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Featured Article

Prevalence of the apolipoprotein E ε4 allele in amyloid β positive subjects across the spectrum of Alzheimer's disease

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Q3 **Abstract**

Introduction: Apolipoprotein E (*APOE*) ε4 is the major genetic risk factor for Alzheimer's disease (AD), but its prevalence is unclear because earlier studies did not require biomarker evidence of amyloid β (Aβ) pathology.

Methods: We included 3451 Aβ+ subjects (853 AD-type dementia, 1810 mild cognitive impairment, and 788 cognitively normal). Generalized estimating equation models were used to assess *APOE* ε4 prevalence in relation to age, sex, education, and geographical location.

Results: The *APOE* ε4 prevalence was 66% in AD-type dementia, 64% in mild cognitive impairment, and 51% in cognitively normal, and it decreased with advancing age in Aβ+ cognitively normal and Aβ+ mild cognitive impairment ($P < .05$) but not in Aβ+ AD dementia ($P = .66$). The prevalence was highest in Northern Europe but did not vary by sex or education.

Discussion: The *APOE* ε4 prevalence in AD was higher than that in previous studies, which did not require presence of Aβ pathology. Furthermore, our results highlight disease heterogeneity related to age and geographical location.

Keywords: APOE; Prevalence; Amyloid; PET; CSF; Alzheimer's disease; Mild cognitive impairment; Subjective cognitive decline; Age; Sex; Education; Geographical location

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and a major cause of morbidity and mortality worldwide [1]. Pathological metabolism and accumulation of amyloid β (Aβ) peptides are thought to be an initiating event in AD, leading to downstream spread of tau pathology, synaptic loss, neurodegeneration, and cognitive decline [2–4]. The main risk factors for the development of AD are increasing age and the ε4 allele of the apolipoprotein E (*APOE*) gene [5–7], the strongest genetic risk factor for sporadic AD [8,9]. *APOE* encodes for apolipoprotein E, which is a major lipid transporting protein in the brain [10]. In humans, the gene exists in three allele variants called ε2, ε3, and ε4. Compared with *APOE* ε3/ε3 (the most common genotype), *APOE* ε4 heterozygosity increases the risk for developing clinical AD by about 3–4 times and *APOE* ε4 homozygosity by about 10–15 times [8,11]. The overall prevalence of *APOE* ε4 positivity has been reported to be approximately 15%–20% in the normal population [11,12] and 50%–60% in patients with AD dementia [8,9,13]. These numbers, however, vary widely and may depend on different characteristics of the study population, including ethnicity [14] and geographical location [13]. In addition, most previous studies included clinically diagnosed AD patients without neuropathological confirmation and/or supportive pathophysiological AD biomarkers. Studies applying cerebrospinal fluid (CSF) and positron emission tomography (PET) have revealed that a substantial proportion of patients with a clinical diagnosis of AD dementia have no evidence of Aβ pathology [15–18], which makes the underlying AD pathology highly unlikely. This mismatch between the clinical diagnosis and Aβ biomarkers seems especially prevalent in *APOE* ε4 noncarriers, as illustrated by a clinical trial in which 36% of *APOE* ε4-negative patients with a diagnosis of "AD dementia" lacked Aβ pathology as determined by PET [19]. Earlier studies emphasize the importance of the matter, as *APOE* ε4 was found to be more strongly associated with biomarker evidence of Aβ pathology (irrespective of clinical status) than a clinical diagnosis of AD [20]. Similarly, the effect size of *APOE* ε4 increased if the presence or absence of Aβ pathology was neuropathologically confirmed [21].

Another critical point of previous studies is the focus on the dementia stage of AD. AD is believed to follow a long trajectory in which Aβ pathology is present, and clinical symptoms gradually develop before the threshold for dementia is reached [22–24]. Few studies have investigated *APOE* ε4 positivity in prodromal AD [25], that is, mild cognitive impairment (MCI) due to AD (Aβ biomarker positive), but prevalence rates around 25%–55% have been reported. Similarly, not many studies reported the proportion of *APOE* ε4 carriers among people with preclinical AD, that is, presence of Aβ pathology without clinical symptoms [26–29].

In the present study, we aimed to investigate the prevalence of *APOE* ε4 positivity across the clinical and preclinical spectrum of AD in a large sample of Aβ biomarker–positive individuals, including cognitively normal (CN) controls, MCI, and AD dementia. We also tested whether the prevalence of *APOE* ε4 positivity varied by age, sex, and geographical location. For comparison, we included a group of Aβ-negative participants.

2. Methods

2.1. Participants

We used data from the Amyloid Biomarker Study Group, which is a worldwide collaborative project on Aβ PET and CSF biomarkers in conjunction with demographic, clinical, and genetic variables [5,30,31]. From all contributing sites, we received individual participant-level data on 9480 individuals (3903 CN, 4189 MCI, 1359 probable AD dementia, and 538 non-AD dementia). Because we aimed to investigate the prevalence of *APOE* ε4 across the spectrum of AD, we applied the following selection procedure for this study: (1) we excluded patients with a clinical diagnosis of non-AD dementia; (2) among CN, MCI, or AD dementia participants, we selected Aβ-positive (Aβ+) individuals as determined by PET and/or CSF and their Aβ-negative (Aβ−) counterparts for comparison; and (3) we excluded individuals who lacked information on *APOE* ε4 status.

Normal cognition was defined as normal scores on cognitive tests, the absence of cognitive complaints (for which medical help was sought), or both [5,31]. Some of the CN participants had subjective cognitive decline (SCD, n = 533 [102 Aβ+ and 431 Aβ−]), defined as the presence of a cognitive complaint but normal cognition on neuropsychological tests [32]. We combined the SCD subjects with the other CN participants [24,33], except for one subanalysis (Section 3.7). MCI and probable AD dementia were defined according to established diagnostic criteria [22,23,34]. Aβ− "AD dementia" cases most likely do not have AD as the underlying cause of their cognitive impairment, although it should be noted that Aβ biomarkers could misclassify subjects, especially when biomarker signals are close to the cutoffs [35,36].

2.2. PET or CSF procedures

Individual PET scans were dichotomized (Aβ+ or Aβ−) using quantitative thresholds or visual reads according to the method used at the study site [5,30]. CSF biomarkers were dichotomized as negative (normal) or positive (abnormal) using study-specific cutoffs [5]. For AD dementia patients, we only had PET data available [30]. For CN and MCI patients, we selected the first available biomarker in time if a participant had both PET and CSF data [5]. Detailed PET or CSF procedures for each site are presented in Supplementary Table 1.

2.3. APOE genotyping

By design, all participants in this study had data on *APOE* ε4 status. For 2955/3114 (95.5%) CN and 3054/3335 (91.6%) MCI subjects, we had specific genotypes (e.g., ε3/ε4, in addition to *APOE* ε4 status), which allowed breakdown into *APOE* ε4 noncarriers, heterozygotes, and homozygotes. Specific genotypes were not available for AD dementia patients, as they were only collected for CN and MCI participants in our previous studies [5,30].

2.4. Age, sex, education, and geographical location

Information on age at time of clinical assessment was available for all participants. There were missing data for sex (130/7,419, 1.8%) and years of education (1137/7,419, 15.3%). We used a previously published classification system for geographical location [13] to divide the participants into Southern Europe (n = 653 [215 Aβ+, 438 Aβ−]), Central Europe (n = 832 [343 Aβ+, 489 Aβ−]), Northern Europe (n = 1667 [792 Aβ+, 875 Aβ−), Australia (n = 395 [190 Aβ+, 205 Aβ−]), North America (n = 3359 [1292 Aβ+, 2067 Aβ−]), or Asia (n = 315 [114 Aβ+, 201 Aβ−]). Some participants (n = 637 [303 Aβ+, 334 Aβ−], 8.1%) could not be classified, as they were included in a multicenter study that covered multiple geographical locations.

2.5. Statistical analyses

Baseline differences were assessed using analysis of variance (with post hoc Bonferroni correction) and χ^2 tests. The prevalence of *APOE* ε4 positivity was defined by calculating the percentage of *APOE* ε4-positive individuals of the total number of participants in each diagnostic group. Generalized estimating equations were used to estimate the effects of age, sex, education, and geographical location on the prevalence of *APOE* ε4 positivity. Generalized estimating equations were the method of choice for the study as it allows analysis of binary-correlated data, such that participant-level data from all cohorts can be modeled while simultaneously accounting for participants within studies. A logit link function for binary outcomes with an exchangeable correlation structure was assumed to account for within-study correlation. Analyses were conducted using the total study population, unless specified otherwise. Age was entered as a continuous measure centered at the mean. We tested two- and three-way interactions between variables, and these terms were retained in the model if they appeared significant by the Wald statistical test. The generalized estimating equations derived unstandardized β coefficients, and standard errors of the main effect were reported. Significance was set at $P < .05$ (two-sided). SPSS software (IBM, version 23.0) was used for statistics.

3. Results

3.1. Participants

Demographic and clinical information for each diagnostic group is provided in Table 1. We included 7419 subjects, among which 970 with a clinical diagnosis of AD dementia (853 Aβ+ and 117 Aβ−), 3335 with MCI (1810 Aβ+ and 1525 Aβ−), and 3114 CN subjects (788 Aβ+ and 2326 Aβ−). Demographic differences among the diagnostic groups included fewer males in the CN group ($P < .05$) and less education in the MCI group compared with the other groups ($P < .001$). Furthermore, in the dementia group, Aβ status was only determined using PET, whereas in the MCI group, the proportion of subjects with CSF data (78%) was greater than that in the CN group (64.9%). In Aβ+ individuals, comparisons within diagnostic groups between *APOE* ε4 positive and negative groups showed that the mean age was lower in *APOE* ε4-positive than that in *APOE* ε4-negative CN and MCI patients ($P < .01$) (Supplementary Table 2). Supplementary Table 3 shows the demographic and clinical characteristics

Table 1
Participant characteristics Q5

	CN			MCI			AD dementia		
	Total	Aβ−	Aβ+	Total	Aβ−	Aβ+	Total	Aβ−	Aβ+
N	3552	2764	788	3335	1525	1810	970	117	853
Age*, mean	67.3 ± 11.8	65.8 ± 12.0	72.6 ± 9.4	70.2 ± 8.6	68.4 ± 8.9	71.8 ± 8.0	69.4 ± 9.4	71.6 ± 9.6	69.1 ± 9.3
Age, range	18–109	18–93	32–109	36–97	36–91	44–97	37–95	48–90	37–95
Sex† (% male)	43.9	42.9	47.2	53.6	54.8	52.7	56.4	64.1	55.3
MMSE‡, mean	29.0 ± 1.2	29.0 ± 1.2	28.8 ± 1.3	26.9 ± 2.5	26.7 ± 2.6	26.5 ± 2.6	21.8 ± 4.8	22.9 ± 4.0	21.6 ± 4.9
Education§, yrs	14.3 ± 3.7	14.3 ± 3.7	14.3 ± 3.8	12.4 ± 4.4	11.9 ± 4.3	12.9 ± 4.4	13.8 ± 3.6	13.6 ± 3.6	13.9 ± 3.6
Modality for Aβ positivity‖ (% PET vs. % CSF)	41.6/58.4	42.9/57.1	36.1/63.9	22.0/78.0	21.0/79.0	22.8/77.2	100/0	100/0	100/0
APOE ε4 positivity¶ (%)	30.5	24.6	50.9	47.2	27.9	63.5	61.1	24.8	66.1
Region									
North America, n	1469	1044	425	1077	412	665	375	50	325
% *APOE* ε4 positive	432 (29.4)	238 (22.8)	194 (45.6)	522 (48.5)	96 (23.3)	426 (64.1)	227 (60.5)	7 (14)	220 (67.7)
Australia, n	200	140	60	76	26	50	118	4	114
% *APOE* ε4 positive	76 (38)	38 (27.1)	38 (63.3)	42 (55.3)	4 (15.4)	38 (76.0)	72 (61.0)	-	72 (63.2)
Northern Europe, n	712	568	144	714	365	349	241	38	203
% *APOE* ε4 positive	251 (35.3)	164 (28.9)	87 (60.4)	375 (52.5)	125 (34.2)	250 (71.6)	166 (68.9)	16 (42.1)	150 (73.9)
Central Europe, n	195	154	41	536	304	232	101	12	89
% *APOE* ε4 positive	60 (30.8)	36 (23.4)	24 (58.5)	223 (41.6)	92 (30.3)	131 (56.5)	60 (59.4)	2 (16.7)	58 (65.2)
Southern Europe, n	269	221	48	343	163	180	41	1	40
% *APOE* ε4 positive	61 (22.7)	43 (19.5)	18 (37.5)	135 (39.4)	37 (22.7)	98 (54.4)	19 (46.3)	0 (0)	19 (47.5)
Asia, n	80	71	9	141	76	65	94	12	82
% *APOE* ε4 positive	18 (22.5)	14 (19.7)	4 (44.4)	47 (33.3)	10 (13.2)	37 (56.9)	49 (52.1)	4 (33.3)	45 (54.9)

Abbreviations: Aβ, amyloid β; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini–Mental State Examination; PET, positron emission tomography; CSF, cerebrospinal fluid; *APOE*, apolipoprotein E.

NOTE. Data are presented as mean ± SD unless indicated otherwise. Differences between diagnostics groups (assessed separately for Aβ-positive and Aβ-negative groups) were assessed using analysis of variance (age, education, and MMSE) and χ^2 tests (sex, modality, and *APOE* ε4 status) with post hoc Bonferroni tests.

*Aβ− CN < MCI/AD, $P < .001$, MCI < AD, $P < .01$; Aβ+ CN/MCI > AD dementia, $P < .001$.

†Aβ− CN < MCI/AD, $P < .05$; Aβ+ CN > MCI/AD dementia, $P < .05$.

‡Aβ− CN < MCI/AD, $P < .001$, MCI < AD, $P < .05$; Aβ+ AD dementia < CN/MCI, $P < .001$, MCI < CN, $P < .001$.

§Aβ− MCI < CN/AD, $P < .001$; Aβ+ MCI < CN/AD dementia, $P < .001$.

‖Aβ− AD > MCI/CN, CN > MCI, $P < .001$; Aβ+ AD dementia > CN/MCI, $P < .001$; CN > MCI, $P < .001$.

¶Aβ+ AD dementia/MCI > CN, $P < .001$.

of individuals tested versus not tested for *APOE* in the complete Amyloid Biomarker Study Group data set [5,30,31].

3.2. Prevalence of APOE ε4 positivity

In Aβ+ subjects, the prevalence of *APOE* ε4 positivity was 50.9% in CN, 63.5% in MCI, and 66.1% in AD dementia (Table 1). The prevalence of *APOE* ε4 positivity was higher in Aβ+ MCI and Aβ+ AD dementia than that in Aβ+ CN ($P < .001$), but there was no difference between Aβ+ MCI and Aβ+ AD dementia ($P = .19$). For comparison, the *APOE* ε4 prevalence in Aβ− subjects was 24.5% in CN, 27.9% in MCI, and 24.8% in AD dementia, which was significantly lower than that in Aβ+ counterparts (all $P < .001$).

3.3. Prevalence of APOE ε4 positivity by age, sex, education, and modality

The prevalence of *APOE* ε4 positivity was lower at older age in Aβ+ CN (β for change in prevalence per year ± standard error: −0.02 ± 0.01, $P < .05$, Fig. 1) and Aβ+ MCI (β = −0.03 ± 0.01, $P < .01$). For example, at age 50, the prevalence of *APOE* ε4 positivity was 61% in Aβ+ CN and 75% in Aβ+ MCI, compared with 42% and 47% at age 90, respectively (Supplementary Fig. S1). There was no age effect on AD dementia (β = 0.01 ± 0.01, $P = .66$). There was also no effect of age in AD dementia when excluding patients (n = 91) with a known atypical presentation, who are typically associated with lower prevalence of *APOE* ε4 (β = 0.00 ± 0.01, $P = .99$, Supplementary Fig. S2). In Aβ− subjects, the prevalence of *APOE* ε4 also decreased with age in CN (β = −0.03 ± 0.01, $P < .001$; difference with Aβ+: $P = .62$) and MCI (β = −0.03 ± 0.01, $P < .001$; difference with Aβ−: $P = .82$) but not in AD dementia (β = −0.01 ± 0.02, $P = .55$; difference with Aβ+: $P = .19$). All effects described previously were similar when adjusting for sex and education.

In Aβ+ subjects, sex and education had no direct effects on *APOE* ε4 positivity, either across or within diagnostic groups (all $P > .05$). Furthermore, in Aβ+ subjects, there was an interaction between age and sex ($P < .05$), whereby prevalence decreased with age for women but not for men. Examining the three-way interaction with diagnosis

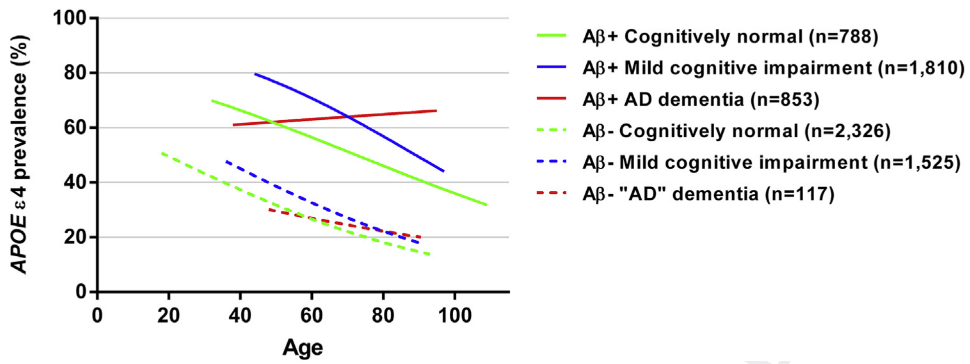

Fig. 1. Prevalence of *APOE* ε4 positivity by age, diagnosis, and Aβ status. Curves were plotted using the point estimates generated by generalized estimating equations and are within the age limits of the diagnostic groups. The models were adjusted for study (site) effect. The 95% confidence intervals are presented in Supplementary Fig. S1. Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; *APOE*, apolipoprotein E.

revealed that the interaction between age and sex was present in MCI ($P < .01$), and at trend level in AD dementia ($P = .053$), but not in CN subjects ($P = .26$). In Aβ− MCI subjects, there was a trend toward higher prevalence of *APOE* ε4 positivity in women (β: 0.19 ± 0.10, $P = .06$). There were no direct of interaction effects for education and no interaction effects (all $P > .05$). The prevalence of *APOE* ε4 positivity was higher for CSF than for PET only in Aβ− MCI subjects ($\chi^2 = 6.68$, $P = .01$; Supplementary Table 4). See Supplementary Table 5 for an overview of all main and interaction effects.

3.4. Prevalence of specific APOE genotypes in CN and MCI

Next, we stratified CN (n = 2955 [751 Aβ+ and 2204 Aβ−]) and MCI (n = 3054 [1638 Aβ+ and 1416 Aβ−]) subjects with *APOE* genotype information available into groups of *APOE* ε4 noncarriers, *APOE* ε4 heterozygotes, and *APOE* ε4 homozygotes, and divided them into quartiles according to age. Both in CN and MCI subjects, the proportion of *APOE* ε4 heterozygotes and *APOE* ε4 homozygotes decreased with advancing age (Fig. 2). Prevalence of the specific genotypes (i.e., *APOE* ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4) is provided in Table 2.

3.5. Prevalence of APOE ε4 positivity by geographical location

Next, we assessed the effect of geographical location on prevalence of *APOE* ε4 positivity. Within Aβ+ subjects, we found that the prevalence of *APOE* ε4 positivity across diagnostic groups was higher in Northern Europe than that in all other geographical locations except Australia (all $P < .001$, Bonferroni corrected; Fig. 3A). In addition, the prevalence of *APOE* ε4 positivity was lower in Southern Europe than that in North America, Central Europe ($P < .05$, uncorrected), and Australia ($P < .001$, Bonferroni-corrected), and higher in Australia than that in Asia ($P < .05$, uncorrected). Within Aβ− subjects, the prevalence of *APOE* ε4 positivity was higher in Northern Europe ($P < .001$, Bonferroni-corrected) and Central Europe ($P < .05$, uncorrected) than that in all other geographical locations (Fig. 3B). These findings were similar when assessing each diagnostic group separately (Supplementary Fig. S3, Supplementary Table 5).

3.6. Predictive effect of APOE ε4 status on disease stage

Finally, to assess whether the *APOE* allele is predictive of AD dementia or MCI beyond its effect on Aβ, we performed binary logistic regression models, including age, sex, education, Aβ status (positive or negative), and *APOE* ε4 status (positive or negative) for CN versus MCI and CN versus AD. We found that *APOE* ε4 status predicted both CN versus MCI (odds ratio: 1.629, 95% confidence interval: 1.348–1.968, $P < .001$) and CN versus AD (odds ratio: 1.811, 95% confidence interval: 1.457–2.251, $P < .001$).

3.7. Prevalence of APOE ε4 positivity by SCD

The prevalence of *APOE* ε4 was higher in participants with SCD than those without, both among Aβ+ (64.7% vs. 48.8%, $P < .05$) and Aβ− (33.6% vs. 22.4%, $P < .05$) subjects (Supplementary Table 6). The relationship between age and *APOE* prevalence was not affected by the presence or absence of SCD (all $P < .05$).

4. Discussion

We found that the prevalence of *APOE* ε4 positivity was 51% in preclinical AD (Aβ+ CN), 64% in prodromal AD (Aβ+ MCI), and 66 % in Aβ+ AD dementia. Among Aβ− subjects, the prevalence of *APOE* ε4 positivity was 25% in CN, 28% in MCI, and 25% in AD dementia. Our estimates of *APOE* ε4 prevalence in Aβ biomarker–verified AD-type dementia are higher than reported in previous studies that defined AD-type dementia based on clinical criteria. This resonates well with studies examining the effect size of *APOE* ε4 in pathology- or biomarker-confirmed cases [20,21] and suggests that the prevalence

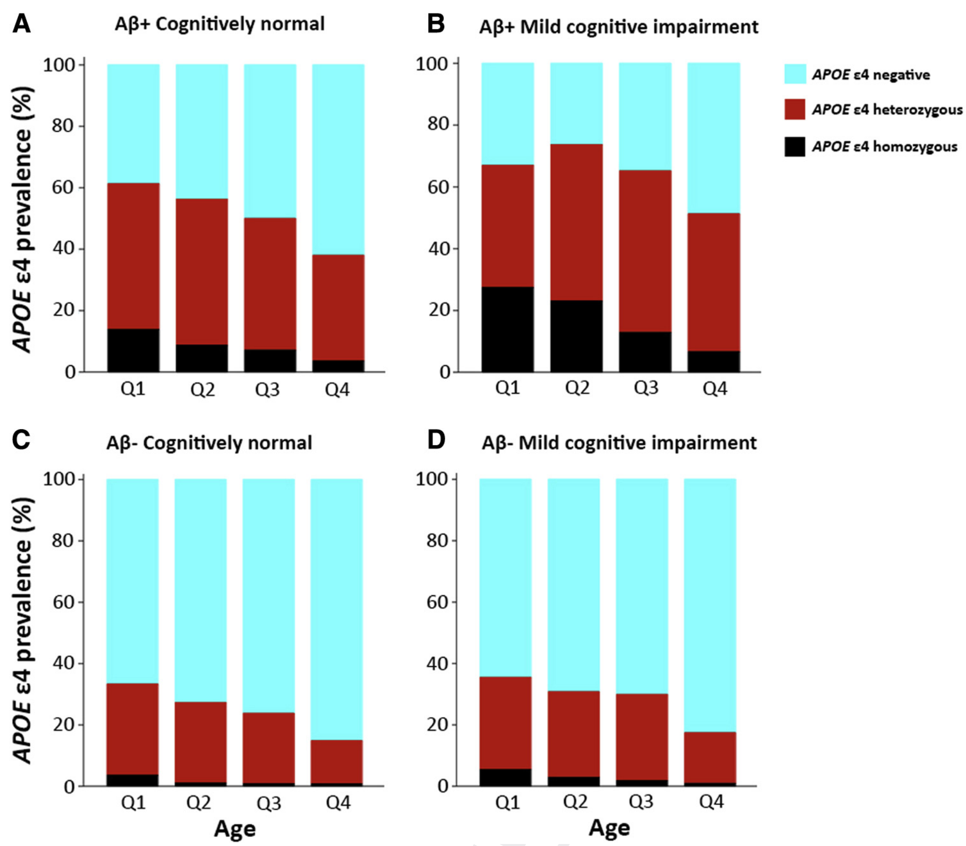

Fig. 2. Distribution of *APOE* ε4 negative, *APOE* ε4 heterozygous, and *APOE* ε4 homozygous subjects across different age quartiles ([A]; Q1 = <67 years, Q2 = 67–73.2, Q3 = 73.21–78.76, Q4 = >78.77 years: [B]; Q1 = <66.67 years, Q2 = 66.68–72.28, Q3 = 72.29–77.19, Q4 = >77.2: [C]; Q1 = <59.5 years, Q2 = 59.5–67.1, Q3 = 67.11–75.65, Q4 = >73.66 years; [D]; Q1 = <62 years, Q2 = 62.01–68.41, Q3 = 68.42–75.0, Q4 = >75.01 years). Abbreviations: Aβ, amyloid β; *APOE*, apolipoprotein E; Q, quartile.

of *APOE* ε4 in AD-type dementia (66%) may have been underestimated in previous studies (50%–60% [8,9,13]).

Another main finding of this study was that the prevalence of *APOE* ε4 decreased with age in preclinical and prodromal AD. There are several possible explanations. First, the additive effects of *APOE* ε4 and Aβ may have resulted in greater conversion from the CN and MCI groups to AD dementia [37]. Higher conversion rates could also be due to earlier and more pronounced accumulation of Aβ load in *APOE* ε4 carriers [38], but the binary nature (Aβ positive or negative) of our data set does not allow testing of this hypothesis. Second, supposedly due to the increased risk for cardiovascular diseases in ε4 carriers, *APOE* ε4 has been linked to increased mortality rates [39–41]. This observation fits our finding that *APOE* ε4 carriership also decreased with age in Aβ− CN and MCI subjects, although the reduction of *APOE* ε4 in Aβ− subjects can also be caused by individuals transitioning from Aβ− to

Table 2
Prevalence of *APOE* genotype in CN and MCI subjects according to Aβ status

Group	*APOE* ε2/ε2	*APOE* ε2/ε3	*APOE* ε2/ε4	*APOE* ε3/ε3	*APOE* ε3/ε4	*APOE* ε4/ε4	*APOE* ε2 carrier	*APOE* ε3 carrier	*APOE* ε4 carrier	Missing
Aβ+/− CN and MCI, n (%)	22 (0.4)	566 (9.4)	126 (2.1)	3028 (50.4)	1845 (30.7)	422 (7.0)	714 (11.9)	5565 (92.6)	6009 (37.7)	440 (6.8)
Aβ+ CN and MCI, n (%)	2 (0.1)	88 (3.7)	61 (2.6)	861 (36.0)	1027 (43.0)	350 (14.7)	151 (6.3)	2037 (85.3)	1377 (57.6)	209 (8.0)
Aβ− CN and MCI, n (%)	20 (0.6)	478 (13.2)	65 (1.8)	2167 (59.9)	818 (22.6)	72 (2.0)	563 (15.6)	3528 (97.5)	890 (24.6)	231 (6.0)
Aβ+ CN, n (%)	1 (0.1)	28 (3.7)	19 (2.5)	336 (44.7)	304 (40.5)	63 (8.4)	48 (6.4)	687 (91.5)	367 (48.9)	37 (4.7)
Aβ+ MCI, n (%)	1 (0.1)	60 (3.7)	42 (2.6)	525 (32.1)	723 (44.1)	287 (17.5)	103 (6.3)	1350 (82.4)	1010 (61.7)	172 (9.5)
Aβ− CN, n (%)	15 (0.7)	311 (14.1)	38 (1.7)	1331 (60.4)	478 (21.7)	31 (1.4)	364 (16.5)	2158 (97.9)	509 (23.1)	122 (5.2)
Aβ− MCI, n (%)	5 (0.4)	167 (11.8)	27 (1.9)	836 (59.0)	340 (24.0)	41 (2.9)	199 (14.1)	1370 (96.8)	381 (26.9)	109 (7.1)

Abbreviations: Aβ, amyloid β; CN, cognitively normal; MCI, mild cognitive impairment; *APOE*, apolipoprotein E.

NOTE. Information on *APOE* genotype was available in 93.2% of subjects with normal cognition and mild cognitive impairment. For subjects with AD dementia, only information on *APOE* status (+ or −) was provided.

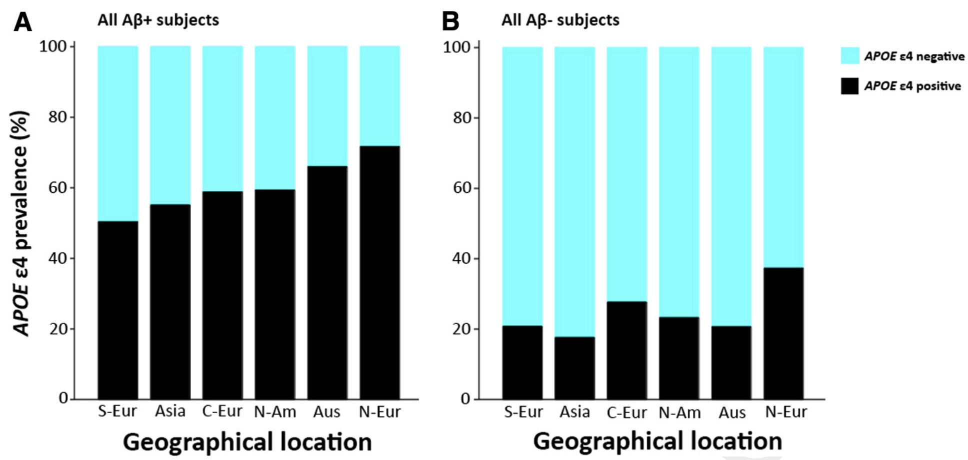

Fig. 3. Distribution of *APOE* ε4 negative and *APOE* ε4 positive subjects by geographical location for all Aβ+ (A) and Aβ− (B) participants across diagnostic groups. A further breakdown into diagnostic groups is provided in Supplementary Fig. S2; 8.1% of participants (n = 637 [303 Aβ+, 334 Aβ−]) could not be classified, as they were included in a multicenter study that covered multiple geographical locations. Abbreviations: Aβ, amyloid β; *APOE*, apolipoprotein E.

Aβ+ with advancing age. Finally, as *APOE* ε4 accelerates the onset of amyloid aggregation by approximately 15 years [5,26], the prevalence of ε4 carriers in Aβ+ subjects will be higher at younger age ranges. Remarkably, the prevalence of *APOE* ε4 did not change with age in AD-type dementia. It may be hypothesized that the higher mortality in *APOE* ε4 carriers is counterbalanced at the dementia stage by individuals transitioning from preclinical and prodromal AD into AD dementia. We also tested whether this lack of an age effect was caused by the inclusion of atypical variants of AD dementia as this group is characterized by lower prevalence of *APOE* ε4 [42,43], but this was not the case (Supplementary Fig. S2). The pathogenesis of early onset AD is complex because this group includes a mix of *APOE* ε4 carriers who develop the disease at younger age and of *APOE* ε4 noncarriers with rapidly progressive AD [44,45]. This may confound relationships between *APOE* ε4 and age, especially in young patients with AD-type dementia. Furthermore, it has been shown that the mortality effect of *APOE* ε4 is less pronounced at older age [46], which may explain the lack of an age effect in AD dementia patients. It is not clear why Aβ+ women had decreasing prevalence of *APOE* ε4 with age. However, a recent large meta-analysis also found an interaction between *APOE* ε4, sex, and age, so that *APOE* ε4 conferred a greater risk for AD in women than in men at younger ages but not in older [47]. It is possible that physiological changes around menopause may interact with *APOE* ε4 in women and increase the risk for Aβ pathology in younger ages [48]. If this leads to an earlier onset of the disease, and earlier death, the *APOE* ε4 prevalence may appear to decrease with age in Aβ+ women.

Another main finding was the lower prevalence of *APOE* ε4 in both Aβ+ and Aβ− CN subjects compared with the MCI and dementia stages. This may be explained by a selection bias, as the vast majority of the MCI and AD dementia subjects visited a memory clinic, while many CN subjects were recruited as research volunteers. Also, *APOE* ε4+ MCI patients may be more likely to seek medical help, and *APOE* ε4 carriers with dementia may be more willing to participate in research due to a positive family history. Another possible reason is that *APOE* ε4 may accelerate the transition from preclinical to clinical AD. For example, *APOE* ε4 may have an effect on brain structure and function through non-Aβ pathways [49–53], which may act synergistically with Aβ pathology to shorten the time between the start of Aβ deposition and cognitive decline. Thus, because *APOE* ε4 carriers will develop symptoms earlier, the prevalence of *APOE* ε4 positivity in CN is lower than that in MCI and dementia cases at the same age range. Finally, *APOE* ε4 noncarriers (which would include *APOE* ε2 carriers) may have mechanisms of resilience (i.e., cognitive reserve) that are less present in ε4 carriers [54].

We also found geographical differences in *APOE* ε4 prevalence, with higher prevalence in AD patients from Northern Europe, Central Europe, and Australia and lower prevalence in patients from Southern Europe and Asia. This is consistent with previous epidemiological studies in clinically diagnosed AD dementia and MCI patients [13,55] and with lower prevalence of *APOE* ε4 in the general population in Southern Europe and Asia compared with Northern Europe [14,55–57]. The novelty of this study is that we confirm these geographical differences in Aβ biomarker–defined AD and throughout the continuum from preclinical to prodromal and dementia stages. The different geographical prevalence of *APOE* ε4 may be important for recruitment of participants in clinical trials and for the use of *APOE* ε4 in algorithms to predict Aβ positivity [58].

Strengths of this study include the large number of Aβ-positive subjects across the spectrum from preclinical to prodromal and dementia stages of AD. Limitations include relatively few participants who came from Asia (n = 315) and Australia (n = 394), and there were no participants from Africa and South America. There were no data on ethnicity of the participants, which may confound the results because ethnicity has been related to both *APOE* ε4 and AD [14,59]. Also, this study is based on an assembly of different study cohorts that may not be representative for typical memory clinic populations or the general population. Finally, Aβ positivity was determined using different modalities (i.e., PET or CSF) and methods (e.g., visual read vs. quantitative threshold for PET and different assays for CSF). There was an unexpected effect of CSF assay (Innotest vs. Luminex), which could be interpreted as a cohort effect as the majority of subjects with CSF analyzed using the Luminex assay are ADNI participants (Supplementary Table 5). We found no effects of modality (PET vs. CSF) on *APOE* ε4 prevalence, and in previous studies using these data, we found only little evidence for heterogeneity related to modality and methodology [5,30].

With about 2/3 of prodromal AD and AD dementia patients being *APOE* ε4 carriers, our results further emphasize the importance of *APOE* ε4 for the development of AD [8,9]. This may be useful for the development of disease-modifying treatments, which may be focused on attenuating the detrimental effects of *APOE* ε4 and for understanding the molecular pathogenesis of AD [60]. Furthermore, the finding that the prevalence of *APOE* ε4 decreases with age in CN and MCI subjects has potential implications for clinical trials in predementia populations, as screening based on *APOE* status to enrich for Aβ positivity may be less effective with advancing age. Finally, it may be of importance to evaluate other proposed AD susceptibility genes [61] in cohorts with known Aβ status, as to date, this has only been assessed in cohorts of clinically diagnosed AD patients and CN elderly.

5. Conclusions

We have quantified the prevalence of *APOE* ε4 in Aβ biomarker–defined preclinical AD, prodromal AD, and AD dementia. The results emphasize the prominent role of *APOE* ε4 in AD, but also point to disease heterogeneity, because *APOE* ε4 positivity is markedly less common in elderly subjects in predementia stages of AD and in people from specific geographical locations, including Southern Europe and Asia. Further studies on phenotypic differences between *APOE* ε4-negative and *APOE* ε4-positive AD patients may be important to understand different pathways that may lead to AD and ultimately to tailor disease-modifying treatments to specific patient subgroups.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.02.009.

RESEARCH IN CONTEXT

1. Systematic review: Previous studies examining the prevalence of apolipoprotein E (*APOE*) ε4 in Alzheimer's disease have included patients based on clinical criteria, without using biomarker information. This may have led to an underestimation of the prevalence of *APOE* ε4 due to misdiagnosis.
2. Interpretation: Our results demonstrate that positron emission tomography or cerebrospinal fluid evidence for the presence of amyloid β is associated with a higher prevalence of *APOE* ε4 (66% vs. 50–60 in previous studies).
3. Future directions: Information on *APOE* ε4 status would improve algorithms to determine risk for amyloid β positivity, for example, to enrich clinical trials. Furthermore, similar studies in amyloid β positive subjects should be performed to determine the prevalence of other Alzheimer's disease susceptibility genes.

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