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C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease

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Abstract

Cardiovascular disease (CVD) is a risk factor for cognitive impairment and dementia. Recent studies implicate homocysteine (HCY) and C-reactive protein (CRP) in this increased risk, as both are associated with cognitive dysfunction in demented and non-demented patients. However, it remains unclear whether they confer added risk in older adults with CVD. A total of 126 older CVD patients underwent blood and neuropsychological evaluation as part of a prospective examination of the neurocognitive consequences of CVD. A subset of these participants ($n = 37$) also underwent neuroimaging to quantify the degree of white matter disease. After adjusting for demographic and medical factors, no significant relationship emerged between HCY and cognitive performance. In contrast, CRP showed significant independent relationships to test performance, including global cognitive performance, attention/psychomotor function, executive function, memory, and visuospatial abilities. Neither HCY nor CRP was related to extent of white matter disease or whole brain volume on magnetic resonance imaging. Further study is needed to identify mechanisms by which inflammatory processes impact on cognitive function and to determine whether reducing circulating levels of inflammatory markers results in improved cognition.

Keywords

Homocysteine; C-reactive protein; Cognition

1. Introduction

With the elderly expected to comprise an increasingly larger proportion of the world's population, dementia is projected to be one of the major health-care problems of coming decades.^{1,2} As a result, there is a growing need to modify known risk factors for cognitive dysfunction. One modifiable risk factor is cardiovascular disease (CVD). Persons with CVD are at elevated risk for Alzheimer's disease and often exhibit cognitive deficits long before onset of stroke or dementia.^{3,4} Deficits of executive dysfunction and psychomotor slowing are most commonly reported, consistent with the close relationship between CVD and cerebrovascular disease.^{5–8}

Recent studies implicate the novel risk factors homocysteine (HCY) and C-reactive protein (CRP) in the relationship of CVD, cerebrovascular disease, and cognitive dysfunction. Both the amino acid HCY and the inflammatory marker CRP have adverse effects on the endothelium, a blood vessel lining crucial for blood flow regulation and blood–brain barrier function.^{9–11} In turn, endothelial dysfunction is a known risk factor for cerebral small vessel

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disease, a condition associated with impaired memory, executive functioning, and psychomotor speed, the same impairments found in older adults with CVD.^{9,10,12–20} This process may help explain the relationship between these biomarkers and Alzheimer's disease, vascular dementia, and cognitive deficits in non-demented populations.^{21–30}

Under this model, elevated levels of HCY and CRP should exacerbate the cerebrovascular changes associated with CVD and thus result in greater cognitive dysfunction. No study to date has determined whether HCY and CRP independently contribute to the cognitive dysfunction found in older adults with CVD, persons at highest risk for their adverse effects. Similarly, no study has examined their relationship to white matter disease in this population. On the basis of findings in other populations, we predicted that both HCY and CRP would be related to cognitive performance and magnetic resonance imaging (MRI) indices of white matter disease and whole brain volume.

2. Methods

The following protocol was approved by the local institutional review board.

2.1. Participants

A total of 128 participants that were enrolled in a larger, prospective study of neurocognitive consequences of CVD were included in the present study. This number represents all participants that underwent a blood draw as part of their baseline assessment at the time of these analyses. For inclusion, participants must have had a documented history of CVD, have been between the ages of 55 and 85, have had a Mini-Mental Status Exam score of >24 ,³¹ and have had no history of neurological or severe psychiatric disorder. Depressive symptoms were measured using the Beck Depression Inventory.³² It is important to note that no participant in the present study had a history of renal failure or significant renal disorder. Only a subset of participants ($n = 37$) completed neuroimaging because of the many MRI contraindications in this population (e.g. pacemakers, stents).

On average, participants were 69.15 ± 7.58 years of age, and had 14.21 ± 2.68 years of education (range 8–20 years). The sample comprised approximately 59% males and 90% white non-Hispanic individuals. See Table 1 for complete demographic and medical information. It should be noted that approximately 40% of participants were on a lipid-lowering medication and 3% were prescribed folic acid/B vitamins.

2.2. Materials

To minimise the risk of hypoglycaemia confounding cognitive performance (particularly in participants with diabetes), nonfasting laboratory measures were employed. These methods have been successfully used in past studies and provide reliable and valid measures of the dependent variables.^{9,33}

2.3. Laboratory measures

HCY was measured by high performance liquid chromatography (Waters, Medford, MA, USA) with fluorescence detection using a modification of the method of Vester and Rasmussen.³⁴ Briefly, samples were reduced with tri-*n*-butylphosphine and the proteins removed by precipitation with perchloric acid. The supernatant was treated with SBD-F in potassium borate and incubated at 60 °C for 1 h. Cooled samples were applied to a C-18 column in 0.1 mol/L sodium acetate (pH 4.0) containing 2% methanol and eluted with a gradient of 2–20% methanol in 0.1 mol/L phosphate buffer (pH 6.0). Mercaptopropionyl glycine was used as an internal standard to control for efficiency of the derivatisation step and for recovery. The intra-assay

coefficient of variation was 5% and the interassay coefficient of variation ranged from 9% to 11%.

CRP was determined on a Beckman CX4 autoanalyser using reagents obtained from Pointe Scientific (Lincoln Park, MI, USA). The assay range was 0.5–1.0 mg/dL and the interassay coefficient of variation was 2.0%. Laboratory values for the sample are shown in Table 1.

Vitamin B12 and folic acid were measured by a solid phase, no-boil radioimmunoassay using a commercial kit (Diagnostic Products Corporation, Los Angeles, CA, USA). Vitamin B6 was analysed by a radioassay kit (ALP-CO, Windham, NH, USA), which measures the conversion of tritiated tyrosine to tyramine by the vitamin B6-dependent enzyme tyrosine decarboxylase.

2.4. Neuropsychological measures

Six domains of cognitive functioning were assessed:

- global cognitive function (Dementia Rating Scale (DRS) total score³⁵)
- attention/psychomotor functioning (Trail Making Test Part A time to completion,³⁶ Digit Symbol-Coding total raw score,³⁷ Digit Span total raw score,³⁷ Grooved Pegboard Test time to completion for dominant and non-dominant hand³⁸)
- executive functioning (Controlled Oral Word Association Test total words (COWAT³⁹), Similarities total raw score,³⁷ Stroop Color Word Test: color word correct responses⁴⁰)
- memory (California Verbal Learning Test (CVLT Trials 1–5, Short Free Recall, Long Free Recall, Discrimination⁴¹), Brief Visuospatial Memory Test-Revised (BVM-T-R Trials 1–3, Delayed Recall, Discrimination⁴²)
- language (Boston Naming Test total raw score,⁴³ Category Fluency total raw score⁴⁴)
- spatial skills (Hooper Visual Organization Test total raw score,⁴⁵ Block Design total raw score,³⁷ Complex Figure Test: copy total raw score (CFT)⁴⁶).

2.5. Brain MRI and white matter hyperintensity quantification

Brain MRI scans were obtained using a Siemens Symphony 1.5 Tesla unit (Siemens AG, Munich, Germany). A standard imaging protocol consisting of both sagittal T1-(TR/TE = 500/30) and T2-(TR/TE = 2500/80) weighted conventional spin-echo localiser images as well as axial T1-, T2-, and fluid attenuated inversion recovery (FLAIR)-weighted (TR/TE = 6000/105) images were obtained. Only the FLAIR sequences were used in this study, given the ability of this sequence to suppress the signal of the cerebrospinal fluid and the sensitivity of this sequence for visualising hyperintensity. The slice thickness for all images was 5 mm with a 2-mm intersection gap. A 192 × 256 matrix with one excitation was used. Each participant's scan was screened for other confounding neurological disorders.

The FLAIR images were used to quantify hyperintensities utilising semi-automated threshold methods with good intra- and inter-rater reliability (>0.90). For each participant, hyperintensities were quantified separately for three anatomical regions: (1) hyperintensities observed in the neocortical white matter (that is, white matter of the corona radiata), (2) hyperintensities confluent with the lateral ventricles (that is, periventricular areas), and (3) hyperintensities adjacent to subcortical grey matter nuclei (that is, caudate, lentiform nuclei, and thalamus). Briefly, the raw FLAIR imaging data was imported into the commercially available Mayo Clinic software program ANALYZE (Mayo Clinic, Rochester, MN, US). First, the skull was stripped and the brain stem and cerebellum were removed, leaving only the total

cerebral brain parenchyma. Second, using the threshold tool in ANALYZE, we isolated the hyperintense regions from surrounding parenchyma for each patient. Using anatomical landmarks, hyperintensities were separated and labelled. The total number of pixels from each anatomical region was then summed across the slices and across regions to quantify white matter hyperintensities (WMH). Total cerebral brain volume (TCBV) was quantified using threshold histogram values that were only consistent with brain parenchyma, and this value was used to correct WMH (formula = (hyperintensity pixel total/brain pixel total) $\times$ 100). This method provides a ratio of hyperintensity load relative to the total amount of brain tissue for each patient and reflects the degree or extent of brain volume impacted by hyperintensity abnormalities. It also allows for a more direct comparison between patients controlling for variability in brain size and generalised atrophy. Finally, this value was log-transformed to promote statistical analysis.

2.6. Procedure

After providing informed consent, participants underwent a blood draw and were administered the neuropsychological battery by a trained research team member. Blood samples were collected in tubes and refrigerated within 10 min of collection. Plasma was separated within 4 h and samples were stored at -70°C until analyses were performed. Neuroimaging was completed on a separate day.

2.7. Data analysis

Descriptive data regarding subject characteristics, biochemistry values, and test performance was generated. Pearson and Spearman correlation was then used to determine relationships among demographic, medical history, and chemistry variables. Finally, one-tailed Pearson correlation and partial correlation analyses were conducted to determine the relationships among the biomarkers, test performances, and MRI indices. Modelled after past studies,⁴⁷ simple bivariate correlation was conducted first, followed by partial correlation adjusting for (1) age and sex; and (2) age, sex, hypertension, diabetes, and history of smoking. Partial correlation procedures involving HCY also controlled for B6, B12, and folic acid levels. Given the exploratory nature of the analyses, we did not correct for multiple comparisons.

3. Results

3.1. Relation to demographic and medical variables

HCY was associated with age, hypertension, and diabetes, but not with a history of smoking (Table 2). CRP showed a significant association with a history of heart failure. The HCY and CRP values were unrelated ($r = 0.02$).

3.2. HCY and neuropsychological test performance

The relationship between HCY and cognitive performance is presented in Table 3. Simple correlation analyses showed significant relationships between HCY and tasks testing attention/psychomotor functioning, including Digit Symbol Coding and both Dominant and Non-dominant Grooved Pegboard performance. This relationship between HCY and psychomotor function remained significant after adjusting for age and sex (Dominant and Non-dominant Grooved Pegboard). No other significant relationships emerged between HCY and cognitive performance when adjusting for demographic factors, and no significant relationships were found when adjusting for both demographic and medical variables.

3.3. CRP and neuropsychological test performance

The relationship between CRP and cognitive performance is presented in Table 4. Using simple correlation, significant relationships emerged between CRP and cognitive performance,

including global cognitive abilities (DRS total score), executive functioning (Similarities), memory (BVM-T-R Trials 1–3), and visuospatial abilities (Complex Figure Test-Copy, Block Design, Hooper Visual Organization Test).

After adjusting for age and sex, significant relationships remained in multiple cognitive domains, including global abilities (DRS total score), executive function (Similarities), memory (CVLT Short Free Recall, BVM-T-R Trial 1–3, BVM-T-R), and visuospatial abilities (Block Design, Hooper Visual Organization Test). Additional relationships also emerged on attention/psychomotor speeded tasks (Trail Making Test A, Digit Symbol Coding, Non-dominant Pegboard).

Finally, when adjusting for demographic and medical conditions, significant correlation with global cognitive abilities (DRS total score), attention/psychomotor speed (Trail Making Test A), executive function (Similarities), memory (CVLT Short Free Recall, BVM-T-R Trial 1–3, BVM-T-R Delayed Recall), and visuospatial abilities (Block Design, Hooper Visual Organization Test) was found.

3.4. Relation to MRI indices

Contrary to predictions, neither HCY nor CRP was significantly related to TCBV or WMH (Table 5). Modest relationships in the opposite direction were found between HCY and WMH.

4. Discussion

The results of the present study suggest that CRP, but not HCY, is independently associated with cognitive dysfunction in older adults with CVD. Our finding of a relationship between CRP and cognitive performance is consistent with the results of past studies and the growing understanding of the downstream consequences of inflammatory processes on the brain.^{29, 30,48,49} For example, CRP is known to promote endothelial injury, which was recently shown to result in the release of neurotoxic thrombin.^{14,50} At a broader level, inflammatory markers are also known to increase with age, coinciding with the development of both normal age-related cognitive decline and pathological conditions such as Alzheimer's disease and vascular dementia.^{30,51} Through the use of an expanded test battery, the present study showed that CRP is related to performance in multiple cognitive domains, including global cognitive performance, attention/psychomotor function, executive function, memory, and visuospatial abilities. This finding extends the findings of previous studies, which typically employed an abbreviated battery that assessed function in only a few cognitive domains. These significant associations emerged even when adjusting for demographic and medical conditions known to influence CRP levels, suggesting that its effects are independent of and additive to CVD.

In contrast, HCY was found to be unrelated to cognitive performance after adjusting for demographic and medical conditions. This finding is in contrast to the growing number of studies that demonstrate such a relationship.^{21,23,24} One possible explanation for the differential findings across studies is sample selection, as many past studies include persons with and without CVD. However, CVD is independently associated with both HCY levels and cognitive impairment, and may thus mediate their observed relationship in past studies.^{52,53}

Contrary to predictions, HCY was not related to whole brain volume or white matter disease on MRI. Past studies have typically shown that higher HCY levels are associated with greater white matter disease, although this pattern is not universal.^{21,24,47,54} Several possible explanations exist, including that CVD mediates the relationship between HCY and white matter disease. Another possible explanation involves medication effects. Many of the CVD patients in the present study were taking medications known to influence HCY and CRP levels (including lipid-lowering drugs).^{55,56} However, given that nearly half of all adults have total

cholesterol levels above 200 mg/dL, it appears likely that many persons included in past studies were prescribed similar medications.⁵⁷ If these findings were to be replicated in a larger sample, they would suggest that the relationship between these medications, biomarkers, and cognitive performance may be more complicated than originally believed.

To our knowledge, the present study is the first to directly examine the relationship between CRP and white matter disease on MRI. As for HCY, we found no relationship between CRP and MRI indices in this sample of older adults with CVD. This finding emerged despite finding consistent relationships between CRP and cognitive test performance, identifying a need to research alternative mechanisms by which CRP may impact on cognition. Past studies showing a relationship between CRP and cognitive dysfunction identify white matter disease as a causative factor, although the present findings argue against this.^{29,30} Clearly, further work is needed.

Characteristics unique to our sample of older CVD patients warrant brief discussion. First, we found that few subjects had hyperhomocysteinaemia, as just 16% had HCY values greater than 15 $\mu\text{mol/L}$. Increased awareness and treatment of this condition has likely reduced its prevalence in CVD patients. Interestingly, no differences in cognitive performance emerged when comparing patients with and without hyperhomocysteinaemia in our sample (data not shown).

The present study offers insight into the relationship between HCY, CRP, and cognitive dysfunction, but may not generalise to all other samples. Although the observed relationships were statistically significant and similar to those found in past studies, they were often modest in size. Such findings remind us that CRP may contribute to cognitive dysfunction in this population, but much of the variability in performance is governed by other factors. Also, as noted earlier, some participants were taking medications known to influence HCY and CRP levels, and little is known about the possible interactive effects of these medications on biomarker levels and cognitive performance. A large epidemiological study may provide greater insight into this possible interaction.

The present study encourages further research on the relationships among biomarkers, cognition, and structural brain changes in older adults. In particular, a better understanding of the mechanisms by which CRP and other inflammatory markers affect the brain is needed. Such studies may prove enormously beneficial, as identification of the mechanisms underlying these modifiable risk factors may lead to improved treatments and benefit at a societal level.

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Table 1

Demographic characteristics, serum biochemistry, and medical history in older adults with cardiovascular disease

Measure	Mean	SD	%
Age (years)	69.15	7.58	
Education (years)	14.21	2.68	
MMSE	28.54	1.50	
Homocysteine ($\mu\text{mol/L}$)	11.67	4.86	
C-reactive protein (mg/L)	2.04	1.72	
B6 (nmol/L)	103.91	95.97	
B12 (pg/mL)	479.73	267.41	
Folate (ng/mL)	38.85	26.43	
Atrial fibrillation			15
Hypertension			73
Coronary artery bypass graft			36
Heart failure			16
Type 2 diabetes mellitus			24
Myocardial infarction			45
Transient ischaemic attack			9
Smoking			53
Depression			20

MMSE = Mini-mental state examination.

Table 2

Relationship among demographic, medical, and chemistry variables in older adults with cardiovascular disease

	Homocysteine	C-reactive protein
Age	0.21 *	−0.12
Sex	0.05	0.05
Beck depression inventory total score	−0.03	−0.03
Myocardial infarction	−0.01	0.00
Heart failure	0.12	0.20 *
Cardiac surgery	0.06	0.01
Pacemaker	0.13	−0.03
Hypertension	0.19 *	0.03
Diabetes	0.21 *	0.09
Smoking	−0.18	0.15

* Two-tailed significance at the 0.05 level.

Table 3
Correlation between homocysteine and cognitive test performance in older adults with cardiovascular disease

	Uncorrected	Demographic ^a	Demographic and medical ^b
Global cognitive abilities			
Dementia rating scale	−0.17	−0.08	−0.09
Attention/psychomotor speed			
Digit span	−0.08	−0.07	−0.05
Trail making test A	0.07	0.00	0.01
Digit symbol coding	−0.16 [*]	−0.09	−0.02
Grooved pegboard: Dominant	0.22 [*]	0.14 [*]	0.12
Grooved pegboard: Non-dominant	0.23 [*]	0.17 [*]	0.18
Executive function			
Trail making test B	0.12	0.06	0.06
Similarities	−0.02	−0.01	0.02
Stroop color word test	−0.07	0.06	0.00
COWAT	−0.12	−0.09	−0.07
Learning and memory			
CVLT trials 1–5	−0.13	−0.08	−0.07
CVLT short free recall	−0.12	−0.07	−0.03
CVLT long free recall	−0.05	0.00	0.04
CVLT discrimination	0.01	0.09	0.09
BVMT-R trials 1–3	−0.10	−0.03	−0.01
BVMT-R delayed recall	−0.06	0.00	0.00
BVMT-R discrimination	0.06	0.11	0.15
Language			
Boston naming test	0.02	0.05	0.03
Animal fluency	0.07	0.13	0.14
Visuospatial abilities			
Complex figure test: Copy	0.02	−0.01	0.07
Block design	0.05	0.10	0.10
Hooper visual organization test	0.01	0.05	0.05

COWAT = Controlled oral word association test.

CVLT = California verbal learning test.

BVMT-R = Brief visuospatial memory test-revised.

^aCorrected for age and sex.

^bCorrected for age, sex, hypertension, diabetes, smoking, B6, B12, and folic acid.

^{*}One-tailed significance at the 0.05 level.

Table 4
Correlation between C-reactive protein and cognitive test performance in older adults with cardiovascular disease

	Uncorrected	Demographic ^a	Demographic and medical ^b
Global cognitive abilities			
Dementia rating scale	-0.17*	-0.21*	-0.21*
Attention/psychomotor speed			
Digit span	-0.11	-0.11	-0.11
Trail making test A	0.14	0.19*	0.20*
Digit symbol coding	-0.10	-0.15*	-0.11
Grooved pegboard: Dominant	0.05	0.12	0.10
Grooved pegboard: Non-dominant	0.12	0.18*	0.17
Executive function			
Trail making test B	0.04	0.07	0.07
Similarities	-0.20*	-0.21*	-0.19*
Stroop color word test	0.04	0.11	0.09
COWAT	0.05	-0.08	-0.06
Learning and memory			
CVLT trials 1–5	-0.06	-0.11	-0.12
CVLT short free recall	-0.14	-0.20*	-0.19*
CVLT long free recall	-0.06	-0.11	-0.12
CVLT discrimination	-0.05	-0.11	-0.09
BVMT-R trials 1–3	-0.18*	-0.22*	-0.21*
BVMT-R delayed recall	-0.14	-0.19*	-0.24*
BVMT-R discrimination	0.02	-0.01	0.00
Language			
Boston naming test	0.03	0.02	0.02
Animal fluency	-0.16*	-0.20*	-0.18
Visuospatial abilities			
Complex figure test: Copy	-0.15*	-0.14	-0.07
Block design	-0.24**	-0.28**	-0.32**
Hooper visual organization test	-0.18*	-0.20*	-0.19*

COWAT = Controlled oral word association test.

CVLT = California verbal learning test.

BVMT-R = Brief visuospatial memory test-revised.

^a Corrected for age and sex.

^b Corrected for age, sex, hypertension, diabetes, and smoking.

* One-tailed significance at the 0.05 level.

** One-tailed significance at the 0.01 level.

Table 5
Correlation between biochemical and MRI findings in older adults with cardiovascular disease

	Uncorrected	Demographic ^a	Demographic/medical ^b
HCY			
WMH	−0.03	−0.15	−0.06
TCBV	−0.08	−0.18	−0.35
CRP			
WMH	0.01	0.01	−0.12
TCBV	−0.02	0.07	−0.20

HCY = Homocysteine.

CRP = C-reactive protein.

WMH = White matter hyperintensities

TCBV = Total cerebral brain volume.

^aCorrected for age and sex.

^bCorrected for age, sex, hypertension, diabetes, and smoking.