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The risk of coronary heart disease (CHD) may be influenced by genetic mutations in the production of apolipoprotein E via alterations to the metabolism of CHD-related blood lipids such as low-density lipoprotein cholesterol and triglycerides. A common polymorphism in the APOE gene (NCBI Entrez Gene 348) results in the *E2, *E3, and *E4 allelic isoforms and 6 corresponding genotypes (*E3/*E3, *E3/*E4, *E2/*E3, *E4/*E4, *E2/*E4, and *E2/*E2, ranked from most to least common). Relative to the *E3/*E3 group, carriers of the *E2 allele tend to have increased levels of ApoE and decreased LDL-C, whereas *E4 carriers tend to have decreased ApoE and increased high-density lipoprotein cholesterol (HDL-C) levels. It has been estimated that between 1% and 8% of variation in LDL-C level can be accounted for by APOE genotype. The variation in LDL-C levels by APOE genotype has been attributed to increased hepatic receptor–mediated LDL-C removal and decreased conversion of very-low-density lipoprotein cholesterol to LDL-C among *E2 carriers, with the reverse effects proposed among *E4 carriers.

The results of epidemiologic studies that examined the relationship between APOE genotypes and CHD outcomes are inconsistent, despite well-established differences in lipid metabolism by APOE genotype. Earlier meta-analyses of published studies pointed more strongly to increased CHD risk among *E4 carriers, with no association noted for *E2 carriers. More recently, a meta-analysis of 17 published and previously unpublished studies with relatively large sample sizes indicated that the risk of coronary disease was decreased among carriers of the *E2 allele and marginally increased among *E4 carriers. However, with all the meta-analyses of the as-

**Background:** The risk of coronary heart disease (CHD) may be related to genetic mutations in the production of apolipoprotein E via alterations to the metabolism of CHD-related blood lipids such as low-density lipoprotein cholesterol and triglycerides.

**Methods:** The relationship between APOE genotype (*E3/*E3, *E3/*E4, *E2/*E3, *E4/*E4, *E2/*E4, and *E2/*E2) and fatal and nonfatal CHD was examined among 10,355 men and 12,134 women, aged 44 to 79 years, from the Norfolk, England, arm of the European Prospective Into Nutrition and Cancer Study (1993-2007). During an average of 11 years of follow-up, 2,712 CHD events were documented.

**Results:** The hazard ratio for CHD was 0.88 (95% confidence interval, 0.77-0.99) for *E2 carriers (*E2/*E2 and *E2/*E3) and 1.09 (1.00-1.19) for *E4 carriers (*E3/*E4 and *E4/*E4) compared with homozygous *E3/*E3 individuals after age and sex adjustment. Similar values were obtained when systolic blood pressure, body mass index, diabetes mellitus, alcohol intake, physical activity, and smoking were added to the model. After additional adjustment for baseline levels of the ratio of low-to-high-density lipoprotein cholesterol, the hazard ratios (and 95% confidence intervals) for *E2 and *E4 carriers were 0.97 (0.85-1.10) and 1.06 (0.97-1.15), respectively, when compared with *E3 homozygotes. No interactions by sex, smoking status, or age groups were observed.

**Conclusion:** In the largest prospective cohort study to date, CHD risk was not associated with APOE genotype after controlling for a variety of cardiovascular risk factors, particularly the ratio of low- to high-density lipoprotein cholesterol.

Arch Intern Med. 2009;169(15):1424-1429
association between APOE and CHD, the studies that were pooled had included a variety of covariates in their analyses and the specific effect of adjustment for lipid profile on an individual basis was less clear.

We aimed to examine the prospective association between APOE genotype and risk of fatal and nonfatal CHD events and the effects of adjustment for lipid profile on these associations. The European Prospective Investigation Into Nutrition and Cancer (EPIC)–Norfolk cohort is the largest prospective cohort study with APOE genotype data available that we are aware of. Within this cohort, it was observed previously that the LDL-C level was relatively higher among *E2 carriers and lower among *E4 carriers; however, the association between APOE and CHD risk within EPIC-Norfolk was not characterized in previous analyses. The availability of follow-up data for this population provided the opportunity to examine the relationship between APOE genotype and CHD outcome, and to explore the role of LDL-C within these associations. Furthermore, age, sex, and smoking status were examined as potential effect modifiers of the association between APOE and CHD in accordance with suggestions from previous studies.6,9-20

**METHODS**

**STUDY DESIGN AND PARTICIPANTS**

Between 1993 and 1997, men and women aged 40 to 79 years were recruited from general practitioners’ registers for the prospective EPIC-Norfolk study.21 A health examination was attended by 25,630 individuals. A second health examination was attended by 13,786 participants in 1997 to 2000, during which a second blood sample was collected.

**RISK FACTOR ASSESSMENT**

Participants completed a self-administered health and lifestyle questionnaire, which included questions on smoking, physical activity, personal medical history, and medication use.21 Never-smokers were identified as participants who responded no when asked if they had ever smoked 1 cigarette per day for at least 1 year-period. Former smokers were those who responded yes to the foregoing question but were no longer smoking at the time the questionnaire was completed. Participants were asked to indicate whether they had been diagnosed by their physician as having a heart attack or diabetes mellitus. Medication use during the past week, including dose and frequency, was also addressed in the health and lifestyle questionnaire. Intake of alcohol during the past year was also addressed in the health and lifestyle questionnaire, which included questions on smoking, physical activity (including dose and frequency, and continued to smoke. Physical activity level was derived from the combination of a 4-level classification of occupational activity and a 4-level category of time spent in cycling and other physical exercise.21 Participants were asked to indicate whether they had been diagnosed by their physician as having a heart attack or diabetes mellitus. Medication use during the past week, including dose and frequency, was also addressed in the health and lifestyle questionnaire. Intake of alcohol during the past year was assessed by a nutrition questionnaire that was mailed to participants along with an invitation to attend the health examination. The interactions between dummy variables for APOE genotype and CHD could be accounted for by lipid levels (n=633). All statistical analyses were conducted with SAS version 8 statistical software (SAS Institute Inc, Cary, North Carolina), and statistical significance was noted at \( P < 0.05 \).

**CASE ASCERTAINMENT**

All participants were followed up through record linkage with national death certification and hospital record linkage (ENCORE). Fatal and nonfatal CHD events were identified by means of the International Classification of Diseases (Ninth Revision, codes 410-414, or 10th Revision, codes 120-125). End point data were collected between 1993 and 2007, with an average length of follow-up of 11 years.

**APOE GENOTYPING**

DNA for genotyping was extracted fromuffy coat from EDTA-treated blood samples collected at the second health examination in 13,786 individuals. For individuals who did not have an available blood sample from the second health examination, DNA for genotyping was extracted from Buffy coats collected at the first health check.21 Details of the DNA sequencing (Pyrosequencing; Qiagen, Valencia, California) assessment of the APOE genotype have been published elsewhere.8 For quality control, 135 samples were genotyped by means of restriction fragment length polymorphism24 and the DNA sequencer to check for reproducibility, and they were fully concordant.

**STATISTICAL ANALYSIS**

Differences in baseline cardiovascular risk characteristics across APOE genotypes were tested separately among men and women by means of analysis of variance and \( \chi^2 \) analyses for continuous and categorical data, respectively. As an exception, an exact test was used to compare the prevalence of previous myocardial infarction and diabetes status across genotype because there were several categories that contained fewer than 5 observations. Cox proportional hazards regression with days of follow-up as the time variable was used to assess the association between APOE genotype and CHD with different covariates.

A 3-level APOE allele group variable was formed, wherein *E2/*E3 was combined with *E2/*E2 (*E2* ), *E3/*E4 was combined with *E4/*E4 (*E4* ), and *E3/*E4 served as the reference category. *E2/*E4 was excluded from the APOE allele grouping in the main analysis because the *E2* and *E4* alleles are proposed to have opposite effects on CHD risk and because less than 1% of the EPIC-Norfolk cohort carried this genotype.8 However, exploratory analyses were conducted wherein the *E2*/*E4 individuals were included in either the *E2*+ or the *E4*+ in the fully adjusted models. The CHD risk was examined in relation to the APOE allele groups first in an age-and sex-adjusted model, followed by additional adjustment for systolic blood pressure, body mass index categories (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0), and “missing,” calculated as weight in kilograms divided by height in meters squared), diabetes mellitus (yes or no), alcohol intake (grams per day), physical activity (inactive, moderately inactive, moderately active, and active), and smoking status (current, nonsmoker, and “missing”). Never-smokers and former smokers were combined to form the nonsmoker group. Finally, the LDL-C/HDL-C ratio was entered into the model to examine how the extent to which the relationship between genotype and CHD could be accounted for by lipid levels. The interactions between dummy variables for APOE group and age, sex, and smoking status were tested separately for significance by likelihood ratio tests that compared models with and without the interaction terms. A sensitivity analysis was conducted wherein individuals who had self-reported myocardial infarction at baseline were excluded from the fully adjusted models (n=633). All statistical analyses were conducted with SAS version 8 statistical software (SAS Institute Inc, Cary, North Carolina), and statistical significance was noted at \( P < 0.05 \).
Table 1. Cardiovascular Risk Factors at Baseline by APOE Genotype in the EPIC-Norfolk Study

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>*E2/*E4</td>
<td>60</td>
<td>59.1 (9.8)</td>
</tr>
<tr>
<td>*E2/*E3</td>
<td>1263</td>
<td>59.1 (9.4)</td>
</tr>
<tr>
<td>*E3/*E4</td>
<td>2309</td>
<td>59.2 (9.3)</td>
</tr>
<tr>
<td>*E4/*E4</td>
<td>247</td>
<td>59.2 (9.3)</td>
</tr>
<tr>
<td>*E4/*E2</td>
<td>246</td>
<td>59.2 (9.1)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; EPIC, European Prospective Investigation Into Nutrition and Cancer; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

SI conversion factors: To convert HDL-C and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*P* values were obtained from one-way analysis of variance for continuous variables and chi² tests for categorical variables (exact test was used for previous MI and diabetes status).

RESULTS

The present analyses were based on 22 169 men and women who had complete data on APOE genotype and lipid profile. During 11 years of follow-up, CHD events were identified in 2712 individuals.

The distribution of cardiovascular risk factors by APOE genotype among men and women is presented in Table 1. For both men and women, mean levels of LDL-C, HDL-C, and serum triglycerides differed across APOE genotypes. Covariate data were missing on fewer than 3% of the participants. The distribution of physical activity levels did not differ across APOE genotypes among men or women (data not shown).

When the APOE genotypes were clustered by allele, the risk of CHD was decreased among *E2*+ group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.77-0.99) and was marginally increased among the *E4*+ group (HR, 1.09; 95% CI, 1.00-1.19) in the age- and sex-adjusted models (Table 2). These associations were unchanged following additional adjustment for systolic blood pressure, body mass index, diabetes mellitus, alcohol intake, physical activity, and smoking (Table 2). However, adjustment for baseline levels of LDL-C-HDL-C attenuated the associations previously detected among the *E2*+ group (HR, 0.97; 95% CI, 0.85-1.10) and *E4*+ group (1.06; 0.97-1.15). Interaction tests of the most fully adjusted models (including LDL-C) indicated that the association between APOE allele groups and CHD risk differed marginally by sex (P=0.09) but did not differ by smoking status or age (P=0.17 and 0.87, respectively). When the analyses were stratified by sex, none of the APOE allele groups were associated with the risk of CHD among men or women after adjustment for LDL-C:HDL-C (Table 2), including models in which hormone therapy use and menopausal status were in the models for women (data not shown). Exclusion of individuals with self-reported myocardial infarction at baseline did not materially alter the point estimates, nor did the inclusion of *E2*/*E4+ individuals in either the *E2*+ group or the *E4*+ group (data not shown). The LDL-C:HDL-C ratio was associated with increased risk of CHD in multivariate models with systolic blood pressure, body mass index, alcohol intake, physical activity, and smoking (HR, 1.17; 95% CI, 1.14-1.19); the inclusion of APOE genotype in the multivariate models did not affect the point estimates or the CIs (data not shown).

COMMENT

The respective higher and marginally lower CHD risk observed among the *E2*+ and *E4*+ groups in the age- and
sex-adjusted analyses of the EPIC-Norfolk cohort is similar to results obtained in the recent meta-analysis of 17 studies, in which the odds ratios were 0.80 (95% CI, 0.70-0.90) for *E2* carriers and 1.06 (0.99-1.13) for *E4* carriers relative to the *E3* homozygous group. Previous research has observed higher serum cholesterol levels among *E4* carriers and corresponding lower serum cholesterol levels among *E2* carriers. It has been proposed that the mechanism responsible for this effect is defective binding at lipoprotein receptors noted among *E2* carriers, which results in decreased cholesterol delivery to the hepatocytes and a subsequent upregulation of hepatic sterol synthesis and LDL receptors. Conversely, the relatively stronger binding to lipoprotein receptors observed in *E4* carriers increases the delivery of cholesterol to the hepatocytes, which results in the downregulation of hepatic sterol synthesis, a decrease in LDL receptors, and a consequent increase in blood LDL-C concentrations.

Adjustment for LDL-C level has not resulted in consistent attenuation of the relationship between APOE genotype and CHD risk in some previous studies. In case-control or cross-sectional studies in which LDL-C was added to the model in a stepwise fashion, no alteration to the significance of the association between APOE and CHD risk was noted. However, LDL-C has not always been included as an analytic covariate in case-control studies of APOE and CHD risk. In prospective studies, adjustment for LDL-C either served to attenuate previously significant associations between APOE and CHD, though only among *E4/*E4 men and *E3/*E3 smokers, or did not affect the results. Thus far, meta-analyses of the association between APOE and CHD have not had the individual-level data required to adjust for serum cholesterol, including the most recent meta-analysis of 37,850 CHD cases and 82,727 nonevents.

Age and sex have been proposed as potential effect modifiers of the association between APOE and CHD risk because there is evidence that genotypic influence on mortality can vary by birth year and that estrogen and APOE may jointly affect lipid levels. Both age and sex have been explored as effect modifiers in only a limited number of studies, with evidence to suggest that increased CHD risk associated with *E4* carriers is either not different or weaker among older adults, or present among men only, independent of serum cholesterol level. Although APOE genotype did not demonstrate any interactive effects with age in the present study, there was a marginally significant interaction with sex. These results must be interpreted with caution because stratification of each allele group by age and sex resulted in a substantially smaller number of cases and controls per stratum and, as such, the power to examine such interactions was somewhat limited. As a reinforcement of the conclusion for the full cohort, though, the association between APOE genotype and CHD risk was null for both men and women after adjustment for blood lipid levels.

**Table 2. Association Between APOE Allele and CHD Risk in the EPIC-Norfolk Study**

<table>
<thead>
<tr>
<th>APOE Allele</th>
<th>CHD Event, No. of Cases/No. in Cohort</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E2</em>/*E2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>314/2567</td>
<td>0.88 (0.77-0.99)</td>
<td>0.88 (0.78-0.99)</td>
<td>0.97 (0.85-1.10)</td>
</tr>
<tr>
<td><em>E2</em>/E3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1587/11443</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>E2</em>/E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>740/4963</td>
<td>1.09 (1.00-1.19)</td>
<td>1.09 (1.00-1.19)</td>
<td>1.06 (0.97-1.15)</td>
</tr>
<tr>
<td><em>E3</em>/E3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>197/1126</td>
<td>0.81 (0.70-0.95)</td>
<td>0.81 (0.70-0.95)</td>
<td>0.89 (0.77-1.04)</td>
</tr>
<tr>
<td><em>E3</em>/E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1065/4845</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>E4</em>/E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>483/2073</td>
<td>1.08 (0.97-1.20)</td>
<td>1.08 (0.97-1.21)</td>
<td>1.06 (0.95-1.18)</td>
</tr>
<tr>
<td><em>E2</em>/*E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>117/1441</td>
<td>1.00 (0.82-1.23)</td>
<td>1.02 (0.83-1.25)</td>
<td>1.12 (0.91-1.38)</td>
</tr>
<tr>
<td><em>E3</em>/E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>522/6598</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>E4</em>/E4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>257/2880</td>
<td>1.08 (0.93-1.26)</td>
<td>1.09 (0.94-1.27)</td>
<td>1.03 (0.88-1.20)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein; CHD, coronary heart disease; CI, confidence interval; EPIC, European Prospective Investigation Into Nutrition and Cancer; HR, hazard ratio.

<sup>a</sup>Adjusted for age and sex.

<sup>b</sup>Adjusted for age, sex, body mass index category (<18.5, 18.5-24.9, 25.0-29.9, ≥30, and “missing”), calculated as weight in kilograms divided by height in meters squared), smoking status, diabetes mellitus (yes/no), alcohol intake (grams per day), physical activity (inactive, moderately inactive, moderately active, and active), and systolic blood pressure.

<sup>c</sup>Adjusted for age, sex, body mass index category (<18.5, 18.5-24.9, 25.0-29.9, ≥30, and “missing”), smoking status, diabetes mellitus (yes/no), alcohol intake (grams per day), physical activity (inactive, moderately inactive, moderately active, and active), systolic blood pressure, and ratio of low- to high-density lipoprotein cholesterol.

<sup>d</sup>*E2* includes *E2*/E2 and *E2*/E3 genotypes; *E4* includes *E3*/E4 and *E4*/E4 genotypes.
were not at increased risk of CHD.\textsuperscript{17,20,31} The lack of agreement across the aforementioned studies may be owing to the heterogeneity of smoking prevalence, choice of reference group, study design, and classification of smoking history. Stratification by smoking status in the EPIC-Norfolk study failed to produce any significant associations among smokers, even without adjustment for cholesterol (data not shown). Among the Whitehall II population, the absence of an interaction between APOE genotype and smoking was attributed to the relatively low proportion of current smokers in the population.\textsuperscript{20} The proportion of current smokers in EPIC-Norfolk was lower than that of the Whitehall II population; therefore, it is possible that there were an insufficient number of subjects exposed to smoking for divergent associations to be detected in the present study. It is worth noting that the results of the present study were unchanged when former smokers were included in the current smoker category rather than the nonsmoker category (data not shown).

There are a number of limitations to the present study. The LDL-C values could not be calculated for individuals with triglyceride levels greater than 354 mg/dL; however, only 3% of the sample had lipid levels above this cutoff point (n = 772). The APOE genotype is also known to affect levels of C-reactive protein,\textsuperscript{37} an inflammatory marker that has been associated with CHD risk.\textsuperscript{38,39} In the present study, the detected association between APOE genotype and CHD risk became nonsignificant after adjustment for lipid levels, although a small remnant risk of 1.05 (95% CI, 0.96-1.15) was retained among \textit{E4} carriers. This suggests that APOE may have an influence on CHD risk beyond circulating LDL-C and HDL-C levels, potentially via an acute-phase reactant such as C-reactive protein. However, we were unable to explore this association because data on C-reactive protein levels among EPIC-Norfolk participants were not available. Furthermore, although the multivariate analyses controlled for a variety of cardiovascular risk factors, including alcohol intake and physical activity, it is also possible that the observed attenuation after adjustment for LDL-C:HDL-C ratio was due to confounding between the cholesterol ratio and another cardiovascular risk factor. The associations observed in the age- and sex-adjusted analyses were not very strong, and the possibility that they were observed as a result of residual confounding cannot be ruled out. Finally, it is possible that some silent myocardial infarction cases were not identified because electrocardiograms were not included in the present study, thereby potentially reducing the study’s power. In turn, with sufficient numbers of the less common APOE genotypes, it might have been possible to avoid the use of combined allele carrier groups and to achieve greater statistical power for the tests of interaction across age, sex, and smoking status. However, given the consistent attenuation of the association between APOE allele carrier risk and CHD on adjustment for LDL-C:HDL-C ratio and the lack of significant interactions across age, sex, and smoking status, it appears unlikely that analysis of the 6 genotypes would have yielded notably different results.

Despite the availability of extensive lifestyle data, the results from the present analysis of the largest prospective cohort study to date with APOE genotype information indicated that CHD risk was not associated with APOE genotype after controlling for a variety of cardiovascular risk factors, particularly the LDL-C:HDL-C ratio. Variation in serum cholesterol level according to APOE genotype is well established and appeared to be the main cause of attenuation of the association between CHD and APOE relative to models without the LDL-C:HDL-C ratio. Because the possibility of residual confounding cannot be ruled out, APOE may be related to CHD through factors in addition to the LDL-C:HDL-C ratio.

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**Author Contributions:** Study concept and design: Ward, Luben, Wareham, Khaw, and Bingham. Acquisition of data: Bowman, Luben, Wareham, and Khaw. Analysis and interpretation of data: Ward, Mitrou, Khaw, and Bingham. Drafting of the manuscript: Ward, Mitrou, and Bingham. Critical revision of the manuscript for important intellectual content: Ward, Mitrou, Bowman, Luben, Wareham, Khaw, and Bingham. Statistical analysis: Ward, Mitrou, and Bingham. Obtained funding: Wareham, Khaw, and Bingham. Administrative, technical, and material support: Bowman, Luben, and Khaw. Study supervision: Mitrou, Wareham, and Bingham.

**Financial Disclosure:** None reported.

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**REFERENCES**


Errors in Text. In the Original Investigation titled “APOE Genotype, Lipids, and Coronary Heart Disease Risk: A Prospective Population Study” by Ward et al, published in the August 10/24 issue of the Archives (2009;169[15]:1424-1429), errors occurred in the last paragraph of the “Introduction” on page 1425. The third sentence should have read, “Within this cohort, it was previously observed that the LDL-C level was relatively lower among *E2 carriers and higher among *E4 carriers; however, the association between APOE and CHD risk within the EPIC-Norfolk cohort was not characterized in previous analyses.” An error also occurred in the first paragraph of the “Comment” section on pages 1426 and 1427. The first sentence should have read, “The respective lower and marginally higher CHD risk observed among *E2+ and *E4+ groups in the age- and sex-adjusted analyses of the EPIC-Norfolk cohort is similar to the results obtained in the recent meta-analysis of 17 studies, in which the odds ratios were 0.80 (95% CI, 0.70-0.90) for *E2 carriers and 1.06 (0.99-1.13) for *E4 carriers relative to the *E3 homozygous group.”