Polipoprotein E (apoE) is a multifunctional protein that plays a key role in the metabolism of cholesterol and triglycerides by binding to receptors on the liver to help mediate clearance of chylomicrons and very low-density lipoproteins from the bloodstream. Although individuals carrying the ε4 allele have higher and those carrying the ε2 allele have lower total cholesterol levels than people with the commonest ε3/ε3 genotype, studies of lipid markers have typically involved too few participants to characterize relationships with different lipid fractions across the 6 common genotypes. A previous review of 48 published studies among a total of 15,492 disease cases reported that, compared with ε3/ε3 individuals, ε4 carriers have a much greater risk of coronary disease and that ε2 carriers have a neutral risk. But about half of those data were from studies with fewer than 500 coronary cases, which may be more liable to publication biases.

Our reassessment of associations of apoE genotypes with circulating lipid levels and with coronary risk uses the following approach to maximize power and minimize bias: (1) we report updated meta-analyses of studies of apoE genotypes with total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or triglycerides (involving data on up to 86,067 participants in 82 studies) and with coronary outcomes (involving data on up to 37,850 cases and 82,727 controls in 121 studies), with tabular data sought from investigators to supplement and update published data; (2) we contacted principal investigators listed.

**Context** Previous reviews of associations of apolipoprotein E (apoE) genotype and coronary disease have been dominated by smaller studies that are liable to biases.

**Objective** To reassess associations of apoE genotypes with circulating lipid levels and with coronary risk.

**Data Sources** We conducted an updated meta-analysis including both published and previously unreported studies, using MEDLINE, EMBASE, BIOSIS, Science Citation Index, and the Chinese National Knowledge Infrastructure Database published between January 1970 and January 2007, reference lists of articles retrieved, and a registry of relevant studies.

**Study Selection** Eighty-two studies of lipid levels (86,067 healthy participants) and 121 studies of coronary outcomes (37,850 cases and 82,727 controls) were identified, with prespecified principal focus on studies with at least 1000 healthy participants for lipids and those with at least 500 coronary outcomes.

**Data Extraction** Information on genotype frequencies, lipid levels, coronary outcomes, and laboratory and population characteristics were recorded independently by 2 investigators and/or supplied by study investigators.

**Results** In the most extreme comparison, people with the ε2/ε2 genotype had 1.14 mmol/L (95% confidence interval [CI], 0.87-1.40 mmol/L [44.0 mg/dL; 95% CI; 33.6-51.1 mg/dL]) or about 31% (95% CI, 23%-38%) lower mean low-density lipoprotein cholesterol (LDL-C) values than those with the ε4/ε4 genotype. There were approximately linear relationships of apoE genotypes (when ordered ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4) with LDL-C and with coronary risk. The relationship with high-density lipoprotein cholesterol was inverse and shallow and that with triglycerides was nonlinear and largely confined to the ε2/ε2 genotype. Compared with ε3/ε3, the odds ratio for coronary disease was 0.80 (95% CI, 0.70-0.90) in ε2 carriers and was 1.06 (95% CI, 0.99-1.13) in ε4 carriers.

**Conclusions** There are approximately linear relationships of apoE genotypes with both LDL-C levels and coronary risk. Compared with individuals with the ε3/ε3 genotype, ε2 carriers have a 20% lower risk of coronary heart disease and ε4 carriers have a slightly higher risk.

©2007 American Medical Association. All rights reserved.
in a registry of coronary genetic studies to seek unreported data; and (3) we pre-
specified that principal analyses would be based on studies of lipid fractions with
at least 1000 healthy participants and on studies of coronary disease with at least
500 cases, involving only studies that had adequately assessed apoE status and lipid
levels and/or coronary outcomes.

METHODS
We sought studies published between January 1970 and January 2007 on apoE
genotype associations with concentrations of total cholesterol, LDL-C, HDL-C,
or triglycerides or with risk of myocardial infarction (defined by World Health
Organization Multinational Monitoring of Trends and Determinants in Car-
diovascular Disease [MONICA] criteria) or angiographic coronary stenosis
generally defined as at least 50% steno-
sis of ≥1 major coronary arteries). For
lipid fractions, data were used from only
apparently healthy controls (ie, people
without known coronary or other dis-
cases or clinical lipid abnormalities) who
had information on all relevant geno-
types. Electronic searches, not limited to
the English language, were performed
using MEDLINE, EMBASE, BIOSIS, Sci-
cence Citation Index, and the Chinese Na-
tional Knowledge Infrastructure Data-
base by scanning the reference lists of
articles identified for all relevant stud-
ies and review articles (including meta-
analyses), hand searching of relevant
journals, and by correspondence with au-
tors of included studies. The computer-
based searches combined search terms
related to the relevant gene (eg, Apoli-
poprotein E, ApoE genotypes), lipid phe-
notypes (eg, total cholesterol, LDL, HDL,
and triglycerides), and coronary disease
(eg, myocardial infarction, atheroscle-
rosis, coronary heart disease, and coronary
stenosis) without language restriction
(FIGURE 1).

The following data were extracted inde-
dependently by 2 investigators, using a
prepiloted data extraction form: geno-
type frequencies by categorical dis-
case outcome; means and standard de-
viations of lipid fractions by genotype;
mean age of cases; proportions of men

...and ethnic subgroups (defined as
people of white European continental
ancestry, East Asian, or other); fasting
status; genotyping and lipid assay meth-
ods; and use of blinding of laboratory
workers. Discrepancies were resolved
by discussion and by adjudication of a
third reviewer. We used the most up-
to-date information in cases of mul-
tiple publications. We supplemented
published data by a tabular data re-
sue request to authors of published reports
and to investigators of 62 potentially rel-
ent unpublished studies listed in pub-
ished meta-analyses who had pub-
ished on variants other than apoE.

Statistical Analysis
Analyses involved only within-study
comparisons to avoid possible biases,
with principal analyses of larger studies
that had used accepted assessments of
apoE genotype status (eg, polymerase
chain reaction, isoelectric phenotyping),
lipid markers (eg, enzymatic and
precipitation methods), and coronary
outcomes (as described above). Indi-
viduals with the ε3/ε3 genotype were
defined as the reference group. Separate
analyses were conducted for each geno-
type (in the following prespecified order:
ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, and ε4/ε4, with
the position of ε2/ε4 genotype inserted
after data exploration) and for ε2 and ε4
carrier status (this particular analysis
excluded, of course, the ε2/ε4 genotype).

Summary odds ratios (ORs) for coro-
nary disease and mean plasma levels of
total cholesterol, LDL-C, HDL-C, and tri-
glycerides (and differences in mean
plasma levels between each genotype and
the reference group) were calculated for
each genotype using a random effects
model that included between-study
heterogeneity. We avoided any double
counting by analyzing different coro-
nary cases separately before combining
them into a single coronary disease group
for the few studies that included a single
control group and nonoverlapping coro-
nary stenosis cases and nonfatal myocar-
dial infarction cases.

Consistency of findings across stud-
ies was assessed using the I² statistic. Pub-
lication bias was assessed using fun-
nel plots, Egger test and the trim-and-fill
method. Heterogeneity was as-
essed using the Q statistic and by
examining prespecified groupings of
studies characteristics. All analyses were
performed using Stata Statistical Soft-
ware, Release 9 (StataCorp LP, Col-
lege Station, Texas).

RESULTS
ApoE Genotypes and Lipid Outcomes
Eighty-two studies (44 previously
published [19 in MEDLINE journals, 25 in non-MEDLINE journals], 6 ex-
anded and/or updated, and 32 previ-
ously unreported in relation to lipid
markers) were identified with data on
apoE genotypes and lipid outcomes
from a total of 86 067 disease-free par-
ticipants (details of study characteris-
tics available from the authors upon re-

Figure 1. Study Flow Diagram

©2007 American Medical Association. All rights reserved.
and triglycerides, and all used precipitation methods to assess HDL-C; LDL-C was directly measured in 4 studies and calculated in the remainder. All but 6 studies used polymerase chain reaction–based methods to establish apoE genotypes. The overall allele frequencies among people without coronary disease were 0.07 for ε2, 0.82 for ε3, and 0.11 for ε4; the overall genotype frequencies were 0.007 for ε2/ε2, 0.116 for ε2/ε3, 0.022 for ε2/ε4, 0.623 for ε3/ε3, 0.213 for ε3/ε4, and 0.019 for ε4/ε4. These frequencies were broadly similar in men and women and in adults older or younger than 55 years (although in East African populations, the frequencies of ε2 and ε4 were 0.08 and 0.09, respectively).26

Associations of apoE genotypes with levels of total cholesterol or LDL-C were strongly positive and approximately linear when ordered as described above (Figure 2). Comparison of people with ε2/ε2 vs those with ε3/ε4 (which are, apart from ε3/ε3, the most common genotypes) yielded differences in total cholesterol of −0.43 mmol/L (95% confidence interval [CI], −0.36 to −0.51 mmol/L [−16.6 mg/dL; 95% CI, −13.9 to −19.7 mg/dL]) or about −8%; 95% CI, −6% to −9%) and in LDL-C of 0.52 mmol/L (95% CI, −0.44 to −0.61 mmol/L [−20.1 mg/dL; 95% CI, −17.0 to −23.6 mg/dL] or about −14%; 95% CI, −12% to −17%). Comparison of people with ε2/ε2 vs those with ε4/ε4 (ie, the 2 most extreme but rarest, genotypes) yielded differences in total cholesterol of −0.81 mmol/L (95% CI, −0.61 to −1.02 mmol/L [−31.3, mg/dL; 95% CI, −23.6 to −39.4 mg/dL] or about −14%, 95% CI, −11% to −18%) and in LDL-C of −1.14 mmol/L (−0.87 to −1.40 mmol/L [−44.0 mg/dL; 95% CI, −33.6 to −54.1 mg/dL] or about −31%; 95% CI, −23% to −38%). Associations of apoE genotypes with HDL-C levels were weakly inverse, with a difference of 0.07 mmol/L (95% CI, 0.06 to 0.09 mmol/L [2.7 mg/dL (95% CI, 2.3 to 3.5 mg/dL]) or about 5%; 95% CI, 4% to 7%) in people with ε2/ε3 vs those with ε3/ε4, and a difference of 0.07 mmol/L (95% CI, 0.02 to 0.11 mmol/L [2.7 mg/dL; 95% CI, 0.8 to 4.3 mg/dL], or about 5%; 95% CI, 2% to 8%) in people with ε2/ε2 vs those with ε4/ε4. The association of apoE genotypes with triglycerides was nonlinear, with the highest levels in people with the comparatively rare ε2/ε2 genotype and the lowest levels in the common ε3/ε3 reference group, corresponding to a difference between these groups of 0.34 mmol/L (95% CI, 0.18 to 0.50 mmol/L [30.1 mg/dL; 95% CI, 15.9 to 44.2 mg/dL] or about 21%; 95% CI, 11% to 32%). Associations of apoE genotypes with lipid fractions generally did not vary importantly when studies were grouped by potentially relevant characteristics (details available from the authors upon request).

### ApoE Genotypes and Coronary Risk

One hundred twenty-one studies (96 previously published [57 in MEDLINE journals, 39 in non-MEDLINE journals], 7 expanded and/or updated, and 18 previously unreported) were identified with data on apoE genotypes and coronary outcomes from a total of 37 850 cases and 82 727 controls (details of study characteristics available from the authors upon request). The principal prespecified analyses are based on data from 17 of these studies that each involved at least 500 cases (Table 1), collectively com-

### Table 1. Summary of Data Available in the Current Analyses on Apolipoprotein E Genotypes and Circulating Lipid Levels or Coronary Risk

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>86 067b</td>
</tr>
<tr>
<td>Studies involving ≥1000 noncases</td>
<td>22</td>
<td>71 150c</td>
</tr>
<tr>
<td>Studies involving &lt;1000 noncases</td>
<td>60</td>
<td>13 917</td>
</tr>
<tr>
<td>Coronary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>37 850/82 727d</td>
</tr>
<tr>
<td>Studies involving ≥500 CHD cases</td>
<td>17</td>
<td>21 331/47 467e</td>
</tr>
<tr>
<td>Studies involving &lt;500 CHD cases</td>
<td>104</td>
<td>16 519/35 260</td>
</tr>
</tbody>
</table>

Abbreviation: CHD, coronary heart disease.


bData on 50 907 of these participants were derived from previously unreported studies.

cTabular data from the studies’ principal investigators were provided for 42 studies (involving 24 626 cases and 55 305 controls).

dData on 8 028 of these cases and 20 834 of these controls were derived from previously unreported studies.

prising about 21,331 cases and 47,467 controls (or about 56% of the total available data). Of the 17 larger studies (10 of which were published in journals indexed by MEDLINE® and 7 previously unreported**), 13 involved European populations,†† 3 were based in North America,34,35,63 and 1 was from Australia.131 Six of these were prospective cohort studies,23,34,35,63,64,92 and 11 were case-control studies‡‡; there were no case-cohort studies. Studies involved patients either with confirmed myocardial infarction (generally defined by World Health Organization criteria) or with coronary stenosis (defined as 50% or 70% stenosis of ≥1 major coronary arteries). All but 5 studies35,44,48,51,148 used polymerase chain reaction–based genotyping methods, and none reported genotyping call rates.

Figure 3 shows that the combined ORs for coronary disease in the studies with at least 500 cases were 0.80 (95% CI, 0.70-0.90) in e2 carriers and 1.06 (95% CI, 0.99-1.13) in e4 carriers. With the e3/e3 genotype as the reference group, Figure 4 shows that the ORs increased progressively between e2/e2 (0.83; 95% CI, 0.55-1.25), e2/e3 (0.82; 95% CI, 0.72-0.92), e2/e4 (0.93; 95% CI, 0.81-1.07), e3/e4 (1.05; 95% CI, 0.99-1.12), and e4/e4 genotypes (1.22; 95% CI, 1.08-1.38). Recorded features of the populations studied did not explain much of the moderately high degree of heterogeneity among the studies noted in Figure 3. When based on the studies with at least 500 cases, the risk associations were broadly similar in men and women, people older or younger than 55 years, and in studies grouped by various characteristics (P value for interaction >.05 for each characteristic recorded, except data source [P=.003], Figure 5).

Findings in the case-control studies were broadly similar to those in cohort studies, arguing against major sur-

Figure 2. Differences in Lipids by Apolipoprotein E Genotypes in Studies With 1000 or More Healthy Individuals, Using People With the e3/e3 Genotype as the Reference Group

<table>
<thead>
<tr>
<th>Total Cholesterol</th>
<th>High-Density Lipoprotein Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted Mean Difference (95% CI, mmol/L)</td>
<td>Weighted Mean Difference (95% CI, mmol/L)</td>
</tr>
<tr>
<td>e2/e2 (Reference)</td>
<td>e2/e2 (Reference)</td>
</tr>
<tr>
<td>e2/e3</td>
<td>e2/e3</td>
</tr>
<tr>
<td>e2/e4</td>
<td>e2/e4</td>
</tr>
<tr>
<td>e3/e4</td>
<td>e3/e4</td>
</tr>
<tr>
<td>e4/e4 (Reference)</td>
<td>e4/e4 (Reference)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low-Density Lipoprotein Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted Mean Difference (95% CI, mmol/L)</td>
<td>Weighted Mean Difference (95% CI, mmol/L)</td>
</tr>
<tr>
<td>e2/e2 (Reference)</td>
<td>e2/e2 (Reference)</td>
</tr>
<tr>
<td>e2/e3</td>
<td>e2/e3</td>
</tr>
<tr>
<td>e2/e4</td>
<td>e2/e4</td>
</tr>
<tr>
<td>e3/e4</td>
<td>e3/e4</td>
</tr>
<tr>
<td>e4/e4 (Reference)</td>
<td>e4/e4 (Reference)</td>
</tr>
</tbody>
</table>

Sizes of data markers are proportional to the inverse of the variance of the weighted mean difference (e3/e3 is represented by a square with an arbitrary fixed size) and the vertical lines represent 95% confidence intervals (CIs). To convert total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol from mmol/L to mg/dL, divide values by 0.0259; triglycerides from mmol/L to mg/dL, divide values by 0.0113.
similar pattern of findings when cut-off levels for numbers of cases in studies were varied. Funnel plots show a clear excess of extreme findings in studies with fewer than 500 coronary outcomes (Egger test, \( P < .001 \)), and trim-and-fill analyses imply that 15 studies of \( e^2 \) and 35 studies of \( e^4 \) are required to make the funnel plots symmetrical. A cumulative meta-analysis, subdivided by study sample size, showed that this divergence in ORs by study size was evident by about the year 2000 (details available from the authors upon request).

**Figure 3.** Odds Ratios for Coronary Disease With Apolipoprotein E Genotype in 17 Studies With at Least 500 Cases

<table>
<thead>
<tr>
<th>Source</th>
<th>( e^2 ) Carriers</th>
<th>( e^2 ) Controls</th>
<th>( e^4 ) Carriers</th>
<th>( e^4 ) Controls</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katoaka et al,35 1996a</td>
<td>771</td>
<td>13 (1.7)</td>
<td>556 (72.4)</td>
<td>3370</td>
<td>102 (3.0)</td>
</tr>
<tr>
<td>Kolovou et al,36-38 2003</td>
<td>502</td>
<td>38 (7.6)</td>
<td>374 (74.5)</td>
<td>145</td>
<td>27 (18.6)</td>
</tr>
<tr>
<td>Marques-Vidal et al,37 2003</td>
<td>560</td>
<td>55 (9.4)</td>
<td>378 (67.5)</td>
<td>361</td>
<td>40 (11.4)</td>
</tr>
<tr>
<td>Grell et al,39 2000a</td>
<td>982</td>
<td>86 (8.7)</td>
<td>693 (70.2)</td>
<td>215</td>
<td>34 (9.0)</td>
</tr>
<tr>
<td>Matomasa et al,40 2002</td>
<td>710</td>
<td>47 (6.6)</td>
<td>416 (59.0)</td>
<td>639</td>
<td>52 (7.8)</td>
</tr>
<tr>
<td>Lenzen et al,41 1996</td>
<td>570</td>
<td>52 (9.1)</td>
<td>360 (60.3)</td>
<td>624</td>
<td>57 (12.0)</td>
</tr>
<tr>
<td>Ye et al,42 2003</td>
<td>1170</td>
<td>144 (12.3)</td>
<td>718 (61.4)</td>
<td>331</td>
<td>46 (13.9)</td>
</tr>
<tr>
<td>Utermann et al,43 1984</td>
<td>523</td>
<td>75 (14.3)</td>
<td>333 (63.7)</td>
<td>1141</td>
<td>244 (21.4)</td>
</tr>
<tr>
<td>Kardan et al,44 2000</td>
<td>661</td>
<td>68 (10.3)</td>
<td>456 (69.0)</td>
<td>229</td>
<td>199 (8.4)</td>
</tr>
<tr>
<td>Bennet et al,45 2006a</td>
<td>1172</td>
<td>95 (8.1)</td>
<td>707 (60.3)</td>
<td>1521</td>
<td>186 (12.2)</td>
</tr>
<tr>
<td>Luc et al,46 1994</td>
<td>1290</td>
<td>133 (10.3)</td>
<td>754 (58.5)</td>
<td>1406</td>
<td>178 (12.7)</td>
</tr>
<tr>
<td>Frick-Schmidt et al,47 2000</td>
<td>940</td>
<td>93 (9.9)</td>
<td>528 (56.2)</td>
<td>9241</td>
<td>1216 (13.2)</td>
</tr>
<tr>
<td>Orth et al,48 1999</td>
<td>239</td>
<td>300 (12.8)</td>
<td>1490 (63.7)</td>
<td>1187</td>
<td>125 (10.5)</td>
</tr>
<tr>
<td>März et al,49 2004</td>
<td>2230</td>
<td>244 (10.9)</td>
<td>1428 (64.0)</td>
<td>1033</td>
<td>165 (16.0)</td>
</tr>
<tr>
<td>Sturgeon et al,50 2005</td>
<td>1037</td>
<td>137 (13.2)</td>
<td>558 (53.8)</td>
<td>1294</td>
<td>184 (14.0)</td>
</tr>
<tr>
<td>Slocot et al,51 2004</td>
<td>1385</td>
<td>176 (12.2)</td>
<td>722 (59.4)</td>
<td>822</td>
<td>696 (13.8)</td>
</tr>
<tr>
<td>Keavney et al,52 2004</td>
<td>4484</td>
<td>474 (10.6)</td>
<td>2566 (57.2)</td>
<td>3757</td>
<td>730 (12.7)</td>
</tr>
<tr>
<td>Total</td>
<td>21331</td>
<td>47467</td>
<td></td>
<td></td>
<td>0.80 (0.70-0.90)</td>
</tr>
</tbody>
</table>

Assessment of heterogeneity: \( e^2 \) carriers vs \( e^3/e^3 \): I\(^2\)=72% (95% confidence interval [CI], 54%-83%; \( P < .001 \)), \( e^4 \) carriers vs \( e^3/e^3 \): I\(^2\)=44% (95% CI, 2%-68%; \( P = .03 \)). Size of data markers indicates the weight of each study in the analysis.

\(^{a}\)Although these studies did not previously report on apolipoprotein E genotypes and coronary risk, principal investigators have provided the references shown to describe the methods used in their study.
COMMENT

Because previous reviews of apoE genotypes have been dominated by many smaller reports that are liable to biases, we conducted a more detailed analysis focusing on larger studies, both published and previously unreported, which fulfilled quality criteria in relation to assessment of apoE status, lipid levels, and coronary outcomes. We have demonstrated approximately linear relationships of apoE genotypes (when ordered ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4) with LDL-C levels and with coronary risk. The LDL-C levels were approximately 30% lower in people ε2/ε2 than with ε4/ε4 genotypes, a difference comparable with that produced by “statin” medication. The relationship of apoE genotypes with HDL-C was shallow and nonlinear and largely confined to the ε2/ε2 genotype, with the latter about 2 times weaker than previously reported (TABLE 3). We found that, in comparison with the commonest ε3/ε3 genotype, ε2 carriers had a 20% reduced coronary risk, in contrast with previous estimates that ε2 carriage is neutral for coronary risk. We noted strong evidence of selective publication in previous estimates based on smaller studies. This is a serious concern given that apoE genotypes and coronary risk had hitherto been considered among the few quantitatively secure associations in cardiovascular disease genetics. Our findings may have several implications, as described below.

The precise mechanisms by which ε2 carriage (and, hence, apo E2 isoforms) might confer advantageous lipid profiles (or other possible cardioprotective effects) are only partially understood. They may relate to comparatively more binding efficiency of apo E2 isoforms with}

![Figure 4. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes Using Individuals With the ε3/ε3 Genotype as the Reference Group, Based on Data From 21 331 Cases and 47 467 Controls in Studies With 500 or More Cases](image)

![Figure 5. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes in Studies With 500 or More Cases](image)

**TABLE 3** Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes in Studies With 500 or More Cases

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>18 152</td>
<td>28 131</td>
</tr>
<tr>
<td>North America</td>
<td>3179</td>
<td>19 336</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>15 367</td>
<td>14 184</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>5964</td>
<td>33 283</td>
</tr>
<tr>
<td>Publication status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Published</td>
<td>13 303</td>
<td>25 505</td>
</tr>
<tr>
<td>Unpublished</td>
<td>8028</td>
<td>21 962</td>
</tr>
<tr>
<td>Data source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tabular data from PI</td>
<td>19 528</td>
<td>45 063</td>
</tr>
<tr>
<td>Data from publication</td>
<td>1 803</td>
<td>2 404</td>
</tr>
<tr>
<td>Genotyping method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>15 838</td>
<td>39 739</td>
</tr>
<tr>
<td>Phenotype</td>
<td>5493</td>
<td>7728</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14 228</td>
<td>23 580</td>
</tr>
<tr>
<td>Women</td>
<td>5870</td>
<td>22 028</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>8906</td>
<td>20 183</td>
</tr>
<tr>
<td>≥55</td>
<td>9837</td>
<td>25 184</td>
</tr>
<tr>
<td>CHD end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI or fatal CHD</td>
<td>13 489</td>
<td>44 132</td>
</tr>
<tr>
<td>Stenosis</td>
<td>7702</td>
<td>7421</td>
</tr>
<tr>
<td>Overall</td>
<td>21 331</td>
<td>47 467</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI confidence interval; MI, myocardial infarction; PCR, polymerase chain reaction; phenotype, use of isoelectric methods to classify apolipoprotein E genotype; and PI, principal investigator of study. Exploration of potential sources of heterogeneity yielded P = .05 for location, publication status, and genotyping method, P = .03 for study design, and P = .003 for data source in ε2 carriers. All corresponding P values were > .05 in ε4 carriers. Size of the data markers is proportional to the inverse of the variance of the odds ratios.

aTotal number for exposed and reference groups.

bIncludes 1 Australian study.

cRefers to status of the source study at the time of current analysis.

©2007 American Medical Association. All rights reserved.
heparin (which could enhance remnant lipoprotein metabolism through heparan sulfate proteoglycans receptors on the liver) and with small, phospholipid-enriched HDL (which could enhance reverse cholesterol transport).168,169 Although apo E2 isoforms bind to LDL receptors much more weakly than do apo E3 or apo E4 isoforms, most ε2 carriers have, as demonstrated by the current data, advantageous lipid profiles and reduced coronary risk, perhaps due to compensatory up-regulation of LDL receptors. (By contrast, about 5% of ε2/ε2 homozygotes develop type III hyperlipoproteinemia, a disorder characterized by increased levels of cholesterol and triglycerides and premature cardiovascular disease.170) The differing effects of different apoE genotypes on coronary risk might also be explained by influences on additional lipid-related phenotypes (eg, on levels of apoE,171 apolipoproteins A-I or apolipoprotein B,172,173 or very low-density lipoprotein174) and/or on markers of inflammation,173,175 immunity,176 or oxidative status.177 Our findings should stimulate further investigation into possible mechanisms.

Given that the prevalence of the ε2 allele is only about 7% in Western populations, even if the 20% lower coronary risk associated with it were to be entirely causal, it would still explain only a few percent of coronary disease cases in Western populations. Although the magnitude of this relative risk is insufficiently strong to justify population-wide screening for apoE genotypes,1 it has been proposed that the effects of apoE genotypes may be particularly strong in certain subgroups, such as in women.3 The current data, however, do not support the existence of such interactions in relation to sex and several other characteristics. Individual participant data would, however, need to be accessed any interactions with other potentially relevant characteristics not recorded in the present study (such as

![Figure 6. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes in Studies With Fewer Than 500 Cases](image)
obesity, diet, medication use, smoking, and glycemic status. More detailed work is needed to help understand reasons for the comparatively modest amount of heterogeneity observed among the larger studies of apoE and coronary disease, such as factors related to assessment of apoE status, coronary outcomes, and study populations.

Our approach to identify previously unreported data yielded information on an extra 8028 cases of coronary disease from 7 studies with at least 500 cases and on an extra 50 907 participants from 13 studies of lipid outcomes with at least 1000 healthy participants. This experience reinforces the rationale for registry-based initiatives such as the Human Genome Epidemiology Network (HuGENet). Our cumulative meta-analysis showed that, in retrospect, the analysis showed that, in retrospect, the current study merit consideration. Our inference that individual data, we could not control

in our estimates, any effect should be minor compared with that in previous estimates because of the comprehensive nature of the current review and its focus on larger studies. Our inference that the large discrepancy between ORs in smaller and larger studies was mainly due to selective publication is based on evidence from statistical tests (showing, for example, an excess of extreme findings in the smaller studies of ε4) and on lack of any other plausible explanations for the observed differences (eg, genotyping procedures used and departure from Hardy-Weinberg equilibrium did not differ much between smaller and larger studies, nor among published and unreported studies; unfortunately, studies were not able to provide genotyping call rates). Because we did not have access to individual data, we could not control

<p>| Table 2. Odds Ratios for Coronary Disease According to Different Cut-off Levels of Study Size Used in Meta-analyses |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 2 Carriers vs 3/3 | 4 Carriers vs 3/3 |</p>
<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Odds Ratios for Coronary Disease</th>
<th>No. of Cases</th>
<th>Odds Ratios for Coronary Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1000</td>
<td>0.85 (0.74-0.97)</td>
<td>1.05 (0.97-1.13)</td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>0.80 (0.70-0.90)</td>
<td>1.06 (0.99-1.13)</td>
<td></td>
</tr>
<tr>
<td>≥250</td>
<td>0.85 (0.75-0.95)</td>
<td>1.10 (1.02-1.18)</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>0.94 (0.86-1.03)</td>
<td>1.35 (1.25-1.46)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CHD, coronary heart disease.

Prespecified principal analysis.

| Table 3. Comparison of Findings of the Current Analyses With Those Reported in the Most Recent Previous Meta-analyses of Apolipoprotein E Genotypes |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| ϵ2/3 vs ϵ3/3 | ϵ3/4 vs ϵ3/3 |
| No. of Participants | Weighted Mean Difference in Lipid Levels (95% CI) | No. of Participants | Weighted Mean Difference in Lipid Levels (95% CI) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Cholesterol, mmol/L | −0.34 (−0.41 to 0.27) | 10 799 | −0.30 (−0.36 to 0.25) | 53 309 |
| LDL | NA | NA | NA | NA |
| HDL | −0.02 (−0.05 to 0.01) | 69 48 | 0.04 (0.02 to 0.08) | 50 295 |
| Triglycerides, mmol/L | 0.15 (0.07 to 0.22) | 9 190 | 0.08 (0.05 to 0.11) | 5 021 |

Abbreviations: CI, confidence interval; NA, not available.

S1 conversions: To convert total cholesterol, HDL, and LDL from mmol/L to mg/dL, divide by 0.0259; triglycerides from mmol/L to mg/dL, divide by 0.0113.

©2007 American Medical Association. All rights reserved.
CONCLUSIONS
There are approximately linear relationships of apoE genotypes with both LDL-C levels and coronary risk. Compared with ε3/ε3 individuals, ε2 carriers have a 20% reduced risk of coronary disease whereas ε4 carriers have a slightly increased risk.

Author Contributions: Drs Danesh and Di Angelantonio had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bennet, Di Angelantonio, Wensley, Dahlin, Collins, Wiman, de Faire, Danesh.

Acquisition of data: Bennet, Di Angelantonio, Ye, Wensley, Dahlín, Keavney, Collins, Wiman, de Faire, Danesh.

Analysis and interpretation of data: Bennet, Di Angelantonio, Wensley, Keavney, Collins, Wiman, de Faire, Danesh.

Drafting of the manuscript: Bennet, Di Angelantonio, Danesh.

Critical revision of the manuscript for important intellectual content: Bennet, Di Angelantonio, Ye, Wensley, Dahlín, Aliborn, Keavney, Collins, Wiman, de Faire, Danesh.

Statistical analysis: Bennet, Di Angelantonio, Wensley.

Obtained funding: de Faire, Danesh.

Administrative, technical, or material support: Bennet, Di Angelantonio, Ye, Wensley, Dahlín, Aliborn, Keavney, Collins, Wiman, de Faire, Danesh.

Study supervision: Bennet, Wiman, de Faire, Danesh.

Financial Disclosures: None reported.

Funding/Support: This work was supported by the British Heart Foundation, an unrestricted educational grant from GlaxoSmithKline, the Raymond and Beverly Sackler Foundation in Israel, the Royal Netherlands Academy of Sciences, Swedish Research Council (grant 05193), the Swedish Heart and Lung Foundation, an unrestricted educational grant of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. Am J Epidemiol. 2006;167(4):609-614.


APOE GENOTYPES, CIRCULATING LIPID LEVELS, AND CORONARY RISK


Apolipoprotein E gene polymorphism and coronary artery disease: the Southampton Ath-


98. Zhao M, Zhao CS, Bai XJ, Zhao YY, Zhang M, Chen CX. Role of lipid levels and gene polymorphisms of apolipoprotein E in siblings with family history of pre-


105. Corbo RM, Vilardo T, Ruggeri M, Gemma AT, Scacchi R. Apolipoprotein E genotype and plasma lev-


107. Dizinni M, Meyer BF, Hussian SS, Basco AC, Afrane A. Hales Z. Relevance of apolipoprotein E polymor-


108. Eichner JE, Kuller LH, Orchard TJ, et al. Relation of apolipoprotein E phenotype to myocardial in-

109. Eto M, Watanabe K, Makino I. Increased fre-


111. Garcés C, Maicas C, Grande R, et al. epsilon 3/4 polymorphism as genotype risk of myocardial in-


bolic factors clustering, lipoprotein cholesterol, apo-

lipoprotein B, lipoprotein (a) and apolipoprotein E phe-


113. Gerdes LU, Gerdes C, Kervinen K, et al. The apo-

lipoprotein epsilon 4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction: a substudy of the Scandi-


115. Guan SW, Liw W, Zhang YH, Qi BL, Ke QM. Rela-

116. Hergenc F, Taka T, Kerek M, Cikagolu B. Apo-

lipoprotein E genotype in Turkish myocardial infarct-


118. Lenzen HJ, Assmann G, Buchwalsky R, Schulte H. Association of apolipoprotein E polymorphism, low-

119. Humphries SE, Talmud PJ, Hawe E, Bolla M, Day IN, Miller GJ. Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospec-

120. Kusui T, Nieminen MS, Ehnholm C, et al. Apo-


122. Lehtinen S, Lehtimaki T, Sisto T, et al. Apolipo-

protein E polymorphism, serum lipids, myocardial infarction, and severity of angiographically verified coro-


124. Li W, Guan SM, Oi BL, Ke QM, Zhang HP. The clinical significance of the detection of apolipopro-


126. Liao MZ, Jan BF, Xu CH, Xu CH, Hu FG, Huang XR. The study of relationship between apolipo-


127. Liu HX, Cao LC, Fu GL, Du Pe, Fu SB. Corre-

128. Liu S, Ma J, Ridker PM, Breslow JL, Stampfer MJ. A prospective study of the association between


