



Published in final edited form as:

Neurology. 2006 May 9; 66(9): 1399–1404. doi:10.1212/01.wnl.0000210447.19748.0b.

## Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers

M.S. Beeri, PhD, M. Rapp, MD, PhD, J.M. Silverman, PhD, J. Schmeidler, PhD, H.T. Grossman, MD, J.T. Fallon, MD, D.P. Purohit, MD, D.P. Perl, MD, A. Siddiqui, MD, G. Lesser, MD, C. Rosendorff, MD, and V. Haroutunian, PhD

The Mount Sinai School of Medicine, Departments of Psychiatry (M.S.B., M.R., J.M.S., J.S., H.T.G., D.P. Purohit, D.P. Perl, A.S., G.L., V.H.), Biostatistics (J.S.), Pathology (J.T.F., D.P. Purohit, D.P. Perl), and Medicine (C.R.), New York, NY; Bronx VA Medical Center (H.T.G., C.R., V.H.), Bronx, NY; and Jewish Home and Hospital (G.L.), New York, NY

### Abstract

**Objective**—To examine the associations between postmortem Alzheimer disease (AD) neuropathology and autopsy-verified cardiovascular disease.

**Methods**—The authors examined 99 subjects (mean age at death = 87.6; SD = 8.7) from the Mount Sinai School of Medicine Department of Psychiatry Brain Bank who were devoid of cerebrovascular disease-associated lesions or of non-AD-related neuropathology. Density of neuritic plaques (NPs) and neurofibrillary tangles (NFTs) as well as coronary artery and aortic atherosclerosis, left ventricular wall thickness, and heart weight were measured. Partial correlations were used to assess the associations of the four cardiovascular variables with NPs and NFTs in the hippocampus, entorhinal cortex, and multiple regions of the cerebral cortex after controlling for age at death, sex, dementia severity, body mass index, and ApoE genotype. These analyses were also repeated separately for ApoE4 carriers and noncarriers.

**Results**—The extent of coronary artery disease and to a lesser extent atherosclerosis were significantly associated with the density of cardinal neuropathologic lesions of AD in this autopsy sample (significant correlations between 0.22 and 0.29). These associations were more pronounced for the ApoE4 allele carriers (n = 42; significant correlations between 0.34 and 0.47).

**Conclusions**—The degree of coronary artery disease is independently associated with the cardinal neuropathological lesions of Alzheimer disease. These associations are primarily attributable to individuals with the ApoE4 allele.

The prevalence of dementia rises steeply with age, doubling every 4 to 5 years from age 60 years, so that more than one-third of individuals older than 80 years are likely to have a dementia.<sup>1</sup> Alzheimer disease (AD) remains the most common cause of dementia in the elderly.<sup>2</sup> Postmortem studies suggest that the hippocampus and entorhinal cortex are the first brain areas to be affected, with cortical association areas being increasingly involved as the disease progresses.<sup>3,4</sup>

Cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, and homocystinemia are associated with vascular dementia, but recent studies have suggested that they are also independently associated with AD.<sup>5</sup> However, few studies have examined

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Address correspondence and reprint requests to Dr. Vahram Haroutunian, Psychiatry Research, 4F-33B, Bronx VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468; vahram.haroutunian@mssm.edu.

Disclosure: The authors report no conflicts of interest.

the specific association of cardiovascular damage with the cardinal neuropathologic lesions of AD directly. The Rotterdam study examined wall thickness and plaques of the carotid arteries, assessed by ultrasonography, and found that both clinically diagnosed probable AD and vascular dementia were associated with atherosclerosis.<sup>6</sup> An interaction between apolipoprotein E genotype (ApoE) and atherosclerosis in the etiology of AD (specifically, an augmented risk of AD in subjects with both a high atherosclerosis score and an ApoE4 allele) was also found in that study. Other investigators have reported that ApoE4 but not cardiovascular disease (measured postmortem) was associated with the extent of AD neuropathology.<sup>7</sup>

The current study was designed a priori to examine the contribution of vascular disease specifically to AD neuropathology (neuritic plaques [NPs] and neurofibrillary tangles [NFTs]), uncomplicated by other factors such as stroke, Lewy bodies, and frontotemporal dementia. The density of NPs and NFTs in the hippocampus, entorhinal cortex, and cerebral cortex were assessed postmortem and related to measures of end organ cardiovascular disease, namely, coronary artery and aortic atherosclerosis, left ventricular wall thickness, and heart weight.

## Methods

### Subjects

Analyses were based on the study of 256 consecutive brain donations that also had a full body autopsy over a period of 17 years. Of these cases, 39 had cerebrovascular disease, and 118 other cases had missing values in at least one of the critical variables (e.g., APOE). Because the objective of this study was to investigate the association between AD neuropathology and end organ cardiovascular disease (i.e., coronary artery disease, aortic atherosclerosis, left ventricular wall thickness, and heart weight), subjects with macroscopic cerebrovascular disease according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)<sup>8</sup> neuropathologic criteria were excluded.<sup>9,10</sup> Therefore, the analysis was limited to the 99 subjects with no discernible neuropathology or AD neuropathology only (CERAD<sup>8</sup> categories 1 = normal brain [n = 18], 2 = definite AD [n = 57], 3 = probable AD [n = 12], and 4 = possible AD [n = 12]). These subjects did not differ significantly from the excluded subjects in age at death, sex, or years of education. Postmortem donations were received by the Mount Sinai School of Medicine Department of Psychiatry Brain Bank, from the next of kin of deceased residents of the Jewish Home and Hospital (JHH) in Manhattan, NY, and Bronx, NY, participating in studies of aging and early dementia. Psychiatric cases were excluded from this cohort. Brain donations were accompanied by full body autopsies allowing objective measures of the presence and magnitude of cardiovascular pathology. All assessments were approved by the institutional review boards of both the JHH and the Mount Sinai School of Medicine. Autopsies were performed after receiving consent from the legal next of kin. Research staff reviewed detailed medical records, which were available on all residents, and whenever possible conducted in-depth interviews with staff and family caregivers to obtain information about antemortem functional and cognitive status.

The Clinical Dementia Rating (CDR) assesses cognitive and functional impairments associated with dementia and provides specific severity criteria for classifying subjects as nondemented (CDR = 0), questionably demented (CDR = 0.5), or increasing levels of severity of dementia from CDR = 1 to CDR = 5.<sup>11,12</sup> A previously described<sup>10,13</sup> multistep approach was applied to the assignment of postmortem CDR scale scores based on cognitive and functional status during the last 6 months of life.

### Assessment of ApoE genotype

After DNA isolation from frozen, never-thawed, brain tissue specimens (50 mg) using Promega Wizard® Genomic DNA purification kit, ApoE genotyping was performed using a modification of published PCR techniques.<sup>14</sup> Participants were categorized as ApoE4 positive if they carried at least one copy of the E4 allele.

### Neuropathologic assessment

The neuropathologic assessment procedures used have been extensively described previously<sup>10,13</sup> and were performed without knowledge of the donor's medical, cognitive, or functional status. Standardized representative blocks from superior and midfrontal gyrus, orbital cortex, basal ganglia with basal forebrain, amygdala, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex (angular gyrus), calcarine cortex, hypothalamus with mammillary bodies, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere were examined using hematoxylin and eosin, modified Bielschowsky, modified thioflavin S, anti- $\beta$ -amyloid, and anti-tau. Any case showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent anti-ubiquitin staining of representative cerebral cortical sections for the identification of cortical Lewy bodies.<sup>15,16</sup> Neuropathologists were blinded to all clinical and psychometric data while evaluating the slides for the presence and extent of relevant neuropathologic lesions. Neuropathologic and final diagnoses were based on a consensus diagnosis (H.T.G., D.P.Perl, V.H., and clinical neuropsychologists) and derived after review of all medical and research records according to procedures described in detail previously.<sup>10,13</sup>

Every case was evaluated for the extent of neuropathologic lesions using the CERAD neuropathologic battery.<sup>8</sup> Sections from each of the tissue blocks described above were rated for the extent of NPs and NFTs using the CERAD four-point scale of 0 = none, 1 = sparse, 3 = moderate, or 5 = severe as described previously.<sup>13</sup> NP and NFT scores derived from examination of the neocortical blocks aggregated by addition into a single summary variable and the entorhinal cortex and hippocampus were used in the primary analyses reported here because previous studies had shown that NP and NFT densities in the subcortical regions assessed were not informative with respect to dementia severity.<sup>10,13</sup> In addition, ancillary exploratory analyses revealed that the inclusion of NP and NFT density estimates from the subcortical fields assessed as part of the CERAD neuropathology battery did not substantively contribute to the findings described.

### Cardiovascular pathology assessment

All cardiovascular pathology assessments were performed using standard protocols. Coronary artery disease was assessed on 2- to 4-mm interval cross sections of all the major epicardial coronary arteries either on the heart or after removal and decalcification. Aortic atherosclerosis was assessed by semiquantitative estimation (scored on a four-point scale of severity with 1 representing no atherosclerosis and 4 representing severe atherosclerosis) of grossly notable plaque involvement of the aortic intimal surface after opening the aorta lengthwise from the ascending to the iliac bifurcation. Heart weight was measured after washing and removal of postmortem clots. Left ventricular wall thickness was measured along the lateral wall 1 cm below the mitral valve annulus.

The cardiovascular and neuropathology assessments were performed independently by different pathologists (neuropathology [D.P. Purohit and D.P. Perl] vs cardiovascular pathology [J.T.F.]) who were blind to each other's data.

## Statistical analysis

Factor analysis was used to create parsimonious summarizing variables, because it was anticipated that the cardiovascular risk variables would have some substantial intercorrelation. Principal components analysis with varimax rotation was performed on the four cardiovascular variables (coronary artery and aortic atherosclerosis, left ventricular wall thickness, and heart weight). Two eigen values were above 1, suggesting that two summarizing variables sufficed. One rotated factor was highly loaded on coronary artery and aortic atherosclerosis (called “atherosclerosis”), and the other was highly loaded on left ventricular wall thickness and heart weight (called “heart size”). Partial correlations were used to assess the associations of the two factors as well as the four cardiovascular variables with NPs and NFTs in the hippocampus, entorhinal cortex, and cerebral cortex after controlling for age at death, sex, CDR (making the subjects who died at different stages of the disease comparable), body mass index (BMI; measured by the JHH staff within 12 months before death and collected from subjects’ medical charts) and ApoE genotype. Because ApoE4 has been found to potentiate the association of atherosclerosis and AD,<sup>6</sup> we repeated the analyses separately for ApoE4 allele carriers and noncarriers.

## Results

Characteristics of the sample as a whole and according to CERAD diagnostic categories are presented in table 1. The sample was relatively old at death (mean age 87.6 years) and predominantly female (81.9%); 13.3% were not demented, 32.4% were severely demented according to the CDR (Levels 3, 4 and 5), and 42.4% had at least one ApoE4 allele. Thirty-seven percent of the sample had a BMI reflecting underweight (less than 18.5 kg/m<sup>2</sup>) and 5% had a BMI reflecting overweight (30 kg/m<sup>2</sup> or greater) according to the American Heart Association classification.<sup>17</sup> Analyses of variance comparing cases with normal brain and the three CERAD AD categories (definite, probable, and possible) found significant results for coronary artery disease and heart weight. We also tested for linear trends (reordering the categories by AD severity) and found significant relationships for these two cardiovascular variables; coronary artery disease severity increased with severity of AD neuropathology, whereas heart weight decreased.

Partial correlations between cardiovascular and neuropathologic measures are presented in table 2. The atherosclerosis factor (coronary artery disease and aortic atherosclerosis) was significantly associated with all three NP variables (correlations ranging from 0.20 and 0.25) but with none of the NFT variables. Coronary artery disease was significantly associated with all three NP variables and also with NFTs in the hippocampus (correlations ranging from 0.22 and 0.29). In contrast, aortic atherosclerosis was not significantly associated with any of the neuropathologic variables. The heart size factor (heart weight and left ventricular wall thickness) had a correlation of  $-0.23$  with NFTs in the cerebral cortex. Left ventricular wall thickness had a correlation of  $-0.22$  with NFTs in the cerebral cortex), but heart weight was not significantly associated with any of the neuropathologic variables.

Table 3 presents the correlations when the sample was divided according to the presence or absence of an ApoE4 allele. In the subgroup with an ApoE4 allele ( $n = 42$ ), all associations that were significant in the entire sample for the atherosclerosis factor were larger and still significant, and the association of atherosclerosis with NFTs in the entorhinal cortex also achieved significance (correlations ranging from 0.32 and 0.41). Similarly, all associations that were significant in the entire sample for the extent of coronary artery disease were larger and still significant, and so were their associations with NFTs in the entorhinal cortex (correlations ranging from 0.34 and 0.47). In addition, the correlation between the extent of aortic atherosclerosis and the density of NPs in the hippocampus ( $r = 0.33$ ) reached significance. None of the correlations between heart size factor, or its constituents, with the

neuropathologic variables were significant. In contrast to the ApoE4 subgroup, in the subgroup without an ApoE4 allele (n = 57), there were no significant correlations between any cardiovascular and neuropathologic variables. For each combination of coronary artery disease and neuropathology of AD, the correlation was stronger in the ApoE4 subgroup. The Fisher Z transformation was applied to each correlation to test the significance of the difference between correlations. None of the comparisons between correlations in the APOE4 carriers and noncarriers were significant. Finally, the APOE subgroups did not differ significantly from each other in the extent of any of the cardiovascular variables.

## Discussion

These results are consistent with and provide evidence for the hypothesis that coronary artery disease contributes significantly to the extent of AD-associated neuropathology independently of other risk factors such as age and sex. Atherosclerosis, particularly coronary artery disease, and the density of cardinal neuropathologic lesions of AD were significantly associated with each other. These associations were primarily attributable to ApoE4 allele carriers. The only significant results found for the heart size composite factor and left ventricular wall thickness were negative associations with NFTs in the cerebral cortex.

These results are consistent with others in which nondemented patients dying of critical coronary artery disease had more abundant senile plaques compared with subjects dying of other causes.<sup>18</sup> Two other studies<sup>7,19</sup> examining postmortem cardiovascular disease and AD neuropathology found no significant associations. One study<sup>19</sup> had few subjects (32 patients with definite AD and 6 age-matched control subjects) and possibly lacked statistical power. In a Finnish study,<sup>7</sup> a cardiovascular index was calculated that combined heart weight and atherosclerosis of the coronary arteries, aorta, and circle of Willis and found no associations with NPs, NFTs,  $\beta$ -A4, PHF- $\tau$ , and cerebral amyloid angiopathy. This study did not statistically control for age, sex, or body mass index, and the cardiovascular disease composite variable that was used may have masked relationships for individual constituents of the composite score. In the current study, all but one of the partial correlations between heart weight and neuropathology of AD were negative, suggesting that the smaller the heart is, the larger the amount of AD neuropathology is. Moreover, when examining these associations without controlling for BMI, the negative correlations were stronger and some reached significance (data not shown). The direction of these associations is only surprising at face value because, in general, heart weight is positively associated with hypertension,<sup>20</sup> which in turn seems to be associated with AD.<sup>21</sup> The lower heart weight with increasing AD neuropathology results may be inherent to postmortem studies that include cases with severe or terminal dementia and may be a consequence of the extreme weight loss, including heart weight loss, experienced by many of these subjects.<sup>22,23</sup> As noted above, 37% of the subjects in the current study could be classified as underweight. This percentage was even higher in those subjects that had CDR scores of 4 or greater or those who were classified as definite AD by CERAD neuropathologic criteria (approximately 70% of those considered underweight). Because the cardiovascular index in Finnish study included heart weight, and BMI was not included as a covariate in the analyses, we speculate that these factors offset the contribution of other cardiovascular components leading to negative results.

A possible explanation for the association between coronary artery disease and neuropathology of AD is that the former is associated with cerebrovascular arterial atherosclerosis.<sup>24</sup> This, in turn, is associated with AD. For example, circle of Willis atherosclerosis has been shown to be associated with AD,<sup>25,26</sup> and a recent study showed that cerebrovascular arterial atherosclerosis was strongly associated with an increased frequency of NPs.<sup>27</sup> In the current study, aortic atherosclerosis showed a lower association

with AD neuropathology (only for NPs in the hippocampus of the ApoE4 subgroup) than coronary artery disease. This distinction between coronary artery and aortic atherosclerosis is supported by recent epidemiologic studies suggesting that aortic atherosclerosis is less strongly associated with cerebrovascular disease.<sup>28,29</sup>

In addition to a direct relationship between coronary artery disease and AD neuropathology, another possible explanation may be that they share a common underlying causative factor. Specifically, our results suggest that the currently observed associations between coronary artery disease and AD neuropathology were primarily attributable to carriers of at least one ApoE4 allele. ApoE4 per se increases the risk for coronary artery disease<sup>30</sup> and for AD.<sup>31</sup> In addition, ApoE has been shown to interact with several cardiovascular risk factors, such as hypertension,<sup>32</sup> cholesterol,<sup>33</sup> insulin resistance,<sup>34</sup> and transient ischemic attacks,<sup>35</sup> to increase the incidence of AD and to accelerate its course. In view of these direct and indirect associations, ApoE might be serving as a common intermediary of both coronary artery disease and AD neuropathology. However, when controlling for ApoE genotype in the entire sample analysis, there were significant relationships between coronary artery disease and NP density. This result suggests that although ApoE genotype contributes strongly to the association, a relationship between coronary artery disease and AD neuropathology may exist independently of ApoE genotype. Other possible common causes include cholesterol metabolism,<sup>36</sup> diabetes,<sup>37</sup> or homocysteine levels.<sup>38</sup> Each of these has been implicated in the processing of  $\beta$ -amyloid, the major constituent peptide in the NP, as well as with tau, the major component of NFTs (for review, see Religa and Winblad<sup>39</sup>). However, in view of the strong associations between these cardiovascular risk factors and coronary artery disease, distinguishing between their relative or independent contributions to AD neuropathology may be difficult to document in humans and may be most readily clarified by studies of animal model systems.

The main strengths of this study are the relatively large sample size and the systematic and quantitative independent measurement of both AD and cardiovascular pathology. A weakness of the study is that the autopsy sample came from a single institution; subjects were mostly white women and from a relatively stable socioeconomic environment, potentially limiting generalizability of these results to more diverse populations. In addition, it is possible that the associations between postmortem AD and cardiovascular pathology differ from these associations in the population before death, because of different distributions of these pathologies.

## Acknowledgments

Supported by NIA grants AG02219 (PI: Vahram Haroutunian), and 1 K01 AG023515-01A2 (PI: Michal Schnaider Beeri). AG05138 (PI: Mary Sano).

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Table 1

Description of the sample (n = 99) and by CERAD categories

Characteristic/ CERAD category	Normal, n = 18	Definite, n = 57	Probable AD, n = 12	Possible AD, n = 12	Whole sample
Age at death	85.7 (10.6); 62–102	88.9 (7.2); 62–103	87.6 (9.3); 67–101	85.4 (10.6); 64–100	87.6 (8.7); 62–103
Sex, % female	72.2	86.0	83.3	66.7	81.9
ApoE, % E4 allele	33.3	47.4	33.3	41.7	42.4
CDR	1.5 (1.8); 0–5	3.3 (1.3); 1–5	2.3 (1.5); 1–5	2.4 (1.4); 0–5	2.8 (1.6); 0–5
BMI, kg/m <sup>2</sup>	23.0 (6.4); 13.1–40.4	20.0 (4.3); 11.7–31.5	20.8 (2.3); 17.6–24.1	21.0 (6.4); 12.9–32.8	20.7 (4.8); 11.7–40.4
Coronary artery disease	3.4 (1.6); 1–5	4.1 (1.1); 1–5	3.5 (1.5); 1–5	2.7 (1.4); 1–5	3.7 (1.4); 1–5
Aortic atherosclerosis	4.0 (1.2); 1–5	4.4 (1.0); 1–5	4.3 (0.99); 3–5	4.3 (1.3); 1–5	4.3 (1.1); 1–5
Left ventricular thickness, cm	1.7 (0.33); 1.2–2.3	1.6 (0.39); 0.30–2.6	1.6 (0.28); 1.2–2.1	1.5 (0.38); 0.80–2.2	1.6 (0.4); 0.3–2.6
Heart weight, g	460.0 (134.6); 230–850	361.4 (100.6); 120–630	397.1 (133.4); 250–670	394.6 (91.7); 230–570	385.0 (114.8); 120–850
NFTs hippocampus*	1.9 (1.8); 0–5	4.4 (1.3); 0–5	2.5 (1.7); 1–5	2.4 (1.8); 0–5	3.4 (1.9); 0–5
NFTs entorhinal cortex*	2.3 (1.7); 0–5	4.6 (0.98); 1–5	2.2 (1.8); 1–5	3.0 (1.9); 1–5	3.7 (1.7); 0–5
NFTs cerebral cortex <sup>†</sup>	0 (0); 0–0	6.7 (5.0); 0–16	0.42 (0.90); 0–3	0.42 (0.67); 0–2	4.1 (5.0); 0–16
NPs hippocampus*	0.1 (0.24); 0–1	2.3 (1.3); 0–5	1.2 (1.5); 0–5	0.50 (0.52); 0–1	1.6 (1.5); 0–5
NPs entorhinal cortex*	0.4 (0.8); 0–3	3.1 (1.4); 0–5	2.3 (1.7); 0–5	0.83 (0.84); 0–3	2.3 (1.7); 0–5
NPs cerebral cortex <sup>†</sup>	1.8 (2.8); 0–10	13.8 (4.7); 4–20	7.7 (2.9); 3–14	5.4 (3.6); 0–10	10.0 (6.3); 0–20

Data are presented as mean (SD); range.

\* 0 = none, 1 = sparse, 3 = moderate, 5 = severe.

<sup>†</sup> Summary of four cerebral cortex areas (midfrontal gyrus, superior middle temporal gyrus, inferior parietal gyrus, and occipital primary visual cortex) by addition of scores on the same scale as in \*.

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; AD = Alzheimer disease; CDR = Clinical Dementia Rating; BMI = body mass index; NFT = neurofibrillary tangle; NP = neuritic plaque.

**Table 2**

Partial correlations of cardiovascular and AD neuropathology characteristics (df = 92)\*

AD neuropathology	Coronary artery disease	Aortic atherosclerosis	Atherosclerosis factor	Left ventricular thickness	Heart weight	Heart size factor
NFTs hippocampus	0.24 <sup>‡</sup>	0.01	0.14	0.11	0.05	0.09
NFTs entorhinal cortex	0.16	0.08	0.16	0.06	-0.16	-0.06
NFTs cerebral cortex	0.13	0.02	0.10	-0.22 <sup>‡</sup>	-0.19	-0.23 <sup>‡</sup>
NPs hippocampus	0.26 <sup>‡</sup>	0.13	0.25 <sup>‡</sup>	0.06	-0.05	-0.01
NPs entorhinal cortex	0.29 <sup>‡</sup>	0.05	0.22 <sup>‡</sup>	-0.07	-0.18	-0.15
NPs cerebral cortex	0.22 <sup>‡</sup>	0.10	0.20 <sup>‡</sup>	-0.09	-0.11	-0.12

\* Covariates were age at death, Clinical Dementia Rating, sex, ApoE4 genotype, and body mass index.

<sup>‡</sup>  $p \leq 0.05$ .

<sup>‡</sup>  $p \leq 0.005$ .

AD = Alzheimer disease; NFT = neurofibrillary tangle; NP = neuritic plaque.

Table 3

Partial correlations of cardiovascular and AD neuropathology characteristics for subjects carrying or not carrying an ApoE4 allele\*

AD neuropathology	Coronary artery disease	Aortic atherosclerosis	Atherosclerosis factor	Left ventricular thickness	Heart weight	Heart size factor
Absence of an ApoE4 allele ( <i>df</i> = 51)						
NFTs hippocampus	0.13	-0.05	0.04	0.12	0.10	0.13
NFTs entorhinal cortex	0.01	0.04	0.04	0.04	-0.09	-0.02
NFTs cerebral cortex	0.05	-0.02	0.04	-0.16	-0.23	-0.21
NPs hippocampus	0.19	-0.003	0.13	-0.06	-0.11	-0.09
NPs entorhinal cortex	0.15	-0.004	0.11	-0.12	-0.18	-0.16
NPs cerebral cortex	0.14	0.02	0.11	-0.16	-0.13	-0.12
Presence of an ApoE4 allele ( <i>df</i> = 36)						
NFTs hippocampus	0.38 <sup>†</sup>	0.11	0.29	0.05	-0.01	0.003
NFTs entorhinal cortex	0.34 <sup>†</sup>	0.16	0.32 <sup>†</sup>	0.03	-0.26	-0.18
NFTs cerebral cortex	0.25	0.10	0.22	-0.28	-0.13	-0.23
NPs hippocampus	0.35 <sup>†</sup>	0.33 <sup>†</sup>	0.41 <sup>†</sup>	0.14	-0.02	0.01
NPs entorhinal cortex	0.47 <sup>‡</sup>	0.14	0.38 <sup>†</sup>	-0.15	-0.21	-0.23
NPs cerebral cortex	0.36 <sup>†</sup>	0.20	0.33 <sup>†</sup>	-0.11	-0.06	-0.11

\* Covariates were age at death, Clinical Dementia Rating, sex, and body mass index.

<sup>†</sup>  $p \leq 0.05$ .

<sup>‡</sup>  $p \leq 0.005$ .

AD = Alzheimer disease; NFT = neurofibrillary tangle; NP = neuritic plaque.