Mortality, Dementia, and Apolipoprotein E Genotype in Elderly White Women in the United States

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OBJECTIVES: To assess the risk of death in relation to apolipoprotein E (APOE) genotype and to evaluate how APOE genotype interacts with dementia and with other major medical conditions to affect survival.

DESIGN: A 6-year prospective cohort study of dementia, APOE genotype and survival.

SETTING: Health maintenance organization in southern California.

PARTICIPANTS: One thousand eight hundred forty-two white women aged 75 and older.

MEASUREMENTS: Dementia was determined using a multistage assessment procedure, medical record, and death certificate review.

RESULTS: With women with the APOE 3/3 genotype as the referent, age-adjusted hazard ratios (HRs) for death according to genotype were 1.25 (95% confidence interval [CI] = 1.00–1.56) for APOE 2/4, 3/4, or 4/4 and 0.83 (95% CI = 0.62–1.13) for APOE 2/3 or 2/2. Survival was associated with APOE genotype (log rank test P = .02). Women with the APOE 2/4, 3/4, or 4/4 genotype died at an earlier age, and those with APOE 2/2 or 2/3 died later than those with the APOE 3/3 genotype. After adjustment for age, education, and hormone use, HRs for death were significantly higher in women with the APOE 2/4, 3/4, or 4/4 genotype who developed dementia (HR = 3.74; 95% CI = 2.81–4.99) and the APOE 2/3 genotype (HR = 3.23; 95% CI = 1.97–5.28) than in women without dementia and the APOE 3/3 genotype. The HRs for death were greater with other medical conditions, but no interaction with any APOE genotype was found.

CONCLUSION: In this population of elderly women, although having at least one e4 allele increased the chances of an earlier death, having dementia increased the risk of death regardless of APOE genotype.

Key words: dementia; APOE; genotype

There are three major alleles of the apolipoprotein E (APOE) gene in the population: e2, e3, and e4, resulting in six unique genotypes: 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4.1 The most common genotype is 3/3, although frequencies can vary in certain ethnic and geographic areas. In studies of older populations, in general, the frequency of the e4 allele is lower and the e2 allele is higher.2 The different frequencies according to age will affect the relationships between APOE genotype and mortality according to age.

The association between APOE genotype and mortality has been studied extensively, yet results are not uniform. Some studies report that any e4 allele3,4 or only the 4/4 genotype5 is associated with higher overall early mortality; others find that the association is not present in a population aged 85 and older.6,7 One study found that people with the APOE 3/4 genotype had a greater risk of mortality and that the risk was even higher in people with the 4/4 genotype at age 50 and then moved toward 1.0 with older age.8

There are several ways in which APOE genotype might be related to mortality. Higher mortality in people with at least one APOE e4 allele could be due to a role of APOE e4 in increasing the chances of developing dementia, which is itself a condition with a high mortality rate. The e4 allele of the apolipoprotein gene (APOE 4) is associated with a greater risk of developing dementia attributed to Alzheimer’s disease3,9–13 and with accelerated development of cognitive impairment.3,9,14 One study15 found that having at least one e4 allele shortened the time between the onset of Alzheimer’s disease and death in men.

An effect of APOE genotype on mortality might also be due to an effect of the APOE genotype on the development of conditions other than dementia that have high mortality. Studies have shown that in the presence of the 4 allele, mortality is greater with cardiovascular disease and cerebrovascular disease16,17 and stroke.18 Another study showed more colon and rectal cancer in people who lacked...
the ε3 allele, although no association between cancer, survival, and APOE was found. There are also studies that have found no association between all-cause mortality and APOE and no association between mortality after ischemic stroke, cerebral infarction, or cardiovascular disease and APOE.

Various studies have linked having one or more APOE ε4 alleles with mortality from various different unique causes, in particular, dementia, cerebrovascular disease, ischemic heart disease, and cancer. The aims of the present analysis was to assess the association between APOE genotype and mortality, to assess the interaction between these major medical conditions and the APOE alleles, and to determine their influence on mortality risk in a large cohort of elderly (≥75) white women.

**METHODS**

The Women's Memory Study is a prospective cohort study with a primary aim of assessing the relationship between hormone therapy and dementia. The Kaiser Permanente Southern California (KPSC) institutional review board reviewed and approved the study. Women consented verbally to the telephone interview. Written consent was obtained before the drawing of a blood specimen for genotyping.

Details on study recruitment methods and methods of assessing cognitive status and dementia have been published elsewhere. Evaluation of the validity of the multistage approach to identifying dementia showed sensitivity of 0.83 and specificity of 1.00 in separating women with dementia from those without dementia.

**Subjects**

In brief, recruitment to the study was based on the use of computer-stored prescription data from the KPSC Pharmacy Information Management System to identify women aged 75 and older on July 1, 1998, who had had at least one prescription for oral hormones filled in a KPSC pharmacy in every calendar year from 1992 to 1998 and a comparison group of hormone non-users, who were women who did not have prescriptions for hormone therapy during the same period.

Of the 6,542 women asked to participate in the study, 3,924 enrolled and completed baseline interviews themselves (n = 3,681) or had baseline data provided by a proxy (n = 243). Of the 3,924 women with a baseline interview, 2,048 also provided a blood sample for genotyping, from which DNA was recovered for 2,043. This analysis is restricted to the 1,842 of these women who reported that their race and ethnicity was white, non-Hispanic or who a proxy reported to be white, non-Hispanic. The remaining 201 women from other ethnic and racial groups were not included in the analysis, because there were an insufficient number of participants to analyze the different racial and ethnic groups separately according to APOE genotype. Figure 1 shows the flow of subjects into this analysis.

**Assessment of Cognitive Status and Dementia Using Multistage Assessment**

The baseline interview and follow-up assessments were used to classify the women according to presence of dementia. This assessment was based on the Telephone Interview of Cognitive Status-modified (TICS-m), the Telephone Dementia Questionnaire (TDQ), and medical record review. Women who did not have dementia at baseline were followed up with annual telephone interviews to collect updated information on health, to reassess cognitive status, and to identify new cases of dementia using the same multistage procedure.

**APOE Genotyping**

APOE genotyping was performed using a method previously developed.

**Ascertainment of Deaths**

To ascertain deaths, all 3,924 women with baseline data on cognitive status and dementia were followed through December 31, 2005, through linkage to the California Death Index, Kaiser Permanente hospital discharge records, and proxy report or other reports obtained during follow-up. The date for closing the ascertainment of deaths was based on the availability of information from the annual versions of the California Death Index. Copies of death certificates for deceased women were obtained from the California Department of Vital Statistics and from other states when state law permitted.

**Classification with Dementia and Other Major Medical Conditions**

Women who had dementia at baseline or at any follow-up multistage assessment through December 31, 2005, were
classified as having dementia. Women who had dementia as the cause of death on the death certificate and women with a mention of dementia elsewhere on the death certificate as a secondary or underlying condition were also classified with dementia. Women with dementia recorded as a clinical diagnosis based on updated medical record review after the multistage assessment were also classified with dementia. Age at dementia was defined as the youngest recorded age available through the multistage assessment or subsequent medical chart review. For women classified with dementia based only on death certificates, it was the date of death.

Major medical conditions (cerebrovascular disease (stroke, other unspecified cerebrovascular disease), ischemic heart disease (IHD; coronary heart disease, coronary artery disease, congestive heart failure, myocardial infarction), and cancer) were ascertained through death certificates, medical records, and interviews. International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 codes (for deaths after 2000) were used. ICD-9 codes used were 290, 294, and 331 for dementia; 430–438 for cerebrovascular disease; 410–414, 428–429 for IHD; and 140–208 for cancer. ICD-10 codes used were F01–F03 and G30 for dementia; I160–169 for cerebrovascular disease; 125 and 150 for IHD; and C00–C97 for cancer.

Analyses
Descriptive statistics were generated for each APOE genotype according to demographic variables from self-reported data at baseline, and cerebrovascular disease, IHD, and cancer were derived from self-report, medical records, and death certificates from baseline through 2005 follow-up. Because of the small number of 2/2 and 4/4 genotypes, most subsequent analyses were performed using these categories: 2/2 or 2/3; 3/3; or 2/4, 3/4, or 4/4. The chi-square statistic was used to assess the statistical significance of the association between APOE genotype and the demographic and medical condition variables. Analysis of variance was used to test the significance of differences in age at dementia between APOE genotypes.

The Kaplan-Meier method was used to assess survival in relation to APOE genotype group using age as the time variable. Differences between groups were compared using log rank test.

The Cox proportional hazards model was used to assess the association between APOE genotype group and other variables and survival, again using age as the time scale.29,30 All medical conditions were treated as time-dependent covariates. The interaction between APOE genotype group and dementia (or other medical conditions) was also included in the models to examine whether the presence of dementia (or other medical conditions) modified the effect of APOE genotype group survival. Exact 95% confidence intervals (CIs) were calculated. A two-sided probability value less than .05 was considered statistically significant.

RESULTS
The mean age at baseline for the 1,842 women included in the analysis was 78.7 (range 75–95). Based on the multistage assessment, medical records, and death certificates, 397 women were classified as having dementia. Women with any e4 allele (APOE genotype 2/4, 3/4, or 4/4) had a mean age at dementia diagnosis of 82.4 ± 3.8, compared with 84.3 ± 4.6 for those with the 2/3 genotype and 83.2 ± 4.2 for those with the 3/3 genotype. The mean age at dementia for the 4/4 genotype alone was 79.7 ± 4.2, compared with 84.3 ± 4.6 for the 2/3 genotype, a difference of 4.6 years (P = .02). There were no dementia cases during the 6 years of follow-up in the 11 women with the 2/2 genotype.

Table 1 shows the number and percentage distribution of APOE genotype for women included in the analysis according to characteristics of the women at baseline and medical condition variables at baseline and during follow-up. The most common genotype was APOE 3/3, found in 62.3% of women. Only 14.1% of women had APOE 2/2 (0.6%) and 2/3 (13.5%) genotypes. Only 27 (1.5%) had the 4/4 genotype, but 436 (23.7%) had at least one e4 allele. These percentages are consistent with those in other population-based studies of women aged 75 and older.13 The frequency of e4 alleles in the current sample was slightly lower than has been found in younger populations.31 Age, education, cerebrovascular disease, IHD, cancer, and hormone use were not associated significantly with APOE genotype. Dementia was associated with APOE genotype; 38.3% of the women with dementia had at least one e4 allele.

There were 427 deaths through December 31, 2005. The mortality rate for all women in the study was 23.2%. Of the 427 deaths, 153 died with dementia (35.8%) and 274 died without dementia (64.2%).

Figure 2 shows the Kaplan-Meier survival curves according to APOE genotype. Survival was significantly associated with APOE genotype (log rank test P = .02).

Table 2 shows age-adjusted hazard ratios (HRs) according to APOE genotype, education, medical condition, and hormone use, with age at death as an outcome. The HRs for death were 0.83 (95% CI = 0.62–1.13) for women in the 2/2 and 2/3 genotype group, indicating survival to an older age and 1.25 (95% CI = 1.00–1.56) for women with any e4 allele, indicating death at a younger age than with the APOE 3/3 genotype. There was no significant association between education, hormone use, or cancer and survival. The presence of dementia and the other medical conditions were all associated with higher HRs, indicating an earlier age at death (HR = 1.97, 95% CI = 1.61–2.41) for women in the 2/2 and 2/3 genotype group, cerebrovascular disease (HR = 2.26, 95% CI = 1.86–2.74), or IHD (HR = 2.78, 95% CI = 2.23–3.47) compared to people; without these conditions.

After adjusting for age, education, and hormone use in a Cox model, the interaction between APOE and dementia was significant (P = .04). In contrast, the interactions between APOE and other medical conditions (cerebrovascular disease, IHD, or cancer) were not significant. Table 3 shows adjusted HRs stratified according to APOE genotype group and the presence or absence of dementia. The adjusted HRs for dementia were significantly higher, indicating shorter survival, in women with dementia for all three genotype groups (HR = 3.74, 95% CI = 2.81–4.99 for any 4 allele; HR = 3.23, 95% CI = 1.97–5.28 for the 2/2, 2/3 genotype group; and HR = 2.68, 95% CI = 2.02–3.56 for the 3/3 genotype) than in women without dementia and APOE 3/3.
In contrast, genotype was not significantly associated with HRs for survival in women without dementia for any \( e^4 \) allele or the 2/2, 2/3 genotype group.

DISCUSSION

An overall association was found between APOE genotype and survival. Consistent with findings in a recent study, overall survival was longer in those with the 2/2 or 2/3 genotype.\(^{32}\) Survival was shorter in women with any \( e^4 \) allele. As expected, dementia was strongly associated with shorter survival. Dementia was present at an earlier age in women with any \( e^4 \) allele and later in women with the 2/3 genotype. None of the women with the APOE 2/2 genotype were classified as having dementia. Although the numbers are small, if this observation is real, it could suggest the presence of a pathway through which genotype may prevent the development of dementia.

The effect of APOE genotype on survival was manifest only when dementia was present. Although survival was also shorter in women with cerebrovascular disease or IHD, APOE did not modify this association. The lack of a statistically significant association between cancer and survival in these women is noteworthy. However, although this association was not statistically significant, the slight

![Figure 2. Kaplan-Meier plot of survival according to apolipoprotein E genotype.](image-url)
association found may be consistent with the idea that there were mostly cured survivors with only a few who were at greater risk. Women entered the study at age 75 and older, and those with a history of cancer at baseline may represent cured survivors of cancer. Newly occurring cancer cases may not have had sufficient time to affect survival given the 6-year follow-up period.

Some longitudinal studies have found an association between APOE and mortality; others have not. Five studies reported no association between APOE e4 and mortality in populations that included older subjects.\textsuperscript{5,33–36} In other studies similar to the current one that included people aged 75–79, there was restricted to white women; the results may not be generalizable to women in other racial and ethnic groups or to men. Those women who were eligible but could not be interviewed at baseline were significantly older, which could potentially cause a bias, although the population was not significantly different from the elderly U.S. female white population.\textsuperscript{39} Other researchers have reported differences in the interaction between APOE genotype, sex, and dementia development.\textsuperscript{40,41} Second, women entered the study cohort at age 75 and older, and the findings may be due to the advanced age of the study population. The study reflects the mortality experience of a group that has already been subject to important causes of early mortality in women, most prominently breast cancer. Furthermore, if APOE is linked to earlier mortality from causes such as cerebrovascular disease and IHD, those people would have died before the start of the study. The distribution of e4 alleles in the sample was also slightly lower than in younger populations, suggesting a selective loss of people carrying these alleles as the population ages.\textsuperscript{37}

Third, not all eligible women elected to participate, and not all women who enrolled in the main study consented to genotyping. Women with dementia or other chronic conditions were less likely to give blood. The effect of this selection for participation on conclusions cannot be estimated, but it is reassuring to note that the distribution of the APOE genotypes is similar to the distribution in the Study of Osteoporotic Fracture, which also included older women who were predominantly white.\textsuperscript{8}

One strength of the study was classification of death with dementia based on sources of information other than the death certificate. Death certificates are notoriously poor at recording the existence of dementia, as was found in this study as well. Only 70 of the 153 deaths with dementia (45.8\%) had dementia mentioned on the death certificate. Underreporting of dementia also occurs in clinical practice.\textsuperscript{42} Not all of the women classified as having dementia had clinical diagnoses in their medical charts. Moreover, 22 (6.3\%) cases of dementia were identified according to death certificate only. The study included more-comprehensive sources of information about dementia. Using the validated multistage classification method, medical records, and death certificates as sources of information greatly enhanced dementia case identification. A second strength was the large number of subjects and the large number of dementia cases in them. It was possible to examine dementia in women with the rare 2/2 genotype because of the size of the study and the large number of cases.

In summary, these data provide two intriguing findings. First, having at least one e4 allele increased the likelihood of early mortality. Second, the association between any APOE genotype and risk of death being limited to only those with dementia, although not to those without dementia, further

### Table 2. Age-Adjusted Risk of Death According to Apolipoprotein E (APOE) Genotype, Education, and Medical Conditions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Deaths, n (%)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>1,262</td>
<td>232 (18)</td>
<td>*</td>
</tr>
<tr>
<td>80–84</td>
<td>473</td>
<td>145 (31)</td>
<td>*</td>
</tr>
<tr>
<td>≥85</td>
<td>107</td>
<td>50 (47)</td>
<td>*</td>
</tr>
<tr>
<td>APOE genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2, 2/3</td>
<td>259</td>
<td>52 (20)</td>
<td>0.83 (0.62–1.13)</td>
</tr>
<tr>
<td>Any 4</td>
<td>436</td>
<td>118 (27)</td>
<td>1.25 (1.00–1.56)</td>
</tr>
<tr>
<td>3/3</td>
<td>1,147</td>
<td>257 (22)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>162</td>
<td>46 (28)</td>
<td>1.26 (0.87–1.81)</td>
</tr>
<tr>
<td>High school grad</td>
<td>446</td>
<td>107 (24)</td>
<td>1.24 (0.94–1.64)</td>
</tr>
<tr>
<td>Some college</td>
<td>753</td>
<td>172 (23)</td>
<td>1.16 (0.90–1.49)</td>
</tr>
<tr>
<td>≥College</td>
<td>476</td>
<td>100 (21)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Hormone use</td>
<td>1,050</td>
<td>237 (23)</td>
<td>0.96 (0.79–1.17)</td>
</tr>
<tr>
<td>Medical conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>397</td>
<td>153 (39)</td>
<td>1.97 (1.61–2.41)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>616</td>
<td>219 (36)</td>
<td>2.26 (1.86–2.74)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>926</td>
<td>314 (34)</td>
<td>2.78 (2.23–3.47)</td>
</tr>
<tr>
<td>Cancer</td>
<td>928</td>
<td>233 (25)</td>
<td>1.16 (0.95–1.41)</td>
</tr>
</tbody>
</table>

* Five subjects with missing values were excluded.

### Table 3. Risk of Death with or without Dementia According to Apolipoprotein E Genotype Adjusted for Age, Education, and Hormone Use

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Dementia</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2*, 2/3</td>
<td>Yes</td>
<td>3.23 (1.97–5.28)</td>
</tr>
<tr>
<td>Any 4</td>
<td>Yes</td>
<td>3.74 (2.81–4.99)</td>
</tr>
<tr>
<td>3/3</td>
<td>Yes</td>
<td>2.68 (2.02–3.56)</td>
</tr>
<tr>
<td>2/2, 2/3</td>
<td>No</td>
<td>0.71 (0.49–1.02)</td>
</tr>
<tr>
<td>Any 4</td>
<td>No</td>
<td>0.83 (0.61–1.12)</td>
</tr>
<tr>
<td>3/3</td>
<td>No</td>
<td>1.00 (Referent)</td>
</tr>
</tbody>
</table>

* There were no cases of dementia in the 2/2 allele.
focusses attention on the effects of this genotype on mortality, specifically through the mechanism of dementia.

ACKNOWLEDGMENTS

This study was funded by National Institute on Aging Grant AG14745. Dr. Crooks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this manuscript.

Author Contributions: All authors have read and approved the manuscript for submission. Each participated in the preparation of the manuscript, including all or in part, acquisition of subjects and data, conception and design of the study, and analysis and interpretation of the data.

Sponsor’s Role: The funding organization (NIA) did not have any role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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