Apolipoprotein E genotype, dementia, and mortality in the oldest old: The 90+ Study

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Abstract

Background: Although the apolipoprotein E (APOE) ε4 allele is a major genetic risk factor for Alzheimer’s disease (AD), it is not clear whether this relationship persists among the oldest old. Several European studies suggest that the effect of the APOE ε4 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 APOE ε4 or APOE ε2 alleles is 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 years and older from The 90+ Study. Eight hundred twenty (89%) participants were genotyped and included in the prevalent dementia and mortality analyses. The 520 initially nondemented participants were included in the incident dementia analyses and were evaluated for dementia every 6 months.

Results: The APOE ε4 allele was significantly associated with prevalent dementia (odds ratio = 2.06) and AD (odds ratio = 2.37) in women but not in men. The APOE ε2 allele was not related to prevalent dementia in either sex. After an average follow-up of 2.4 years, 188 incident dementia cases were identified. Neither the APOE ε4 nor the APOE ε2 allele was related to incident dementia or AD. Five hundred ten (64%) participants died after an average follow-up of 2.3 years, and their mortality was not related to the presence of either the APOE ε2 or APOE ε4 allele.

Conclusions: Our findings suggest that the associations between APOE ε4, dementia, and mortality are age dependent, and that APOE ε4 no longer plays a role in dementia and mortality at very old ages.

Keywords: Apolipoprotein E; Dementia; Alzheimer’s disease; Mortality; Oldest-old

1. Introduction

The ε4 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 ε2 allele is more controversial. Whereas many studies report a protective effect of the APOE ε2 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 ε4 allele on the risk of dementia and mortality diminishes or disappears in advanced age. In our own cohort, we previously found the APOE ε2 allele to be associated with increased odds of AD pathology but decreased odds of dementia, whereas the APOE ε4 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 years 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 years 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 nonparticipants 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, 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.

2.2. Assessments

The neuropsychological battery included a variety of tests previously described [19], including the Mini-Mental State Examination (MMSE) [20]. The neurological examination, 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 6 months. In some situations, in-person follow-up was not possible owing 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 follow-up included the Cognitive Abilities Screening Instrument-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.

2.3. 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, fourth edition criteria for dementia [27] and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for AD [28]. Although National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria exclude people aged 90 years 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 cutoff scores for dementia derived from this cohort [29].

Cognitive status during follow-up 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 Cognitive Abilities Screening Instrument-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 participants’ 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.

2.4. Data analysis

A flowchart of participant inclusion for the different analyses is shown in Figure 1. Analyses of allele and genotype frequencies included 802 genotyped participants and were compared using $\chi^2$ 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 follow-up ($N = 520$). 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 follow-up evaluation when determined to be demented or the date of last follow-up 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 (alive were censored at their age on December 31, 2010. Mortality 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 ε2 and APOE ε4 alleles were assessed by including dummy coded variables (1 if present and 0 if absent) for both APOE ε2 and APOE ε4 and using the APOE ε3/ε3 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 ε4 as well as sex and APOE ε2. 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: 90–105), 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 with 65% of men (P = .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%), and had an average age of 94.7 years; about half were demented (53%). Compared with participants included in this study, the excluded participants did not differ in sex (P = .43) or education (P = .92), but were older (P = .01), less likely to be Caucasian (P = .05), and more likely to have a diagnosis of dementia at baseline (P = .001).

The frequency of the different APOE genotypes and alleles is shown in Table 1. The most common genotype was ε3/ε3 (68%), followed by ε3/ε4 (15%) and ε2/ε3 (15%). Three participants had the ε4/ε4 genotype, and three had the ε2/ε2 genotype. The APOE allele frequencies were 8.7% for APOE ε2, 82.5% for APOE ε3, and 8.9% for APOE ε4 in the overall sample. Compared with allele frequencies in younger Caucasian populations (APOE ε2 = 7.8%, APOE ε3 = 76.5%, and APOE ε4 = 15.8%) [31], the APOE ε4 allele frequency was lower and the APOE ε3 allele frequency was higher. Men and women did not differ significantly on allele frequencies (P = .49), genotype frequencies (P = .60), or proportions of APOE ε4 carrier status (men: 15.2%, women: 18.1%; P = .35) or APOE ε2 carrier status (men: 18.6%, women: 16.4%; P = .47).

#### 3.1. Prevalent dementia

The presence of an APOE ε4 allele was significantly associated with prevalent dementia and AD in women but not in men (Table 2). Women with an APOE ε4 allele had more than twice the odds of having dementia (odds ratio [OR] = 2.06) or AD (OR = 2.37) compared with women with
the APOE ε3/ε3 genotype. Conversely, in men, we found nonsignificant lower odds of prevalent dementia (OR = 0.73) and AD (OR = 0.63) among APOE ε4 carriers. Of interest, two of the three participants (one man and one woman) with an ε4/ε4 genotype did not have dementia at their baseline evaluation. In analyses of men and women combined, the interactions between sex and the APOE ε4 allele were not statistically significant for all-cause dementia (P = .12) or AD (P = .12) but were suggestive of a sex difference.

The associations between the presence of an APOE ε2 allele and dementia were not significant but were also suggestive of a sex difference. Women with an APOE ε2 allele had decreased odds of dementia (OR = 0.73) or AD (OR = 0.79), whereas men with an APOE ε2 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 ε2 allele were not statistically significant for all-cause dementia (P = .10) or AD (P = .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: 90–103) and average length of follow-up 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 nondemented participants because they had no follow-up evaluation. The reasons for no follow-up were as follows: 13 died, 3 withdrew, 15 had a baseline evaluation <6 months before study end, and 15 had not yet had a follow-up visit, although time since their baseline evaluation was >6 months. These 46 participants were mostly women (74%), had at least some college education (70%), and had an average age of 92.2 years, 11% were APOE ε4 carriers, and 11% were APOE ε2 carriers. Thus, the excluded participants did not differ in terms of sex (P = .44), education (P = .82), APOE ε4 (P = .38), or APOE ε2 carrier status (P = .22), but were younger (P = .003) than participants included in the analyses.

The presence of an APOE ε4 allele or an APOE ε2 allele was not associated with incident all-cause dementia or AD in women or men (Table 3). Of note, the two participants with an ε4/ε4 genotype who were not demented at baseline developed dementia during the follow-up period.

In combined analyses of men and women, the interactions between sex and the APOE ε4 allele and sex and the APOE ε2 allele were not significant (P > .20) for all-cause dementia and AD.

3.3. Mortality

Of the 802 participants, 510 (64%) died during follow-up at an average age of 97.2 years (range: 90–108) (Table 1). The average follow-up for mortality was 2.8 years (range: 0.02–81). Presence of an APOE ε4 allele or an APOE ε2 allele was not related to mortality either in women or 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 ε4 allelic frequency, with an equivalent higher APOE ε3 frequency, in this sample of oldest-old participants compared with younger subjects in other studies. Although APOE ε4 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 ε4 allele disappears at very old age. Our results are consistent with that hypothesis, as we found increased

| Subjects | APOE group | All-cause dementia | AD |
|----------|------------|-------------------|-----|
|          | Number of subjects | Number of cases | OR (95% CI) | P value | Number of subjects | Number of cases | OR (95% CI) | P value |
| All      | ε2+        | 136 37 | 0.90 (0.58-1.38) | .62 | 125 99 | 1.01 (0.62-1.66) | .96 |
|          | ε3/ε3      | 543 152 | 1.00 (reference) | – | 485 94 | 1.00 (reference) | – |
|          | ε4+        | 139 52 | 1.70 (1.14-2.54) | .009 | 126 39 | 1.97 (1.26-3.07) | .003 |
| Women    | ε2+        | 97 28 | 0.73 (0.45-1.21) | .23 | 88 19 | 0.79 (0.45-1.41) | .43 |
|          | ε3/ε3      | 400 131 | 1.00 (reference) | – | 352 83 | 1.00 (reference) | – |
|          | ε4+        | 107 48 | 2.06 (1.32-3.22) | .002 | 96 37 | 2.37 (1.46-3.86) | <.001 |
| Men      | ε2+        | 39 9 | 1.72 (0.73-4.07) | .21 | 37 7 | 2.59 (0.94-7.06) | .06 |
|          | ε3/ε3      | 143 21 | 1.00 (reference) | – | 133 11 | 1.00 (reference) | – |
|          | ε4+        | 32 4 | 0.73 (0.24-2.26) | .59 | 30 2 | 0.63 (0.14-2.90) | .55 |

Table 2
Association of APOE with prevalent dementia, The 90+ Study

Abbreviations: OR, odds ratio; CI, confidence interval; ε2+, one or more APOE ε2 alleles; ε4+, one or more APOE ε4 alleles; AD, Alzheimer’s disease.

*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.

ORs and 95% CI for all analyses are adjusted for age and for analyses in all participants combined are additionally adjusted for sex.

†There were 14 subjects (10 women and 4 men) and 3 AD cases (3 women) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups.
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 allele frequency in the oldest old [32–36]. The most common finding is a decrease in the APOE ε4 frequency with a corresponding increase in the APOE ε2 frequency in nonagenarians and centenarians compared with younger groups. We found a similar decrease in the frequency of the APOE ε4 allele, but the frequency of the APOE ε3, not the APOE ε2, was increased. Our results are consistent with a recent pooled analysis of case–control studies of older people of European ancestry [37] that assessed the change in allele frequency with age between <60 years and >90 years. That study found a significant decrease in frequency of APOE ε4, a significant increase in frequency of APOE ε3, and no change in the frequency of APOE ε2. Furthermore, the allele frequencies in our study (APOE ε2 = 8.7%, APOE ε3 = 82.5%, APOE ε4 = 8.9%) are similar to the allele frequencies in those aged >90 years in the pooled analysis (APOE ε2 = 8.3%, APOE ε3 = 83.3%, APOE ε4 = 8.3%).

We found increased odds of prevalent dementia and AD among those with an APOE ε4 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 years 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 ε4 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 ε4 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 ε4 allele is no longer harmful at very advanced ages.

In our study, the significant association between APOE ε4 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 ε4 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 owing to the relatively small number of men in our study.

Few studies have reported on the association between an APOE ε2 allele and prevalent dementia. We found nonsignificant lower odds of dementia (OR = 0.73) and AD (OR = 0.79) among women, whereas in men, we found nonsignificant 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 nonsignificant association of APOE ε2 and dementia in women (OR = 0.69), but found significantly decreased odds in men (OR = 0.22). The Gothenburg study found nonsignificant lower odds for dementia (OR = 0.7) and AD (OR = 0.5) in 412 men and women

| Subjects | APOE group | Number of subjects* | Number of cases* | HR (95% CI) | P value |
|----------|------------|---------------------|------------------|-------------|---------|
| All      | ε2+        | 94                  | 38               | 1.19 (0.83–1.72) | .34     |
|          | ε3/ε3      | 355                 | 122              | 1.00 (reference) | −       |
|          | ε4+        | 82                  | 32               | 1.04 (0.71–1.53) | .83     |
| Women    | ε2+        | 66                  | 27               | 1.22 (0.79–1.88) | .37     |
|          | ε3/ε3      | 243                 | 89               | 1.00 (reference) | −       |
|          | ε4+        | 54                  | 20               | 1.01 (0.63–1.64) | .96     |
| Men      | ε2+        | 28                  | 11               | 1.10 (0.54–2.23) | .79     |
|          | ε3/ε3      | 112                 | 33               | 1.00 (reference) | −       |
|          | ε4+        | 28                  | 12               | 1.11 (0.58–2.13) | .75     |

Abbreviation: HR, hazard ratio.

*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.

| Study | Number of subjects* | Number of cases* | HR (95% CI) | P value |
|-------|---------------------|------------------|-------------|---------|
| All   | 11                  | 4                | 0.72 (0.45–1.14) | .16     |
|       | 3                    | 22               | 0.93 (0.38–2.29) | .87     |

Table 4
Association of APOE with mortality, The 90+ Study

| Subjects | APOE group | Number of subjects* | Number of deaths* | HR (95% CI) | P value |
|----------|------------|---------------------|------------------|-------------|---------|
| All      | ε2+        | 136                 | 89               | 0.92 (0.73–1.15) | .45     |
|          | ε3/ε3      | 543                 | 338              | 1.00 (reference) | −       |
| Women    | ε2+        | 139                 | 93               | 0.94 (0.75–1.18) | .59     |
|          | ε3/ε3      | 400                 | 249              | 1.00 (reference) | −       |
| Men      | ε2+        | 39                  | 24               | 0.84 (0.53–1.33) | .45     |
|          | ε3/ε3      | 143                 | 89               | 1.00 (reference) | −       |

*There were 16 subjects (12 women and four men) and 10 deaths (eight women and two men) who were APOE ε2/ε4 and are included in both ε2+ and ε4+ groups.

HRs and 95% CI for all analyses are adjusted for age and for analyses in all participants combined are additionally adjusted for sex.
aged 85 years and older [9]. The discrepancy of results seen among studies seems to be among men, a problem that will be difficult to sort out because 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 ε4 was related to increased odds and APOE ε2 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 ε2 or APOE ε4 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 with 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 ε4/ε4 homozygotes can reach very old age without dementia. We had two APOE ε4/ε4 participants who were not demented at their baseline evaluation. They did, however, develop dementia during follow-up.

We found no association between APOE ε4 or APOE ε2 and incident dementia in our 520 initially nondemented 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 APOE ε4 and incident dementia in 187 initially nondemented 85+ year olds. The Gothenburg study analyzed the risk of dementia between ages 85 and 88 in 320 subjects and found neither APOE ε4 nor APOE ε2 to be related to all-cause dementia [9]. Similarly, the Kungsholmen Project reported data for 187 people aged 85 years and older and found no association between APOE ε4 or APOE ε2 and AD [12]. It seems apparent that the APOE gene has no effect on the risk of dementia on people who survive to very old age without dementia; thus, it must exert its effects at an earlier age.

We also found no association between APOE ε4 or APOE ε2 and mortality after age 90. Our results are consistent with most studies in not finding an association between APOE ε4 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 1551 nonagenarians from the Danish 1905 birth cohort [15]. In contrast, in the Kungsholmen Project [13], the APOE ε4 allele was related to increased mortality and the APOE ε2 allele was related to decreased mortality among people 85 years and older who were not demented. In our study, APOE was not associated with mortality in either demented or nondemented 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 nondifferential 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, to our knowledge, it is 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 after age 90 APOE ε4 is related to prevalent dementia, but not to incident dementia or mortality, support the hypothesis previously set forth that the effects of the APOE ε4 allele change with age. Although APOE ε4 is a strong risk factor for AD, dementia, and mortality in younger elderly individuals, it has little effect in the very old.

Acknowledgments

The authors thank the participants and their relatives and the staff of The 90+ Study. They also thank Dr. Pamela Ward for the APOE genotyping.

This study was supported by the National Institute on Aging grant R01AG21055.

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