# Apolipoprotein E, health, and mortality in Taiwanese older adults

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## *Introduction*

Apolipoprotein E (ApoE), a commonly investigated genetic marker, has been linked to health outcomes and longevity. ApoE has three common alleles: E2, E3, and E4, with E3 being the most prevalent allele in most populations. The E4 allele is a common genetic risk factor for Alzheimer and cardiovascular disease (Corder et al., 1996; Eichner et al., 2002; Lahoz et al., 2001; Rosvall et al., 2009), and in some populations, shorter lifespans (Ewbank, 2004, 2007; Schachter et al., 1994; Smith, 2002). It has also been suggested that the E2 allele has neuroprotective effects on the brain (Higgins et al., 1997; Rebeck, Kindy, LaDu, 2002), as it may play a direct role as an anti-oxidant agent (Miyata & Smith, 1996). While several studies have examined the relationship between ApoE and cardiovascular risk factors, few studies have examined the relationship of ApoE to a variety of other biological indicators of health or to indicators of performance-based measures of physical and cognitive function or depressive symptoms. The purpose of this study is to investigate these relationships between ApoE and biomarkers of health as well as ApoE and mortality.

## *Methods*

We use the Social, Environment, and Biomarkers of Aging Study (SEBAS) of Taiwanese adults ages 54 and older to examine how ApoE relates to outcomes that have been previously reported in the literature. Specifically, we will investigate the relationship between ApoE and mortality (from 2000 to 2008), cardiovascular (e.g., blood pressure) and metabolic (e.g., total cholesterol [total-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, body mass index [BMI], and waist-hip ratio [WHR]) markers; and indicators of infection and inflammation (C-reactive protein [CRP], interleukin-6 [IL-6]).

Using established at-risk cutpoints, we compare the proportion of ApoE4 carriers and non-carriers (as well as ApoE2 carriers and non-carriers) with at-risk levels of a set of biologic markers (sampled in 2000). When investigating the relationship between mortality and ApoE genotype, participants with blood samples taken for genotyping in 2000 were followed until 2008.

At-risk levels of biomarkers were examined in relation to the presence of an ApoE2 and ApoE4 allele. We will also examine change in biomarkers (calculated as values in 2006 subtract values in 2000) for those with evaluations at both 2000 and 2006.

In models linking ApoE genotype to survival, participants with blood samples taken for genotyping in 2000 are followed until 2008.

*Results*

The average age of the study sample was 67 years old, with slightly more men than women (57%) (Table 1). The majority of respondents were married (75%), and 29% had a secondary education or higher. For ApoE, the E3 allele was the most prevalent (85%), with a near equal representation of the E2 and E4 alleles (8% and 7%, respectively). By the end of 2008, 21% of the sample had died.

Our preliminary analyses, which do not include controls for age or other covariates, find that ApoE (presence or absence of E2 or E4) was not associated with death after 8-years of follow-up (Table 2). When examining the relationship of various biomarkers of health to ApoE, at-risk levels of blood lipids were associated with the ApoE2 allele (Table 3). A greater proportion of E2 non-carriers had at-risk levels of both total-C and HDL-C than among E2 carriers. The E2 allele appears to have a protective effect on total-C and HDL-C: they were less likely to have at-risk levels (9% and 16%, respectively) compared with non-carriers (16% and 30%, respectively).

Future analyses will examine the association between ApoE and 6-year change in biomarkers.

*Conclusions*

Our findings suggest that ApoE is associated with blood lipid levels. This relationship of ApoE to cholesterol levels has been similarly reported in other populations in France, Finland, and the U.S. (Dufouil et al., 2005; Kivipelto et al., 2002; Lahoz et al., 2001). From this preliminary analysis, the absence of an association between ApoE and mortality, which has been reported in the other studies (Ewbank, 2002, 2004, 2007), is likely due to our relatively small sample size and our crude analysis which did not adjust for contributing factors like age. However, other analyses that examined age-specific mortality rates using an age-based hazard model did not find an effect for ApoE (results not shown). Future additional analyses that more thoroughly examine these relationships will better contribute to our understanding of the relationship between ApoE, health, and mortality.

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Table 1. Sample characteristics of Taiwanese older adults at baseline (2000)

| | N | Mean ± SD or %* |
|---|---|---|
| Age | 1023 | 66.5± 8.2 |
| Men (%) | 1023 | 56.6 |
| Marital status (%) | 1023 | |
| Never married | | 2.9 |
| Married | | 74.5 |
| Separated, divorced, or widowed | | 22.6 |
| Education (%) | 1023 | |
| No formal education | | 28.3 |
| Any primary education | | 43.0 |
| Secondary education or higher | | 28.7 |
| Number of medical conditions† | 1023 | 0.8 ± 0.9 |
| ApoE alleles (%) | 1020 | |
| E2 | | 8.0 |
| E3 | | 84.7 |
| E4 | | 7.3 |
| ApoE genotype (%) | 1020 | |
| E2E2 | | 0.5 |
| E3E2 | | 13.6 |
| E3E3 | | 71.0 |
| E4E2 | | 1.5 |
| E4E3 | | 13.2 |
| E4E4 | | 0.3 |
| *Biomarkers* | | |
| Body mass index (kg/m$^2$) | 1022 | 24.5 ± 3.6 |
| Waist-hip ratio | 1020 | 0.9 ± 0.1 |
| Systolic blood pressure (mm Hg) | 1023 | 137.6 ± 21.0 |
| Diastolic blood pressure (mm Hg) | 1023 | 82.6 ± 11.4 |
| Total cholesterol (mg/dl) | 1022 | 200.9 ± 39.5 |
| High-density lipoprotein cholesterol (mg/dl) | 1022 | 49.0 ± 13.9 |
| Triglycerides (mg/dl) | 1022 | 123.5 ± 93.5 |
| C-reactive protein (mg/dl) | 1000 | 0.3 ± 0.7 |
| Interleukin-6 (pg/ml) | 1006 | 3.5 ± 5.4 |
| Died by end of 2008 | 1023 | 21.3 |

†Includes self-reported history of: high blood pressure, kidney disease, high cholesterol, heart disease, diabetes mellitus, lung disease, stroke

ApoE=apolipoprotein E; ADLs=activities of daily living; IADLs=instrumental activities of daily living

*Mean or % values based on weighted analyses

Table 2. Percent ApoE2 and E4 carriers and non-carriers and dead at end of 2008*

| | ApoE2 | | | ApoE4 | | |
|---|---|---|---|---|---|---|
| | Carrier N=158 | Non-carrier N=862 | p-value | Carrier N=147 | Non-carrier N=873 | p-value |
| Survived | 15.9 | 84.1 | 0.51 | 15.4 | 84.6 | 0.40 |
| Died | 14.1 | 85.9 | | 13.2 | 86.8 | |

*Sample based on the cohort of respondents age 54+ who were examined 2000 (N=1020), % based on weighted analyses

Table 3. Percent with at-risk levels of biomarkers (in 2000) by the presence or absence of ApoE2 and ApoE4*

| | | | ApoE2 | | | ApoE4 | | |
|---|---|---|---|---|---|---|---|---|
| At-risk biomarker levels | Cutpoint | N | Carrier | Non-carrier | p-value | Carrier | Non-carrier | p-value |
| Body mass index (kg/m$^2$) | >30 | 1019 | 9.1 | 6.7 | 0.28 | 6.8 | 7.2 | 0.87 |
| Waist-hip ratio | males ≥0.95; females ≥0.80 | 1017 | 47.1 | 44.8 | 0.58 | 49.4 | 44.4 | 0.25 |
| Systolic blood pressure (mm Hg) | ≥140 | 1020 | 45.5 | 45.4 | 0.96 | 46.5 | 45.2 | 0.75 |
| Diastolic blood pressure (mm Hg) | ≥90 | 1020 | 28.7 | 27.2 | 0.70 | 30.7 | 26.9 | 0.33 |
| Total cholesterol (mg/dl) | ≥240 | 1020 | **8.9** | **15.8** | **0.02** | 16.3 | 14.4 | 0.55 |
| High-density lipoprotein cholesterol (mg/dl) | <40 | 1020 | **15.6** | **29.7** | **<.01** | 32.6 | 26.6 | 0.12 |
| Triglycerides (mg/dl) | ≥200 | 1020 | 13.6 | 10.1 | 0.18 | 11.02 | 10.5 | 0.86 |
| C-reactive protein (mg/L) | ≥3 | 1000 | 26.2 | 25.1 | 0.78 | 19.2 | 26.3 | 0.06 |
| Interleukin-6 (pg/ml) | ≥4.64 | 1005 | 20.3 | 18.6 | 0.61 | 14.4 | 19.7 | 0.12 |

Bold indicates significance at the p<.05 level

*Sample is based on the cohort of respondents who were examined in 2000, % based on weighted analyses