Relationship Between ApoE, MRI Findings, and Cognitive Function in the Cardiovascular Health Study

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Background and Purpose—We determined the relationship between apolipoprotein (Apo)E, MRI, and low cognitive scores.

Methods—The relationship between age, education, ApoE genotype, MRI examination of the brain, subclinical and clinical cardiovascular disease, and low (<80) score on the Modified Mini-Mental State Examination (3MSE, as modified by Teng and Chui) was evaluated for 3469 black and white participants in the Cardiovascular Health Study (CHS) in years 5 and 6 of the study. The participants were followed for up to 3 years.

Results—The prevalence of scores <80 in years 5 and 6 of the CHS was 8.2% for participants without and 20.4% for those with prior history of stroke. Age, race, and education were important determinants of low 3MSE scores. The prevalence of ApoE-4 (odds ratio [OR], 1.6 [1.1 to 2.1]) was directly related to scores <80, as was high ventricular volume (OR, 1.6 [1.2 to 2.3]), high white matter grade (OR, 1.4 [1.1 to 1.9]), and infarctlike lesions (OR, 1.6 [1.2 to 2.1]) on the MRI in the multivariate analysis. A five-point or greater decline in scores over up to 3 years was more often observed for participants with low 3MSE scores at year 5, at older ages, with lower education, and experiencing incident stroke (OR, 3.6 [1.2 to 10.6]), ApoE-4 genotype (OR, 1.8 [1.4 to 2.3]), and with MRI findings of high ventricular volume (OR, 2.0 [1.5 to 2.7]), and infarctlike lesions (OR, 1.2 [0.9 to 1.5]).

Conclusions—These results demonstrate that vascular changes on MRI, measures of brain atrophy, ApoE-4, and age, education, and race are associated with low cognitive scores among older individuals. The MRI of the brain provides valuable information related to cognitive tests and decline over time. The potential exists for using MRI measurements to identify high-risk individuals for dementia and to test potential interventions to reduce the risk of dementia. (Stroke. 1998;29:388-398.)

Key Words: apolipoproteins ■ dementia ■ magnetic resonance imaging ■ stroke ■ vascular disease

In this report from the CHS, we investigated (1) the association of ApoE genotype with cognitive function as measured by the 3MSE (Teng et al)1,2; (2) the association between ApoE-4 and subclinical and clinical CVD at baseline with MRI findings at years 5 and 6 of the CHS and low score (<80) on 3MSE at years 5 or 7 of CHS; and (3) the relationship between MRI findings and subclinical and clinical cardiovascular disease, ApoE, incident cardiovascular disease, and stroke after the MRI with five-point or greater decrease in the 3MSE scores between years 5 and 7.3

The analyses are based on a very large population-based sample of 3480 older black and white participants who had an MRI of the brain, ApoE genotyping, assessment of incident stroke, MI, angina pectoris, and CHF, and evaluation of subclinical CVD.

This report focuses on the interrelationship of age, race, education, MRI findings, ApoE-4, low cognitive scores, and decline in scores over 3 years after the MRI in older adults.

Knowledge of the association of vascular disease and dementia has been evolving with increasing use of cerebral MRI and CT, which have shown that subclinical vascular pathology in the brain (such as “silent infarction” and white matter changes) of probable vascular origins may be associated with cognitive decline and dementia.4-7

Improved survival of patients after a stroke and a growing population of older individuals who are at higher risk of incident stroke suggest that the number of cases of vascular dementia may increase in the future. It is currently estimated that approximately 20% to 25% of incident stroke cases subsequently become demented.8-10 In addition, case-fatality rates are higher among stroke patients who become demented than those who are not demented.11

The neuronal cellular loss13 that accompanies the increase in β-amyloid and neuronal fibrillary tangles can be identified on CT and MRI brain scans as brain atrophy.13 It remains difficult to separate brain atrophy and Alzheimer’s disease from normal...
aging in the early stages of Alzheimer’s disease. Patients with Alzheimer’s disease have been reported to have greater ventricular volume and greater increase in ventricular volume over time compared with that in control subjects. Major changes in Alzheimer’s disease are often found in the hippocampus, amygdala, and temporal lobe. There is no specific diagnostic pattern on an MRI to separate Alzheimer’s disease from “aging.”

Abnormal white matter findings on MRI are common among older individuals and have been associated with older age and hypertension. White matter lesions are likely related to vascular disease in the long, penetrating arteries in the brain. White matter abnormalities have been associated with a cognitive loss in some but not all studies.

The association of ApoE-4 genotype with Alzheimer’s disease has been repeatedly documented in both case-control and longitudinal studies. Individuals who have ApoE-4 genotype have a higher prevalence and earlier age of onset of Alzheimer’s disease. The association of ApoE-4 with other causes of dementia, especially vascular dementia, is less certain.

Methods

The design of the CHS has been published. The original sample of the CHS included 5201 adults 65 years of age or older recruited from a defined sample of the Medicare files in four communities in the United States: Forsyth County, NC; Sacramento County, Calif; Washington County, Md; and Pittsburgh, Pa. The eligible participants were not institutionalized and were expected to remain in the area for at least the next 3 years. They were able to give informed consent that did not require a proxy respondent at baseline. Participants were recruited to the study between June 1989 and May 1990. The original sample of 5201 participants was 57% women and 95% Caucasian. In 1992 to 93 (year 5), 687 additional African-American participants were recruited to the study in three of the four communities (Forsyth County, NC; Sacramento, Calif; and Pittsburgh, Pa) (year 5) by similar methods as in the original recruitment from the Medicare files. These participants are referred to as the new CHS cohort.

Cognitive Testing

The baseline evaluation included home interviews and physical examinations. At the baseline examination for the original cohort (year 2), participants completed the MMSE. Participants were then seen yearly in the clinic. Beginning in year 3 of the study, the 3MSE replaced the MMSE (see “Appendix”) and was administered annually at all clinic visits and on home visits when appropriate.

The 3MSE samples a wider range of cognitive abilities, extends the ceiling and floor of the test, and enhances the reliability and validity of the scores. The components of the MMSE include short-term and delayed recall and temporal and spatial orientation. The scores on the MMSE range from 0 to 30, and on the 3MSE range from 0 to 100. Teng and coworkers reported that the mean score was 43 for demented patients on the MMSE, with a standard deviation of 26, and for normal control subjects 94, with a standard deviation of 6. The scores on the MMSE and the 3MSE previously have been reported to be highly correlated with age and education.

In this report, we have used a cut-point of 80 for the 3MSE on the basis of recommendations of the author of the 3MSE (E.L. Teng, PhD, personal communication, 1995). The 3MSE, just before or immediately after MRI (within 60 days) was used in the year 5 and 6 analysis. A decrease of five or more points in the 3MSE between the MRI and year 7 was considered a “significant change” in the test score. All of the cut-points and changes in scores were defined before the analysis of the results. The Spearman correlation between 3MSE at years 3 and 5 to 6 for white participants in the CHS without clinical stroke was .67 (data not shown). The digit symbol substitution test (DSST) and the Benton Visual Retention Test (“C” form) (years 6, 7, and 8 only) were also administered to the participants.

The DSST is a measure of attention and speed. The Spearman correlation between the digit symbol substitution test at year 5 and the 3MSE at year 5 was .55. A low digit symbol score was classified as <30.

The Benton Visual Retention Test form C consists of 10 designs: The participant sees the design for 10 seconds and then is asked to copy it. We classified the Benton as 0, 1, or 2 correct versus 3 to 10 positive.

MRI Examination

At years 5 and 6 of the study (1992 to 1994), all subjects were invited to have a MRI of the brain to assess the extent and severity of cerebral vascular disease. A detailed description of the MRI techniques and methods of analyses have been published.

The scanning protocol included unenhanced sagittal and axial spin–echo T1–weighted images (repetition time [TR], 500 msec; echo time [TE], 20 msec) and axial spin-density and T2–weighted images (TR, 3000 msec; TE, 30 and 100 msec) in sections of 5-mm thickness, with no interslice gaps, as detailed in the previously reported pilot study. Axial scans were parallel to a line between the anterior and posterior commissures (AC–PC line). All scans were performed without administration of contrast.

Ventricle scores extended from slitlike ventricles (grade 0) to markedly enlarged ventricles (grade 9). Sulci grades ranged in a similar fashion. White matter changes were estimated by the total extent of periventricular and subcortical white matter signal abnormality on spin density weighted axial images graded by successive increase from no changes or barely detectable changes (grades 0 and 1, respectively) to almost all white matter involved (grade 9). ILL were defined as focal, nonmass lesions in a vascular distribution, hyperintense to grey matter on both spin density and T2–weighted images.

The MRI examinations were completed for 3660 (62%) of 5888 participants in the CHS, including 3073 (62%) of 4927 white subjects, 566 (62%) of 916 black subjects, and 21 of other races. There were 2132 women and 1528 men who had MRI examinations. Having an MRI examination was inversely related to age: 1350 age 65 to 69 years (67%), 1237 age 70 to 74 (59%), 706 age 75 to 79 (50%), 284 age 80 to 84 (37%), and 83 age 85 or older (36%) underwent MRI examinations. There were no differences in distinction of ApoE between the total cohort and participants who had an MRI. Participants who completed MRIs had higher scores on the 3MSE and the MMSE at year 2. They were better educated (25.5% college or higher) compared with 18% for those who did not have an MRI. Of those who had an MRI, 28% had a history of clinical cardiovascular disease compared with 37% with a history of clinical cardiovascular disease for participants who did not have an MRI at years 5 to 6. The analysis of the MRI cohort underestimated the prevalence of low 3MSE in the population.

The reasons for not having an MRI included the following: the patient died before the MRI examination (374); no clinic visit in years 5 to 6 (477); patient refused (506); MRI contraindications (277); patient unable to complete MRI (439); and other.

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Selected Abbreviations and Acronyms

Apo = apolipoprotein
CHF = congestive heart failure
CHS = Cardiovascular Health Study
CI = confidence interval
clinical/subclinical CVD = clinical/subclinical cardiovascular disease
ILL = infarctlike lesions
MI = myocardial infarction
MMSE = Mini-Mental State Examination
MRI = magnetic resonance imaging
OR = odds ratio
3MSE = Modified Mini-Mental State Examination

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We classified the MRI parameters both as continuous variables and as categorical variables (ie, high and low categories). For categorical analysis in this report, we coded variables as follows: for infarcts (>3 mm) 0 versus 1 to 5 ILH; for white matter grades 0 to 2 versus grades 3 to 9; for sulci width 1 to 4 versus 5 to 8; and for ventricle size 1 to 4 versus 5 to 9. Several studies describing the results of the initial MRI examination in the CHS have recently been published.26–29

**Measurement of ApoE**

The three major allelic forms of the ApoE gene were determined in the Core Molecular Genetics facility at the University of Vermont College of Medicine by the method of Hixson and Vernier.30 The two primers used for polymerase chain reaction amplification, done in 96-well microtiter plates, were 5’GGCAGGGCTTCAAGGA3’ and 5’ACAGAATTCGGCCCGCTGTGTA3’. AmpliTaq T4 DNA polymerase was obtained from Perkin-Elmer; the restriction enzyme HhaI was obtained from New England BioLabs. DNA samples known to be E4/E4 and E2/E3 were analyzed with each batch as positive controls. The restriction patterns were determined from gels stained with ethidium bromide. DNA samples known to be E4/E4 and E2/E3 were analyzed with each batch as positive controls. The restriction patterns were determined from gels stained with ethidium bromide.

**Subclinical and Clinical Vascular Disease and Stroke**

At baseline (year 2) for the original cohort and at year 5 for the new cohort, prevalence and extent of clinical cardiovascular disease was assessed. Clinical vascular disease was defined as a confirmed history of heart disease, including MI, angina pectoris, CHF, coronary bypass surgery, atrial fibrillation as detected by electrocardiogram, use of a cardiac pacemaker, history of stroke or transient ischemic attack or carotid artery surgery, and history of intermittent claudication or peripheral vascular surgery. Note that clinical CVD includes both cardiovascular, cerebrovascular, and lower extremity peripheral vascular disease.

Subclinical CVD was defined as ankle-arm index <0.9 mm Hg, internal carotid wall thickness >80th percentile, common carotid wall thickness >80th percentile, carotid stenosis >25%, major electrocardiogram abnormalities, or Rose Questionnaire positive for claudication or angina.32

**Statistical Methods**

Tests for linear trend involved the use of Cochran-Mantel $\chi^2$ tests. Logistic regression models were used to model low cognitive function scores or large changes in cognitive function scores between two examinations. The logistic analyses included age, sex, race, education level, subclinical and clinical disease status, and presence of ApoE-4 as variables in the models. For models looking at change in cognitive scores between two time points, the cognitive test score at the first time point was included as a covariate in the logistic model. Stepwise logistic regression with the above variables forced into the model allowed for assessment of the significance of interactions.

**ApoE, MRI Findings, and Cognitive Function**

<table>
<thead>
<tr>
<th>Total No.</th>
<th>No History of Stroke</th>
<th>History of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
</tr>
<tr>
<td>White men</td>
<td>1237</td>
<td>1132</td>
</tr>
<tr>
<td>White women</td>
<td>1698</td>
<td>1628</td>
</tr>
<tr>
<td>Black men</td>
<td>197</td>
<td>183</td>
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<td>320</td>
</tr>
<tr>
<td>Total</td>
<td>3469</td>
<td>3263</td>
</tr>
</tbody>
</table>

The distribution of ApoE genotype for the entire CHS cohort was measured. There were 5457 participants who had ApoE measurements, and 3480 (64%) of these participants (Table 1) also had an MRI examination. The frequency of the ApoE-4 genotype was 1.6%, and 25.6% of the 5457 participants had at least one ApoE-4 gene. The distribution of ApoE was similar when restricted to participants who had an MRI examination.

The percentage of participants with at least one ApoE-4 allele was significantly higher among black subjects (31.6%) than white subjects (24.4%). This race difference persisted after adjustment for age. The percentage of participants with ApoE-4 decreased with age: 27.3% of participants 65 to 69 years old compared with 21.2% older than 80 had at least one ApoE-4 allele. The distribution of ApoE genotypes was not significantly different for men and women, and there was no consistent relationship between levels of education and ApoE-4 genotypes (not shown). The observed distribution of ApoE genotypes was similar to that seen in other studies of older individuals.34,35

**Results**

Characteristics of the CHS participants, those who had an MRI, ApoE, and 3MSE cognitive testing at year 5 to 6 and are included in the analysis are shown in Table 1. The mean age at entry to the CHS was 71 years. There were 3469 white and black participants, including 206 with a history of stroke before the MRI examination.

**ApoE Measurements**

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**Relationship of ApoE-4 to Subclinical and Clinical Disease and MRI Measurements**

At CHS baseline, 31% of white participants and 36% of black participants had clinical CVD by CHS criteria, 42% of white participants and 41% of black participants had subclinical CVD, and 28% of white participants and 23% of black participants
TABLE 2. Relationship Between MRI Variables and Modified Mini-Mental State Examination at Years 5 to 6 by Race, No Prior History of Stroke

<table>
<thead>
<tr>
<th>MRI Years 5 to 6</th>
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<th>White</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>White matter grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>3–9</td>
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<td>30</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Sulci width</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>62</td>
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<td>30</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>No. infarcts ≥3 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>18</td>
</tr>
<tr>
<td>1–5</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Ventricle volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>20</td>
</tr>
<tr>
<td>5–9</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>43</td>
</tr>
</tbody>
</table>

Modified Mini-Mental State Examination

The 3MSE scores were substantially lower in black subjects than in white subjects (Table 1). The percent of participants with 3MSE <80 increased with age and lower education. In bivariate analysis the percentage with low 3MSE varied from 9.3% for black subjects and 2.5% for white subjects 65 to 69 years old to 51.7% for black subjects and 22% for white subjects 80 or older. Approximately 42% of black subjects and 13% of white subjects with less than a high school education had low 3MSE scores. However, for those with college education or more, the percentage with a low score was similar for black subjects (3.3%) and white subjects (2.2%). The prevalence of scores <80 was greater for participants with a history of stroke before the MRI (Table 1).

Relationship of MRI ApoE to Low Modified Mini-Mental State Score at Time of MRI

In the bivariate analysis for participants without a prior history of stroke, a low score (<80) on the 3MSE measurement at the time of the MRI was significantly related to several MRI variables, white matter grade, infarctlike lesions, ventricular volume, and sulci width (Table 2). The association of MRI findings with 3MSE low scores was not significantly different for men compared with women or for black subjects compared with white subjects. For stroke cases, the prevalence of the MRI changes was higher and the mean 3MSE was lower. For white subjects, the number of previous 3MSE tests before MRI could have been 3 to 4 times, whereas for the new cohort of black subjects, the year 5 test was their first 3MSE evaluation. Learning effects for the 3MSE therefore could affect differences in scores between black subjects and white subjects. However, the scores were similar for black subjects in the original cohort recruited in year 2, the same time as for white subjects and the year 5 new cohort of black subjects.

The association of low 3MSE scores with age, education, sex, subclinical disease at baseline, ApoE-4, and MRI findings was evaluated with the use of logistic regression; the 3MSE score was the dependent variable (<80). The analysis excluded participants with a history of stroke before the MRI and is presented in Table 3.

Overall, high ventricle volume scores, high white matter grade scores, presence of MRI ILL ≥3 mm, and presence of ApoE-4 were related to low 3MSE (<80) scores at year 5 to 6 in the multiple logistic regression analysis that included adjustment for confounding by age, education, and sex. These associations were very similar for black subjects and white subjects.

The association of MRI variables and low 3MSE scores (<80) was different for men and women. For women, large ventricles (OR, 2.7; 1.7 to 4.4) was the stronger risk factor on MRI. For men, sulci width (OR, 1.7; 1.1 to 2.8), was most highly related to a low 3MSE score. The association of low 3MSE with MRI ILL and white matter score were similar in men and women.

The determinants of low score on the digit symbol substitution test were similar to the results for the 3MSE (not shown) for both black subjects and white subjects.

MRI and Changes in the Modified Mini-Mental State Scores, Years 5 to 7

There were 3253 white subjects and 584 black subjects alive at year 7 (excluding those with a prior stroke history) who had repeat 3MSEs. Of the 3253 white subjects, 655 (20.6%) had a decrease of at least 5 points on the 3MSE between years 5 to 7 compared with 133 (22.7%) of 584 black subjects. The percentage with declining scores was not significantly different (OR, 0.97; 0.74 to 1.26) (Table 4) for black subjects and white subjects (Table 5) and for men and women (not shown). The probability of a decline of five or more points was related to age (15%, 65 to 69 years at entry versus 42%, 80 or older; P = .001) and to education (30% in those with less than high school education to 17% in those with a college diploma) (not shown) (P = .001).
The decline in scores between years 5 to 7 was related to scores at year 5 as 43.6% (24 of 55) participants with year 5 scores, 70 versus 18.8% with year 5 scores of $90 had declined five points between years 5 to 7 ($p = .0001$) (Table 5).

The decline of 5 points from years 5 to 7 was also related to the presence of ApoE-4 gene (Figure). Several of the variables measured by the MRI at year 5 were also related to a 5-point decline, including number of infarcts $\geq 3$ mm, high sulci width, white matter grade, and size of ventricles ($p < .001$) for all MRI variables (Figure). In the multivariate model (Table 4) high white matter grade, MRI infarcts, high ventricular volume, ApoE-4, and subclinical cardiovascular disease at baseline were predictors of decline of five or more points.

Among white participants with no clinical cardiovascular disease before MRI (including stroke), the decline in the MMSE between years 5 to 7 was directly related to an incident stroke after MRI ($n = 29$; OR, 3.6; 1.2 to 10.2) but weakly related to incident MI ($n = 47$; OR, 1.5; 0.6 to 4.2), or angina pectoris ($n = 116$; OR, 1.4; 0.8 to 2.5). These results were based on the logistic regression analysis that included age, education, sex, MRI measures, and prevalent subclinical/clinical disease (Table 6). The association of stroke with decline of five points in score between years 5 and 7 was especially strong for white women (OR, 6.0; 1.5 to 24.0) compared with men (OR, 1.6; 0.4 to 9.2; not shown). Further inclusion of low MMSE at year 5 to 6 (OR, 1.4; 0.9 to 2.2) or duration of follow-up between examinations (0.7, 0.5 to 1.0) did not affect the results. There were too few events among black subjects between years 5 and 6 (seven strokes and seven MIs) to analyze this subgroup.

### Modified Mini-Mental State Examination at Year 7 Prospective Analysis

In multivariate analysis the primary predictors of a low 3MSE at year 7 were similar to years 5 to 6 (Table 4) education indicators, low 3MSE at years 5 to 6, ApoE-4 (OR, 1.6; 1.2 to 2.2), high ventricular volume (OR, 1.5; 1.1 to 2.2), high white matter grade (OR, 1.4; 1.0 to 1.9), and ILL on MRI (OR, 1.4; 1.0 to 2.5). These results were based on the logistic regression analysis that included age, education, sex, MRI measures, and prevalent subclinical/clinical disease (Table 6). The association of stroke with decline of five points in score between years 5 and 7 was especially strong for white women (OR, 6.0; 1.5 to 24.0) compared with men (OR, 1.6; 0.4 to 9.2; not shown). Further inclusion of low MMSE at year 5 to 6 (OR, 1.4; 0.9 to 2.2) or duration of follow-up between examinations (0.7, 0.5 to 1.0) did not affect the results. There were too few events among black subjects between years 5 and 6 (seven strokes and seven MIs) to analyze this subgroup.

#### TABLE 3. Factors Associated With Modified Mini-Mental State Score <80 in Older Adults at Years 5 to 6*

<table>
<thead>
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<th>Black</th>
<th>White</th>
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<tbody>
<tr>
<td></td>
<td>Odds</td>
<td>Ratio</td>
<td>CI</td>
</tr>
<tr>
<td>Age, y†</td>
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<td></td>
</tr>
<tr>
<td>70–74</td>
<td>1.5</td>
<td>(0.8, 3.0)</td>
<td>1.1</td>
</tr>
<tr>
<td>75–79</td>
<td>2.9</td>
<td>(1.4, 5.9)</td>
<td>2.6</td>
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<td>≥80</td>
<td>7.2</td>
<td>(3.2, 16.2)</td>
<td>6.2</td>
</tr>
<tr>
<td>Sex</td>
<td>1.0</td>
<td>(0.6, 1.6)</td>
<td>1.3</td>
</tr>
<tr>
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<td>...</td>
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<td>(4.3, 25.4)</td>
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<tr>
<td>Some college</td>
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<td>(0.6, 4.1)</td>
<td>1.8</td>
</tr>
<tr>
<td>MRI, infarct 0, (1–5)</td>
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<td>(1.1, 3.1)</td>
<td>1.5</td>
</tr>
<tr>
<td>High ventricular volume (1–4), (5–9)</td>
<td>1.0</td>
<td>(0.5, 2.0)</td>
<td>1.9</td>
</tr>
<tr>
<td>Increased sulci width (1–4), (5–8)</td>
<td>1.6</td>
<td>(0.8, 3.2)</td>
<td>1.2</td>
</tr>
<tr>
<td>High white matter grade (0–2), (3–9)</td>
<td>1.5</td>
<td>(0.9, 2.5)</td>
<td>1.5</td>
</tr>
<tr>
<td>ApoE-4</td>
<td>1.5</td>
<td>(0.9, 2.5)</td>
<td>1.6</td>
</tr>
<tr>
<td>Clinical CVD at baseline</td>
<td>1.0</td>
<td>(0.5, 1.9)</td>
<td>1.4</td>
</tr>
<tr>
<td>Subclinical CVD at baseline</td>
<td>0.8</td>
<td>(0.4, 1.5)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*In participant with no history of stroke.
†College education or higher ≥1, age 65–69 = 1.

#### TABLE 4. Multivariate Analysis of Determinants of Decline of Five or More Points, Years 5 to 6 and Year 7 (Excluding Stroke Cases)*

<table>
<thead>
<tr>
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<th>White</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>ApoE-4</td>
<td>1.30</td>
<td>(0.78, 2.15)</td>
<td>1.68</td>
</tr>
<tr>
<td>MRI, infarct 0, (1–5)</td>
<td>0.94</td>
<td>(0.55, 1.61)</td>
<td>1.24</td>
</tr>
<tr>
<td>High ventricular volume (1–4), (5–9)</td>
<td>1.31</td>
<td>(0.64, 2.68)</td>
<td>2.02</td>
</tr>
<tr>
<td>High sulci width (1–4), (5–8)</td>
<td>0.74</td>
<td>(0.34, 1.58)</td>
<td>1.20</td>
</tr>
<tr>
<td>High white matter grade (0–2), (3–9)</td>
<td>1.62</td>
<td>(0.94, 2.77)</td>
<td>1.17</td>
</tr>
<tr>
<td>Clinical CVD at baseline</td>
<td>1.94</td>
<td>(1.0, 3.76)</td>
<td>1.07</td>
</tr>
<tr>
<td>Subclinical CVD at baseline</td>
<td>1.45</td>
<td>(0.78, 2.67)</td>
<td>1.29</td>
</tr>
<tr>
<td>Black</td>
<td>...</td>
<td>...</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Other significant variables included in model: age, education, sex, low 3MSE at years 5 to 6.
TABLE 5. Five-Point Decrease or Greater in Modified Mini-Mental Scores Over a 3-Year Period After MRI by Age Group

<table>
<thead>
<tr>
<th>Years 5 to 6</th>
<th>Blacks With Five-Point Decrease</th>
<th>%</th>
<th>No.</th>
<th>Whites With Five-Point Decrease</th>
<th>%</th>
<th>No.</th>
<th>Total With Five-Point Decrease</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3MSE Score*</td>
<td>No.</td>
<td></td>
<td></td>
<td>No.</td>
<td></td>
<td></td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>32</td>
<td>12</td>
<td>37.5</td>
<td>23</td>
<td>12</td>
<td>52.2</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>70–79</td>
<td>50</td>
<td>14</td>
<td>28.0</td>
<td>89</td>
<td>35</td>
<td>39.3</td>
<td>139</td>
<td>49</td>
</tr>
<tr>
<td>80–89</td>
<td>159</td>
<td>31</td>
<td>19.5</td>
<td>438</td>
<td>108</td>
<td>24.7</td>
<td>597</td>
<td>139</td>
</tr>
<tr>
<td>≥90</td>
<td>188</td>
<td>42</td>
<td>22.3</td>
<td>1934</td>
<td>357</td>
<td>18.5</td>
<td>2122</td>
<td>399</td>
</tr>
<tr>
<td>Total†</td>
<td>429</td>
<td>99</td>
<td>23.1</td>
<td>2484</td>
<td>512</td>
<td>20.6</td>
<td>2913</td>
<td>611</td>
</tr>
</tbody>
</table>

P for linear trend: P = .042 (Blacks), P = .001 (Whites), P = .001 (Total)

*Score closest to MRI.
†Excludes “other” race categories (n=20).

Discussion

The CHS is one of the largest longitudinal studies of older individuals that includes measures of cognition, ApoE, MRI of the brain, and clinical and subclinical vascular disease.

The DSM IV diagnostic criteria for dementia includes the development of multiple cognitive deficits, one of which must be memory impairment, which causes impairment in social and occupational functioning and a decline in functioning over time. Low scores on screening tests such as the MMSE are not synonymous with dementia but are powerful risk factors for dementia.

There are four variables that are related to both low 3MSE scores (<80) at year 5 and decline in scores between years 5 to 7, including (1) demographic factors (low education levels and increasing age), (2) measures of possible brain atrophy on MRI (higher ventricular volume), (3) measures of vascular disease (prevalent and incident stroke, MRI infarcts >3 mm and higher white matter grade), and (4) genetic factors/host susceptibility (prevalence of ApoE-4).

Education and Age

Education and age were very powerful determinants of a low 3MSE score at years 5 to 6 and 7. Cognitive scores declined with increasing age. Lower prior education levels are associated with poorer cognitive scores and probably, a higher incidence and prevalence of dementia of the Alzheimer’s type. The CHS was unique in having included a large sample of older individuals with less than a high school education and more than a college degree. Black participants had a much higher prevalence of low 3MSE scores (<80) (21.6%) compared with 5.7% for white participants. For both black and white participants there was a very strong association of age and education to low scores. The very large OR for low 3MSE scores for black participants with less than a high school education compared with college-educated black participants (45-fold) (Table 3) demonstrates the importance of education on cognitive function tests. For each age and education group, low 3MSE scores were more prevalent among black participants compared with white participants. However, the prevalence of scores <80 on the 3MSE among college-educated black participants was similar to the prevalence of low 3MSE for college-educated white participants (3.8% and 2.5%, respectively) and much lower than for black or white participants with no high school diploma.

The educational attainment of this older cohort (mean age of 73 years at entry) is related to education and socioeconomic factors 50 to 60 years ago (1930 to 1940s). In the CHS sample, 23% of white subjects had less than a high school education, 54% high school and/or some college, and 23% college education or greater compared with 39% of black subjects with less than a high school education, 43% high school and/or some college, and 18% with a college education. The difference in prevalence of low scores (<80 on 3MSE) among black subjects with less than a high school compared with a high school education (41.5% versus 3.3%) may be due to effects of education, to effects of environmental agents on the brain and cognitive function early in life, to subsequent differences in lifestyle after completing their education, or to effects of hypertension, diabetes, and vascular disease, which have higher prevalence in less-educated black subjects and white subjects, and may be risk factors for low cognitive scores and MRI abnormalities. The prevalence of MRI abnormality in this study, however, were similar for black subjects and white subjects. The differences in level of “formal education” do not measure the quality of formal education years ago nor the effect of informal educational experiences that could have affected the test results.

ILL, ventricular volume, high white matter grade on MRI, and ApoE-4 were all related to low scores on the Benton Visual Retention Test (form C), DSST, and 3MSE for both black and white subjects, and there was relatively little difference in the strength of the associations among the three tests for black subjects compared with white subjects. The results were also similar for the original black cohort recruited in 1989 to 1990 and the new black cohort (1992 to 1993) that had not been previously tested.

The five-point decline in 3MSE scores between years 5 and 7 was related to both age and education and were similar for black subjects and white subjects. The follow-up (maximum approximately 3 years) is short, and further long-term follow-up may identify other determinants of change in 3MSE scores.
Determinants of decrease in Modified Mini-Mental State of five or more points between years 5 and 6 to 7 (MRI measures, years 5 to 6) (comparison of black and white participants).

The CHS does not include a measure of clinical dementia. The 3MSE is biased as a screening instrument for possible dementia, as are many other neuropsychological screening instruments. Many investigators have noted differences by education and race in the sensitivity and specificity of screening instruments compared with clinical diagnosis of dementia.47,48 Prior education and experience with some of the items on the neuropsychological tests may influence the test scores. The results of the Benton were also similar to the 3MSE and DSST. None of these tests, however, have been extensively used for evaluating population samples of black subjects. There is no population data demonstrating the relationship of test scores to clinical dementia within the black populations.

Ventricular Atrophy

Measures of brain morphology based on the MRI examination, as indicated by ventricle size and white matter lesions, and MRI infarct were related to low scores on the 3MSE and to a decline in scores over time. Most of these associations were similar for black subjects and white subjects. The confidence limits overlapped unity for black subjects in some analyses. This could be due to the smaller sample size in this racial group.

One of the most important observations of the study was the strong and independent association of large ventricles (as measured by the MRI) with low scores on the 3MSE and DSST, and measure of disability.53 Some investigators have noted differences by education and race in the sensitivity and specificity of screening instruments compared with clinical diagnosis of dementia.47,48 Prior education and experience with some of the items on the neuropsychological tests may influence the test scores. The results of the Benton were also similar to the 3MSE and DSST. None of these tests, however, have been extensively used for evaluating population samples of black subjects. There is no population data demonstrating the relationship of test scores to clinical dementia within the black populations.

TABLE 6. Factors Associated With Five-Point or More Decrease in 3MSE Over 3 Years After MRI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>(Confidence Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>1.1</td>
<td>(0.8, 1.5)</td>
</tr>
<tr>
<td>75–79</td>
<td>1.6</td>
<td>(1.3, 2.4)</td>
</tr>
<tr>
<td>≥80</td>
<td>3.1</td>
<td>(2.0, 4.8)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.2</td>
<td>(0.9, 1.5)</td>
</tr>
<tr>
<td>No high school</td>
<td>2.8</td>
<td>(2.0, 4.0)</td>
</tr>
<tr>
<td>Some college*</td>
<td>1.5</td>
<td>(1.1, 2.1)</td>
</tr>
<tr>
<td>MRI, ILL†, 0, (1–5)</td>
<td>1.2</td>
<td>(0.9, 1.5)</td>
</tr>
<tr>
<td>High ventricular volume† (1–4), (5–9)</td>
<td>2.0</td>
<td>(1.5, 2.7)</td>
</tr>
<tr>
<td>High sulci width† (1–4), (5–8)</td>
<td>1.2</td>
<td>(0.9, 1.6)</td>
</tr>
<tr>
<td>High white matter grade† (0–2), (3–9)</td>
<td>1.0</td>
<td>(0.8, 1.3)</td>
</tr>
<tr>
<td>ApoE-4</td>
<td>1.8</td>
<td>(1.4, 2.3)</td>
</tr>
<tr>
<td>Incident stroke after MRI</td>
<td>3.6</td>
<td>(1.2, 10.6)</td>
</tr>
<tr>
<td>Incident CHF after MRI</td>
<td>0.6</td>
<td>(0.3, 1.3)</td>
</tr>
<tr>
<td>Incident angina after MRI</td>
<td>1.4</td>
<td>(0.8, 2.5)</td>
</tr>
<tr>
<td>Incident MI after MRI</td>
<td>1.5</td>
<td>(0.6, 4.2)</td>
</tr>
<tr>
<td>Subclinical disease baseline†</td>
<td>1.0</td>
<td>(0.7, 1.5)</td>
</tr>
</tbody>
</table>

*College education or higher=1, age 65–69=1.
†See text for definitions.

ApoE, MRI Findings, and Cognitive Function

Vascular Disease in the Brain

Both white matter grade and number of ILL on MRI were related to low score (<80) at years 5 to 7 and declines in 3MSE scores between years 5 to 7. The ILL and white matter abnormalities are likely related to vascular disease.18,29 Various measures of subclinical disease such as carotid artery wall thickness, stenosis, or decreased ankle-brachial blood pressure are risk factors for MRI infarcts26 and white matter abnormal-
patients are not included in large clinic follow-ups, such as in dementia clinics. It is also likely that some patients have unrecognized dementia before their stroke. Stroke cases that became demented also have a shorter life expectancy.

Approximately 5% of the population over age 65 years have prevalent stroke. Approximately 25% of stroke patients become demented after their stroke. One study has estimated that there are 430,000 stroke cases that are demented over the age of 65 in the United States and that 62% (266,000) have their dementia directly related to stroke. Prevention of stroke could possibly substantially reduce the prevalence and incidence of dementia in the population.

Low scores on cognitive tests have also been reported to be a risk factor for clinical stroke. It is possible that risk factors such as hypertension, diabetes, and hyperlipidemia may lead to brain changes such as ILL and high white matter grade that are associated with lower scores on cognitive function tests and therefore also on increased risk of clinical stroke. Treatment of risk factors could possibly reduce both risk of clinical stroke and cognitive decline.

Subclinical cardiovascular disease at baseline was related to a 3MSE score <80 at age 5, white subjects only, and decline in scores between years 5 and 7, black subjects and white subjects, after adjustment for confounding by age, education, and MRI measures (Tables 3 and 4). These results are consistent with a recent report from the Rotterdam Study, which found that carotid artery wall thickness, ankle-brachial blood pressure, and ApoE-4 were strong predictors of both vascular and Alzheimer’s disease–related dementia. However, these associations were cross-sectional. In the CHS (for the white cohort), the measures of subclinical disease were done at baseline, approximately 3 years before the 3MSE evaluation. The measures of subclinical disease for most of the black cohort were done concurrently with the 3MSE and MRI at year 5 or 6.

In the Rotterdam Study (age 55 to 94 years), histories of both MI and stroke were associated with a low score on the MMSE at baseline examination. In the CHS, the OR for MI was increased 1.5, but confidence limits were wide (0.6 to 4.2) because of the small number of incident MI cases.

ApoE
ApoE-4 was associated with both low 3MSE scores (<80), in black subjects and white subjects at years 5 and 7 (approximately a twofold difference stronger in white subjects than black) and a decline of five or more points between years 5 to 7 in white subjects only. Several studies have also shown that ApoE-4 is related to a more rapid decline in cognitive scores over time and early changes in brain metabolism. The combination of lower initial scores on cognitive tests and ApoE-4 may be an important determinant of risk of dementia.

The association of ApoE polymorphism and vascular dementia is more controversial than for Alzheimer’s disease. ApoE-4 is associated with higher levels of LDL cholesterol, premature atherosclerosis, and higher incidence of clinical coronary heart disease. There is relatively little evidence for a relationship between ApoE-4 genotype, extent of cardiovascular disease, and risk of dementia. The prevalence of subclinical or clinical cardiovascular disease and MRI changes were not significantly different for participants who had or did not have ApoE-4 genotype in the CHS. The association of ApoE-4 with lower cognitive scores was not due to higher prevalence of atherosclerotic vascular disease associated with ApoE-4. Individuals with ApoE-4 genotype at postmortem examination have a higher prevalence of neuropathological changes of Alzheimer’s disease, extracellular deposition of β-amyloid, and the intracellular neurofibrillary tangles. A population-based study in New York City and Rotterdam, The Netherlands, reported that the prevalence of ApoE-4 was significantly higher (OR, 1.8; 1.2 to 2.7) for heterozygote ApoE-4 stroke cases with dementia compared with control subjects.

In the Zutphen Study of older men, ApoE-4 was associated with a 2-fold increased risk of impaired cognitive function. There was a very strong association of cerebrovacular disease, ApoE-4, and decline in scores. The prevalence of both an ApoE-4 and stroke was associated with a 17-fold greater risk of cognitive decline compared with those with no history of stroke and not ApoE-4. The results are similar to the current CHS study.

**Diagnosis of Dementia**

The CHS does not include a clinical diagnosis of dementia and included only screening tests for possible dementia (3MSE, DSST, and the Benton Visual Retention Test). The sensitivity and specificity of a cut-point of 80 on the 3MSE test is very high for diagnosis of dementia. The Canadian Study of Aging and Health used the 3MSE to establish the prevalence of dementia in five regions of Canada. A cut-point of 77 to 78 was used to select individuals for further evaluation. Of the 8949 screened, 1614 (18%) scored below 78. The subjects who scored below 78 and all institutionalized participants had a further detailed neurological and psychiatric evaluation. Approximately 50% (1125) were subsequently diagnosed as being demented, 772 as having cognitive loss without dementia, and 523 as normal, including 358 (36%) of 1006 community control subjects who initially scored below 77 to 78. There were 494 individuals who had a “normal 3MSE” >78, and only 7 (1.4%) were found to be demented by further detailed neurological and psychiatric evaluation.

The 3MSE is very similar to the Cognitive Abilities Screening Instrument (CASI) used in the Honolulu-Asia aging study. A score of 82 on the CASI is equivalent to approximately 25 to 26 on the MMSE. In the Honolulu-Asia study, 92% of the dementia cases diagnosed by DSM IIIIR criteria scored <82 on the CASI.

Isolated memory loss was recently documented in the Seattle Dementia Study to be a strong predictor of subsequent clinical dementia; 10 of 21 individuals (48%) with isolated memory loss became clinically demented during a 48-month follow-up period. Verbal memory loss is also an early sign of dementia.

The positive prediction of being demented, given a low score on a cognitive screening test such as the 3MSE, is still not very high, given the relatively low prevalence or incidence of dementia in the population. If the prevalence of dementia was 10% among 1000 participants and the sensitivity and specificity of low scores for identifying dementia were both 90%, then only 50% of individuals with low score (<80)
would be classified as demented and 10 (1.2%) of the 820 who scored ≥ 80 would be demented. Over time, however, many of the individuals who scored < 80 will be classified as demented. Therefore, it is likely that some CHS participants with scores < 80 on the 3MSE were not clinically demented at the time of the cognitive testing or MRI. The association of MRI changes and/or 3MSE scores < 80 or decline in scores over time could be stronger for participants with low scores (< 80) and clinical dementia or “vascular dementia” or be related to low scores (< 80) but not to clinical dementia.

A decline in score over time is an important criterion for dementia.38 For white subjects in the CHS, it was possible to determine the relationship between cognitive scores at baseline year 2 by using the MMSE and the 3MSE at years 5 to 6 to determine whether the white participants who had a low score at years 5 to 6 had entered the study with lower scores. Among the 2946 white participants with MRI and ApoE measurements, 95 (3.2%) scored < 24 on the MMSE at entry to the CHS and 45 of these 95 (42%) scored < 80 at year 5 to 6. These 45 participants who scored < 80 at year 2 accounted for 24% of the scores < 80 at years 5 to 6. In addition, 34 of the 45 participants who scored < 70 at year 5 (approximately 75%) had a decrease of at least five points on the 3MSE between years 3 and 5 of the CHS.

These results suggest that the lower scores at years 5 and 7 (at least for the white cohort in CHS) were a function of both lower scores at entry (year 2) and decline between years 2 to 5 and 7. The majority of the black cohort entered the study in year 5 and have had a relatively short follow-up.

There are several other reasons for low cognitive scores other than “possible dementia.” There was a relatively weak association between depression as measured by the 10-item version of the Center for Epidemiology Studies’ (CES-D)39 depression scale and low cognitive scores.

Reported alcohol consumption was very low in the CHS and was not a major factor in the 3MSE scores. Prevalent stroke was excluded from much of the analysis because of the strong association between stroke and low 3MSE scores. A history of Parkinson’s disease (29 men and 30 women in the original cohort of 5201 at year 2 and only 1 in the new cohort at year 5) was low in the CHS. The major drugs used in the CHS were primarily for the treatment of hypertension. There was only a weak relationship between antihypertensive therapy and 3MSE. Only approximately 10% of the cohort was using antidepressant drugs; of 399 participants in the original cohort who scored < 80 at year 5 to 6, 33 (8.4%) were taking benzodiazepines.

We also asked participants whether they had vision or hearing problems. In the original cohort of 5201 participants, 100 (25%) of 399 had a vision problem and 76 (19.3%) had hearing problems among those that scored < 80 on the 3MSE at year 5 compared with 15% with vision and 10% with hearing problems who scored > 80. The prevalence of vision problems and especially hearing problems increase with age and may contribute to some of the lower 3MSE score results. Efforts were made by the staff at yearly examinations to evaluate hearing and vision problems. It is unlikely that any of these variables had a major effect on low 3MSE scores.

Conclusions

This study documents that the prevalence of low scores on neuropsychological test of cognition and decline in scores over time are related to MRI vascular findings, ILL, white matter grade, and to the size of the ventricles. ApoE-4 has an independent association with prevalence of low scores and decline in scores. The MRI findings and ApoE-4 are generally independent of the powerful effects of age and education on cognitive test scores.

In the immediate future, it will be very important to determine whether the measures on MRI and subclinical vascular disease, genetic polymorphisms (such as ApoE) will be strong predictors of clinical dementia and types of dementia.

Appendix


Acknowledgments

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Relationship Between ApoE, MRI Findings, and Cognitive Function in the Cardiovascular Health Study

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