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APOE genotype, dementia and mortality in the oldest-old: The 90+ Study

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Abstract

Background—Although the ApolipoproteinE (APOE) ε4 allele is a major genetic risk factor for Alzheimer's disease (AD), it is not clear if this relationship persists among the oldest-old. Several European studies suggest that the effect of the APOEε4 allele on dementia and mortality disappears in very old age. We describe the APOE allele and genotype frequencies and examine whether the presence of the APOEε4 or APOEε2 alleles are related to prevalent dementia, incident dementia, and mortality in a population-based cohort of oldest-old participants in the United States.

Methods—We studied 904 participants aged 90 and older from The 90+ Study. 802 (89%) participants were genotyped and included in the prevalent dementia and mortality analyses. The 520 initially non-demented participants were included in the incident dementia analyses and were evaluated for dementia every six months.

Results—The APOEε4 allele was significantly associated with prevalent dementia (odds ratio [OR]=2.06) and AD (OR=2.37) in women, but not in men. The APOEε2 allele was not related to prevalent dementia in either sex. After an average followup of 2.4 years, 188 incident dementia cases were identified. Neither the APOEε4 nor the APOEε2 allele was related to incident dementia or AD. 510 (64%) participants died after an average followup of 2.3 years and their mortality was not related to the presence of either the APOEε2 or APOEε4 alleles.

Conclusions—Our findings suggest that the associations between APOEε4, dementia and mortality are age dependent and that APOEε4 no longer plays a role in dementia and mortality at very old ages.

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María Corrada, Daniel Berlau, Annlia Paganini-Hill, and Claudia Kawas report no conflicts of interest.

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Keywords

Apolipoprotein E; Dementia; Alzheimer's disease; Mortality; Oldest-old

1. Introduction

The $\epsilon 4$ allele of the Apolipoprotein e (APOE) gene is firmly established as a susceptibility gene for Alzheimer's disease (AD) [1] and other dementias [2]. The role of the APOE $\epsilon 2$ allele is more controversial. Whereas many studies report a protective effect of the APOE $\epsilon 2$ allele, others, particularly population-based studies, do not [3–4]. Several studies, all in Europe, have evaluated the role of APOE in relation to dementia [5–12] and mortality [9, 11, 13–15] in the oldest-old. Most suggest that the influence of the APOE $\epsilon 4$ allele on the risk of dementia and mortality diminishes or disappears in advanced age. In our own cohort, we previously found the APOE $\epsilon 2$ allele to be associated with increased odds of AD pathology but decrease odds of dementia whereas the APOE $\epsilon 4$ allele was associated with increased odds of both AD pathology and dementia [16], suggesting a complex role of APOE in dementia and neuropathology in the oldest-old and prompting us to further examine the role of APOE in this age group.

With the large geographic variation of APOE genotypes, the rapidly growing oldest-old population throughout much of the world, and the very high risk of dementia in this age group [17], it is important to understand the relationship between APOE and dementia in the oldest-old in the United States. In this study, we describe the APOE allelic and genotypic frequencies and examine their association with prevalent dementia, incident dementia, and mortality in a large population-based cohort of participants aged 90 years and older living in the United States.

2. Methods

2.1 Subjects

Participants were members of *The 90+ Study*, a population-based longitudinal study of aging and dementia in people aged 90 and older. Participants were originally members of the Leisure World Cohort Study, an epidemiological health study of a California retirement community initiated in the early 1980s. Leisure World Cohort members alive and aged 90 and older as of January 1, 2003 or January 1, 2008 and later were invited to join *The 90+ Study*. Of all eligible cohort members, 83% joined the study. Participants did not differ from non-participants on sex (78% vs. 79% women), age at the time of the invitation to *The 90+ Study* (mean=93 years for both groups), or chronic disease history and lifestyle characteristics at time of entry into the Leisure World Cohort. Additional details about participant recruitment are published elsewhere [18]. As of December 31, 2010, a total of 904 individuals had been recruited and agreed to longitudinal in-person evaluations that included demographics, medical history, neurological examination, neuropsychological testing, functional assessment, informant questionnaires, and the option to provide DNA for APOE genotyping.

2.1 Assessments

The neuropsychological battery included a variety of tests previously described [19], among them the Mini-Mental State Exam [20]. The neurological exam, performed by trained physicians or nurse practitioners, included mental status testing covering multiple domains and items on functional abilities. A DNA sample for APOE genotyping was obtained from either blood or a cheek swab.

Evaluations were repeated every six months. In some situations, in-person followup was not possible due to participant's declining health, frailty, or disability. In such cases, information was obtained over the phone or by mail with participants themselves or their informants. The phone followup included the CASI-short, a short cognitive screening instrument [21]. Information from informants included the Dementia Questionnaire [22–23] administered over the phone and mailed questionnaires regarding participants cognitive [24] and functional abilities [25–26]. Detailed methods and procedures used in this cohort have been previously published elsewhere [17, 19].

All participants or their informants provided informed consent and the Institutional Review Board of the University of California, Irvine, approved all procedures performed.

2.2 Determination of cognitive status

Cognitive status at baseline was determined from the neurological examination (90% of participants) or the MMSE score (10% of participants). The neurological examiner determined the presence or absence of dementia based on the participant's cognitive and functional status during the neurological evaluation using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dementia [27] and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease [28]. Although NINCDS-ADRDA criteria exclude people 90 years of age and older, we applied the criteria despite the older age of our participants. When using the MMSE to determine cognitive status, we used age- and education-specific cut scores for dementia derived from this cohort [29].

Cognitive status during followup was determined from an in-person evaluation whenever possible (76% of participants). When an in-person evaluation was unavailable, we used information from informant questionnaires or the CASI-short. Detailed information about the application of these criteria to diagnose dementia is described elsewhere [17, 30]. All evaluations and determination of cognitive status were completed blinded to the APOE genotype of the participants.

Information about participant's deaths was obtained from family members, local newspapers obituaries, and ascertainment of death certificates. We had 100% ascertainment of participant's vital status at the end of this study's period.

2.3 Data analysis

A flowchart of participant inclusion for the different analyses is shown in the Figure. Analyses of allele and genotype frequencies included 802 genotyped participants and were compared using chi square tests. We used logistic regression to examine the association between APOE genotype and prevalent dementia at the time of the participant's baseline evaluation (N=802). We examined the association between APOE genotype and incident dementia using only participants who were not demented at baseline and who had additional followup (N=520). Cox regression was used with age as the time scale, age at dementia diagnosis as the outcome of interest, and age at baseline examination as delayed entry. Participants were considered at risk of dementia and contributed person-years from the date of their baseline evaluation until the date of the followup evaluation when determined to be demented or the date of last followup evaluation when determined not to be demented. Analyses included evaluations done between January 1, 2003 and December 31, 2010. Mortality analyses included all participants in the prevalent analyses (N=802) and used Cox regression with age at death as the outcome of interest. Participants were considered at risk of death and contributed person-years from the date of their baseline evaluation until the

date of death. Participants who were still alive were censored at their age on December 31, 2010. Regression analyses were performed for all participants (adjusting for age and sex) and separately for men and women (adjusting for age). The independent effects of the APOE ϵ 2 and APOE ϵ 4 alleles were assessed by including dummy coded variables (1 if present and 0 if absent) for both APOE ϵ 2 and APOE ϵ 4 and using the APOE ϵ 3/ ϵ 3 genotype as the reference. We also tested for sex by APOE interactions by including in the regression models the product terms for sex and APOE ϵ 4 as well as sex and APOE ϵ 2. All analyses were performed using SAS software version 9.2 for Windows (SAS Institute Inc., Cary, NC).

3. Results

Table 1 gives the characteristics of the 802 participants (89%) for whom APOE genotype was available. Most participants were women (74%), Caucasian (99%), and had at least some college education (66%). At the baseline evaluation, participants were on average 93.7 years of age (range: 90 to 105) and about a third (29%) were diagnosed with dementia, most of whom had AD (77%). The proportion diagnosed with AD varied by sex, as 79% of women with dementia were diagnosed with AD compared to 65% of men ($p=0.02$).

The 102 participants not genotyped and thus excluded from the analyses were mostly women (77%), Caucasian (97%), had at least some college education (66%), had an average age of 94.7 years, and about half were demented (53%). Compared with participants included in this study, the excluded participants did not differ in sex ($p=0.43$) or education ($p=0.92$) but were older ($p<0.01$), less likely to be Caucasian ($p=0.05$), and more likely to have a diagnosis of dementia at baseline ($p<0.001$).

The frequency of the different APOE genotypes and alleles are shown on Table 1. The most common genotype was ϵ 3/ ϵ 3 (68%) followed by ϵ 3/ ϵ 4 (15%) and ϵ 2/ ϵ 3 (15%). Three participants had the ϵ 4/ ϵ 4 genotype and three had the ϵ 2/ ϵ 2 genotype. The APOE allele frequencies were 8.7% for APOE ϵ 2, 82.5% for APOE ϵ 3, 8.9% for APOE ϵ 4 in the overall sample. Compared with allele frequencies in younger Caucasian populations (APOE ϵ 2=7.8%, APOE ϵ 3=76.5%, and APOE ϵ 4=15.8%) [31], the APOE ϵ 4 allele frequency was lower and APOE ϵ 3 allele frequency higher. Men and women did not differ significantly on allele frequencies ($p=0.49$), genotype frequencies ($p=0.60$) or proportions of APOE ϵ 4 carrier status (men: 15.2%, women: 18.1%; $p=0.35$) or APOE ϵ 2 carrier status (men: 18.6%, women: 16.4%; $p=0.47$).

3.1 Prevalent dementia

The presence of an APOE ϵ 4 allele was significantly associated with prevalent dementia and AD in women but not in men (Table 2). Women with an APOE ϵ 4 allele had more than twice the odds of having dementia (OR=2.06) or AD (OR=2.37) compared with women with the APOE ϵ 3/ ϵ 3 genotype. Conversely in men, we found non-significant lower odds of prevalent dementia (OR=0.73) and AD (OR=0.63) among APOE ϵ 4 carriers. Of interest, two of the three participants (one man and one woman) with an ϵ 4/ ϵ 4 genotype did not have dementia at their baseline evaluation. In analyses of men and women combined, the interactions between sex and the APOE ϵ 4 allele were not statistically significant for all-cause dementia ($p=0.12$) or AD ($p=0.12$) but were suggestive of a sex difference.

The associations between the presence of an APOE ϵ 2 allele and dementia were not significant but were also suggestive of a sex difference. Women with an APOE ϵ 2 allele had decreased odds of dementia (OR=0.73) or AD (OR=0.79), whereas men with an APOE ϵ 2 allele had increased odds of dementia (OR=1.72) and AD (OR=2.59). In combined analyses of men and women, the interactions between sex and the APOE ϵ 2 allele were not

statistically significant for all-cause dementia ($p=0.10$) or AD ($p=0.06$) but were suggestive of a sex difference.

3.2 Incident dementia

Most of the 520 participants in the incident analyses were women (69%) and had at least some college education (70%) (Table 1). Their average age at baseline was 93.4 years (range: 90 to 106) and average length of followup was 2.4 years, during which 188 incident cases of dementia were diagnosed. Of those diagnosed as demented by an examination ($N=150$), most were diagnosed with AD (76%).

Analyses of incident dementia excluded 46 non-demented participants because they had no followup evaluation. The reasons for no followup were: 13 died, 3 withdrew, 15 had a baseline evaluation less than 6 months before study end, and 15 had not yet had a followup visit although time since their baseline evaluation was more than 6 months. These 46 participants were mostly women (74%), had at least some college education (70%), had an average age of 92.2 years, 11% were APOE ϵ 4 carriers, and 11% were APOE ϵ 2 carriers. Thus, the excluded participants did not differ in terms of sex ($p=0.44$), education ($p=0.82$), APOE ϵ 4 ($p=0.38$) or APOE ϵ 2 carrier status ($p=0.22$), but were younger ($p=0.003$) than participants included in the analyses.

Neither the presence of an APOE ϵ 4 allele nor an APOE ϵ 2 allele was associated with incident all-cause dementia or AD in women or men (Table 3). Of note, the two participants with an ϵ 4/ ϵ 4 genotype who were not demented at baseline, developed dementia during the followup period.

In combined analyses of men and women, the interactions between sex and the APOE ϵ 4 allele and sex and the APOE ϵ 2 allele were not significant ($p>0.20$) for all-cause dementia and AD.

3.3 Mortality

Of the 802 participants, 510 (64%) died during followup at an average age of 97.2 years (range: 90–108) (Table 1). The average followup for mortality was 2.8 years (range: 0.02 – 8.1). Presence of an APOE ϵ 4 allele or an APOE ϵ 2 allele was not related to mortality either in women or in men (Table 4).

4. Discussion

Our study extends the available literature on the APOE allele and genotype frequencies and their relationships with dementia and mortality to oldest-old in the United States. We found a lower APOE ϵ 4 allelic frequency, with an equivalent higher APOE ϵ 3 frequency, in this sample of oldest-old participants compared with younger subjects in other studies. Although APOE ϵ 4 has emerged as a clear genetic susceptibility factor for dementia in younger subjects, only a handful of studies, all in Europe, have examined the association in the oldest-old [5–12]. The consensus seems to be that the increased risk associated with the APOE ϵ 4 allele disappears at very old age. Our results are consistent with that hypothesis as we found increased odds of prevalent dementia at baseline but no association with the development of incident dementia after age 90 or with mortality in people who survived to that age.

Several studies have looked at the APOE allelic frequency in the oldest-old [32–36]. The most common finding is a decrease in the APOE ϵ 4 frequency with a corresponding increase in the APOE ϵ 2 frequency in nonagenarians and centenarians compared with younger groups. We found a similar decrease in the frequency of the APOE ϵ 4 allele but the

frequency of the APOE ϵ 3, not the APOE ϵ 2, was increased. Our results are consistent with a recent pooled analysis of case-control studies of older people of European ancestry [37] which assessed the change in allele frequency with age between <60 years and >90 years. That study found a significant decrease in frequency of APOE ϵ 4, a significant increase in frequency of APOE ϵ 3, and no change in the frequency of APOE ϵ 2. Furthermore, the allele frequencies in our study (APOE ϵ 2=8.7%, APOE ϵ 3=82.5%, APOE ϵ 4=8.9%) are similar to the allele frequencies in those aged older than 90 in the pooled analysis (APOE ϵ 2=8.3%, APOE ϵ 3=83.3%, APOE ϵ 4=8.3%).

We found increased odds of prevalent dementia and AD among those with an APOE ϵ 4 allele in women but not men. Our results are very similar to those of The Vantaa 85+ study in Finland of 510 people aged 85 and older which found increased odds in women (OR=3.5) but not in men (OR=1.4) [10]. Other studies of oldest-old participants have not reported results by sex but overall find the presence of an APOE ϵ 4 allele to be related to prevalent dementia [8–9] or AD [5, 7, 9]. In contrast, a study of centenarians in Finland [6] did not find APOE ϵ 4 carriers to be at increased odds of AD. Although this last result is different from others, it supports the hypothesis that the effect of the APOE ϵ 4 allele is no longer harmful at very advanced ages.

Our significant association between APOE ϵ 4 and prevalent dementia in women but not men is likely, at least in part, to be due to a differential survival between men and women. Studies in younger populations suggest that men with dementia have higher mortality than women with dementia [38–39] and that the presence of an APOE ϵ 4 allele shortens survival in men with AD but not in women [40]. The lack of a statistically significant association in men may also be due in part to low statistical power due to the relatively small number of men in our study.

Few studies have reported on the association between an APOE ϵ 2 allele and prevalent dementia. We found non-significant lower odds of dementia (OR=0.73) and AD (OR=0.79) among women, whereas in men we found non-significant higher odds of dementia (OR=1.72) and a trend toward higher odds of AD (OR=2.59). The Vantaa 85+ Study [10] found a similar non-significant association of APOE ϵ 2 and dementia in women (OR=0.69) but found significantly decreased odds in men (OR=0.22). The Gothenburg study found non-significant lower odds for dementia (OR=0.7) and AD (OR=0.5) in 412 men and women aged 85 and older [9]. The discrepancy of results seen among studies seems to be among men, a problem which will be difficult to sort out since studies include few oldest-old men with dementia.

The differences by sex in the association between prevalent dementia and APOE seen in our study are not just in significance but also in the direction of the effect. Whereas in women APOE ϵ 4 was related to increase odds and APOE ϵ 2 to decreased odds of dementia, the effects in men were in the opposite direction. As the number of men with prevalent dementia who were also APOE ϵ 2 or APOE ϵ 4 carriers in our study was small, these sex differences may not be real. If real, however, these sex differences could be related to differences by sex in dementia types (a lower proportion of men were diagnosed with AD compared to women in this study), in the relation between vascular risk factors and APOE [41], or in the relation between AD neuropathology and APOE [42]. Studies including more men and pathologically confirmed cases are necessary to further explore these potential sex differences.

Consistent with other studies [5, 9] we found that APOE ϵ 4/ ϵ 4 homozygotes can reach very old age without dementia. We had two APOE ϵ 4/ ϵ 4 participants who were not demented at their baseline evaluation. They did, however, develop dementia during followup.

We found no association between APOEε4 or APOEε2 and incident dementia in our 520 initially non-demented 90+ year olds. Only a few studies have explored this association in the oldest-old. Similar to our findings, the Vantaa 85+ study [11] found no association between APOEε4 and incident dementia in 187 initially non-demented 85+ year olds. The Gothenburg study analyzed the risk of dementia between ages 85 and 88 in 320 subjects and found neither APOEε4 nor APOEε2 to be related to all cause dementia [9]. Similarly, the Kungsholmen Project reported data for 187 people aged 85 and older and found no association between APOEε4 or APOEε2 and AD [12]. It seems apparent that the APOE gene has no effect on the risk of dementia on people that survive to very old age without dementia and thus it must exert its effects at an earlier age.

We also found no association between APOEε4 or APOEε2 and mortality after age 90. Our results are consistent with most studies in not finding an association between APOEε4 and mortality, including a 3-year mortality in the Vantaa 85+ study [11], a 3-year mortality in the Gothenburg study [9], a 5-year mortality in the Helsinki Ageing Study [14], or a 6-year mortality in a study of 1,551 nonagenarians from the Danish 1905 birth cohort [15]. In contrast, in the Kungsholmen Project [13], the APOEε4 allele was related to increased mortality and the APOEε2 allele was related to decreased mortality among people 85 and older who were not demented. In our study, APOE was not associated with mortality in either demented or non-demented participants (results not shown).

Our study has several limitations. Common to all studies of the oldest-old is the difficulty in diagnosing dementia in these older persons. Applying current diagnostic criteria to the oldest-old may not be appropriate and may result in misdiagnosing participants. Sensory and motor limitations, fatigue, and comorbidities can complicate the administration and interpretation of our diagnostic assessments. However, diagnosis occurred without knowledge of APOE genotype and any misclassification would be non-differential among genotypes. Another limitation is the small number of men diagnosed with dementia, which makes findings for men less precise. Finally, our study excluded 102 participants on whom genotyping could not be done. These participants were older and more likely to be demented than those analyzed. Inclusion of these participants would be expected to change allele frequencies by only a small amount and should not change the observed associations much.

Despite its limitations, our population-based study of well-characterized oldest-old individuals is one of the largest. In addition, it is to our knowledge, the first study in the United States to report APOE allele and genotype frequencies and to explore the associations with dementia and mortality in the oldest-old.

Our results showing that APOEε4 is related to prevalent dementia but neither incident dementia nor mortality after age 90 support the hypothesis previously set forth that the effects of the APOEε4 allele change with age and although APOEε4 is a strong risk factor for AD, dementia, and mortality in younger elderly, it has little effect in the very old.

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Figure.
Flow chart of participant inclusion

Table 1

Characteristics of participants, The 90+ Study

Characteristic	Prevalent Dementia and Mortality Analyses (n = 802)		Incident Dementia Analyses (n = 520)	
	Mean	Range	Mean	Range
Age at baseline, years	93.7	90 – 105	93.4	90 – 103
Followup, years [*]	2.8	0.02 – 8.1	2.4	0.1 – 7.7
Age at death, years [†]	97.2	90 – 108	--	--
	Number	%	Number	%
Women	592	73.8	356	68.5
Education				
High school	268	33.6	156	30.0
Any college	364	45.7	247	47.5
Any graduate school	165	20.7	117	22.5
Subjects with dementia [‡]	236	29.4	188	36.2
APOE genotype				
e2/e2	3	0.4	2	0.4
e2/e3	117	14.6	81	15.6
e2/e4	16	2.0	11	2.1
e3/e3	543	67.7	355	68.3
e3/e4	120	15.0	69	13.3
e4/e24	3	0.4	2	0.4
APOE allele frequency				
e2	139	8.7	96	9.2
e3	1323	82.5	860	82.7
e4	142	8.9	84	8.1

Abbreviations: APOE = Apolipoprotein E

^{*} For mortality analyses, followup is the years between study baseline and death or 12/31/2010; For analyses of incident dementia, followup is the years between study baseline and dementia diagnosis or time when last known to be nondemented

[†] Age at death of 510 (64%) participants who died during followup

[‡] 'Subjects with dementia' are the participants with dementia at baseline for analyses of prevalent dementia and the participants who developed dementia during followup for analyses of incident dementia

Table 2

Association of apolipoprotein E with prevalent dementia, The 90+ Study

Subjects	APOE Group	All-Cause Dementia				Alzheimer's Disease			
		No. Subjects [†]	No. Cases [‡]	OR (95% CI) [*]	p-value	No. Subjects [‡]	No. Cases [‡]	OR (95% CI) [*]	p-value
All	ε2+	136	37	0.90 (0.58 – 1.38)	0.62	125	99	1.01 (0.62 – 1.66)	0.96
	ε3/ε3	543	152	1.00 (reference)	--	485	94	1.00 (reference)	--
	ε4+	139	52	1.70 (1.14 – 2.54)	0.009	126	39	1.97 (1.26 – 3.07)	0.003
Women	ε2+	97	28	0.73 (0.45 – 1.21)	0.23	88	19	0.79 (0.45 – 1.41)	0.43
	ε3/ε3	400	131	1.00 (reference)	--	352	83	1.00 (reference)	--
	ε4+	107	48	2.06 (1.32 – 3.22)	0.002	96	37	2.37 (1.46 – 3.86)	<0.001
Men	ε2+	39	9	1.72 (0.73 – 4.07)	0.21	37	7	2.59 (0.94 – 7.06)	0.06
	ε3/ε3	143	21	1.00 (reference)	--	133	11	1.00 (reference)	--
	ε4+	32	4	0.73 (0.24 – 2.26)	0.59	30	2	0.63 (0.14 – 2.90)	0.55

Abbreviations: APOE = Apolipoprotein E; OR = odds ratio; CI = Confidence Interval; ε2+ = 1 or more APOEε2 alleles; ε4+ = 1 or more APOEε4 alleles

^{*} Odds ratios and 95% CI for all analyses are adjusted for age and for analyses in all participants combined are additionally adjusted for sex.

[†] There were 16 subjects (12 women and 4 men) and 5 dementia cases (5 women) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups

[‡] There were 14 subjects (10 women and 4 men) and 3 Alzheimer's disease cases (3 women) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups

Table 3

Association of apolipoprotein E with incident dementia, The 90+ Study

Subjects	APOE Group	All-Cause Dementia				Alzheimer's Disease			
		No. Subjects [†]	No. Cases [‡]	HR (95% CI) [*]	p-value	No. Subjects [‡]	No. Cases [‡]	HR (95% CI) [*]	p-value
All	ε2+	94	38	1.19 (0.83 – 1.72)	0.34	75	19	1.05 (0.63 – 1.75)	0.85
	ε3/ε3	355	122	1.00 (reference)	--	309	76	1.00 (reference)	--
	ε4+	82	32	1.04 (0.71 – 1.53)	0.83	71	21	1.14 (0.71 – 1.84)	0.60
Women	ε2+	66	27	1.22 (0.79 – 1.88)	0.37	55	16	1.19 (0.67 – 2.08)	0.56
	ε3/ε3	243	89	1.00 (reference)	--	209	55	1.00 (reference)	--
	ε4+	54	20	1.01 (0.63 – 1.64)	0.96	49	15	1.20 (0.68 – 2.11)	0.53
Men	ε2+	28	11	1.10 (0.54 – 2.23)	0.79	20	3	0.61 (0.18 – 2.11)	0.44
	ε3/ε3	112	33	1.00 (reference)	--	100	21	1.00 (reference)	--
	ε4+	28	12	1.11 (0.58 – 2.13)	0.75	22	6	0.93 (0.38 – 2.29)	0.87

Abbreviations: APOE, apolipoprotein E; HR, hazard ratio; CI, confidence interval; ε2+ = 1 or more APOEε2 alleles; ε4+ = 1 or more APOEε4 alleles

^{*} Hazard ratios and 95% CI for all analyses are adjusted for age and for analyses in all participants combined are additionally adjusted for sex

[†]There were 11 subjects (7 women and 4 men) and 4 dementia cases (2 women and 2 men) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups

[‡]There were 9 subjects (7 women and 2 men) and 2 Alzheimer's disease cases (2 women) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups

Table 4

Association of apolipoprotein E with mortality, The 90+ Study

Subjects	APOE Group	No. Subjects [†]	No. Deaths [‡]	HR (95% CI)*	p-value
All	ε2+	136	89	0.92 (0.73 – 1.15)	0.45
	ε3/ε3	543	338	1.00 (reference)	--
	ε4+	139	93	0.94 (0.75 – 1.18)	0.59
Women	ε2+	107	71	0.93 (0.71 – 1.21)	0.58
	ε3/ε3	400	249	1.00 (reference)	--
	ε4+	97	65	1.03 (0.79 – 1.33)	0.85
Men	ε2+	39	24	0.84 (0.53 – 1.33)	0.45
	ε3/ε3	143	89	1.00 (reference)	--
	ε4+	32	22	0.72 (0.45 – 1.14)	0.16

Abbreviations: APOE = Apolipoprotein E; HR = hazard ratio; CI = Confidence Interval; ε2+ = 1 or more APOEε2 alleles; ε4+ = 1 or more APOEε4 alleles

[†]Hazard ratios and 95% CI for all analyses are adjusted for age and for analyses in all participants combined are additionally adjusted for sex

[‡]There were 16 subjects (12 women and 4 men) and 10 deaths (8 women and 2 men) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups