Apolipoprotein E, Carbon Dioxide Vasoreactivity, and Cognition in Older Adults: Effect of Hypertension

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Abstract

Objectives—To investigate the associations between the apolipoprotein E (APOE) $\varepsilon 4$ allele, carbon dioxide (CO\textsubscript{2}) vasoreactivity, and cognitive performance and to explore the effect of CO\textsubscript{2} vasoreactivity and hypertension on the associations between APOE and cognition.

Design—Observational.

Setting—Community.

Participants—Older adults (N=625) enrolled in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study

Measurements—Change in cerebral blood flow velocity in response to CO\textsubscript{2} challenge (CO\textsubscript{2} vasoreactivity) measured using transcranial Doppler ultrasonography, Trail-Making Test Part B – A (TMT), Hopkins Verbal Learning Test delayed recall (HVLT).

Results—APOE-$\varepsilon 4$ was associated with lower CO\textsubscript{2} vasoreactivity (p=.009) and poorer performance on the TMT (p<.001) and HVLT (p<.001). Having hypertension and APOE-$\varepsilon 4$ was associated with worse cognitive and CO\textsubscript{2} vasoreactivity measures than having neither or either alone (p<.001 for TMT and HVLT, p=.01 for CO\textsubscript{2} vasoreactivity). The association between APOE-$\varepsilon 4$ and cognition was only significant if it was present concurrent with low CO\textsubscript{2} vasoreactivity, defined as below the median of the sample (APOE by CO\textsubscript{2} vasoreactivity: p=.04 for TMT, p=.04 for HVLT). In hypertension, the association between APOE-$\varepsilon 4$ and executive
function was also only significant in participants with lower CO\textsubscript{2} vasoreactivity (p=.005 for APOE by CO\textsubscript{2} vasoreactivity)

**Conclusion**—Individuals at risk of Alzheimer’s disease (AD) because they have APOE-\varepsilon4 may have lower CO\textsubscript{2} vasoreactivity, which in turn may be contributing to the observed lower cognitive performance associated with this allele. The cognitive effect of APOE-\varepsilon4 are magnified in hypertension and low CO\textsubscript{2} vasoreactivity. This study offers evidence that APOE-\varepsilon4 may be associated with microvascular brain injury even in the absence of clinical AD.

**Keywords**

hypertension; apolipoprotein E; cognition; CO\textsubscript{2} vasoreactivity

The \varepsilon4 allele of the gene that codes apolipoprotein E (APOE) has been consistently found to be a risk factor for Alzheimer’s disease (AD) and other cognitive disorders.\textsuperscript{1} APOE-\varepsilon4 may also be associated with poor cognitive performance in older adults without dementia\textsuperscript{2,3} and is associated with hypertension, which in turn may increase the risk of cognitive impairment.\textsuperscript{4,5} Prior studies suggest that hypertension and APOE have a cumulative effect on the risk of AD,\textsuperscript{6} but fewer studies have explored the combined effect on cognition in older adults without dementia. For example in the Honolulu–Asia Aging Study, midlife high systolic blood pressure had a stronger negative effect on global measures of cognition in participants with APOE-\varepsilon4.\textsuperscript{7}

APOE is a protein involved in the maintenance of lipid homeostasis in the brain by taking up lipids produced after neuronal degeneration and redistributing them for cellular repair.\textsuperscript{8} Carriers of the APOE-\varepsilon4 allele have lower levels of APOE lipoprotein than carriers of the other alleles.\textsuperscript{9} In addition to neurotoxic manifestations of this allele, recent evidence suggests possible harmful cerebrovascular effects.\textsuperscript{10} In an in vitro blood–brain barrier (BBB) model, APOE was found to be involved in the regulation of the integrity of tight junctions in an isoform-dependent fashion.\textsuperscript{11} Mice models suggest that APOE-\varepsilon4 disrupts BBB integrity through cyclophilin A.\textsuperscript{12} As reviewed recently, most of the observations regarding APOE and cerebral microvascular effects were derived from animal models or postmortem studies; few human in vivo studies exist.\textsuperscript{10} Measuring the cerebral blood flow response to changes in end-tidal carbon dioxide (CO\textsubscript{2}) (CO\textsubscript{2} vasoreactivity) is a noninvasive in vivo method of assessing the integrity and function of the brain microcirculation.\textsuperscript{13} Low CO\textsubscript{2} vasoreactivity has been observed in individuals with AD and vascular dementia.\textsuperscript{14,15} Previous work suggests that CO\textsubscript{2} vasoreactivity is low in individuals with hypertension and is linked to poor executive function.\textsuperscript{16,17} It was hypothesized that APOE-\varepsilon4 carriers would have low CO\textsubscript{2} vasoreactivity, which also might be related to cognitive performance.

The associations between APOE, CO\textsubscript{2} vasoreactivity, and cognitive function were examined in a population-based study of older adults, and the potential effect of CO\textsubscript{2} vasoreactivity and hypertension on the relationship between APOE-\varepsilon4 and cognition was investigated.
METHODS

The current analyses used data collected during the baseline evaluations of the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study (MOBILIZE Boston), which has been described previously.\textsuperscript{18} Briefly, it is a population-based prospective observational study funded by the National Institute on Aging. The institutional review board at Hebrew SeniorLife approved MOBILIZE Boston, and each participant provided a written informed consent. The institutional review board at the University of Southern California approved this analysis.

Participants

Eligibility criteria included aged 70 and older, able to speak and understand English, and living in the recruitment area for at least 2 years after enrollment. Exclusion criteria included a Mini-Mental State Examination (MMSE) score less than 18, hearing or visual impairment that interfered with communication, having a terminal illness, and inability to walk 20 feet without assistance. Participant assessments included anthropometric and blood pressure measurement, health habits, medical history, medication inventory, and cognitive evaluations. Hypertension was defined as high blood pressure (≥140/90 mm Hg) or receiving antihypertensive medication. Neuropsychological assessments included the Trail Making Test (TMT) Parts A and B\textsuperscript{19} and the Hopkins Verbal Learning Test (HVLT). The TMT is a benchmark test for executive function. TMT Part B minus Part A (B–A), which adjusts the test for the motor speed and dexterity of the participant, was calculated.\textsuperscript{20} HVLT scores included delayed recall and recognition abilities.

Cerebral Hemodynamics Cerebral hemodynamics were assessed on a subset of subjects using transcranial Doppler ultrasonography (TCD; MultiDop X4, DWL-Transcranial Doppler Systems, Inc., Sterling, VA). Subjects without TCD evaluations were of the same age but were more likely to be female and nonwhite and to have diabetes mellitus, hypertension, and lower MMSE than those with TCD evaluations, as reported previously.\textsuperscript{21} A heart rate and beat-to-beat arterial pressure monitor (Finapres, Ohmeda Monitoring Systems, Englewood, CO) was attached to subjects, as previously described.\textsuperscript{22} End-tidal CO\textsubscript{2} was measured using a CO\textsubscript{2} analyzer (Vacumed, Ventura, CA) attached to a nasal cannula. Mean blood flow velocity (BFV) was measured in the middle cerebral artery at a depth of 50 to 60 mm. A well-trained dedicated TCD technician performed TCD procedures. BFV in the middle cerebral artery was measured continuously while subjects inspired a gas mixture of 8% CO\textsubscript{2}, 21% oxygen, and 71% nitrogen for 2 minutes and then mildly hyperventilated to an end-tidal CO\textsubscript{2} of approximately 25 mmHg for 2 minutes. CO\textsubscript{2} itself may also affect blood pressure, so cerebrovascular conductance (cerebral blood flow/mean arterial blood pressure) was derived, and CO\textsubscript{2} vasoreactivity was calculated as the slope of the change in cerebrovascular conductance versus the change in end-tidal CO\textsubscript{2}.\textsuperscript{23}

Genotyping

Genotyping was conducted at the Harvard Medical School–Partners Healthcare Center for Genetics and Genomics. Multiplex polymerase chain reaction assays were designed using Sequenom Spectro DESIGNER software version 3.0.0.3 (San Diego, CA) by inputting
sequences containing the single nucleotide polymorphism (SNP) site and 100 base pairs of flanking sequences on either side of the SNP. Quality control was conducted using a subsample (5%) of duplicate genotyping to identify any discordance in the results. APOE status was determined according to the genotypes at the rs429358 and rs7412 SNPs and was defined as APOE-ε4+ if the individual had at least one APOE-ε4 allele and APOE-ε4− if the individual had no APOE-ε4 alleles.

**Statistical Analysis**

Linear models were used to compare cognitive and cerebral hemodynamics between the two APOE-ε4 groups and between the following three groups: combination (hypertension and APOE-ε4+), either alone (hypertension or APOE-ε4+), and neither (normotension and APOE-ε4−). The modifying effects of the interactions between CO₂ vasoreactivity and APOE and between hypertension and APOE on cognitive performance were explored by including an interaction variable (APOE by CO₂ vasoreactivity and APOE by hypertension) in the models. A categorical variable was used for the interaction analysis (low and high CO₂ vasoreactivity divided at the median measure of the sample).

All models were adjusted for demographic characteristics, education, body mass index (BMI), blood pressure, and stroke. P-values were adjusted for multiple testing using simulation-based multiple comparison. The results are presented in the tables and figures as least square means (adjusted for the covariates) to account for confounding in gene-association studies. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used for the analyses.

**RESULTS**

The sample included 625 participants who were evaluated at baseline (mean age 78, 80% white, 63% female, mean MMSE score 27, mean 14.5 years of education). As shown in Table 1, APOE-ε4− participants were more likely to be white, have lower cholesterol, and score higher on the MMSE. Of the 625 participants, 74% had hypertension, and 24% had at least one APOE-ε4 allele. (Eight participants were homozygous APOE-ε4+.) Cerebral hemodynamic data were gathered on 374 (60%) participants. There was no difference in the genotypic distribution between those with (26% APOE-ε4+) and without (22% APOE-ε4+) hemodynamic data (p=.17), but those without hemodynamic data had lower cognitive performance on the TMT Part B–A (p<.001) and HVLT delayed recall (p=.01).

**APOE, Cognition and CO₂ Vasoreactivity**

After adjustment for demographic characteristics, BMI, systolic blood pressure, educational level, and prior history of stroke, the APOE-ε4 allele was associated with lower CO₂ vasoreactivity (p=.009) and poorer performance on the TMT part B (p<.001) and Part B–A (p<.001) and the HVLT delayed recall (P<.001) and recognition (p.006). There was no difference in resting BFV between the two APOE-ε4 groups (P=.24) (Table 2).

When the effect of CO₂ vasoreactivity on the associations between APOE-ε4 and cognition was investigated, it was observed that participants with APOE-ε4 and lower (below the median of the sample) CO₂ vasoreactivity had worse cognition (APOE by CO₂...
vasoreactivity: p=.04 for TMT Part B–A, p=.04 for HVLT delayed recall, after adjusting for
covariates). In participants with higher CO\textsubscript{2} vasoreactivity, APOE-ε4 had no significant
association with cognitive performance (APOE effect: p=.63 for TMT Part B–A, p=.99 for
HVLT delayed recall; Figure 1A).

**APOE, hypertension, and CO\textsubscript{2} vasoreactivity**

Participants with hypertension and APOE-ε4 had poorer performance on executive function
and memory tests (APOE by hypertension for TMT Part B–A and HVLT delayed recall, p < .001) and lower CO\textsubscript{2} vasoreactivity (p=.01) than those with neither or either alone. There
were no differences in BFV between the three groups. These results with pairwise
comparisons are shown in Table 3.

When investigating the effect of CO\textsubscript{2} vasoreactivity on the associations between APOE-ε4
and cognition according to hypertension status it was observed that, in individuals with
hypertension, only those with low CO\textsubscript{2} vasoreactivity demonstrated the negative association
between APOE-ε4 and executive function (APOE effect in those with low CO\textsubscript{2}
vasoreactivity p =.03 vs high CO\textsubscript{2} vasoreactivity p=.75, p=.005 for APOE by CO\textsubscript{2}
vasoreactivity; Figure 1B). There was no interaction between hypertension, APOE, and CO\textsubscript{2}
vasoreactivity with respect to the memory measure.

**DISCUSSION**

Older adults with APOE-ε4 may have lower CO\textsubscript{2} vasoreactivity and poorer executive
function and memory performance compared to those without. Concurrent hypertension and
low CO\textsubscript{2} vasoreactivity with the APOE-ε4 allele is linked to poor cognitive performance in
older adults. Multiple neuropathological findings have been reported to be relevant to the
APOE-ε4-related risk of AD and cognitive impairment, including low amyloid clearance
and high aggregation, high tau phosphorylation, synaptic deficits, mitochondrial
dysfunction, and neuroinflammation. (For a review, see 27.) Prior studies have also
demonstrated that APOE-ε4 may be linked to disruption of BBB integrity and endothelial
dysfunction.\textsuperscript{28, 29} APOE-ε4 is associated with low peripheral endothelial-mediated
vasoreactivity.\textsuperscript{30} CO\textsubscript{2} vasoreactivity is linked to low peripheral endothelial function and is
low in individuals with AD and prodromal AD.\textsuperscript{14, 31} The results of the current study extend
these observations to suggest that individuals at risk of developing AD by virtue of their
APOE-ε4 allele have impaired CO\textsubscript{2} vasoreactivity function. This may serve as an early
vascular biomarker for the risk of cognitive decline related to APOE-ε4. To the knowledge
of the authors of the current study, this is the first evidence that APOE-ε4 carriers may have
lower CO\textsubscript{2} vasoreactivity than noncarriers.

As in previous studies, we demonstrated that the combination of APOE-ε4 and hypertension
is associated with worse cognitive performances.\textsuperscript{7} We also found that this combination is
associated with decreased CO\textsubscript{2} vasoreactivity suggesting an increased impact on the
cerebral microvasculature.

CO\textsubscript{2} vasoreactivity may be contributing to the association between APOE and cognition. In
particular, when CO\textsubscript{2} vasoreactivity is not impaired, APOE-ε4 was not linked to lower
cognitive performance. Stated differently, in this sample of older adults, CO₂ vasoreactivity above the median was protective against the negative effect of APOE-ε4 on cognition. This observation is novel and supports the hypothesis that microvascular injury may be an important mechanism by which APOE leads to cognitive impairment, but because of the cross-sectional nature of this analysis, this observation does not imply causality. Nevertheless, it is possible to deduce a mechanistic role of CO₂ vasoreactivity in associations between APOE and cognition because a genetic marker by definition precedes CO₂ vasoreactivity and cognitive performance. Because other potential mechanisms, such as amyloid deposition, mitochondrial dysfunction, and inflammation, were not measured, this role of CO₂ vasoreactivity needs to be confirmed in a more-comprehensive risk factor assessment study.

An association between APOE and resting BFV was not found. One possible explanation is that the effect of APOE-ε4 may be exerted on some but not all regions of the brain. It was not possible to assess regional variations in cerebral blood flow velocity using transcranial Doppler. Results of this study should be interpreted in the context of its limitations, which include the cross-sectional nature of the phenotypic measures (cognition and hemodynamics) and the small number of subjects with available CO₂ vasoreactivity data. The latter limitation was accounted for by adjusting for factors associated with the lack of CO₂ vasoreactivity data (age, education, sex, race). A difference in the APOE-ε4 allele distribution was not observed according to presence or absence of cerebral hemodynamic data.

CONCLUSION

Individuals at risk for AD because they have the APOE-ε4 allele have low CO₂ vasoreactivity, and the effects of this allele on cognition and CO₂ vasoreactivity may be greater when concurrently present with hypertension. Having higher CO₂ vasoreactivity may offer a protective mechanism against cognitive impairment in individuals with the APOE-ε4 allele. This study provides in vivo evidence that APOE-ε4 carriers have cerebral microcirculatory dysfunction, which may play a role in its cognitive manifestations.

Acknowledgments

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References


Figure 1.
Cognitive scores in the two APOE-ε4 groups according to (A) carbon dioxide (CO₂) vasoreactivity status (low and high) and (B) CO₂ vasoreactivity (VR) and hypertension (HTN) status in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study. All p-values adjusted for multiple testing using simulation approach; scores (least square means) and p-values adjusted for age, sex, race, body mass index, stroke history, educational level, and systolic blood pressure. P-value for the interaction between APOE and CO₂ vasoreactivity obtained from the parameter for APOE by CO₂ vasoreactivity in the corresponding models. HVLT=Hopkins Verbal Learning Test; NTN=normotension.
Table 1
Demographic, Social, and Clinical Characteristics According to Apolipoprotein E (APOE)-ε4 Status of Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>APOE-ε4**, n=478</th>
<th>APOE-ε4+, n=147</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>78.2±5.5</td>
<td>77.2±4.7</td>
<td>.08</td>
</tr>
<tr>
<td>Female, %</td>
<td>61%</td>
<td>67%</td>
<td>.18</td>
</tr>
<tr>
<td>White, %</td>
<td>82%</td>
<td>73%</td>
<td>.02</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>27.7±5.2</td>
<td>27.3±4.8</td>
<td>.46</td>
</tr>
<tr>
<td>Alcohol nondrinker, %</td>
<td>25%</td>
<td>29%</td>
<td>.34</td>
</tr>
<tr>
<td>Never smoked, %</td>
<td>42%</td>
<td>43%</td>
<td>.19</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg, mean±SD</td>
<td>129.1±17.7</td>
<td>130.5±18.4</td>
<td>.42</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg, mean±SD</td>
<td>69.7±8.8</td>
<td>70.7±8.6</td>
<td>.28</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>10%</td>
<td>9%</td>
<td>.76</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>74%</td>
<td>73%</td>
<td>.97</td>
</tr>
<tr>
<td>Antihypertensive therapy, %</td>
<td>68%</td>
<td>65%</td>
<td>.58</td>
</tr>
<tr>
<td>Heart disease, %</td>
<td>27%</td>
<td>24%</td>
<td>.53</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>5%</td>
<td>5%</td>
<td>.96</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>17%</td>
<td>16%</td>
<td>.64</td>
</tr>
<tr>
<td>Low density lipoprotein, mg/dL, mean±SD</td>
<td>106.4±33</td>
<td>112.1±35.7</td>
<td>.08</td>
</tr>
<tr>
<td>Cholesterol, mg/dL, mean±SD</td>
<td>183.3±39.7</td>
<td>191.6±37.5</td>
<td>.03</td>
</tr>
<tr>
<td>Mini-Mental State Examination score, mean±SD</td>
<td>27.4±2</td>
<td>26.7±3</td>
<td>.003</td>
</tr>
</tbody>
</table>

P-values were obtained from the t-test or chi-square test comparing the two APOE groups.

SD=standard deviation.
Table 2
Cognitive (n=625) and Cerebral Hemodynamic (n=374) Measures According to Apolipoprotein E (APOE)-ε4 Status in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study

<table>
<thead>
<tr>
<th>Measure</th>
<th>APOE-ε4⁻</th>
<th>APOE-ε4⁺</th>
<th>P-Valueᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Least Square Mean (Standard Error)ᵇ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂ vasoreactivity, cm/s per mmHg/partial pressure of CO₂(\text{mmHg}\times10^{-2})</td>
<td>1.10 (0.05)</td>
<td>0.95 (0.07)</td>
<td>.009</td>
</tr>
<tr>
<td>Blood Flow Velocity, cm/s</td>
<td>43.19 (1.26)</td>
<td>42.13 (1.54)</td>
<td>.24</td>
</tr>
<tr>
<td>Trail-Making Test, seconds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>62.5 (2.4)</td>
<td>65.7 (3.0)</td>
<td>.36</td>
</tr>
<tr>
<td>Part B</td>
<td>165.4 (5.6)</td>
<td>187.7 (7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Part B–A</td>
<td>105.8 (4.8)</td>
<td>124.7 (6.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed recall</td>
<td>5.8 (0.3)</td>
<td>4.7 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recognition</td>
<td>11.6 (0.2)</td>
<td>10.9 (0.2)</td>
<td>.006</td>
</tr>
</tbody>
</table>

ᵃResults obtained from generalized linear models adjusted for age, sex, race, educational level, body mass index, systolic blood pressure, and stroke.

ᵇObtained from model comparing the two APOE groups adjusted for the same covariates. CO₂=carbon dioxide.
# Table 3

Cognitive and Cerebral Hemodynamic Measures According to Apolipoprotein E (APOE)-ε4 and Hypertension Status in the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston Study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normotension and APOE-ε4⁺, n=126</th>
<th>Hypertension or APOE-ε4⁺, n=391</th>
<th>Hypertension and APOE-ε4⁺, n=108</th>
<th>APOE by Hypertension, P-Valueᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Least Square Means (Standard Error)ᵇ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-Making Test, seconds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>59.9 (3.4)ᶜ</td>
<td>62.9 (2.4)ᶜ</td>
<td>66.2 (3.3)ᶜ</td>
<td>.03</td>
</tr>
<tr>
<td>Part B</td>
<td>156.6 (7.7)</td>
<td>169.7 (5.7)</td>
<td>185.4 (7.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Part B–A</td>
<td>98.5 (6.5)</td>
<td>109.6 (4.8)</td>
<td>122.1 (6.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed recall</td>
<td>6.1 (0.4)ᶜ</td>
<td>5.6 (0.3)ᶜ</td>
<td>4.8 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recognition</td>
<td>11.8 (0.3)ᶜ</td>
<td>11.4 (0.2)ᶜ</td>
<td>11.0 (0.3)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood flow velocity, cm/s</td>
<td>42.6 (1.6)ᶜ</td>
<td>42.9 (1.3)ᶜ</td>
<td>42.0 (1.7)ᶜ</td>
<td>.61</td>
</tr>
<tr>
<td>CO₂ vasoreactivity, cm/s per mmHg/ partial pressure of CO₂/mmHg x10⁻²</td>
<td>1.06 (0.07)ᶜ</td>
<td>1.09 (0.05)ᶜ</td>
<td>0.97 (0.07)</td>
<td>.01</td>
</tr>
</tbody>
</table>

ᵃ Adjusted for age, sex, race, body mass index, stroke, systolic blood pressure, and educational level.
ᵇ Obtained from models adjusted for the same covariates with the interaction parameter (APOE by hypertension).
ᶜ Not significantly different from each other (after adjusting for pairwise multiple testing).