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## Effects of Hypertension and Hypercholesterolemia on Cognitive Functioning in Patients with Alzheimer's Disease

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### Abstract

This study investigated the relationship between the vascular comorbidities of hypertension and hypercholesterolemia and the cognitive phenotype of Alzheimer's disease (AD). Seventy four AD patients underwent objective measurement of blood pressure and serum cholesterol levels, and they received a detailed neuropsychological evaluation examining attention, memory, language, visuomotor/visuospatial skills, and executive functioning. Multiple regression analyses controlling for demographic variables, overall cognitive status, and the presence of diabetes/cardiac disease indicated that an increase in the number of vascular comorbidities, but not their severity, was associated with poorer verbal and visual recall, visuoconstructive and spatial analysis, verbal reasoning, and set shifting. The findings demonstrate that VCs are associated with specific aspects of cognitive functioning in AD patients. The mechanisms likely involve the effects of VCs on cerebrovascular disease including white matter disruption. The results highlight the importance of controlling these risk factors in patients who carry the diagnosis of AD.

### Keywords

Alzheimer's Disease; Hypertension; Hypercholesterolemia; Cognitive Functioning

### Introduction

Research has examined whether vascular comorbidities (VCs) including high and low blood pressure and hypercholesterolemia are associated with an increased risk of Alzheimer's disease

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(AD). A number of epidemiological studies support this relationship,<sup>1–8</sup> but have found that these effects may be stronger in midlife as opposed to closer to the disease onset, and may be modified by the presence of the apolipoprotein E  $\epsilon$ 4 allele, a genetic risk factor for AD.<sup>2–4, 6, 8</sup> Animal models have reported associations between high cholesterol diets and increased accumulation of brain AB in rabbits and transgenic mice,<sup>9–10</sup> and clinical trials with the cholesterol lowering agent Simvastatin have found reduced cerebrospinal fluid AB in mild AD patients.<sup>11–13</sup> On the other hand, conflicting findings exist as well concerning a relationship between hypertension and hypercholesterolemia and the risk of AD.<sup>14–17</sup> Hayden and colleagues<sup>14</sup> recently reported that neither hypertension nor hypercholesterolemia were risk factors for AD in a sample of over 3,000 elderly participants in the Cache County Study. They raised the possibility that the use of self-report or informant measurement of these comorbidities may have weakened the association, either due to the unawareness of persons that they had these conditions or conversely, better medical follow-up of these conditions in persons who were aware.

These studies have led to an appreciation of the potential contribution of VCs to the pathogenesis of AD. However, little is known about the effects of these comorbidities on the clinical features of the disease, despite evidence that VCs are quite prevalent in this patient group.<sup>18–19</sup> Research in non-demented older adults has established relationships between hypertension and poorer cognitive performance on measures of memory and executive functioning, including working memory.<sup>20–23</sup> Relationships between hypercholesterolemia and cognitive functioning, specifically memory performance, have been less consistent.<sup>24–26</sup> Zhang et al<sup>26</sup> found a U-shaped relationship between serum cholesterol values and memory performance, suggesting that the assumption of a monotonic association may account for some of the discrepancies.

A previous investigation by our group<sup>27</sup> in African American AD patients found that those with Stage 3 hypertension (systolic BP >160 mm Hg, diastolic BP >90 mm Hg)<sup>28</sup> performed worse than normotensive patients on the Conceptualization and Initiation/Perseveration subscales of the Mattis Dementia Rating Scale.<sup>29</sup> These patients did not have a history of stroke or transient ischemic attacks, or evidence of large vessel strokes on neuroimaging. The results suggested the subtle effects of hypertension on executive functioning. The above sample was limited to patients with severe hypertension versus normotensive patients and also did not examine the presence of other comorbidities. Bellew et al.<sup>19</sup> reported that cognitive decline was greater over a six month period for AD patients with hypertension versus normotensive patients. However, their study used global measures including the Alzheimer's Disease Assessment Scale Cognition portion<sup>30</sup> and the Mini-Mental State Exam (MMSE)<sup>31</sup> and did not analyze whether certain abilities are more vulnerable than others.

The current study examined the overlap between VCs and cognitive performance in patients who have AD. We investigated whether the presence and severity of hypertension and hypercholesterolemia are associated with specific cognitive deficits. Patients underwent a detailed neuropsychological evaluation measuring cognitive domains of attention, memory, language, visuomotor/visuospatial performance, and executive functioning. Hypertension and hypercholesterolemia were objectively measured in order to obtain an indication of their severity as well as the frequency of their occurrence in our patients since self/family reports can be unreliable.<sup>28,32</sup> It was hypothesized that AD patients with vascular comorbidities would exhibit more severe executive functioning and memory deficits, in line with studies demonstrating an association in nondemented adults<sup>20–24, 26</sup> and our previous study of hypertension and AD.<sup>27</sup>

## Method

### Participants

Patients with mild-moderate AD were prospectively recruited from the outpatient memory assessment clinics at The Wesley Woods Center on Aging and Grady Memorial Hospital. The study was approved by the Emory University Institutional Review Board, and signed informed consent was obtained from all participants and their representatives including spouses and adult children. Patients had probable AD<sup>33</sup> diagnosed by experienced neurologists and geriatricians in the Emory Alzheimer's Disease Research Center. Patients were not selected to participate in the current study on the basis of the presence or absence of hypertension and hypercholesterolemia. Patients were excluded if they had a history of psychiatric (Axis I) disorders, alcohol or substance-related abuse, and co-existing neurologic conditions such as Parkinson's disease and seizures. We excluded participants with large-vessel strokes based on history or imaging. The documented history of stroke included a review of medical records indicating presentation to a hospital for a newly acquired focal neurological deficit which lasted greater than 24 hours and a discharge diagnosis of acute stroke. Participants with a history of transient ischemic attacks via self-report or medical records were also excluded.

The final sample consisted of 74 probable AD patients with MMSE scores  $\geq 9$  points (mean=19.5 points, SD=4.7). The average age was 75.5 years (SD=10.0, Range=50–94) and average education was 12.4 years (SD=3.4, Range=2–20). Sixty-two percent of the sample was female. There were 45 (61%) Caucasian patients and 29 (39%) African American patients.

### Procedure

**Measurement of Vascular Comorbidities**—Patients arrived in the morning and underwent measurement of their blood pressure and cholesterol levels by the clinical research nurse. Patients were seated for at least 5 minutes in a chair with their feet on the floor and their arm supported at heart level. Blood pressure was determined by averaging two readings separated by two minutes, with additional readings taken if they differed by more than 5 mm Hg.<sup>28</sup> Serum lipid profiles were obtained. Sixty one of the 74 patients came in fasting (no caloric intake for at least 8 hours). Published guidelines were used to define the presence or absence of hypertension and hypercholesterolemia.<sup>28,34</sup> Hypertension was defined as systolic BP  $\geq 140$  mm Hg, diastolic BP  $\geq 90$  mm Hg, or taking antihypertensive medication. Hypercholesterolemia was defined as a fasting total cholesterol level of 240 mg/dl or greater, or taking cholesterol lowering agents (e.g., Statins).

**Measurement of Cognitive Functioning**—Patients underwent testing of their cognitive functioning by a psychometrist who was unaware of the patients' vascular status. Fifty-five patients were tested on the same day as the assessment of their VCs, and they were given a light meal prior to receiving the measures. The remaining 19 patients had a mean interval of 28.6 days (SD=18.2) between the measurement of their VCs and their cognitive evaluation.

Five cognitive domains were evaluated involving attention, language, memory, visuospatial/visuomotor performance, and executive functioning. Attention was assessed by the maximum number of digits forward<sup>35</sup> and the number of seconds needed to sequence numbers using a pencil (Trails A).<sup>36</sup> Language was examined via the 15-item CERAD version of the Boston Naming Test.<sup>37</sup> The evaluation of memory included verbal and visual episodic memory (CERAD word list recall and design recall) and semantic memory (timed generation of animal names in 60 seconds).<sup>37</sup> Visuospatial/visuospatial performance was evaluated by having participants copy the four CERAD designs and determine the angular orientation of lines on the five practice trials of the Judgment of Line Orientation Test.<sup>38</sup> Finally, executive functioning was measured via the Similarities subtest of the Wechsler Adult Intelligence Test-

III<sup>39</sup> and the maximum number of digits backwards.<sup>35</sup> Trails B was administered as well, but only 13 patients could complete this measure, and therefore the results were not analyzed due to floor effects in this population.

## Results

### Presence of Vascular Comorbidities and Cognitive Performance

Table 1 shows the relationship between the number of vascular comorbidities broken down by demographic features and MMSE scores. A between group Anova indicated a significant difference in age,  $F(2,71)=7.10$ ,  $p<.01$ . Sheffe posthoc analysis revealed that patients with no VCs were significantly younger than patients with two VCs ( $p<.001$ ), with a trend as well ( $p=.07$ ) for a difference in age from those with one VC. In addition, there was a significant association between gender and the number of VCs (Cochran-Armitage Trend Test,  $p>.05$ ), with more females having 2 VCs compared to males. Education, MMSE scores, and the distribution of race did not significantly differ among those with none, one, or two VCs.

A composite score was derived reflecting the total number of VCs for each patient (range=none to two). Separate multiple regression analyses were performed on the dependent variables of each of the neuropsychological measures. The number of vascular comorbidities was entered as a predictor variable, while also entering years of age and education, gender, race, and MMSE score in the models to control for possible confounding of the relationship between VCs and cognitive performance. We also controlled for the possible effects of other VCs. A review of the medical records revealed that diabetes, either insulin or non-insulin dependent, occurred in 10 (14%) of 74 patients, whereas cardiac disease (e.g., atrial fibrillation, heart attack, angioplasty) was present in an additional 8 (11%) patients.

The results of these analyses are shown in Table 2. An increase in the number of VCs was associated with significantly ( $p<.05$ ) poorer immediate word list recall and delayed recall of designs, poorer performance in judging the angular orientation of lines, lower verbal reasoning performance on Similarities, and fewer digits backwards.

The previous analyses assumed that the effects of the VCs on cognitive performance were additive and/or homogeneous and not whether they may have different effects. We therefore examined the individual or interactive effects of hypertension or hypercholesterolemia in regression models, while also controlling for years of age and education, gender, race, MMSE score, and the presence of diabetes/cardiac disease. There was a trend ( $p=0.09$ ) indicating that hypertension had a different effect on CERAD design recall than did hypercholesterolemia. Under this model, the effect of hypertension on CERAD Design Recall was significant, Coefficient=  $-1.64$  (0.61),  $p < 0.01$ , whereas the effect of hypercholesterolemia was negligible, Coefficient=  $-0.18$  (0.55),  $p = 0.75$ . In addition, there was evidence ( $p<0.001$ ) that the effects of hypertension and hypercholesterolemia on the CERAD design copy task were different and, in fact, were in opposite directions. The presence of hypertension was a significant predictor of poorer visuomotor/visuospatial performance, Coefficient=  $-2.20$  (0.55),  $p<.001$ , while the presence of hypercholesterolemia was associated with better performance on this task, Coefficient=  $1.47$  (0.49),  $p<.01$ . The remaining analyses did not indicate separate effects of hypertension and hypercholesterolemia on cognitive performance.

### Severity of Vascular Comorbidities and Cognitive Performance

We examined the relationship between the severity of blood pressure and cholesterol measures and performance on the cognitive tests. These analyses were limited to the 61 patients who fasted at the time their cholesterol values were obtained. For this group, the mean (SD) systolic BP was 138.41 (20.03) mm Hg, diastolic BP was 80.44 (11.04) mm Hg, and cholesterol level

was 185.23 (43.33) mg/dl. Pearson Product Moment coefficients revealed significant ( $p < .05$ ) correlations between both higher systolic and diastolic blood pressure readings and poorer design copy ( $r = -0.26$ ), and higher cholesterol levels and fewer digits reversed ( $r = -0.29$ ). However, regression models adjusting for potential confounders including age, education, race, gender, MMSE score, and diabetes/cardiac disease were nonsignificant for any of the cognitive measures.

We examined the possibility that since some patients ( $n = 19$ ) were not cognitively tested on the same day as the readings, we may have observed weakened relationships with the actual values. However, separate analyses restricting the sample to the 55 patients who underwent cognitive and vascular measurements on the same day also did not reveal significant correlations.

## Discussion

The results of this study indicate that vascular comorbidities contribute to the cognitive phenotype of patients who have been diagnosed with AD. An increase in the number of VCs, measured by hypertension and hypercholesterolemia, was associated with greater impairments in immediate verbal memory and delayed visual memory, verbal reasoning, set shifting, and visuospatial skills. These impairments were observed after controlling for potential confounders including demographic features and overall cognitive status. The findings extend our previous study<sup>27</sup> demonstrating a relationship between hypertension and executive functioning deficits in AD patients to encompass memory and visuomotor/visuospatial skills as well. In addition, the results are consistent with studies demonstrating a relationship between VCs and cognitive functioning in normal aging.<sup>20–26</sup> However, our study has a relatively small sample size and is limited to patients who are followed in Memory Disorders Clinics. Future large-scale epidemiological studies in AD patients are therefore necessary to confirm these findings.

The presence of hypertension and hypercholesterolemia, but not the actual values of these VCs, were related to cognitive performance. It is possible that the presence of a VC may reflect a more stable and chronic measure as opposed to a reading which is subject to fluctuations. For example, in the current study which used published clinical guidelines<sup>28,34</sup> for determining a condition, a patient could have obtained a normal blood pressure or cholesterol value and still have been classified as having hypertension or hypercholesterolemia based on taking medication for its treatment. We believe that our classification of patients was accurate for several reasons. First, we obtained objective ratings as opposed to relying on patient/family reports which can be unreliable due to unawareness of these conditions.<sup>28, 32, 40–41</sup> Moreover, our estimates of the frequency of the VCs (77% hypertension, 70% hypercholesterolemia) is similar to the reported frequency in other studies of AD patients and in population based investigations of the elderly.<sup>19, 42–44</sup>

Although our patients did not have neuroimaging evidence of large vessel strokes, we did not assess the relationships of other potential cerebral correlates of cognitive performance. Patients with an increased number of VCs may have had more “silent” strokes, a risk factor for dementia and for a steeper decline in cognitive functioning.<sup>45</sup> Neuropathological studies of AD brains reveal that co-existing cerebrovascular disease is common, affecting more than one-third of AD patients, and that pure vascular dementia without AD pathology is rare.<sup>46–48</sup> The degree of brain atrophy may also have been greater in patients as a function of an increase in the number of VCs. Cerebrovascular risk factors are associated with brain atrophy. The latter, in turn, is associated with poorer cognitive performance.<sup>49–52</sup> Seshadri et al.<sup>52</sup> found that an increase in the score on the Framingham Stroke Risk Profile was related to smaller total brain

volumes. Moreover, poorer performance on measures of attention, executive functioning, and visuospatial performance were related to smaller brain volumes as well.

Another mechanism for the observed effects of VCs on cognition in the present study may involve white matter (WM) disruption, a marker of small vessel damage. An increased number of WM hyperintensities on MRI is associated with many of the same risks for AD including high blood pressure, high cholesterol, diabetes mellitus, atrial fibrillation, and high plasma homocysteine levels.<sup>53–57</sup> Yoshita and colleagues<sup>58</sup> recently examined the relationship between the presence of cerebrovascular risk factors, including hypertension and hyperlipidemia, and white matter hyperintensities in normal elderly controls and patients with either mild cognitive impairment or AD. The investigators found that the extent of white matter hyperintensities was related to an increase in the cerebrovascular burden for all three groups. However, there were regional differences in the distribution of WM changes, with posterior regions and the splenium of the corpus callosum especially affected in AD. The investigators proposed that AD pathology and vascular risks factors may be additive. In the context of the current study, it is intriguing to speculate that the finding of a relationship between the presence of VCs on visuospatial and visuomotor performance may reflect the vulnerability of posterior brain regions. Separate analyses testing for the individual or additive effects of hypertension and hypercholesterolemia suggested that hypertension alone exerted a more deleterious effect on both CERAD design copy and recall. In contrast, hypercholesterolemia was associated with better performance on design recall. This latter finding is not easily explained and may represent an artifact. Limitations of our sample size may have affected the power to detect different effects of hypertension and hypercholesterolemia on cognitive functioning. Current research by our group is enrolling additional patients and correlating white matter damage detected via diffusion tensor imaging with the presence of vascular comorbidities and aspects of cognitive performance in patients with mild to moderate AD.

The overall findings that VCs contribute to cognitive functioning in AD suggest the importance of their control. With the exception of a study by Bellew and colleagues,<sup>19</sup> we know of no studies specifically demonstrating that control may lead to a slower progression of the disease. Our findings are clearly limited to a convenience sample and thus may not be representative of the population at large. Moreover, its cross-sectional nature leaves open the necessity of a longitudinal study investigating the effects of VCs on the course of AD.

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Number of Vascular Comorbidities (Hypertension, Hypercholesterolemia) Broken Down by Demographic Features and MMSE Score

Table 1

Number of Vascular Comorbidities	Mean (SD), Age	Mean (SD) Education	N (%) Gender	N (%) Race	Mean (SD) MMSE
None: N=7 (9%)	64.6 (12.9)	13.0 (5.1)	F: 3 (43%) M: 4 (57%)	AA: 1 (14%) C: 6 (86%)	18.1 (7.6)
One: N=25 (34%)*	74.0 (10.0)	13.1 (2.0)	F: 12 (48%) M: 13 (52%)	AA: 9 (36%) C: 16 (64%)	20.3 (5.0)
Two: N=42 (57%)	78.3 (8.1)	11.9 (3.7)	F: 31 (74%) M: 11 (26%)	AA: 19 (45%) C: 23 (55%)	19.2 (4.0)

\* Hypertension alone: n=15; Hypercholesterolemia alone: n=10

**Table 2** Coefficients (Standard Errors) of Multiple Regression Analyses Examining the Relationship Between Number of Vascular Comorbidities (Hypertension, Hypercholesterolemia) and Cognitive Performance

Overall p	# VCs (0-2)	Gender (0=Female, 1=Male)	Age	Race (0=African-American, 1=Caucasian)	Yrs. Ed	MMSE	Presence of Diabetes or Cardiac Disease (0=No, 1=Yes)
ATTENTION							
Trails A ** n=73 (# Secs.)	-6.02 (13.38)	-7.56 (18.69)	0.09 (0.93)	-42.76 (19.74)*	-2.15 (2.81)	-10.50 (1.87)**	-15.56 (18.68)
Digit Span Forward ** n=73 (# Digits)	-0.28 (0.26)	0.14 (0.35)	0.05 (0.02)**	1.06 (0.37)**	0.01 (0.05)	0.08 (0.04)*	0.49 (0.36)
LANGUAGE							
Boston Naming Test ** n=74 (# Correct)	-0.04 (0.48)	0.12 (0.65)	-0.07 (0.03) <sup>†</sup>	1.90 (0.69)**	0.06 (0.10)	0.22 (0.07)**	0.30 (0.65)
EPISODIC MEMORY							
CERAD Total Word Recall ** n=74 (Trials 1-3)	-1.83 (0.63)**	-1.36 (0.86)	0.02 (0.04)	-0.57 (0.92)	-0.16 (0.13)	0.53 (0.09)**	1.18 (0.87)
CERAD Delayed Word Recall ** n=74 (# Words)	-0.33 (0.25)	-0.22 (0.34)	-0.06 (0.02)**	0.42 (0.36)	0.01 (0.05)	0.11 (0.03)**	-0.23 (0.34)
CERAD Design Recall ** n=73 (# Points)	-0.84 (0.40)*	-0.63 (0.55)	-0.04 (0.03)	0.32 (0.59)	0.05 (0.08)	0.17 (0.06)**	0.00 (0.55)
SEMANTIC MEMORY							
Animal Fluency n=74 (# Correct) **	-0.65 (0.60)	1.35 (0.82)	0.02 (0.04)	0.24 (0.87)	-0.00 (0.13)	0.37 (0.08)**	0.33 (0.82)
VISUO-MOTOR/VISUO-SPATIAL							
CERAD Design Copy ** n=73 (# Points)	-0.21 (0.41)	-0.87 (0.56)	0.01 (0.03)	1.18 (0.60) <sup>†</sup>	0.08 (0.09)	0.22 (0.06)**	0.58 (0.56)
Judgment of Line Orientation ** n=66 (# Points)	-0.83 (0.29)**	-0.04 (0.39)	0.02 (0.02)	-0.01 (0.39)	0.07 (0.05)	0.15 (0.04)**	0.55 (0.37)
EXECUTIVE FUNCTIONS							
Similarities ** n=71 (# Points)	-2.39 (1.13)*	-0.51 (1.56)	0.03 (0.08)	2.11 (1.67)	0.40 (0.23) <sup>†</sup>	0.89 (0.15)**	0.17 (1.56)
Digit Span Backward ** n=73 (# Points)	-0.44 (0.22)*	-0.18 (0.30)	0.06 (0.02)**	0.45 (0.32)	0.06 (0.05)	0.15 (0.03)**	0.59 (0.30) <sup>†</sup>

\* p<.05

\*\* p<.01

+ p<.10