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Neocortical β -amyloid area is associated with dementia and *APOE* in the oldest-old

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Abstract

Objective—Apolipoprotein E (*APOE*) ϵ 2 carriers may be protected from dementia because of reduced levels of cortical β -amyloid. In the oldest-old, however, *APOE* ϵ 2 carriers have high β -amyloid plaque scores and preserved cognition. We compared different measures of β -amyloid pathology across *APOE* genotypes in the oldest-old, and their relationship with dementia.

Methods—The study included 96 participants from The 90+ Study. Using all information, dementia diagnoses were made. Neuropathological examination included staging for amyloid plaques and β -amyloid cortical percent area stained by NAB228 antibody.

Results—Both *APOE* ϵ 2 and *APOE* ϵ 4 carriers had high Consortium to Establish a Registry for Alzheimer's Disease plaque scores. However, *APOE* ϵ 2 carriers had low cortical β -amyloid percent areas. β -amyloid percent area was associated with dementia across *APOE* genotypes.

Conclusions—Lower levels of percent area in *APOE* ϵ 2 carriers may reflect lower total β -amyloid and may contribute to *APOE* ϵ 2 carriers' decreased risk of dementia, despite high β -amyloid plaque scores. The relationship between β -amyloid plaques and dementia in the oldest-old may vary by *APOE* genotype.

Keywords

Alzheimer; Apolipoprotein E; Beta-amyloid; Dementia; Oldest-old

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Dr. Berlau performed all statistical analyses at the University of California at Irvine and at Regis University.

Dr Berlau, Dr Corrada, Mr Robinson, Dr Geser, Dr Kawas, and Dr Trojanowski were involved in drafting/revising the manuscript for content, study concept and design, and analysis and interpretation of data.

Dr Arnold and Dr Lee were involved study concept and design.

1. Introduction

Alzheimer's disease (AD) affects more than 5 million people in the United States alone, at far-reaching social and financial costs. Moreover, the incidence of dementia (mostly AD) continues to increase with age and is more than 18%/year in people age 90 years and older (the oldest-old) [1]. The relationship between clinical AD and the hallmark pathology of AD, β -amyloid plaques, is well established in the younger elderly (age, 65–90 years) [2].

However, this relationship is still equivocal in the oldest-old. Several studies have suggested that β -amyloid plaques are not associated with dementia [3,4], whereas others have found that this relationship continues into the oldest-old [5,6]. Based on the recent attention to β -amyloid-based biomarkers, it will become increasingly important to understand this relationship in the oldest-old, the fastest growing age group in the country.

The apolipoprotein E (*APOE*) gene has been identified as the major genetic risk modifier in sporadic AD. *APOE* ϵ 4 carriers have increased risk of clinical and pathological AD [7,8]. Conversely, *APOE* ϵ 2 carriers have consistently lower risks of dementia and clinical AD [9], but the relationship between *APOE* ϵ 2 and all forms of β -amyloid neuropathology is still not clear. Some studies have found that *APOE* ϵ 2 carriers have decreased levels of β -amyloid neuropathology [10,11], whereas others have no decrease [12,13]. Although the precise mechanisms by which *APOE* can affect the pathogenesis of AD are unknown, it has been proposed that the *ApoE* proteins can affect a large variety of AD processes, including tau phosphorylation, neuronal apoptosis, and β -amyloid deposition [14].

We recently found that, in the oldest-old, *APOE* ϵ 2 carriers have a somewhat reduced risk of dementia but increased levels of β -amyloid pathology compared with those with *APOE* ϵ 3/3 [15,16]. These studies assessed β -amyloid pathology using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) plaque scores, which measured β -amyloid plaques. There is significant evidence that diffuse plaques or oligomeric β -amyloid may also be critically involved in AD and cognitive dysfunction [17].

Therefore, it is the purpose of this study to extend our initial studies of the relationship between *APOE* and β -amyloid pathology. Adding to our previous study [16], β -amyloid pathology will be assessed using two different measures: CERAD scoring, which is a semiquantitative measure of neuritic plaques, and a β -amyloid percent area measure, which quantifies β -amyloid via immunostaining using the NAB228 antibody and measures all assembly states of β -amyloid.

2. Methods

2.1. Participants

Participants were drawn from The 90+ Study, a population-based longitudinal study of aging and dementia in persons age 90 years and older. These subjects are survivors from the Leisure World Cohort Study, an epidemiologic investigation of a retirement community in Orange County, CA (Leisure World, Laguna Woods) initiated during the early 1980s. The cohort is primarily white, well educated, upper middle class, and mostly female. The 1151 participants from the original cohort age 90 years and older on January 1, 2003, were invited to join The 90+ Study. Although most of the recruited participants still lived in the same county (60%), many had moved to other parts of California (24%) or out of state (16%). We selected all subjects who had a completed brain autopsy and completed β -amyloid percent area analysis by October 2010, which totaled 103 subjects. However, we excluded three people because they did not have a valid Mini Mental State Examination (MMSE) score, one person for not having *APOE* genotyping, and, to maintain mutually exclusive groups,

three participants who had the *APOE* genotype *APOE* ϵ 2/*APOE* ϵ 4. Thus, 96 people were included in the study.

2.2. Determination of clinical diagnosis

As members of The 90+ Study, all participants received a neurological examination and neuropsychological testing every 6 months, including the MMSE and other tests described previously [18]. Medical history information was obtained and included comorbidities such as depression, stroke, congestive heart failure, atrial fibrillation, and Parkinson's disease. In addition, most participants had available medical records and neuroimaging (computed tomography/magnetic resonance imaging) that were used for the clinical diagnosis. Clinical diagnoses were determined by a consensus diagnostic conference, using all available information and blinded to *APOE* genotype. Dementia diagnosis was established using *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria. Clinical AD diagnoses were established using National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [19] for possible or probable AD. The institutional review board of the University of California, Irvine, approved all procedures.

2.3. Determination of pathological diagnosis

Before dissection, the whole brain was weighed. One hemisphere of each individual was selected for use in the final neuropathology diagnosis based on the neurological examiner's impression of any asymmetry in clinical neurological features. The hemisphere corresponding to any such clinical features was selected for examination. Thioflavin S staining was performed on midfrontal and superior temporal cortex sections, and CERAD criteria were used to determine neuritic plaque scores [20]. For analysis, semiquantitative plaque scores were given numeric values, so that none = 0, sparse = 1, moderate = 2, and frequent = 3.

For the β -amyloid percent area measure, midfrontal and superior temporal cortex sections were stained using anti- β -amyloid (NAB228, an antibody binding to $A\beta_{1-42}$). A representative section of NAB228-stained tissue was selected (holes in the tissue were not included in stained areas), the multithresholder maximum entropy algorithm was applied, and β -amyloid percent area was determined. Detailed methods have been described previously [21,22]. In all analyses, the mean value of the two cortical areas was used.

2.4. Statistical analysis

The levels of neuropathology between demented and nondemented subjects within each *APOE* genotype were analyzed using Student *t* tests. Because of the small number of homozygous individuals for *APOE* ϵ 2 and *APOE* ϵ 4, these individuals were grouped with the heterozygous participants for analysis. We then examined the relationship between age at death, post mortem interval, gender, and education to *APOE* genotype to determine whether these variables should be included as covariates in subsequent analyses. Although none of the variables were associated with the outcome variables, age at death and gender were retained in the model as covariates to maintain statistical continuity with other *APOE* studies. Logistic regression analyses were performed to examine the relationship of *APOE* genotype to several clinical and neuropathological outcomes. The clinical outcomes analyzed were presence or absence of dementia, presence or absence of possible or probable AD, and MMSE score less than 24 (vs ≥ 24). The neuropathological outcomes analyzed were CERAD plaque score (frequent vs none/sparse/moderate) and β -amyloid percent area (above the median vs below the median). Because they are continuous variables, we also used linear regression to examine the effects of *APOE* on MMSE scores and β -amyloid percent area. We used the data from the visit closest to the time of death for analyses of MMSE score. All

statistical analyses were performed using SAS (version 9.2, SAS Institutes Inc., Cary, NC) and SPSS (version 19, IBM, Armonk, NY).

3. Results

The demographic information of the participants is summarized in Table 1. The participants were predominantly female and were highly educated. Participants' median age at death was 96.8 years. *APOE* ϵ 2 was present in 13.5% of participants (one person was *APOE* ϵ 2 homozygous) and *APOE* ϵ 4 in 18.8% (one person was *APOE* ϵ 4 homozygous). Dementia was present in 59.4% of the participants, whereas clinical AD was present in 44.8%. The median percent amyloid area was 3.2% in *APOE* ϵ 2 carriers and 10.6% in *APOE* ϵ 4 carriers.

The relationship between *APOE*, dementia status, and β -amyloid neuropathology is summarized in Fig. 1. CERAD plaque scores did not differentiate demented vs nondemented participants with *APOE* ϵ 2 and *APOE* ϵ 3/3, but β -amyloid percent area did differentiate demented vs non-demented participants in all three *APOE* genotypes.

The dissociations between CERAD plaque score and β -amyloid percent area for participants with an *APOE* ϵ 2 gene are shown in Table 2. All but one of the participants with a β -amyloid percent area value below the median had moderate or frequent CERAD plaque scores. One participant had a low CERAD plaque score, but a β -amyloid percent area score slightly above the median (6.6%).

The associations between *APOE* genotype and clinical and neuropathological outcomes are summarized in Table 3. Neither *APOE* ϵ 2 nor *APOE* ϵ 4 was associated significantly with any clinical outcomes (dementia, clinical AD, or MMSE score < 24). However, all the odds ratios (ORs) for *APOE* ϵ 2 were less than one, suggesting lower odds for all the outcomes; all the ORs for *APOE* ϵ 4 were more than one, suggesting higher odds for all clinical outcomes. For analyses of neuropathological outcomes, *APOE* ϵ 4 carriers were significantly more likely to have frequent β -amyloid plaques (OR, 5.11) and high β -amyloid percent area (OR, 11.50) than *APOE* ϵ 3/3 carriers. In contrast, *APOE* ϵ 2 carriers were significantly more likely to have frequent β -amyloid plaques (OR, 4.51), and were less likely, although not significantly, to have high β -amyloid percent area (OR, 0.42) than *APOE* ϵ 3/3 carriers. When MMSE score was analyzed as a continuous variable, *APOE* ϵ 2 carriers did slightly better on the MMSE ($B = 2.20$, $P = .48$), whereas *APOE* ϵ 4 carriers did slightly worse ($B = -1.72$, $P = .52$) than *APOE* ϵ 3/3 carriers, but the results were not significant. When amyloid area was analyzed as a continuous variable, *APOE* ϵ 2 carriers had slightly (but not significantly) lower β -amyloid percent areas ($B = -0.48$, $P = .79$), whereas *APOE* ϵ 4 carriers had significantly higher β -amyloid percent area ($B = 3.99$, $P = .02$) than *APOE* ϵ 3/3 carriers. In the case of both variables, the interpretations of results from the linear regressions were not different from the results of the dichotomous variables.

4. Discussion

In this study of the oldest-old, we found that β -amyloid percent area but not CERAD plaque score was associated with dementia in all three *APOE* genotypes. These findings may help explain the surprising dissociation between AD neuropathology and dementia that we previously found in *APOE* ϵ 2 carriers in this cohort [16]. In that study, *APOE* ϵ 2 carriers demonstrated significantly higher CERAD plaque scores than *APOE* ϵ 3/3 carriers, despite having decreased odds of dementia.

In the current study, both *APOE* ϵ 2 and *APOE* ϵ 4 carriers had very high CERAD plaque scores. Previous studies have confirmed that *APOE* ϵ 4 is associated with increased AD neuropathology, especially β -amyloid plaques [7]. The mechanism behind this increase in β -

amyloid pathology is still being determined [14]. In contrast, there is little evidence in the literature that *APOE* ϵ 2 is associated with increased β -amyloid plaque scores. Previously, in this oldest-old cohort, we described that *APOE* ϵ 2 carriers have increased plaque scores, as measured by CERAD [16]. However, other researchers examining younger cohorts have found *APOE* ϵ 2 to be associated with decreased β -amyloid pathologies, including β -amyloid plaque density, neuropil thread formation, and amyloid angiopathy [11]. It is possible, therefore, that the extreme age of the subjects in this cohort may be involved in the different neuropathological levels in *APOE* ϵ 2 carriers.

In contrast to the CERAD plaque measure, the β -amyloid percent area measure was strongly associated with dementia and was not elevated in *APOE* ϵ 2 carriers compared with *APOE* ϵ 3/3 carriers. The *APOE* ϵ 2 carriers, despite having high CERAD plaque scores, had relatively low levels of amyloid as measured by β -amyloid percent area. These findings suggest that CERAD plaque scores may not be the best way to measure the relevant β -amyloid pathology in oldest-old *APOE* ϵ 2 carriers. An *APOE* ϵ 2-specific mechanism may exist that increases the numbers of CERAD plaques, while actually reducing β -amyloid in other forms and therefore overall β -amyloid levels. In addition, *APOE* ϵ 2 carriers may have an accelerated formation of β -amyloid into plaques to protect against the more destructive oligomeric form of β -amyloid. The β -amyloid percent area measures many different assembly states of β -amyloid, including diffuse plaques and β -amyloid oligomers. It may be a better marker for overall β -amyloid pathology, or may be measuring other, more relevant forms of β -amyloid, especially in the oldest-old. It is likely that a measure of all types of β -amyloid (such as the NAB228 percent area) relates better than staging to in vivo amyloid measures, because positron emission tomographic scanning may visualize only the more fibrillar β -amyloid deposits, but further research is needed to elucidate this relationship.

There are several limitations to this study that warrant discussion. This analysis focused on the relationship between *APOE* genotype, dementia, and hallmark AD neuropathology, but did not address additional pathologies such as vascular lesions, hippocampal sclerosis, or Lewy bodies. These other pathologies are perhaps involved in the association between *APOE* ϵ 2 genotype and dementia, but this analysis focused specifically on the methodology of measuring β -amyloid neuropathology. Because AD neuropathology alone becomes increasingly rare with advanced age [23], subjects with mixed pathology may be more relevant to clinical situations. Nevertheless, future analyses should examine to what extent these other pathologies are related to *APOE* and dementia. It is also possible that *APOE* ϵ 2 may offer protection against dementia because of a mechanism that is completely independent of neuropathology, such as affecting brain reserve or neuroplasticity, which the current findings do not address. Another limitation to the study was the inclusion of non-AD cases in the analysis. In the oldest-old, many of the non-AD cases have high levels of AD pathology, and we felt that their inclusion was warranted because their clinical diagnosis may have been incorrect or they could have had multiple dementia etiologies including AD. In addition, the current cohort comprises a predominantly female, white population of high educational level, characteristics that could potentially limit the generalizability of our results. However, according to the U.S. Census, most people age 90 years and older are women, white, and at least high school graduates [24]. Thus, despite the lack of representation of minority subjects and having mostly women in the cohort, the composition of the current cohort does reflect that of people age 90 years and older in the United States.

The current findings suggest that the relationship among *APOE*, AD neuropathology, and cognition in the oldest-old is a complex one. Although *APOE* ϵ 4 carriers are more likely to have dementia and β -amyloid neuropathology, *APOE* ϵ 2 carriers show a dissociation between cognition and β -amyloid neuropathology when measured using CERAD plaque scores. However, if β -amyloid pathology is measured using β -amyloid percent area, the

relationship between β -amyloid and cognition is restored, and *APOE* ϵ 2 carriers have better cognition and less β -amyloid percent area. Thus, it appears that β -amyloid continues to be important for cognition after age 90; however, CERAD plaque scores may no longer be the best measure of this neuropathology.

5. Author disclosures

Dr Lee has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd.; has received speaker honoraria from Pfizer, Inc, BMS, and Merck; may accrue revenue on patents re: Modified avidin-biotin technique; Method of stabilizing microtubules to treat Alzheimer's disease; Method of detecting abnormally phosphorylated tau; Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments; Compositions and methods for producing and using homogeneous neuronal cell transplants; Rat comprising straight filaments in its brain; Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries; Diagnostic methods for Alzheimer's disease by detection of multiple mRNAs; Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases; Compositions and methods for producing and using homogenous neuronal cell transplants; Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders; Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype; Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody; and receives research support from the National Institutes of Health, National Institute on Aging (NIA) PO1 AG 17586-10, PO1 AG-032953, National Institute of Neurological Disorders and Stroke (NINDS) P50 NS053488-02, NIA UO1 AG029213-01, and from the Marian S. Ware Alzheimer Program. Dr Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd; has received speaker honoraria from Pfizer, Inc; serves as an associate editor of *Alzheimer's & Dementia*; may accrue revenue on patents re: Modified avidin-biotin technique; Method of stabilizing microtubules to treat Alzheimer's disease; Method of detecting abnormally phosphorylated tau; Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments; Compositions and methods for producing and using homogeneous neuronal cell transplants; Rat comprising straight filaments in its brain; Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries; Diagnostic methods for Alzheimer's disease by detection of multiple mRNAs; Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases; Compositions and methods for producing and using homogenous neuronal cell transplants; Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders; Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype; Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody; and receives research support from the NIH (NIA P01 AG 09215-20 [principal investigator (PI)], NIA P30AG10124-18 [PI], NIA PO1 AG 17586-10 [Project 4 leader], NIA 1PO1 AG-19724-07 [Core C leader], NIA 1 UO1 AG024904-05 [Co-PI Biomarker Core Laboratory], NINDS P50 NS053488-02 [PI], NIA UO1 AG029213-01 [co-investigator]; RC2NS069368 [PI], RC1AG035427 [PI], and NIA P30AG036468 [PI]), and from the Marian S. Ware Alzheimer Program.

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Research In Context

1. **Systematic review:** We searched PubMed for reports with the search items *APOE* Alzheimer's disease, *APOE* Alzheimer neuropathology, and *APOE* amyloid. We targeted studies that examined the relationships among apolipoprotein E (*APOE*), dementia, and Alzheimer's disease (AD) neuropathology.
2. **Interpretation:** These findings help explain the dissociation between AD neuropathology and dementia previously found in *APOE* ϵ 2 carriers. If β -amyloid pathology is measured using β -amyloid percent area, the relationship between β -amyloid and cognition is restored. Thus, it appears that β -amyloid continues to be important for cognition after age 90; however, CERAD plaque scores may no longer be the best neuropathological measure.
3. **Future directions:** The current study demonstrated that β -amyloid percent area correlated with cognition better than CERAD plaques. Because β -amyloid percent area measures all assembly states of β -amyloid, it is unknown which states cause cognitive deficits seen in AD. Future research should use more specific measures of neuropathology to help identify these specific assembly states and to determine how they affect cognition.

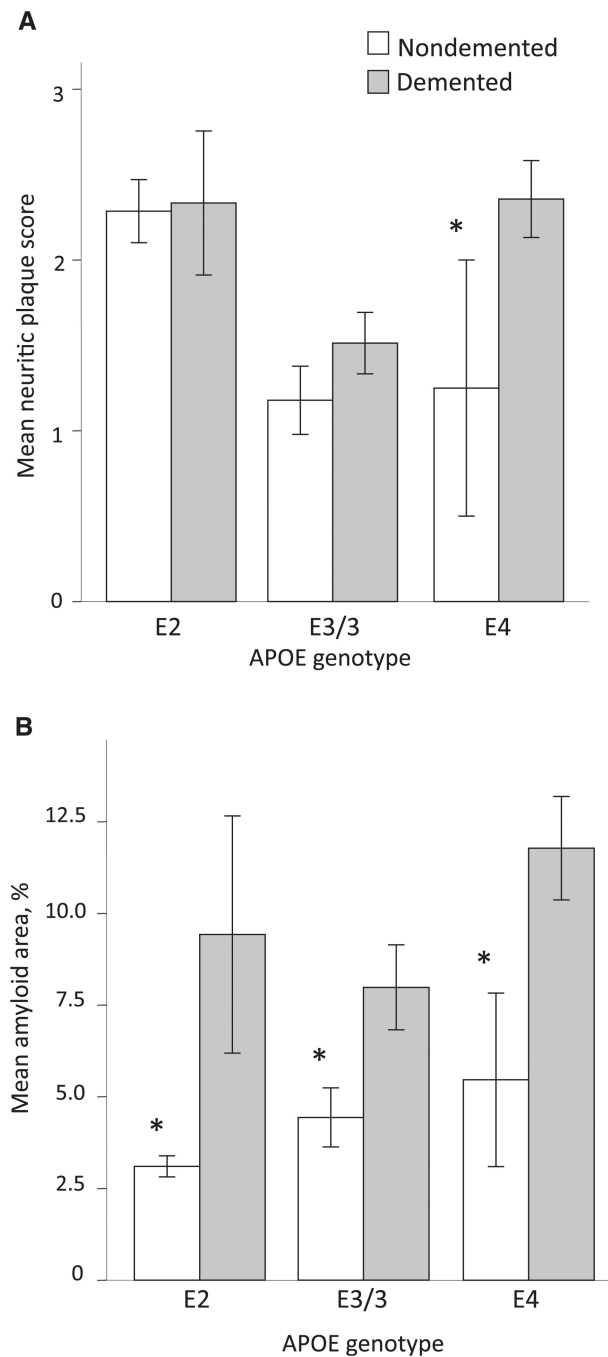


Fig. 1. β -amyloid neuropathology types by apolipoprotein E (*APOE*) genotype and dementia status. (A) *APOE* ϵ 2 carriers have high levels of β -amyloid plaques, regardless of their dementia status. (B) In contrast, nondemented *APOE* ϵ 2 carriers have significantly lower levels of amyloid as measures by β -amyloid percent area. Across all genotypes, β -amyloid percent area effectively differentiates demented from nondemented participants. * $P < .05$ using Student's *t* test. Error bars show ± 1 standard error.

Table 1
Participant characteristics (n = 96)

	All subjects (n = 96)	APOE ε2 (n = 13)	APOE ε3/3 (n = 65)	APOE ε4 (n = 18)
Females, n (%)	67 (76.0)	10 (76.9)	50 (76.9)	13 (72.2)
Education, n (%)				
Less than college	29 (30.2)	7 (53.8)	17 (26.2)	5 (27.8)
Any college	44 (45.8)	5 (38.5)	32 (49.2)	7 (38.9)
Any graduate school	22 (22.9)	1 (7.7)	15 (23.1)	6 (33.3)
All-cause dementia, n (%)	57 (59.4)	6 (46.2)	37 (56.9)	14 (77.8)
Clinical Alzheimer's disease, n (%)	43 (44.8)	6 (46.2)	31 (47.7)	11 (61.1)
CERAD β-amyloid plaques				
None, n (%)	21 (21.9)	0 (0)	19 (29.2)	2 (11.1)
Sparse, n (%)	19 (19.8)	2 (15.4)	14 (21.5)	3 (16.7)
Moderate, n (%)	30 (31.3)	5 (38.5)	21 (32.3)	4 (22.2)
Frequent, n (%)	26 (27.1)	6 (46.2)	11 (16.9)	9 (50.0)
Age at death, years, median (range)	96.8 (90.8–105.9)	97.1 (92.9–101.2)	96.5 (90.8–105.9)	97.8 (92.1–102.8)
Visit–death interval, month, median (range)	3.8 (0.2–29.3)	4.4 (0.5–16.7)	3.7 (0.2–29.3)	3.4 (0.4–9.8)
MMSE, median (range)	20.5 (0–30)	27 (0–29)	21 (0–30)	15.5 (0–29)
Brain weight, g, median (range)*	1134 (872–1403)	1190 (934–1365)	1120 (872–1390)	1150 (902–1403)
Post mortem interval, hours, median (range)†	5.0 (1.0–53.7)	5.3 (3.3–53.7)	5.0 (1.8–34.1)	4.3 (1.0–17.0)
β-amyloid area, %, median (range)	5.2 (0.3–28.5)	3.2 (1.5–23.0)	4.2 (0.3–28.5)	10.6 (1.5–21.8)

Abbreviations: APOE, apolipoprotein E; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini Mental State Exam.

* n = 90.

† n = 94.

Table 2
Subjects with *APOE* ε2 and their dissociation between CERAD score and amyloid percent area

Subject no.	<i>APOE</i> genotype	Dementia	CERAD plaque score	Amyloid area, %	Dissociation between pathologies*
1	23	Alzheimer's	Sparse	1.45	No
2	22	Nondemented	Frequent	1.80	Yes
3	23	Nondemented	Moderate	2.80	Yes
4	23	Alzheimer's	Frequent	3.00	Yes
5	23	Nondemented	Moderate	3.00	Yes
6	23	Nondemented	Moderate	3.13	Yes
7	23	Nondemented	Moderate	3.20	Yes
8	23	Nondemented	Moderate	3.45	Yes
9	23	Nondemented	Frequent	4.35	Yes
10	23	Alzheimer's	Sparse	6.60	No
11	23	Alzheimer's	Frequent	9.05	No
12	23	Alzheimer's	Frequent	13.45	No
13	23	Alzheimer's	Frequent	23.00	No

Abbreviations: *APOE*, apolipoprotein E; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

* Defined as having moderate or frequent CERAD plaques, but below median (5.2%) amyloid percent area levels.

Table 3
Associations between APOE genotype and clinical and neuropathological outcomes

Outcomes	Genotype*			
	APOE ε2/ε	APOE ε3/3	APOE ε4/ε	P value
	OR (95% CI) [†]	OR (95% CI) [†]	OR (95% CI) [†]	
Clinical outcomes				
Dementia	0.65 (0.20–2.18)	1 (reference)	2.81 (0.82–9.66)	.12
Alzheimer's disease	0.94 (0.28–3.14)	1 (reference)	1.80 (0.61–5.30)	.32
MMSE score < 24	0.36 (0.10–1.24)	1 (reference)	1.56 (0.48–5.00)	.48
Neuropathological outcomes				
Frequent β-amyloid plaques	4.51 (1.19–17.08)	1 (reference)	5.11 (1.56–16.78)	.005
High β-amyloid area, % [‡]	0.42 (0.16–2.13)	1 (reference)	11.50 (2.38–55.66)	.003

Abbreviations: APOE, apolipoprotein E; OR, odds ratio; CI, confidence interval; MMSE, Mini Mental State Exam.

* Three participants with the genotype APOE ε2/4 were excluded from all analyses.

[†] From logistic regressions including age at death and gender as covariates.

[‡] Defined as greater than the median value of 5.2%.