5.5 ± 0.9	−2.08	.04
Attention-Executive-Psychomotor				
Trail Making Test Part A, seconds[27]	38.3 ± 13.4	34.3 ± 11.3	3.51	.001
Trail Making Test Part B, seconds[27]	93.1 ± 40.0	89.3 ± 40.2	0.83	.41
Letter Search, Time	92.5 ± 27.5	93.4 ± 25.2	−0.10	.92
Letter Search, Errors	1.6 ± 2.4	1.1 ± 2.2	1.73	.09
Stroop-Word/Color, correct 45 seconds[28]	29.9 ± 7.8	32.2 ± 8.5	−2.56	.01
Controlled Oral Word Association[29]	39.7 ± 12.4	42.1 ± 12.6	−2.24	.03
Grooved Pegboard, Dominant Hand[30]	92.5 ± 27.5	88.5 ± 21.0	1.80	.08
WAIS III Digit Span Subtest[24]	17.8 ± 3.4	17.7 ± 3.9	0.11	.91
WAIS III Symbol Coding Subtest[24]	56.3 ± 14.2	58.7 ± 13.9	−2.48	.02

WAIS = Wechsler Adult Intelligence Scale.

Table 3

Summary of Hierarchical Regression Analysis of Change in Attention-Executive-Psychomotor Cognitive Domain

Step/Variable	Beta†	R^2 Change	Total R^2	Significance
Block 1		0.14	0.14	F (2,75) = 6.26 P =.003
Age	−0.19			
Baseline attention-executive-psychomotor domain *z*-score	−0.41***			
Block 2		0.05	0.20	F (3,74) = 4.20 P =.04
Rank of baseline C-reactive protein	−0.22*			
Overall model				F (3,74) = 5.75 P =.001

*P < .05,

***P < .001.

†The beta reported is the standardized coefficient for the final equation.

R^2 = coefficient of determination.