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APOE genotypes as a risk factor for age-dependent accumulation of cerebrovascular disease in older adults

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Abstract

INTRODUCTION: Apolipoprotein E (*APOE*) is a susceptibility gene for late-onset Alzheimer's disease neuropathology; less is known about the relationship between *APOE* and cerebrovascular disease (CVD) neuropathology.

METHODS: We investigated associations of *APOE* status with arteriolosclerosis, macro- and micro-infarcts, and atherosclerosis in 1,383 adults (65.9–108.2 years at death) with and without dementia. Excluding ε2/ε4 carriers, multivariable regressions for each CVD-related neuropathology compared ε4 and ε2 carriers to ε3/ε3 carriers adjusting for confounders including age and Alzheimer's neuropathology.

RESULTS: 342 individuals (24.7%;~87.7 years at death;39.9% non-demented) were ε3/ε4 or ε4/ε4, 180 (13.0%;~89.9 years at death;66.6% non-demented) were ε2/ε3 or ε2/ε2. ε4 carriers had higher odds of macroinfarcts (OR=1.41,95%CI:1.02–1.94,p=0.03) while ε2 carriers had higher

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Conflicts

The authors have no conflicts of interest to report.

odds of moderate-to-severe arteriolosclerosis (OR=1.68,95%CI:1.15–2.45,p=0.006) compared to ε3/ε3 carriers. Age-stratified analyses suggested these relationships were driven by ε4 carriers<90 years at death and ε2 carriers≥90 years at death, respectively.

DISCUSSION: *APOE* differentially affects type and timing of CVD-related neuropathology.

Keywords

APOE ε4 allele; *APOE* ε2 allele; cerebrovascular disease; neuropathology; oldest old

1. Background

Apolipoprotein E (*APOE*) is a susceptibility gene for late-onset Alzheimer's disease (AD) neuropathology. Most studies from our group [1, 2] and others [3–7] have shown that *APOE* ε4 positive status is specifically related to greater abundance of amyloid pathology including AD pathology and cerebral amyloid angiopathy (CAA). In contrast, while *APOE* ε2 carriers also show increases in CAA [6–9], they show less AD pathology when compared to ε4 carriers [4, 10]. Less is known about the role of *APOE* in non-amyloid cerebrovascular disease (CVD) neuropathology. This is despite the fact that increasing evidence suggests CVD-related neuropathology lowers the threshold for dementia and often coexists with AD-related neuropathology in individuals diagnosed with clinical AD at death (see [11] for review).

Existing post-mortem studies of *APOE* and non-amyloid CVD-related neuropathology have met with conflicting results. Our group has shown that *APOE* ε4 positive status is related to a relatively weak increase in the odds of gross infarcts in older persons [12]. Meanwhile, other studies have shown inconsistent results when investigating the relationship between ε4 and non-amyloid CVD neuropathologies of arteriolosclerosis, infarcts, lacunes, and/or atherosclerosis [4, 5, 10, 13–17]. Even less is known about *APOE* ε2 positive status and non-amyloid cerebrovascular disease; however, studies that do exist report null post-mortem findings [4, 10, 15]. This may be due, in part, to the small number of prospective clinical-pathologic studies that include pathologic data on non-amyloid CVD neuropathologies as well as the potentially limited inclusion of oldest old decedents.

In previous work investigating the relationship of *APOE* and the neuropathology of dementia in the oldest old, we showed that oldest old decedents have a higher prevalence of mixed AD-vascular pathology [18]. While studies of oldest old decedents report that ε2 is associated with the same degree [19, 20] – or less [10] – of senile plaques and tangles in post-mortem tissue as ε4 seen at younger ages of death, less is known about non-amyloid CVD neuropathology. Thus, the current study investigates the relationship of *APOE* ε4 as well as ε2 carrier status with additional CVD-related neuropathologies, i.e., arteriolosclerosis, microinfarcts, and intracranial atherosclerosis, and the role of age at death, i.e., ≥90 years at death, on these associations.

2. Methods

2.1 Participants

Described in detail elsewhere [21–23], subjects of this research were participants in prospective, community-based, clinical-pathologic cohort studies of aging, either ROS (1994-present), MAP (1997-present) or MARS (2004-present). The Institutional Review Board of Rush University Medical Center approved all studies and participants gave written informed consent for all aspects of the study in accordance with the Declaration of Helsinki. They also signed an anatomic gift act for donation of the brain at the time of death. All studies follow the same recruitment, biospecimen and data collection as well as clinical and neuropathological processing and analysis.

As previously outlined [24], dementia status was determined through a review of self-report questionnaires, neurological examination, cognitive testing and participant interview blind to post-mortem neuropathological data. For the purposes of this study, individuals were deemed to have ‘dementia at death’ (based on their last cl inical visit prior to death) that included AD as well as other primary causes of dementia [25]. Mild cognitive impairment (MCI) was also determined if participants were impaired on one or more cognitive domain(s) but did not have a clinical diagnosis of dementia regardless of possible causes for cognitive impairment.

2.2 APOE genotyping

DNA was extracted from peripheral blood or frozen postmortem brain tissue. Genotyping was performed by Polymorphic DNA Technologies (Alameda, CA) by investigators blinded to all clinical and pathologic data. *APOE* alleles and genotypes were determined by sequencing rs429358 (codon 112) and rs7412 (codon 158) at exon 4 of the *APOE* gene [26]. *APOE* ε4 positive status was defined as possessing one or more copies of the ε4 allele, i.e. ε3/ε4 or ε4/ε4, while the following were considered negative for ε4, i.e., non-carriers of the *APOE* ε4 allele: ε2/ ε2, ε2/ε3 or ε3/ ε3. Separate group categorizations were used for the APOE ε2 positive group, i.e., participants with ε2/ε2 or ε2/ε3 haplotypes. Given that we wanted to assess the independent effects associated with the ε4 and ε2 alleles, we excluded participants with the ε2/ε4 haplotype from all analyses.

2.3 Neuropathology

Postmortem samples were obtained from 1,258 aged participants, with details of brain autopsy procedures described elsewhere [21, 22, 27]. Briefly, the post-mortem neuropathological evaluation included a uniform structured assessment with procedures that includes and extends those outlined by the pathologic dataset recommended by the National Alzheimer’s Disease Coordinating Center. Evaluations were performed blinded to clinical data and reviewed by a board-certified neuropathologist.

2.3.1 Outcomes of Interest—We used the term arteriolosclerosis to describe the histological changes commonly found in the small vessels of the brain in aging including intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles with consequent narrowing of the vascular lumen. We evaluated the vessels of the

anterior basal ganglia with a semi-quantitative grading system, i.e., 0 (none) to 7 (occluded) and compressed these levels into none (0), mild (1), moderate (2), and severe (3) as previously reported [12, 28, 29].

Gross infarct, i.e., macroinfarct examination documented age (acute/subacute/chronic), size, and location (side and region) of cerebral infarcts visible to the naked eye on fixed slabs. All grossly visualized and suspected infarcts were dissected for histologic confirmation [25, 27]. A minimum of nine regions in one hemisphere are examined on 6μm paraffin-embedded sections, stained with hematoxylin/eosin (six cortical regions: midfrontal, middle temporal, entorhinal, hippocampal, inferior parietal, and anterior cingulate cortices; two subcortical regions: anterior basal ganglia and thalamus; and midbrain) [12, 30]. For this study, we coded for none versus ≥1 macroinfarcts regardless of location.

Microinfarcts were defined as any chronic infarct seen by microscopic examination using hematoxylin and eosin-stained 6-micron sections that were not identified by gross inspection. They were investigated in at least nine regions including the mid-frontal, middle or superior temporal, anterior cingulate, inferior parietal, and entorhinal cortices, as well as within the hippocampus, anterior basal ganglia, anterior thalamus, and hemisection of the midbrain, including the substantia nigra. Microinfarcts ranged from cavitated to puckered to incomplete in appearance; however, all exhibited acellularity with varying degrees of gliosis and remaining macrophages [30, 31].

The degree of intracranial atherosclerosis of the circle of Willis vessels was recorded on a semi-quantitative scale, i.e., none (0), mild (1), moderate (2), and severe (3), as previously described [32].

2.3.2 Covariates—Global AD-related neuropathology, i.e., plaque and tangle burden, was evaluated using Bielschowsky silver staining to visualize neuritic plaques and neurofibrillary tangles in the mid-frontal, superior temporal, inferior parietal, and entorhinal cortices as well as the CA1/subiculum of the mid-hippocampus at 6mm [33]. CAA was quantified in mid-frontal, mid-temporal, parietal, and calcarine cortices [34]. For each region, meningeal and parenchymal vessels were assessed for amyloid deposition and scored from 0 (no deposition), 1 (scattered segmental but no circumferential deposition), 2 (circumferential deposition up to 10 vessels), 3 (circumferential deposition up to 75% of the total vessels of the region), to 4 (circumferential deposition on more than 75% of the total vessels of the region). The CAA variable used for the current analyses grouped participants by no/mild or moderate/severe regional average of the maximum of the meningeal and parenchymal CAA scores as follows: no (average=0), mild (average<1.5), moderate (1.5 ≤ average≤2.5), and severe (average>2.5).

2.4 Statistical Analyses

Differences between groups (*APOE* ε4, ε2, and ε3/ε3 carriers) in demographic and clinical characteristics were examined using three group comparisons (ANOVA for continuous variables and Chi-square tests for categorical variables). To examine the role of *APOE* gentoypes on the presence of neuropathologically derived levels of arteriolosclerosis, macro- and micro-infarcts, and intracranial atherosclerosis, we conducted a series of multivariable

logistic regressions for each CVD-related neuropathology comparing *APOE* ε4 and ε2 carriers to ε3/ε3 carriers after controlling for a number of a priori covariates. All p values are two sided and the statistical significance was set a $p<0.05$. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

In the first series of models, we adjusted for demographic characteristics (age at death and sex). The second set of models controlled for demographic characteristics as well as other cerebral vessel disease variables of non-interest (e.g., arteriolosclerosis, macroinfarcts, and intracranial atherosclerosis were added to the microinfarct model; arteriolosclerosis, macroinfarcts, and microinfarcts were added to the intracranial atherosclerosis model, etc.). The third set of models further adjusted for global AD-related neuropathology and CAA given the fact that ε4 and ε2 are known to be related to both forms of neuropathology. The final set of models added baseline systolic blood pressure and change in systolic blood pressure over time given the role that hypertension may play in CVD burden [35] and its *APOE* associates [36]. Odds Ratios (ORs) and 95% Confidence Intervals (Cis) were calculated using maximum likelihood estimates from the logistic regression models.

Where indicated secondary to significant results, individual analyses were conducted to explore interactions between ε4 and ε2 carrier status with age at death. Thus, individual interaction terms, e.g., ε4 carrier status x age and ε2 carrier status x age, were included in final models found to be significant on neuropathological outcomes as outlined above. Given previous reports in the oldest old of mixed AD-vascular pathology [18] and differential levels of AD-related neuropathology based on *APOE* genotypes [10], we also grouped participants based on age at death less than or greater than 90 years and conducted stratified analyses to specifically address issues surrounding the oldest old.

3. Results

A total of 1,470 persons had available neuropathological data at the time of these analyses as well as *APOE* allele information and subsequent genotyping. Given that we wanted to assess the independent effects associated with ε4 and ε2, we excluded 87 participants (6.0%) with the ε2/ε4 haplotype from all analyses. Thus, a total of 1,383 individuals, 458 men and 925 women (96% white), with neuropathological data and relevant *APOE* allele information were included in this study (Table 1). Age at death (mean=88.8) ranged between 65.9 and 108.2 years. Participants were highly educated, averaging 16.2 years of education.

Of the 1,383 participants, 342 (24.7%) had *APOE* ε4 (ε3/ε4 or ε4/ε4), 180 (13.0%) had ε2(ε2/ε2 or ε2/ε3), and 861 (62.2%) had ε3/ε3. Sample characteristic analyses compared the 342 ε4 carriers [i.e., ε3/ε4 (n=317) and ε4/ε4 (n=25)], the 180 *APOE* ε2 carriers [i.e., ε2/ε2 (n=7) or ε2/ε3 (n=173)], and the 861 ε3/ε3 carriers. Separate ANOVAs with follow-up least squares mean comparisons revealed that ε4 carriers were younger at time of death, $F(1,380)=7.61$, $p=0.0005$,compared to ε3/ε3 carriers (follow-up p-value=0.004) [and ε2 carriers, follow-up p-value=0.001]. ε4 carriers also reported more years of education, $F(1,380)=5.30$, $p=0.0005$, than their ε3/ε3 counterparts (follow-up p-value=0.03) [and ε2 carriers, follow-up p-value=0.007].Chi-square testing revealed that ε2 carriers were less

likely to be cognitively impaired, i.e., mild cognitive impairment or demented, at death [$\chi^2(2)=51.52$, $p<0.0001$] compared to ε3/ε3 carriers [and ε4 carriers] (Table 1).

3.1 APOE and CVD

3.1.1 Levels of arteriolosclerosis—There were no associations between *APOE* ε4 carrier status and arteriolosclerosis in our sample regardless of adjustments (Table 2). By contrast, regardless of model adjustments, ε2 carriers were at increased odds of moderate to severe levels of arteriolosclerosis compared to ε3/ε3 carriers (Table 2).

3.1.2 Macroinfarcts—Regardless of model adjustments, ε4 carriers were at increased odds of macroinfarcts compared to ε3/ε3 carriers (fully adjusted Model 4: OR=1.41,95%CI: 1.02–1.94,p=0.03). By contrast, there were no associations between *APOE* ε2 carrier status and macroinfarcts in our sample regardless of adjustments (fully adjusted Model 4: OR=0.89,95%CI:0.60–1.31,p=0.55).

3.1.3 Microinfarcts—*APOE* ε4 was not related to microinfarcts regardless of adjustments (Table 3). Similar results were seen when considering ε2 (Table 3).

3.1.4 Levels of intracranial atherosclerosis—There were no associations between *APOE* ε4 carrier status and levels of intracranial atherosclerosis in our sample regardless of adjustments (Table 4). Similar results were seen when considering ε2 carrier status (Table 4).

3.2 APOE, CVD, and Age at death

3.2.1 Interaction term—Age at death was included as an interaction term with *APOE* genotypes in separate macroinfarct and arteriolosclerosis models outlined above; there were no significant results for interactions with ε2 or ε4 in either model (data not shown).

3.2.2 Stratified analyses—When age stratified analyses were restricted to age at death <90 years, ε4 carriers with an age at death <90 years were at increased odds of macroinfarcts compared to ε3/ε3 carriers of a similar age, regardless of adjustments (fully adjusted Model 4: OR=1.81,95%CI:1.15–2.87,p=0.01). There were no significant results for ε2 carrier status in macroinfarct models regardless of adjustments (data not shown). Additionally, there were no significant results for ε4 or ε2 carrier status in arteriolosclerosis models restricted to age at death <90 years, regardless of adjustments (data not shown).

When age stratified analyses were restricted to age at death ≥90 years, there were no significant results for ε4 or ε2 carrier status in macroinfarct models, regardless of adjustments (data not shown). In contrast, regardless of model adjustments, ε2 carriers with an age at death ≥90 years were at increased odds of moderate to severe levels of arteriolosclerosis compared to ε3/ε3 carriers of a similar age (fully adjusted Model 4: OR=1.80,95%CI:1.06–2.98,p=0.02). There were no significant results for ε4 carrier status in these models regardless of adjustments (data not shown).

3.3 Post-hoc analyses

Including the 87 participants with ε2/ε4 as an additional group did not change results for the original *APOE* ε4 and ε2 carrier groups across all analyses previously reported, regardless of adjustments. There were no significant findings for ε2/ε4 compared to ε3/ε3 carriers regardless of adjustments (data not shown) with one exception. Like the original *APOE* ε4 carriers, ε2/ε4 carriers were also at increased odds of macroinfarcts compared to ε3/ε3 carriers in fully adjusted Model 4 (OR=2.40,95%CI:1.10–5.20,p=0.02). These results were driven by ε2/ε4 carriers ≥90 years at death (fully adjusted Model 4: OR=1.80,95%CI:1.06–2.98,p=0.02).

4. Discussion

Current results revealed a significant association between ε2 carrier status (i.e., ε2/ε2 or ε2/ε3) and levels of arteriolosclerosis, regardless of adjustments. Results also confirmed our previous work [12] and the work of others [13, 15] documenting the relationship between *APOE* ε4 and CVD in the form of macroinfarcts and extended it to include ε2/ε4. Age-stratified analyses suggest that the association of ε2 with arteriolosclerosis is driven by ε2 carriers ≥90 years of age at death, whereas, the association of ε3/ε4 or ε4/ε4 with macroinfarcts is driven by those carriers <90 years at death. By contrast, though numbers are small, in those with ε2/ε4, the association with macroinfarcts may be driven by those ≥90 years at death. Overall, results of this study suggest that *APOE* may differentially affect the type and timing of CVD-related neuropathology.

Our results regarding the differential associations between *APOE* genotypes with the type of CVD-related neuropathology contributes to the literature in several ways. First, we report that the presence of ε2/ε2 or ε2/ε3 is associated with greater severity of cerebral small vessel disease. Our work in decedents with and without dementia extends previous reports that these *APOE* haplotypes were not related to macroinfarcts, microinfarcts, lacunes, and hemorrhages [4, 10, 15] given that these studies consisted primarily of decedents with AD and did not look at arteriolosclerosis. Likewise, our results suggesting that the presence of ε4 (including ε2/ε4) is associated with greater odds of gross infarcts adds to a growing body of literature on this topic [12, 13, 15], and provides further support for the null findings from other studies investigating ε4 and other CVD-related neuropathologies [4, 5, 10, 16, 17]. Second, our study may inform previous reports of the relative increase in the frequency of the ε2 allele in decedents with vascular dementia [37] by suggesting that cerebral small vessel disease (and perhaps gross infarcts in those with ε2/ε4) may be a key contributor in affected individuals. Given the relationship between arteriolosclerosis and white matter damage [38], and the role of white matter damage including infarcts [39] in vascular dementia [40], additional work is needed to investigate these potential links; however, our study provides support for the assertion that the ‘protective’ effect of the ε2 allele may, in fact, imply a delayed onset and alternate underlying physiology, rather than a prevention of dementia.

The delayed onset suggested for the ε2 allele may best be interpreted within the context of a differential impact *APOE* genotypes on the timing of CVD-related neuropathology. The age-stratified analyses of this study revealed that the ε2 and arteriolosclerosis association was

particularly robust for ε2 carriers ≥90 years at death while the ε4 and macroinfarcts association was particularly robust for ε3/ε4 or ε4/ε4 carriers <90 years at death. Interestingly, we provide preliminary evidence that the ε2/ε4 and macroinfarcts association was particularly robust for those carriers ≥90 years at death, suggesting that this haplotype may share timing attributes with ε2 but CVD-related neuropathological associations with ε4. It has been reported that AD may partially mediate the association between excess early mortality and *APOE* ε4 positive status [41]; results of our age-stratified analyses suggest that exploration of the role of gross infarcts on these associations and the role of the ε2/ε4 haplotype may also be warranted. In addition, age-stratified ε2 results in our oldest old decedents, when combined with the fact that ε2 has been associated not only with vascular dementia post-mortem [37] but also adverse cerebrovascular events ante-mortem [42, 43], suggest that *APOE* ε2 may play a role in the greater preponderance of mixed AD/vascular pathology reported in the oldest old [18]. Additional work is needed to better understand the mechanisms underlying the role of *APOE* in differentially promoting earlier gross infarcts and later cerebral small vessel disease depending upon carrier status and the complex relationship implied by the results revealed for our small sample of ε2/ε4 carriers.

Our data suggests that at least some of the mechanisms of action for *APOE* ε4 and ε2 may be distinct from beta amyloid – something other researchers have noted [44] – and have specific windows of opportunity. For example, it has been hypothesized that ε2 may contribute to the disruption of vessel wall integrity and increase micro and/or macro intracerebral bleeding ([36] for review). Combined with the fact that ε2 has been associated with adverse vascular events [42, 43,], it seems plausible that the *APOE* ε2 allele may also be contributing to the pathology of cerebral small vessel disease including neuropathologically-confirmed arteriolosclerosis (and perhaps gross infarcts) in the oldest old. More generally, Apolipoprotein E as a plasma lipoprotein constituent (ApoE) is present in perivascular astrocytes as well as the walls of CVD-affected vessels [46]. Thus, it may be that, regardless of haplotypes, ApoE provides a link between AD-related and CVD-related neuropathologies. Furthermore, while *APOE* ε2 and ε4 carrier status appear to contribute at different times to CVD-related neuropathology, results of the current study, if validated, may suggest that studies of disease prevention may require distinct approaches based on *APOE* genotype and age.

This study has strengths and limitations. To our knowledge, this is the largest community-based study that examined postmortem human brain for association of *APOE* ε4 and ε2 alleles with CVD. Uniform clinical and pathologic evaluation protocols are applied across our cohorts by the same group of investigators, which makes it efficient to merge the data for combined analysis. This is particularly important given the possibility of depletion of ε4 in older ages [41] combined with the rarity of ε2 carriers more generally requires a large number of decedents for a study of this type. Case in point, while we explored associations between the ε2/ε4 haplotype and CVD-related neuropathology, this group comprised only 6% of the entire sample, leaving interpretation of the resulting relationships tentative. Another limitation is that this is an association study, thus, our results cannot establish a causal relationship between *APOE* allele carrier status and neuropathology and, as previously stated, discussions of possible underlying mechanisms require directed study. Furthermore, the extent of CVD is likely under-reported in our study given the

neuropathological examination was restricted both in terms of quantification as well as brain areas. This is particularly the case for our semi-quantitative levels of arteriolosclerosis which were restricted to one section of the anterior basal ganglia. While we adjusted for both CVD neuropathology of non-interest as well as global AD-related neuropathology, we may have omitted other less apparent confounders and/or other *APOE* allele by neuropathology interactions. Combined with the fact that our work has shown that neuropathologies are often inter-related and the presence of one neuropathology may exacerbate the brain-behavior associates of another [25, 32], further work is needed to understand the role of distinct *APOE* gene variants on both the separate as well as the interactive effects of these neuropathologies. In conclusion, *APOE* allele carrier status may not only impart differential age of clinical onset [47, 48], results of our study add to the growing body of literature [3, 49] that *APOE* genotypes may also impart a differential pathophysiology and course of disease.

Research in Context

Systematic review:

Using traditional (e.g., PubMed) sources, we found that most studies show *APOE* ε4 positive status specifically related to a greater abundance of amyloid pathology including AD pathology and cerebral amyloid angiopathy (CAA). *APOE* ε2 carriers show increases in CAA, but less AD pathology compared to ε4 carriers. Existing post-mortem studies of *APOE* and non-amyloid CVD-related neuropathology report conflicting results. This may be due to the small number of prospective clinical-pathologic studies including data on non-amyloid CVD-related neuropathologies and/or limited inclusion of oldest old decedents.

Interpretation:

Findings revealing the role of *APOE* in differentially promoting earlier gross infarcts and later cerebral small vessel disease depending upon carrier status suggest that *APOE* may differentially affect the type and timing of CVD-related neuropathology.

Future Directions:

Verification of these findings is needed, as are investigations to understand the role of distinct *APOE* genotypes on the interactive effects of amyloid and non-amyloid neuropathologies.

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Highlights

- We examined *APOE* ε4 & ε2 as related to non-amyloid forms of cerebrovascular disease
- Of 1,383 decedents, 342 were ε3/ε4 or ε4/ε4, 180 were ε2/ε3 or ε2/ε2
- ε3/ε4 & ε4/ε4 carriers had higher odds of macroinfarcts compared to ε3/ε3 carriers
- ε2/ε3 & ε2/ε2 carriers had higher odds of arteriolosclerosis versus ε3/ε3 carriers
- Results were driven by ε4 carriers<90 & ε2 carriers≥90 years at death, respectively

Table 1.

Sample Background and Neuropathology characteristics

	Entire Sample (N=1383)	***APOE* carrier status**		
		ε4+ (n=342)	ε2+ (n=180)	ε3/ε3 (n=861)
Background				
Age at death (yrs)	88.85 ±6.78	87.71 ±6.54	89.91 ±7.20	89.08 ±6.73
Sex (M:F)	458:925	115:227	53:127	290:571
Race (W:B:O)	1329:49:4	321:20:1	173:6:1	835:23:2
Education (yrs)	16.25 ±3.63	16.75 ±3.58	15.74 ±3.31	16.16 ±3.70
MMSE at death	20.81 ±9.25	17.57 ±10.35	22.62 ±8.21	21.73 ±8.67
MCI at death (%)	23.80	19.35	22.22	26.00
Demented at death (%)	43.60	60.11	33.33	39.25
Neuropathology				
Arteriolosclerosis (%)	33.70	33.63	42.22	31.94
Macroinfarcts (%)	35.36	38.90	35.00	34.03
Microinfarcts (%)	30.01	29.82	31.67	29.73
Atherosclerosis (%)	34.20	35.10	37.78	33.10
Global AD-related	0.74 +0.62	1.11 +0.66	0.41 +0.42	0.66 +0.57
CAA (% with moderate/severe)	33.55	51.75	33.33	26.36
NIA Reagan (%)	63.85	81.87	46.11	60.40

Note: all values equal mean±standard deviation unless otherwise noted. Abbreviations: yrs=years; M=male, F=female; W=white, B=black, O=other including Native American and Asian/Pacific Island; MMSE=Mini-Mental State Examination; MCI=mild cognitive impairment; CAA=cerebral amyloid angiopathy; NIA Reagan=AD present by NIA Reagan Pathology criteria (High or Intermediate Likelihood); %=percent.

Table 2.

Role of *APOE* gentoypes (ε4 and ε2) on the presence of neuropathologically derived levels of arteriolosclerosis (severe+moderate versus mild+none).

	Adjusted OR (95% CI)			
	Model 1 (N=1371)	**Model 2 (N=1364)**	**Model 3 (N=1329)**	**Model 4 (N=1231)**
***APOE* ε4 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	1.12 (0.86-1.47)	1.04 (0.78-1.38)	1.00 (0.73-1.37)	0.97 (0.70-1.34)
***APOE* ε2 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	**1.51 (1.09-2.11)** **	**1.46 (1.03-2.07)** *	**1.53 (1.07-2.20)** *	**1.68 (1.15-2.45)** **

OR=Odds Ratio

CI=Confidence Interval

Model 1=adjusted for demographic characteristics (age at death and sex)

Model 2=adjusted for demographic characteristics (age at death and sex) + macroinfarcts, microinfarcts and levels of intracranial atherosclerosis

Model 3= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, microinfarcts and levels of intracranial atherosclerosis + global AD-related neuropathology and CAA

Model 4= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, microinfarcts and levels of intracranial atherosclerosis + global AD-related neuropathology and CAA + subclinical cardiovascular disease (baseline systolic BP, change in systolic BP over time)

** $p \leq 0.01$

* $p < 0.05$

Table 3.

Role of *APOE* genotypes (ε4 and ε2) on the presence of microinfarcts (1≥ versus 0).

	Adjusted OR (95% CI)			
	Model 1 (N=1383)	**Model 2 (N=1364)**	**Model 3 (N=1329)**	**Model 4 (N=1231)**
***APOE* ε4 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	1.04 (0.80-1.37)	0.98 (0.74-1.31)	1.01 (0.74-1.38)	1.03 (0.74-1.42)
***APOE* ε2 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	1.07 (0.75-1.51)	1.03 (0.72-1.48)	0.98 (0.67-1.42)	1.02 (0.70-1.50)

OR=Odds Ratio

CI=Confidence Interval

Model 1=adjusted for demographic characteristics (age at death and sex)

Model 2=adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and levels of intracranial atherosclerosis

Model 3= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and levels of intracranial atherosclerosis + global AD-related neuropathology and CAA

Model 4= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and levels of intracranial atherosclerosis + global AD-related neuropathology and CAA + subclinical cardiovascular disease (baseline systolic BP, change in systolic BP over time)

** $p<0.01$

* $p<0.05$

Table 4.

Role of *APOE* genotypes (ε4 and ε2) on the presence of neuropathologically derived levels of intracranial atherosclerosis (severe+moderate versus mild+none).

	Adjusted OR (95% CI)			
	Model 1 (N=1376)	**Model 2 (N=1364)**	**Model 3 (N=1329)**	**Model 4 (N=1231)**
***APOE* ε4 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	1.14 (0.88-1.50)	1.10 (0.83-1.45)	1.08 (0.80-1.47)	1.10 (0.80-1.51)
***APOE* ε2 carrier status**				
No	Referent	Referent	Referent	Referent
Yes	1.21 (0.86-1.70)	1.10 (0.77-1.57)	1.07 (0.74-1.54)	1.04(0.71-1.54)

OR=Odds Ratio

CI=Confidence Interval

Model 1=adjusted for demographic characteristics (age at death and sex)

Model 2=adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and microinfarcts

Model 3= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and microinfarcts + global AD-related neuropathology and CAA

Model 4= adjusted for demographic characteristics (age at death and sex) + macroinfarcts, arteriolosclerosis and microinfarcts + global AD-related neuropathology and CAA + subclinical cardiovascular disease (baseline systolic BP, change in systolic BP over time)

** $p<0.01$

* $p<0.05$