

Association of Apolipoprotein E Genotypes With Lipid Levels and Coronary Risk

Anna M. Bennet, PhD

Emanuele Di Angelantonio, MD, MSc

Zheng Ye, PhD

Frances Wensley, MSc

Anette Dahlin, BSc

Anders Ahlbom, PhD

Bernard Keavney, MD, FRCP

Rory Collins, FRCP, FMedSci

Björn Wiman, MD, PhD

Ulf de Faire, MD, PhD

John Danesh, MSc, DPhil, FRCP

APOLIPOPROTEIN 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.¹⁻³ Although individuals carrying the $\epsilon 4$ allele have higher and those carrying the $\epsilon 2$ allele have lower total cholesterol levels than people with the commonest $\epsilon 3/\epsilon 3$ genotype, studies of lipid markers have typically involved too few participants to characterize relationships with different lipid subfractions across the 6 common genotypes.⁴ A previous review of 48 published studies among a total of 15 492 disease cases reported that, compared with $\epsilon 3/\epsilon 3$ individuals, $\epsilon 4$ carriers have a much greater risk of coronary disease and that $\epsilon 2$ carriers have a neutral risk.⁵ But about half of those data were from studies with fewer than 500 coronary cases, which may be more liable to publication biases.⁶⁻⁹

Our reassessment of associations of apoE genotypes with circulating lipid levels and with coronary risk uses the following approach to maximize power and

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 $\epsilon 2/\epsilon 2$ 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 $\epsilon 4/\epsilon 4$ genotype. There were approximately linear relationships of apoE genotypes (when ordered $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) 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 $\epsilon 2/\epsilon 2$ genotype. Compared with $\epsilon 3/\epsilon 3$, the odds ratio for coronary disease was 0.80 (95% CI, 0.70-0.90) in $\epsilon 2$ carriers and was 1.06 (95% CI, 0.99-1.13) in $\epsilon 4$ carriers.

Conclusions There are approximately linear relationships of apoE genotypes with both LDL-C levels and coronary risk. Compared with individuals with the $\epsilon 3/\epsilon 3$ genotype, $\epsilon 2$ carriers have a 20% lower risk of coronary heart disease and $\epsilon 4$ carriers have a slightly higher risk.

JAMA. 2007;298(11):1300-1311

www.jama.com

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

Author Affiliations: Department of Public Health and Primary Care, University of Cambridge, Cambridge, England (Drs Bennet, Di Angelantonio, Ye, and Danesh and Ms Wensley); Division of Clinical Chemistry, Department of Molecular Medicine and Surgery (Ms Dahlin and Dr Wiman), Department of Cardiology (Dr de Faire) Karolinska University Hospital, and Divisions of Epidemiology (Dr Ahlbom) and Cardiovascular Epidemiology (Dr de Faire), Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Institute of Human Genetics, Newcastle University, Central Parkway, Newcastle, England (Dr Keavney); and Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, England (Dr Collins).
Corresponding Author: John Danesh, MSc, DPhil, FRCP, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, England CB1 8RN (john.danesh@phpc.cam.ac.uk).

in a registry of coronary genetic studies to seek unreported data; and (3) we prespecified 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 Cardiovascular Disease [MONICA] criteria¹⁰) or angiographic coronary stenosis (generally defined as at least 50% stenosis of ≥ 1 major coronary arteries). For lipid fractions, data were used from only apparently healthy controls (ie, people without known coronary or other diseases or clinical lipid abnormalities) who had information on all relevant genotypes. Electronic searches, not limited to the English language, were performed using MEDLINE, EMBASE, BIOSIS, Science Citation Index, and the Chinese National Knowledge Infrastructure Database by scanning the reference lists of articles identified for all relevant studies and review articles (including meta-analyses), hand searching of relevant journals, and by correspondence with authors of included studies. The computer-based searches combined search terms related to the relevant gene (eg, *Apolipoprotein E*, *ApoE* genotypes), lipid phenotypes (eg, *total cholesterol*, *LDL*, *HDL*, and *triglycerides*), and coronary disease (eg, *myocardial infarction*, *atherosclerosis*, *coronary heart disease*, and *coronary stenosis*) without language restriction (FIGURE 1).

The following data were extracted independently by 2 investigators, using a prepiloted data extraction form: genotype frequencies by categorical disease outcome; means and standard deviations 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 methods; 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 multiple publications. We supplemented published data by a tabular data request to authors of published reports and to investigators of 62 potentially relevant unreported studies listed in published meta-analyses¹¹⁻¹⁴ who had published on variants other than apoE.

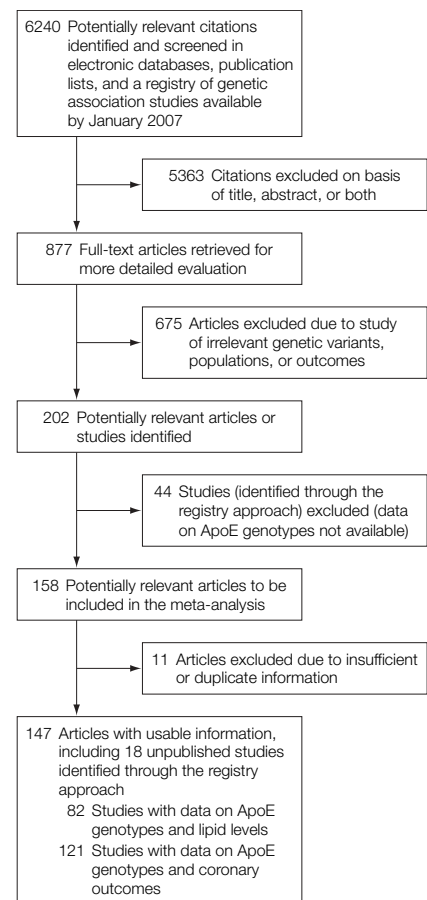
Statistical Analysis

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). Individuals with the $\epsilon 3/\epsilon 3$ genotype were defined as the reference group. Separate analyses were conducted for each genotype (in the following prespecified order: $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$, with the position of $\epsilon 2/\epsilon 4$ genotype inserted after data exploration) and for $\epsilon 2$ and $\epsilon 4$ carrier status (this particular analysis excluded, of course, the $\epsilon 2/\epsilon 4$ genotype).

Summary odds ratios (ORs) for coronary disease and mean plasma levels of total cholesterol, LDL-C, HDL-C, and triglycerides (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 coronary cases separately before combining them into a single coronary disease group for the few studies that included a single control group and nonoverlapping coronary stenosis cases and nonfatal myocardial infarction cases.

Consistency of findings across studies was assessed using the I^2 statistic.¹⁵ Publication bias was assessed using fun-

Figure 1. Study Flow Diagram



nel plots, Egger test¹⁶ and the trim-and-fill¹⁷ method. Heterogeneity was assessed using the Q statistic¹⁸ and by examining prespecified groupings of studies characteristics. All analyses were performed using Stata Statistical Software, Release 9 (StataCorp LP, College Station, Texas).

RESULTS

ApoE Genotypes and Lipid Outcomes

Eighty-two studies¹⁹⁻¹⁰¹ (44 previously published [19 in MEDLINE journals, 25 in non-MEDLINE journals], 6 expanded and/or updated, and 32 previously unreported in relation to lipid markers) were identified with data on apoE genotypes and lipid outcomes from a total of 86 067 disease-free participants (details of study characteristics available from the authors upon re-

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

	No. of Studies	No. of Participants ^a
Lipid outcomes		
Total	82	86 067 ^b
Studies involving ≥1000 noncases	22	72 150 ^c
Studies involving <1000 noncases	60	13 917
		No. of Cases/Controls ^a
Coronary outcomes		
Total	121	37 850/82 727 ^d
Studies involving ≥500 CHD cases	17	21 331/47 467 ^e
Studies involving <500 CHD cases	104	16 519/35 260

Abbreviation: CHD, coronary heart disease.

^aNumber of individuals with data on ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 genotypes.^bTabular data from the studies' principal investigators were provided for 51 studies (involving 79 929 noncases).^cData on 50 907 of these participants were derived from previously unreported studies.^dTabular data from the studies' principal investigators were provided for 42 studies (involving 24 626 cases and 55 305 controls).^eData on 8028 of these cases and 20 834 of these controls were derived from previously unreported studies.

quest). The principal analyses in the current review are based on data from the 22 studies that each involved at least 1000 participants (TABLE 1), collectively comprising about 84% of the total available data (ie, information was available from 72 150 individuals for total cholesterol; 61 463 for LDL-C; 69 142 for HDL-C, and 67 852 for triglycerides). Of these 22 studies (9 of which were previously published* and 13 previously unreported†), 12 involved European populations,‡ 6 were based in North America,^{24,34,35,54,63,87} and 4 in East Asia.^{36,71,77,86} Nine of these studies were based in prospective cohorts^{24,25,34-36,62,63,73,84} (typically recruiting participants from population registers, such as general practitioners lists or electoral rolls), 13 were either cross-sectional surveys or case-control studies§ (with controls sampled from general populations in 4 of the case-control studies^{37,44,48,59} and from blood donors in 1 such study⁵¹). Sixteen of the larger studies|| involved fasted individuals, and 1 did not report fasting status.⁸⁴

All of the studies used enzymatic methods to measure total cholesterol

and triglycerides, and all used precipitation methods to assess HDL-C; LDL-C was directly measured in 4 studies^{44,81,86,87} and calculated in the remainder. All but 6 studies^{35,44,48,51,69,81} 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/ε3 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-

¶References 19-68, 88, 90-94, 96, 100-164.

*References 36, 48, 54, 69, 71, 81, 84, 86, 87.

†References 24, 25, 34, 35, 37, 44, 51, 59, 62, 63, 73, 77, 82.

‡References 25, 37, 44, 48, 51, 59, 62, 69, 73, 81, 82, 84.

§References 37, 44, 48, 51, 54, 59, 69, 71, 77, 81, 82, 86, 87.

||References 24, 35, 36, 44, 48, 54, 59, 63, 69, 71, 73, 77, 81, 82, 86, 87.

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,^{25,34,35,62,63,92} 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 studies^{35,44,48,51,148} 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 $\epsilon 2$ carriers and 1.06 (95% CI, 0.99-1.13) in $\epsilon 4$ carriers. With the $\epsilon 3/\epsilon 3$ genotype as the reference group, FIGURE 4 shows that the ORs increased progressively between $\epsilon 2/\epsilon 2$ (0.83; 95% CI, 0.55-1.25), $\epsilon 2/\epsilon 3$ (0.82; 95% CI, 0.72-0.92;), $\epsilon 2/\epsilon 4$ (0.93; 95% CI, 0.81-1.07), $\epsilon 3/\epsilon 4$ (1.05; 95% CI, 0.99-1.12;), and $\epsilon 4/\epsilon 4$ 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-

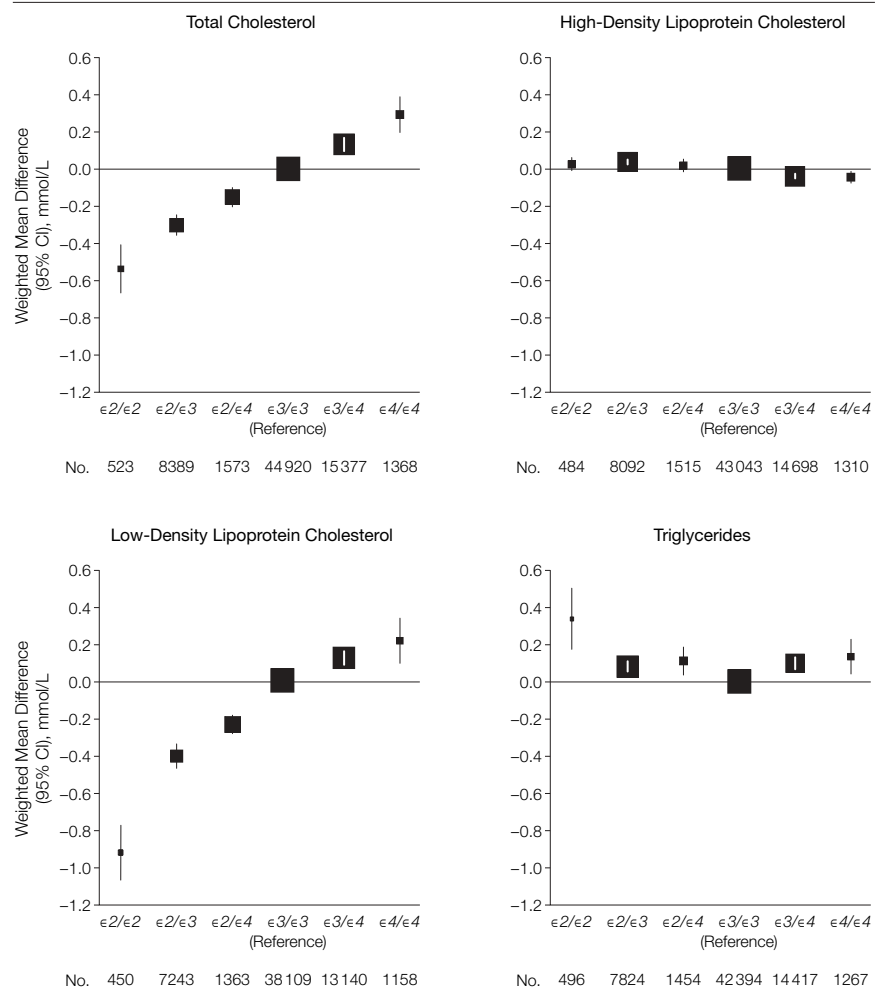
vival bias (Figure 5). By contrast, in the meta-analysis based on studies with fewer than 500 cases, the ORs for coronary disease were 1.00 (95% CI, 0.91-1.11) in $\epsilon 2$ carriers and 1.66 (95% CI, 1.50-1.84) in $\epsilon 4$ carriers. There was a high degree of heterogeneity among findings in the smaller studies, mainly related to differences in geographical location, study design, and type of publication (FIGURE 6). These findings were not materially altered by using fixed effect meta-analysis (which does not incorporate heterogeneity between studies) or exclusion of the few stud-

ies departing from Hardy-Weinberg equilibrium (details available from the authors upon request).

Evidence of Publication Bias

Figure 5 and Figure 6 display different ORs in the prespecified comparison of results for studies with at least 500 cases vs those for smaller studies (combined ORs of 0.80 (95% CI, 0.70-0.90) vs 1.00 (95% CI, 0.91-1.11), respectively, comparing $\epsilon 2$ carriers with $\epsilon 3/\epsilon 3$; or 1.06 (95% CI, 0.99-1.13) vs 1.66 (95% CI, 1.50-1.84), respectively, comparing $\epsilon 4$ carriers with $\epsilon 3/\epsilon 3$). TABLE 2 shows a

Figure 2. Differences in Lipid Levels by Apolipoprotein E Genotypes in Studies With 1000 or More Healthy Individuals, Using People With the $\epsilon 3/\epsilon 3$ Genotype as the Reference Group



Sizes of data markers are proportional to the inverse of the variance of the weighted mean difference ($\epsilon 3/\epsilon 3$ 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.

[#]References 25, 37, 39, 40, 44, 47, 48, 51, 62, 131, 148.

^{**}References 27, 34, 35, 45, 59, 63, 92, 111.

^{††}References 25, 27, 37, 39, 40, 44, 45, 47, 48, 51, 59, 62, 92, 148.

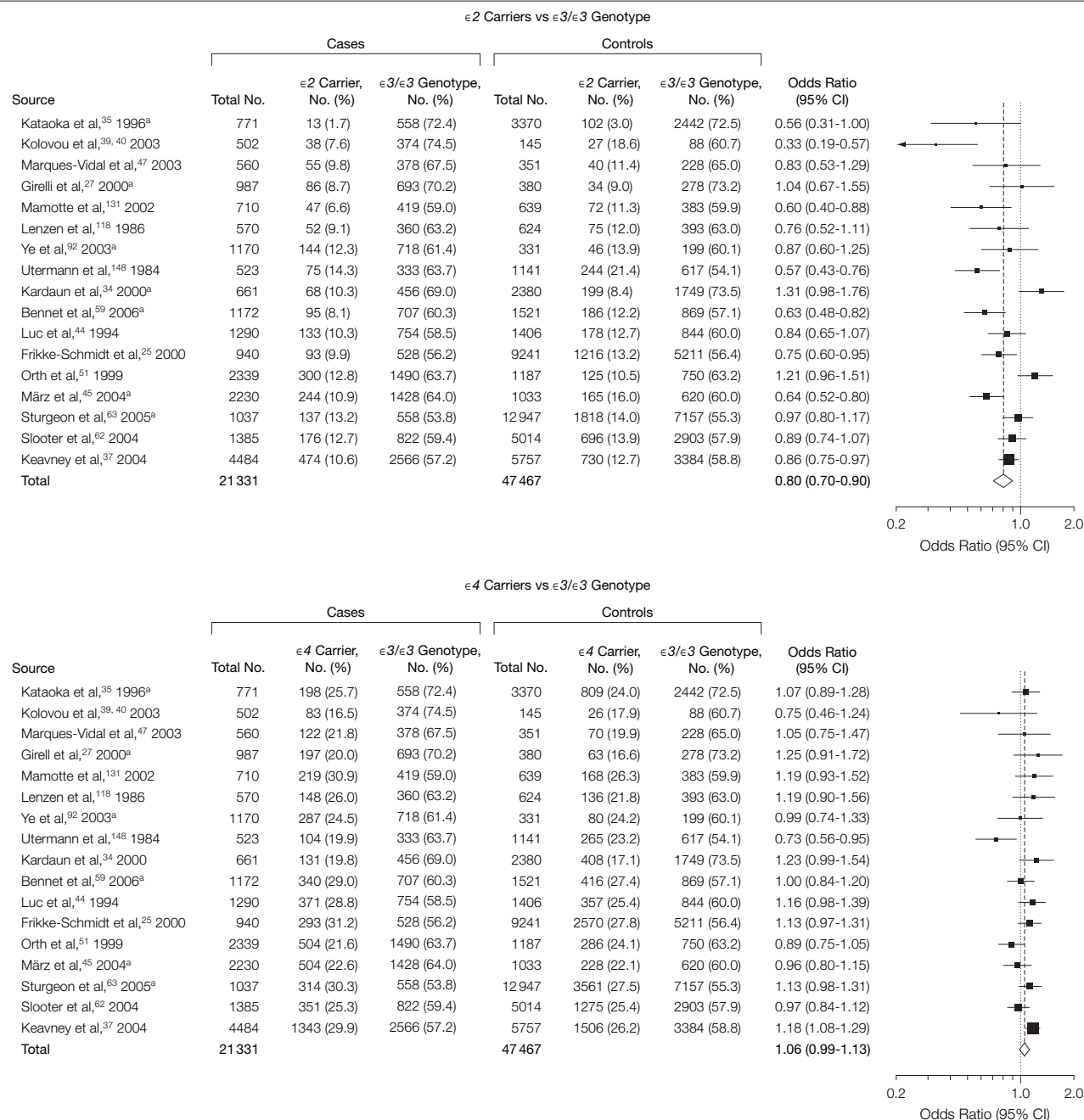
^{‡‡}References 27, 37, 39, 40, 44, 45, 47, 48, 51, 59, 131, 148.

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 out-

comes (Egger test, $P < .001$), and trim-and-fill analyses imply that 15 studies of $\epsilon 2$ and 35 studies of $\epsilon 4$ are required to make the funnel plots symmetrical. A cumulative meta-analysis, subdi-

vided 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



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

^aAlthough 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.

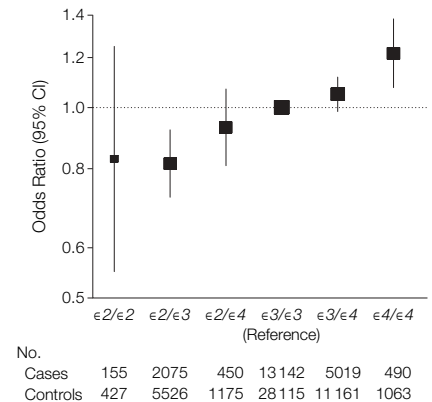
COMMENT

Because previous reviews of apoE genotypes have been dominated by many smaller reports that are liable to biases,^{4,5,165} 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 $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) with LDL-C levels and with coronary risk. The LDL-C levels were approximately 30% lower in people $\epsilon 2/\epsilon 2$ than with $\epsilon 4/\epsilon 4$ genotypes, a difference comparable with that produced by "statin" medication.¹⁶⁶ The relationship of apoE genotypes with HDL-C was shallow and inverse and that with triglycerides was nonlinear and largely confined to the $\epsilon 2/\epsilon 2$ genotype, with the latter about 2

times weaker than previously reported⁴ (TABLE 3). We found that, in comparison with the commonest $\epsilon 3/\epsilon 3$ genotype, $\epsilon 2$ carriers had a 20% reduced coronary risk, in contrast with previous estimates that $\epsilon 2$ carriage is neutral for coronary risk.⁵ 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.

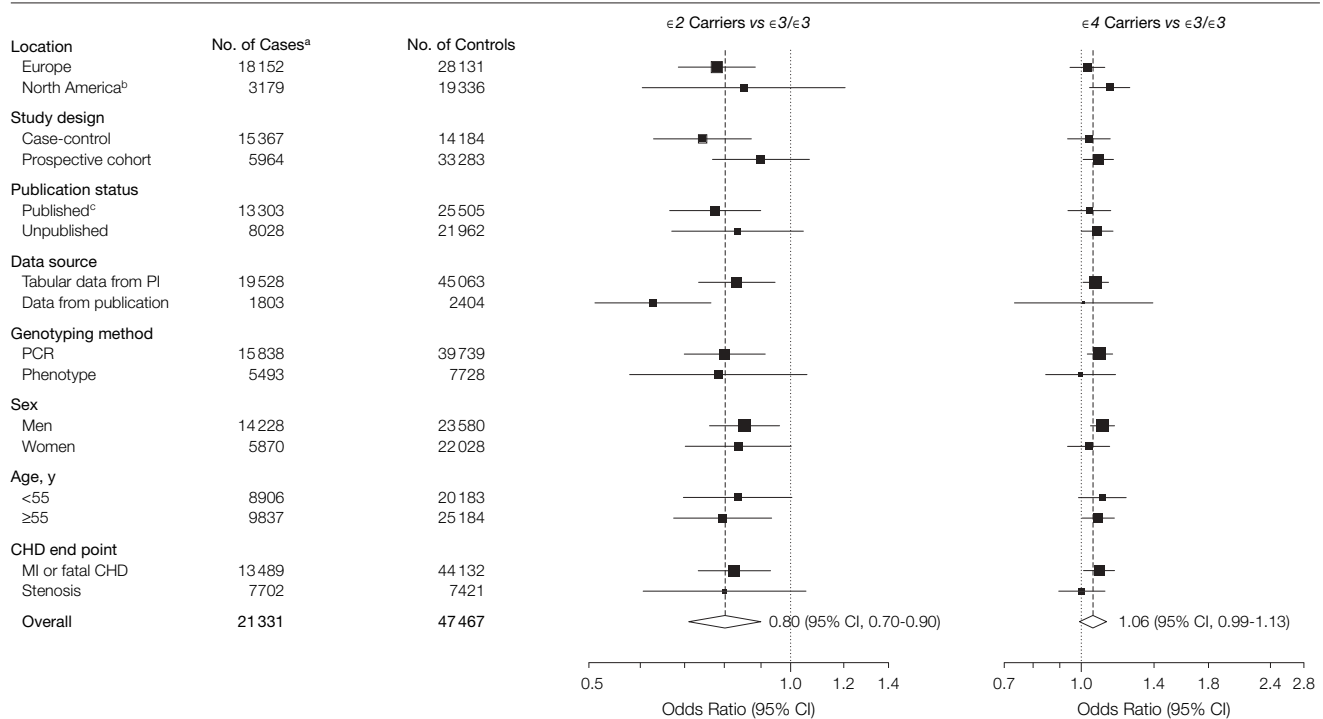
The precise mechanisms by which $\epsilon 2$ carriage (and, hence, apo E2 isoforms) might confer advantageous lipid profiles (or other possible cardioprotective effects) are only partially understood.¹⁶⁷ They may relate to comparatively more efficient binding of apo E2 isoforms with

Figure 4. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes Using Individuals With the $\epsilon 3/\epsilon 3$ Genotype as the Reference Group, Based on Data From 21 331 Cases and 47 467 Controls in Studies With 500 or More Cases



Size of data markers is proportional to the inverse of the variance of the odds ratios ($\epsilon 3/\epsilon 3$ is represented by a square with arbitrarily fixed size) and vertical lines represent 95% confidence intervals (CIs).

Figure 5. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes in Studies With 500 or More Cases



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 $\epsilon 2$ carriers. All corresponding P values were $> .05$ in $\epsilon 4$ 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.

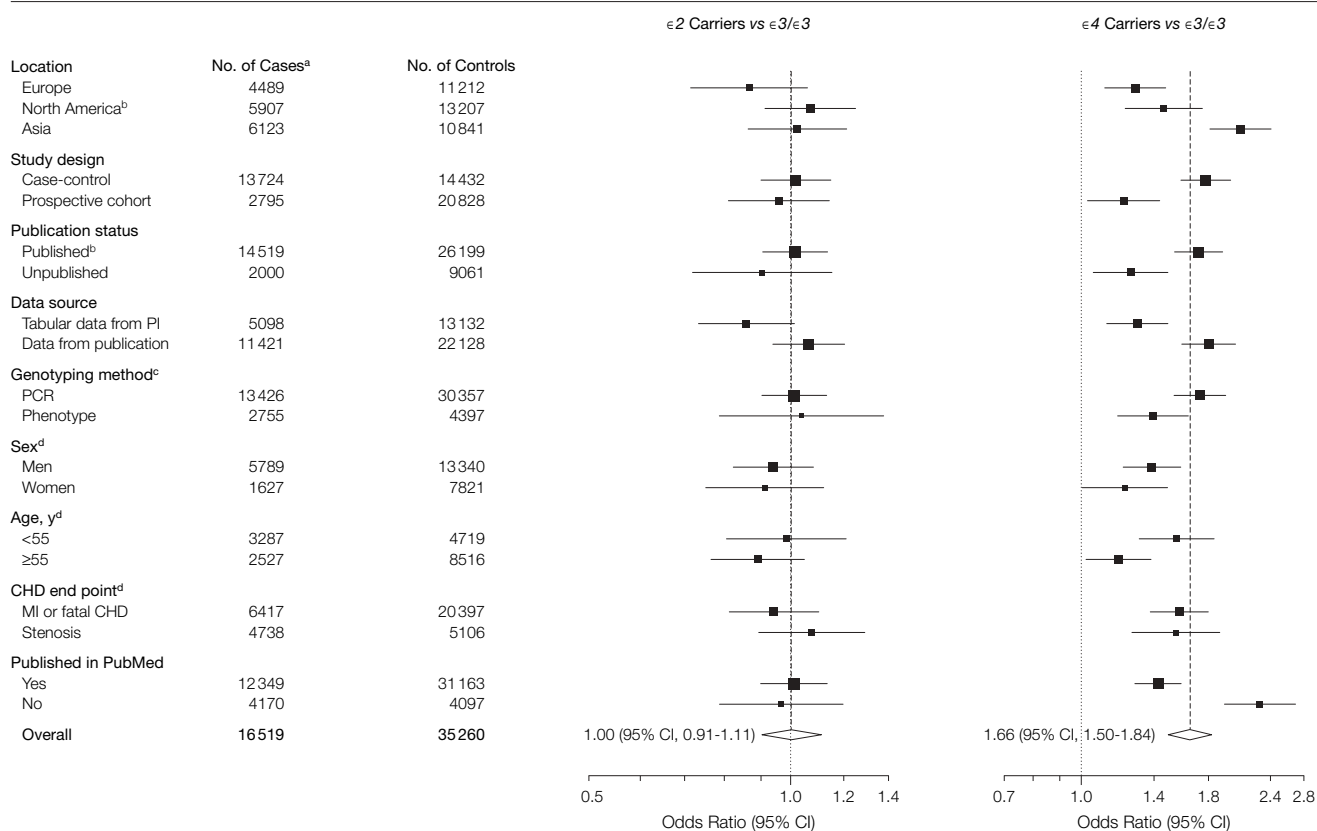
heparin (which could enhance remnant lipoprotein metabolism through heparan sulfate proteoglycans receptors on the liver) and with small, phospholipid-enriched HDL (which could enhance reverse cholesterol transport).^{168,169} Although apo E2 isoforms bind to LDL receptors much more weakly than do apo E3 or apo E4 isoforms, most $\epsilon 2$ 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 $\epsilon 2/\epsilon 2$ 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 $\epsilon 2$ 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 ex-

plain 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.⁵ 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, be needed to assess 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



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. Several characteristics explained a considerable part of the heterogeneity, including study location ($P < .001$), design ($P < .001$), publication status ($P = .004$), data source ($P < .001$), and type of journal ($P < .001$). Size of data markers is proportional to the inverse of the variance of the odds ratios.

^aTotal number for exposed and reference groups.

^bRefers to status of the source study by January 2007.

^cGenotype-specific data was not available from 3 studies.

^dThe weighted average of these strata-specific odds ratios (and the numbers of participants contributing to them) does not equal the overall odds ratio because only partial data were available on these characteristics since they were provided as tabular data by only a subset of relevant studies.

obesity,¹⁷⁸ diet,^{179,180} medication use,¹⁸¹ smoking,^{147,182} and glycemic status¹⁷⁸). 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).¹⁸³ Our cumulative meta-analysis showed that, in retrospect, the divergence in findings between smaller and larger studies was apparent by the year 2000. This observation underscores the potential value of regularly updated reviews for certain rapidly evolving hypotheses, both to enhance understanding and to optimize the use of resources. The observation that previous analyses both underestimated and overestimated effects of particular apoE

genotypes on coronary risk suggests that selective publication could work in surprisingly complex ways. Smaller studies may have preferentially reported striking findings in relation to $\epsilon 4$ and coronary risk but underreported the unexpected inverse association between the uncommon $\epsilon 2$ allele and coronary risk (perhaps because these differences would have been more difficult to detect). This finding encourages further study of the impact of selective publication in different contexts.⁶⁻⁹

The strengths and limitations of the current study merit consideration. Our analyses involved 5 times more data than in any previous relevant analysis, including tabular data from a considerable number of larger studies (both published and previously unreported). Even though we cannot entirely exclude publication bias

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 $\epsilon 4$) 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

Table 2. Odds Ratios for Coronary Disease According to Different Cut-off Levels of Study Size Used in Meta-analyses

Studies Involving, CHD Cases	No. of Studies	Odds Ratios for Coronary Disease	
		$\epsilon 2$ Carriers vs $\epsilon 3/\epsilon 3$	$\epsilon 4$ Carriers vs $\epsilon 3/\epsilon 3$
≥ 1000	8	0.85 (0.74-0.97)	1.05 (0.97-1.13)
$\geq 500^a$	17	0.80 (0.70-0.90)	1.06 (0.99-1.13)
≥ 250	31	0.85 (0.75-0.95)	1.10 (1.02-1.18)
≥ 100	81	0.94 (0.86-1.03)	1.35 (1.25-1.46)

Abbreviation: CHD, coronary heart disease.

^aPrespecified 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

	$\epsilon 2/\epsilon 3$ vs $\epsilon 3/\epsilon 3$				$\epsilon 3/\epsilon 4$ vs $\epsilon 3/\epsilon 3$			
	Previous Meta-analysis		Current Analyses		Previous Meta-analysis		Current Analyses	
	Weighted Mean Difference in Lipid Levels (95% CI) ^a	No. of Participants	Weighted Mean Difference in Lipid Levels (95% CI) ^a	No. of Participants	Weighted Mean Difference in Lipid Levels (95% CI) ^a	No. of Participants	Weighted Mean Difference in Lipid Levels (95% CI) ^a	No. of Participants
Cholesterol, mmol/L								
Total	-0.34 (-0.41 to 0.27)	10 799	-0.30 (-0.36 to 0.25)	53 309	0.14 (0.08 to 0.19)	12 441	0.13 (0.10 to 0.17)	60 297
LDL	NA	NA	-0.40 (-0.46 to 0.33)	44 512	NA	NA	0.13 (0.09 to 0.16)	50 394
HDL	-0.02 (-0.05 to 0.01)	6948	0.04 (0.02 to 0.05)	50 295	-0.03 (-0.05 to 0.01)	8185	-0.04 (-0.05 to 0.03)	56 886
Triglycerides, mmol/L	0.15 (0.07 to 0.22)	9193	0.08 (0.05 to 0.11)	50 214	0.11 (0.06 to 0.15)	10 716	0.10 (0.07 to 0.13)	56 886
	$\epsilon 2$ Carriers vs $\epsilon 3/\epsilon 3$				$\epsilon 4$ Carriers vs $\epsilon 3/\epsilon 3$			
	Previous Meta-analysis		Current Analyses		Previous Meta-analysis		Current Analyses	
	Odds Ratios for Coronary Disease (95% CI) ^b	Case/Control	Odds Ratios for Coronary Disease (95% CI) ^b	Case/Control	Odds Ratios for Coronary Disease (95% CI) ^b	Case/Control	Odds Ratios for Coronary Disease (95% CI) ^b	Case/Control
	0.95 (0.84 to 1.14)	10 085/20 245	0.80 (0.70 to 0.90)	15 372/34 068	1.30 (1.18 to 1.44)	12 255/23 383	1.06 (0.99 to 1.13)	18 651/40 339

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

SI 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.

^aDallongeville et al.⁴

^bSong et al.⁴³

for population stratification nor conduct "mendelian randomization" analyses,³⁷ nor could we adjust for variables in possible intermediate pathways.

CONCLUSIONS

There are approximately linear relationships of apoE genotypes with both LDL-C levels and coronary risk. Compared with $\epsilon 3/\epsilon 3$ individuals, $\epsilon 2$ carriers have a 20% reduced risk of coronary disease whereas $\epsilon 4$ carriers have only 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, Wiman, de Faire, Danesh.

Acquisition of data: Bennet, Di Angelantonio, Ye, Wensley, Dahlin, 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, Dahlin, Ahlborn, 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, Dahlin, Wiman, de Faire, Danesh.

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

Drs Bennet and Di Angelantonio are joint first authors.

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 Award in the Medical Sciences, Swedish Research Council (grant 05193), the Swedish Heart and Lung Foundation (grant 199941395 and 200041272), Wallenberg Consortium North, the King Gustaf V, and Queen Victoria's Foundation.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: The following investigators kindly provided additional information from their studies: Xiaojuan Bai, MD, China Medical University, China; Virginia Bañares, MD, Laboratorio de Genética Molecular, Buenos Aires, Argentina; Elisabeth Barrett-Connor, MD, University of California San Diego; Petr Benes, MD, Faculty of Science, Masaryk University, Czech Republic; Maurizio Cassader, MD, University of Turin, Italy; Juliana Chan, MD, Chinese University of Hong Kong, China; Eliecer Coto, MD, Hospital Central de Asturias, Spain; Roberto Corrocher, MD, University of Verona, Italy; Patrick Couture, MD, Laval University, Quebec City, Quebec; John Crouse, MD, Wake Forest University School of Medicine, Winston-Salem, North Carolina; Anthony Dart, MD, Baker Heart Research Institute, Melbourne, Australia; Jean Davignon, MD, Clinical Research Institute of Montreal, Montreal, Quebec; Janneke Dijk-Brouwer, MD, University Medical Center Groningen, Groningen, the Netherlands; Luc Djoussé, MD, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; Cornelia van Duijn, MD, Erasmus Medical Center,

Rotterdam, the Netherlands; Nduna Dzimir, MD, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; Shuzhi Feng, MD, Tianjin Medical University Hospital, Tianjin, China; Jean Ferrières, MD, Faculté de Médecine, Toulouse, France; Aaron Folsom, MD, School of Public Health, University of Minnesota, Minneapolis; Aídlí Fonseca, MD, Instituto Nacional de Saúde, Lisboa, Portugal; Ruth Frikke-Schmidt, MD, Copenhagen University Hospital, Copenhagen, Denmark; Carmen Garces, MD, Universidad Autonoma de Madrid, Madrid, Spain; Ulrik Gerdes, MD, University Psychiatric Hospital in Aarhus, Risskov, Denmark; Bas Heijmans, MD, Leiden University Medical Centre, Leiden, the Netherlands; Gülay Hergenc, MD, Turkish Society of Cardiology, Istanbul, Turkey; Barbara Howard, MD, MedStar Research Institute, Washington, DC; Aida Inbal, MD, Tel-Aviv University, Tel-Aviv, Israel; Aaron Isaacs, MD, Erasmus Medical Center, Rotterdam, the Netherlands; Turgay Isbir, MD, Istanbul University, Istanbul, Turkey; Jorge Joven, MD, Hospital Universitari de Sant Joan, Reus, Spain; Tomohiro Katsuya, MD, Osaka University Graduate School of Medicine, Osaka, Japan; Genovefa Kolovou, MD, Onassis Cardiac Surgery Center, Athens, Greece; Edward Lakatta, MD, National Institute on Aging, Baltimore, Maryland; Federico Licastro, MD, Università di Bologna, Italy; Gérald Luc, MD, Université de Lille 2, Lille, France; Kalpana Luthra, PhD, Institute of Medical Sciences, New Delhi, India; Antonio Mansur, MD, PhD, University of São Paulo Medical School, São Paulo, Brazil; Winfried März, MD, Synlab Centre of Laboratory Diagnostics, Heidelberg, Germany; Richard Mayeux, MD, Columbia University, New York, New York; Anoop Misra, MD, Institute of Medical Sciences, New Delhi, India; Maggie Ng, PhD, Chinese University of Hong Kong, Hong Kong, China; Viviane Nicaud, MD, Université Pierre et Marie Curie-Paris 6, Paris, France; Matthias Orth, MD, Ruhr-Universität Bochum, Germany; Dao-Quan Peng, MD, PhD, Central South University, Changsha, China; Daniel Petrovič, MD, PhD, University of Ljubljana, Ljubljana, Slovenia; N. Ranjith, MD, University of Kwazulu-Natal, Durban, South Africa; Katarina Raslova, MD, Institute of Preventive and Clinical Medicine, Bratislava, Slovak Republic; Patrick Rump, MD, PhD, Maastricht University, Maastricht, the Netherlands; Nicole Schupf, PhD, Columbia University, New York, New York; José Sorli, MD, University of Valencia, Valencia, Spain; James Terry, MD, Wake Forest University, Winston-Salem, North Carolina; Laurance Tiet, PhD, INSERM U525, Université Pierre et Marie Curie, Paris, France; E. Shyong Tai, MD, Singapore General Hospital, Singapore; Daniel Chun-hang Wai, MD, Singapore General Hospital, Singapore; Yonghong Xie, MD, Fourth Military Medical University, Xi'an, China; Kimiko Yamakawa-Kobayashi, PhD, University of Tsukuba, Tsukuba-shi Ibaraki-ken, Japan; Shu Ye, MD, PhD, William Harvey Research Institute, London, England; Iwona Zak, MD, Medical University of Silesia, Katowice, Poland; Dian-Wen Zhang, MD, Qingdao Hiserver Hospital, Qingdao, China; Jianhua Zhu, MD, Affiliated Hospital of Nantong Medical College, Nantong, China; Martin Bobrow, FRS, University of Cambridge, Cambridge, England; and Adam Butterworth, MSc, Cambridge Genetics Knowledge Park, Cambridge, England commented helpfully. Elena Zotova, BA, Albert Einstein College of Medicine, Bronx, New York, helped with translation of reports published in Russian. None of these individuals received compensation.

REFERENCES

- Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol*. 2002;155(6):487-495.
- Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science*. 1988;240(4852):622-630.

- Utermann G, Langenbeck U, Beisiegel U, Weber W. Genetics of the apolipoprotein E system in man. *Am J Hum Genet*. 1980;32(3):339-347.
- Dallongeville J, Lussier-Cacan S, Davignon J. Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. *J Lipid Res*. 1992;33(4):447-454.
- Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med*. 2004;141(2):137-147.
- Ioannidis JPA, Trikalinos TA, Khoury MJ. Implications of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. *Am J Epidemiol*. 2006;164(7):609-614.
- Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large vs small studies: an empirical assessment. *Lancet*. 2003;361(9357):567-571.
- Khoury MJ, Little J, Gwinn M, Ioannidis JP. On the synthesis and interpretation of consistent but weak gene-disease associations in the era of genome-wide association studies. *Int J Epidemiol*. 2007;36(2):439-445.
- Little J, Bradley L, Bray MS, et al. Reporting, appraising, and integrating data on genotype prevalence and gene-disease associations. *Am J Epidemiol*. 2002;156(4):300-310.
- Tunstall-Pedoe H, Kuusasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation*. 1994;90(1):583-612.
- Casas JP, Cavalleri GL, Bautista LE, Smeeth L, Humphries SE, Hingorani AD. Endothelial nitric oxide synthase gene polymorphisms and cardiovascular disease: a HuGE review. *Am J Epidemiol*. 2006;164(10):921-935.
- Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ*. 2005;331(7524):1053.
- Wheeler JG, Keavney BD, Watkins H, Collins R, Danesh J. Four paroxonase gene polymorphisms in 11 212 cases of coronary heart disease and 12 786 controls: meta-analysis of 43 studies. *Lancet*. 2004;363(9410):689-695.
- Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66 155 cases and 91 307 controls. *Lancet*. 2006;367(9511):651-658.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
- Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
- Bai X, Zhao M, Wang B. Dyslipidemia-related risk factors for myocardial infarction and polymorphism of ApoE gene among myocardial infarction patients and their siblings [in Chinese]. *Zhonghua Yi Xue Za Zhi*. 2001;81(6):340-343.
- Bañares VG, Peterson G, Aguilar D, et al. Association between the APOE*4 allele and atherosclerosis is age dependent among Argentine males. *Hum Biol*. 2005;77(2):247-256.
- Batalla A, Alvarez R, Reguero JR, et al. Synergistic effect between apolipoprotein E and angiotensinogen gene polymorphisms in the risk for early myocardial infarction. *Clin Chem*. 2000;46(12):1910-1915.
- Brouwer DA, Leerink CB, Steward HN, et al. Lip-

- ids, apolipoprotein-E genotypes and other risk factors of patients with coronary artery disease in Curacao. *West Indian Med J*. 1997;46(2):47-52.
23. Dart A, Sherrard B, Simpson H. Influence of apoE phenotype on postprandial triglyceride and glucose responses in subjects with and without coronary heart disease. *Atherosclerosis*. 1997;130(1-2):161-170.
 24. Djousse L, Myers RH, Province MA, et al. Influence of apolipoprotein E, smoking, and alcohol intake on carotid atherosclerosis: National Heart, Lung, and Blood Institute Family Heart Study. *Stroke*. 2002;33(5):1357-1361.
 25. Frikke-Schmidt R, Tybjaerg-Hansen A, Steffenensen R, Jensen G, Nordestgaard BG. Apolipoprotein E genotype: epsilon32 women are protected while epsilon43 and epsilon44 men are susceptible to ischemic heart disease: the Copenhagen City Heart Study. *J Am Coll Cardiol*. 2000;35(5):1192-1199.
 26. Gerdes LU, Klausen IC, Sihm I, Faergeman O. Apolipoprotein E polymorphism in a Danish population compared to findings in 45 other study populations around the world. *Genet Epidemiol*. 1992;9(3):155-167.
 27. Girelli D, Russo C, Ferraresi P, et al. Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. *N Engl J Med*. 2000;343(11):774-780.
 28. Gong W, Peng S, Peng J, Wang J. Association of geriatric coronary heart disease with apolipoprotein E gene polymorphism in relation and its impact on serum lipid levels. *Chin J Gerontol*. 2000;5:149-150.
 29. Heijmans BT, Slagboom PE, Gussekloo J, et al. Association of APOE epsilon2/epsilon3/epsilon4 and promoter gene variants with dementia but not cardiovascular mortality in old age. *Am J Med Genet*. 2002;107(3):201-208.
 30. Inbal A, Freimark D, Modan B, et al. Synergistic effects of prothrombotic polymorphisms and atherogenic factors on the risk of myocardial infarction in young males. *Blood*. 1999;93(7):2186-2190.
 31. Isbir T, Yilmaz H, Agachan B, Karaali ZE. Cholesterol ester transfer protein, apolipoprotein E and lipoprotein lipase genotypes in patients with coronary artery disease in the Turkish population. *Clin Genet*. 2003;64(3):228-234.
 32. Jin W, Lu YS, Xu YH, Zheng MF. Relation of apolipoprotein E polymorphism to myocardial infarction and serum lipids. *Shanghai Med J (Chin)*. 1998;21:697-699.
 33. Joven J, Simo JM, Vilella E, et al. Lipoprotein(a) and the significance of the association between platelet glycoprotein IIIa polymorphisms and the risk of premature myocardial infarction. *Atherosclerosis*. 1998;140(1):155-159.
 34. Kardaun JW, White L, Resnick HE, et al. Genotypes and phenotypes for apolipoprotein E and Alzheimer disease in the Honolulu-Asia aging study. *Clin Chem*. 2000;46(10):1548-1554.
 35. Kataoka S, Robbins DC, Cowan LD, et al. Apolipoprotein E polymorphism in American Indians and its relation to plasma lipoproteins and diabetes: the Strong Heart Study. *Arterioscler Thromb Vasc Biol*. 1996;16(8):918-925.
 36. Katsuya T, Baba S, Ishikawa K, et al. Epsilon 4 allele of apolipoprotein E gene associates with lower blood pressure in young Japanese subjects: the Suita Study. *J Hypertens*. 2002;20(10):2017-2021.
 37. Keavney B, Palmer A, Parish S, et al. Lipid-related genes and myocardial infarction in 4685 cases and 3460 controls: discrepancies between genotype, blood lipid concentrations, and coronary disease risk. *Int J Epidemiol*. 2004;33(5):1002-1013.
 38. Kharrazi H, Vaisi Raygani A, Sabokrohi AR, Pourmotabbed T. Association between apolipoprotein E polymorphism and coronary artery disease in the Kermanshah population in Iran. *Clin Biochem*. 2006;39(6):613-616.
 39. Kolovou G, Yiannakouris N, Hatzivassiliou M, et al. Association of apolipoprotein E polymorphism with myocardial infarction in Greek patients with coronary artery disease. *Curr Med Res Opin*. 2002;18(3):118-124.
 40. Kolovou GD, Daskalova DC, Hatzivassiliou M, et al. The epsilon 2 and 4 alleles of apolipoprotein E and ischemic vascular events in the Greek population—implications for the interpretation of similar studies. *Angiology*. 2003;54(1):51-58.
 41. Letonja M, Guzik-Salobir B, Peterlin B, Petrovic D. Apolipoprotein E gene polymorphism effects triglycerides but not CAD risk in Caucasian women younger than 65 years. *Ann Genet*. 2004;47(2):147-153.
 42. Li WH, Huang DJ, Du XH, Zhang WZ, Hu JL. Effect of apolipoprotein E polymorphisms on serum lipids and relation to coronary heart stenosis. *Chin J Arterioscl (Chin)*. 2000;8:54-57.
 43. Licastro F, Chiappelli M, Caldarera CM, et al. The concomitant presence of polymorphic alleles of interleukin-1beta, interleukin-6 and apolipoprotein E is associated with an increased risk of myocardial infarction in elderly men: results from a pilot study. *Mech Ageing Dev*. 2004;125(8):575-579.
 44. Luc G, Bard JM, Arveiler D, et al. Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction: the ECTIM Study. *Arterioscler Thromb*. 1994;14(9):1412-1419.
 45. März W, Schrnagl H, Hoffmann MM, Boehm BO, Winkelmann BR. The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen risk and cardiovascular health study). *Eur Heart J*. 2004;25(23):2109-2119.
 46. Mansur AP, Annicchino-Bizzacchi J, Favaro D, Avakian SD, Cesar LA, Ramires JA. Angiotensin-converting enzyme and apolipoproteins genes polymorphism in coronary artery disease. *Clin Cardiol*. 2000;23(5):335-340.
 47. Marques-Vidal P, Bongard V, Ruidavets JB, Fauvel J, Perret B, Ferrieres J. Effect of apolipoprotein E alleles and angiotensin-converting enzyme insertion/deletion polymorphisms on lipid and lipoprotein markers in middle-aged men and in patients with stable angina pectoris or healed myocardial infarction. *Am J Cardiol*. 2003;92(9):1102-1105.
 48. Menzel HJ, Kladezky RG, Assmann G. Apolipoprotein E polymorphism and coronary artery disease. *Arterioscl*. 1983;3(4):310-315.
 49. Nakai K, Fusazaki T, Zhang T, et al. Polymorphism of the apolipoprotein E and angiotensin I converting enzyme genes in Japanese patients with myocardial infarction. *Coron Artery Dis*. 1998;9(6):329-334.
 50. Oh JY, Barrett-Connor E. Apolipoprotein E polymorphism and lipid levels differ by gender and family history of diabetes: the Rancho Bernardo Study. *Clin Genet*. 2001;60(2):132-137.
 51. Orth M, Weng W, Funke H, et al. Effects of a frequent apolipoprotein E isoform, ApoE4Freiburg (Leu28→Pro), on lipoproteins and the prevalence of coronary artery disease in whites. *Arterioscler Thromb Vasc Biol*. 1999;19(5):1306-1315.
 52. Orth M, Dierkes J, Luley C. Chylomicron remnant concentrations in patients with coronary artery disease. *Clin Chem Lab Med*. 2003;41(5):652-662.
 53. Ou T, Yamakawa-Kobayashi K, Arinami T, et al. Methylenetetrahydrofolate reductase and apolipoprotein E polymorphisms are independent risk factors for coronary heart disease in Japanese: a case-control study. *Atherosclerosis*. 1998;137(1):23-28.
 54. Pablos-Méndez A, Mayeux R, Ngai C, Shea S, Berglund L. Association of apoE polymorphism with plasma lipid levels in a multiethnic elderly population. *Arterioscler Thromb Vasc Biol*. 1997;17(12):3534-3541.
 55. Peng DQ, Zhao SP, Nie S, Li J. Gene-gene interaction of PPARgamma and ApoE affects coronary heart disease risk. *Int J Cardiol*. 2003;92(2-3):257-263.
 56. Peng S, Peng J, Gong WX. Association of apolipoprotein E gene polymorphism with early-onset coronary heart disease and its effect on plasma lipid levels [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2001;18(5):375-378.
 57. Raslova K, Smolkova B, Vohnout B, Gasparovic J, Frohlich JJ. Risk factors for atherosclerosis in survivors of myocardial infarction and their spouses: comparison to controls without personal and family history of atherosclerosis. *Metabolism*. 2001;50(1):24-29.
 58. Regis-Bailly A, Visvikis S, Steinmetz J, et al. Frequencies of five genetic polymorphisms in coronarographed patients and effects on lipid levels in a supposedly healthy population. *Clin Genet*. 1996;50(5):339-347.
 59. Bennet AM, van Maarse MC, Hallqvist J, et al. Association of TNF-alpha serum levels and TNFA promoter polymorphisms with risk of myocardial infarction. *Atherosclerosis*. 2006;187(2):408-414.
 60. Scaglione L, Bergerone S, Gambino R, et al. Role of lipid, apolipoprotein levels and apolipoprotein E genotype in young Italian patients with myocardial infarction. *Nutr Metab Cardiovasc Dis*. 1999;9(3):118-124.
 61. Scuteri A, Najjar SS, Muller D, et al. ApoE4 allele and the natural history of cardiovascular risk factors. *Am J Physiol Endocrinol Metab*. 2005;289(2):E322-E327.
 62. Slieter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. *Neurology*. 2004;62(7):1196-1198.
 63. Sturgeon JD, Folsom AR, Bray MS, Boerwinkle E, Ballantyne CM. Apolipoprotein E genotype and incident ischemic stroke: the Atherosclerosis Risk in Communities Study. *Stroke*. 2005;36(11):2484-2486.
 64. Terry JG, Howard G, Mercuri M, Bond MG, Crouse JR III. Apolipoprotein E polymorphism is associated with segment-specific extracranial carotid artery intima-media thickening. *Stroke*. 1996;27(10):1755-1759.
 65. von Muhlen D, Barrett-Connor E, Kritzer-Silverstein D. Apolipoprotein E genotype and response of lipid levels to postmenopausal estrogen use. *Atherosclerosis*. 2002;161(1):209-214.
 66. Wang GQ, Wang XL, Yang CR, Li X, Xiao BY, Zhang YZ. Relationship between apolipoprotein E gene polymorphism and longevity, lipids in Uyghur nationality. *Chin J Gerontol (Chin)*. 2001;5:325-327.
 67. Wang XH, Gao HQ. Clinical study of the association between apoE polymorphism and lipid metabolism of patients with CHD. *J Clin Cardiol (Chin)*. 2000;16:440-442.
 68. Wu JH, Lo SK, Wen MS, Kao JT. Characterization of apolipoprotein E genetic variations in Taiwanese: association with coronary heart disease and plasma lipid levels. *Hum Biol*. 2002;74(1):25-31.
 69. Boer JM, Ehnholm C, Menzel HJ, et al. Interactions between lifestyle-related factors and the ApoE polymorphism on plasma lipids and apolipoproteins. European Atherosclerosis Research Study. *Arterioscler Thromb Vasc Biol*. 1997;17(9):1675-1681.
 70. Chen Z, Huang J, Zhu TB, et al. Study on the lipids and apolipoprotein E polymorphism in siblings and offspring of patients with coronary heart disease aged 55 years or younger. *J Clin Cardiol (Chin)*. 2002;18:150-152.
 71. Choi YH, Kim JH, Kim DK, et al. Distributions of ACE and APOE polymorphisms and their relations with dementia status in Korean centenarians. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):227-231.
 72. Cui JB, Wang SJ, Wang JP, et al. The relationship between apolipoprotein E genotypes and levels of plasma lipids in the Henan Han population. *J Henan Med Uni (Chin)*. 2000;35:519-522.
 73. Dufouil C, Richard F, Fievet N, et al. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology*. 2005;64(9):1531-1538.
 74. Ehnholm C, Lukka M, Kuusi T, Nikkila E, Utermann G. Apolipoprotein E polymorphism in the Finnish population: gene frequencies and relation to lipoprotein concentrations. *J Lipid Res*. 1986;27(3):227-235.

75. Fan P, Zhang ZH, Liu Y, Gu HQ, Liu BW. Apolipoprotein E polymorphism, serum lipids and apolipoproteins of 362 Han national subjects in Chengdu area [in Chinese]. *Hua Xi Yi Ke Da Xue Xue Bao*. 1999;30(4):373-374.
76. Guo Y, Guo JJ, Nao JF, Wang FW. The relations between polymorphisms of apolipoprotein E gene and atherosclerotic cerebral infarction. *Chinese J Neurol (Chin)*. 1997;30:236-238.
77. Li X, Zhao D, Liu J, et al. The study on the effects of apolipoprotein E gene polymorphism on serum lipids and its frequency distribution in Beijing natural population. *J Cardiovascul Pulmon Dis (Chin)*. 2002;21:193-197.
78. Liou FE. Measurement of apolipoprotein E genetic variation and serum lipid levels. *Chin J Contemp Pediatr (Chin)*. 2001;3:667-668.
79. Long SY, Zhang XM, Fu MH, Xu YH, Liu BW. Relationship of ApoE gene polymorphism with subclasses of serum high-density lipoprotein in hyperlipidemia [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2004;21(6):615-617.
80. Ng MC, Wang Y, So WY, et al. Ethnic differences in the linkage disequilibrium and distribution of single-nucleotide polymorphisms in 35 candidate genes for cardiovascular diseases. *Genomics*. 2004;83(4):559-565.
81. Ritter MM, Gewitsch J, Richter WO, Geiss HC, Wildner MW, Schwandt P. Apolipoprotein E polymorphism has no independent effect on plasma levels of lipoprotein(a). *Atherosclerosis*. 1997;131(2):243-248.
82. Rodrigues MO, Fonseca A, Matias DC, et al. APOE genotypes and dyslipidemias in a sample of the Portuguese population. *Clin Chem Lab Med*. 2005;43(9):907-912.
83. Rump P, Mensink RP, Hornstra G. Interaction between a common variant of the cholesteryl ester transfer protein gene and the apolipoprotein E polymorphism: effects on plasma lipids and lipoproteins in a cohort of 7-year-old children. *Nutr Metab Cardiovasc Dis*. 2002;12(6):317-324.
84. Salah D, Bohnet K, Gueguen R, Siest G, Visvikis S. Combined effects of lipoprotein lipase and apolipoprotein E polymorphisms on lipid and lipoprotein levels in the Stanislas cohort. *J Lipid Res*. 1997;38(5):904-912.
85. Sorli JV, Corella D, Frances F, et al. The effect of the APOE polymorphism on HDL-C concentrations depends on the cholesterol ester transfer protein gene variation in a Southern European population. *Clin Chim Acta*. 2006;366(1-2):196-203.
86. Tan CE, Tai ES, Tan CS, et al. APOE polymorphism and lipid profile in three ethnic groups in the Singapore population. *Atherosclerosis*. 2003;170(2):253-260.
87. Tremblay AJ, Bergeron J, Gagne JM, Gagne C, Couture P. Influence of apolipoprotein E genotype on the reliability of the Friedewald formula in the estimation of low-density lipoprotein cholesterol concentrations. *Metabolism*. 2005;54(8):1014-1019.
88. Wang X, Wang GQ, Yang CR, Li X. Apolipoprotein E gene polymorphism and its association with human longevity in the Uygur nationality in Xinjiang. *Chin Med J (Engl)*. 2001;114(8):817-820.
89. Xiang W, Zhao S, Peng D. Apolipoprotein E polymorphism and plasma lipid, lipoprotein, apolipoprotein levels in 291 children of Changsha [in Chinese]. *Hunan Yi Ke Da Xue Xue Bao*. 1999;24(3):232-236.
90. Xie YH. Epsilon 4: a genetic factor susceptible to hypercholesterolemia. *Zhonghua Yi Xue Za Zhi (Chin)*. 1989;69:585-587.
91. Yan SK, Zhou X, Ha DW. Influence of apolipoprotein E gene polymorphism on lipids, apolipoproteins and Lp(a) in Han Chinese. *Bas Med Sci Clin (Chin)*. 1998;18:48-52.
92. Ye S, Dunleavy L, Bannister W, et al. Independent effects of the -219 G>T and epsilon 2/epsilon 3/epsilon 4 polymorphisms in the apolipoprotein E gene on coronary artery disease: the Southampton Atherosclerosis Study. *Eur J Hum Genet*. 2003;11(6):437-443.
93. Yuan RY, Liang SL, Mai YM, Chui RZ. The study of interrelationship between apolipoprotein E alleles polymorphism and coronary heart disease. *Chin J Cardiol*. 1998;3:320-322.
94. Zak I, Balcerzyk A, Sarecka B, Niemiec P, Cierniewski Z, Dylag S. Contemporaneous carrier-state of two or three "proatherosclerotic" variants of APOE, ICAM1, PPARA, and PAI-1 genes differentiate CAD patients from healthy individuals. *Clin Chim Acta*. 2005;362(1-2):110-118.
95. Zeng HS, Liu XQ, Wu SQ, Guo ZS, Chen ZY. The effects of apolipoprotein E gene polymorphism on the concentrations of lipids and lipoproteins in Chinese children. *Chin J Child Health Care (Chin)*. 1998;6:83-85.
96. Zhang SM, Cui Y, Fang WH. Effect of genetic variation of apolipoprotein B and apolipoprotein E genetic polymorphism on coronary artery disease. *Chin J Pract Intern Med (Chin)*. 2003;23:475-477.
97. Zhang ST, Liu ZX, Chen WF. The effects of ApoE gene polymorphism and serum lipid levels in the newborn baby. *Xin Sheng Er Ke Za Zhi (Chin)*. 1998;13:241-243.
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 premature coronary heart disease. *J Chin Med Uni (Chin)*. 2002;31:6-8.
99. Zhu CL, Zhou X, Liu F, Hu HL. The relationship between polymorphisms of apolipoprotein E gene and serum lipid levels. *Chin J Arterioscl (Chin)*. 2005;13:203-206.
100. Zhu JH, Pan M, Wang HM, Sun CL, Liu ZH. The effect of apolipoprotein E polymorphism on serum lipids, lipoproteins, and apolipoproteins variation. *J Clin Cardiol (Chin)*. 2002;18:63-65.
101. Zhu JY, Gao HQ, Zhou YK, et al. The association of apolipoprotein E and coronary heart disease. *Clin Med J Chin (Chin)*. 2002;9:224-226.
102. Baitasova NB, Rysmendiev AZ, Shchuratova SG. Apolipoprotein genes in patients with ischemic heart disease [in Russian]. *Klin Med (Mosk)*. 2001;79(12):19-21.
103. Benes P, Muzik J, Benedik J, et al. Single effects of apolipoprotein B, (a), and E polymorphisms and interaction between plasminogen activator inhibitor-1 and apolipoprotein(a) genotypes and the risk of coronary artery disease in Czech male caucasians. *Mol Genet Metab*. 2000;69(2):137-143.
104. Cao W, Chen F, Teng L, Wang S, Fu S, Zhang G. The relationship between apolipoprotein E gene polymorphism and coronary heart disease and atherosclerotic cerebral infarction [in Chinese]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 1999;16(4):249-251.
105. Corbo RM, Vilardo T, Ruggeri M, Gemma AT, Scacchi R. Apolipoprotein E genotype and plasma levels in coronary artery disease: a case-control study in the Italian population. *Clin Biochem*. 1999;32(3):217-222.
106. Cumming AM, Robertson FW. Polymorphism at the apolipoprotein-E locus in relation to risk of coronary disease. *Clin Genet*. 1984;25(4):310-313.
107. Dzimirli N, Meyer BF, Hussain SS, Basco C, Afrane B, Hales Z. Relevance of apolipoprotein E polymorphism for coronary artery disease in the Saudi population. *Arch Pathol Lab Med*. 1999;123(12):1241-1245.
108. Eichner JE, Kuller LH, Orchard TJ, et al. Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. *Am J Cardiol*. 1993;71(2):160-165.
109. Eto M, Watanabe K, Makino I. Increased frequencies of apolipoprotein epsilon 2 and epsilon 4 alleles in patients with ischemic heart disease. *Clin Genet*. 1989;36(3):183-188.
110. Feng S, Wang H, Wang Q, Tian JL. Analysis of apolipoprotein E gene polymorphisms in elderly coronary heart disease. *Geriatr Health Care (Chin)*. 2005;11:174-176.
111. Garcés C, Maicas C, Grande R, et al. epsilon3epsilon4 genotype as risk factor of myocardial infarction in middle-aged people in Spain. *Dis Markers*. 2005;21(3):153-156.
112. Weber M, McNicoll S, Marcl M, et al. Metabolic factors clustering, lipoprotein cholesterol, apolipoprotein B, lipoprotein (a) and apolipoprotein E phenotypes in premature coronary artery disease in French Canadians. *Can J Cardiol*. 1997;13(3):253-260.
113. Gerdes LU, Gerdes C, Kervinen K, et al. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction: a substudy of the Scandinavian Simvastatin Survival Study. *Circulation*. 2000;101(12):1366-1371.
114. Gong W, Peng S, Peng J, Wang J. Association of geriatric myocardial infarction and apolipoprotein E gene polymorphism. *Applied Geriatr (Chin)*. 2000;14:131-133.
115. Guan SM, Li W, Zhang YH, Qi BL, Ke QM. Relativity between apolipoprotein E genotype, level of blood lipids, and lipoprotein in patients with coronary heart disease. *J Clin Cardiol (Chin)*. 2002;18:166-168.
116. Hergenc G, Taga Y, Emerk K, Cirakoglu B. Apolipoprotein E genotyping in Turkish myocardial infarction survivors and healthy controls. *J Biomed Sci*. 1995;2(1):46-49.
117. Kim IJ, Hong BK, Lee BK, et al. Apolipoprotein E polymorphism in non-diabetic patients with acute coronary syndrome. *Yonsei Med J*. 1999;40(4):377-382.
118. Lenzen HJ, Assmann G, Buchwalsky R, Schulte H. Association of apolipoprotein E polymorphism, low-density lipoprotein cholesterol, and coronary artery disease. *Clin Chem*. 1986;32(5):778-781.
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 prospective study. *Lancet*. 2001;358(9276):115-119.
120. Kuusi T, Nieminen MS, Ehnholm C, et al. Apolipoprotein E polymorphism and coronary artery disease: increased prevalence of apolipoprotein E-4 in angiographically verified coronary patients. *Arteriosclerosis*. 1989;9(2):237-241.
121. Attila G, Acarturk E, Eskandari G, et al. Effects of apolipoprotein E genotypes and other risk factors on the development of coronary artery disease in Southern Turkey. *Clin Chim Acta*. 2001;312(1-2):191-196.
122. Lehtinen S, Lehtimäki T, Sisto T, et al. Apolipoprotein E polymorphism, serum lipids, myocardial infarction, and severity of angiographically verified coronary artery disease in men and women. *Atherosclerosis*. 1995;114(1):83-91.
123. Li HM, Pan M, Liang S, Wang HM, Chua ZC, Zhu HJ. Effect of apolipoprotein E, angiotensin-converting enzyme gene on coronary heart disease in Chinese population. *Chin J Mod Med (Chin)*. 2003;13:35-37.
124. Li W, Guan SM, Qi BL, Ke QM, Zhang HP. The clinical significance of the detection of apolipoprotein E polymorphism for coronary heart disease in the elderly population. *Chin J Geriatr (Chin)*. 2003;22:214-217.
125. Liu XC, Peng HY, Qin GF. The relationship of ApoE polymorphisms with the serum concentration of ApoE in coronary heart disease. *Shanghai J Med Lab Sci (Chin)*. 2003;18:36-39.
126. Liao MZ, Jian BF, Xu CH, Xu CH, Hu FG, Huang XR. The study of relationship between apolipoprotein E polymorphism and coronary heart disease. *Pract Prev Med (Chin)*. 2004;11:691-693.
127. Liu HX, Cao LC, Fu GL, Du PeG, Fu SB. Correlation between apolipoprotein E gene polymorphism and coronary heart disease and cerebral thrombosis. *China J Mod Med (Chin)*. 1999;9:78-80.
128. Liu S, Ma J, Ridker PM, Breslow JL, Stampfer MJ. A prospective study of the association between

- APOE genotype and the risk of myocardial infarction among apparently healthy men. *Atherosclerosis*. 2003; 166(2):323-329.
129. Lu YS, Wu WJ, Xu X, Zhuang QQ, Wu MP, Mei MZ. Relationship between apolipoprotein E polymorphisms, serum lipid levels and myocardial infarction. *Chin J Arterioscl (Chin)*. 1999;7:110-112.
 130. Yang Z, Zhu T, Ma G, et al. Apolipoprotein E polymorphism in the early onset of coronary heart disease. *Chin Med J (Engl)*. 2001;114(9):983-985.
 131. Mamotte CD, Burke V, Taylor RR, van Bockxmeer FM. Evidence of reduced coronary artery disease risk for apolipoprotein epsilon2/3 heterozygotes. *Eur J Intern Med*. 2002;13(4):250-255.
 132. Damaraju S, Yu QT, Safavi F, Marian AJ. Apolipoprotein epsilon 4 is not a genetic risk factor for coronary artery disease or restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 1995; 75(16):1181-1183.
 133. Marshall HW, Morrison LC, Wu LL, et al. Apolipoprotein polymorphisms fail to define risk of coronary artery disease: results of a prospective, angiographically controlled study. *Circulation*. 1994;89(2):567-577.
 134. Biggart S, Chin D, Fauchon M, et al. Association of genetic polymorphisms in the ACE, ApoE, and TGF beta genes with early onset ischemic heart disease. *Clin Cardiol*. 1998;21(11):831-836.
 135. Kumar P, Luthra K, Dwivedi M, Behl VK, Pandey RM, Misra A. Apolipoprotein E gene polymorphisms in patients with premature myocardial infarction: a case-controlled study in Asian Indians in North India. *Ann Clin Biochem*. 2003;40(Pt 4):382-387.
 136. Mustafina OE, Shagisultanova EI, Tuktarova IA, Khushnutdinova EK. Polymorphism of the apolipoprotein E gene and the risk of myocardial infarction [in Russian]. *Mol Biol (Mosk)*. 2002;36(6):978-984.
 137. Niao Q, Liang ZD, Hu SH, Li NM, Lu XM. The relationship of apolipoprotein E gene polymorphism and coronary heart disease in Guang Xi, Zhuang population. *J Sichuan Univ (Med Sci Edition) (Chin)*. 2004;35:285-286.
 138. Lahoz C, Schaefer EJ, Cupples LA, et al. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis*. 2001; 154(3):529-537.
 139. Pan YY, Hu J, Li Dong X, Pan ZH, Wang YC. Effects of ApoE polymorphism on plasma lipid levels and coronary disease. *J Clin Intern Med (Chin)*. 2001; 18:267-269.
 140. Baroni MG, Berni A, Romeo S, et al. Genetic study of common variants at the ApoE, Apo AI, Apo CIII, Apo B, lipoprotein lipase (LPL) and hepatic lipase (LIPC) genes and coronary artery disease (CAD): variation in LIPC gene associates with clinical outcomes in patients with established CAD. *BMC Med Genet*. 2003; 4:8-14.
 141. Peng J, Gong WX, Peng S, Wang J, Shi L, Lin XF. Effect of apolipoprotein E gene polymorphism on plasma lipid levels and association with coronary heart disease. *Chin J Arterioscl (Chin)*. 1999;7:307-310.
 142. Ranjith N, Pegoraro RJ, Rom L, Rajput MC, Naidoo DP. Lp(a) and apoE polymorphisms in young South African Indians with myocardial infarction. *Cardiovasc J S Afr*. 2004;15(3):111-117.
 143. Salazar LA, Hirata MH, Giannini SD, et al. Seven DNA polymorphisms at the candidate genes of atherosclerosis in Brazilian women with angiographically documented coronary artery disease. *Clin Chim Acta*. 2000;300(1-2):139-149.
 144. Yan S, Zhou X, Lin Q, Song Y. Association of polymorphism of apolipoprotein E gene with coronary heart disease in Han Chinese. *Chin Med J (Engl)*. 1999;112(3):224-227.
 145. Stengård JH, Pekkanen J, Ehnholm C, Nissinen A, Sing CF. Genotypes with the apolipoprotein epsilon4 allele are predictors of coronary heart disease mortality in a longitudinal study of elderly Finnish men. *Hum Genet*. 1996;97(5):677-684.
 146. Talmud PJ, Lewis SJ, Hawe E, et al. No APOEepsilon4 effect on coronary heart disease risk in a cohort with low smoking prevalence: the Whitehall II study. *Atherosclerosis*. 2004;177(1):105-112.
 147. Talmud PJ, Stephens JW, Hawe E, et al. The significant increase in cardiovascular disease risk in APOEepsilon4 carriers is evident only in men who smoke: potential relationship between reduced antioxidant status and ApoE4. *Ann Hum Genet*. 2005; 69(Pt 6):613-622.
 148. Utermann G, Hardewig A, Zimmer F. Apolipoprotein E phenotypes in patients with myocardial infarction. *Hum Genet*. 1984;65(3):237-241.
 149. Wang C, Zhou X, Ye S, et al. Combined effects of apoE-CII cluster and LDL-R gene polymorphisms on chromosome 19 and coronary artery disease risk. *Int J Hyg Environ Health*. 2006;209(3): 265-273.
 150. Wang CH, Zhou X, Zhou GD, et al. Genetic association of apoE and apoCII gene polymorphisms with coronary heart disease [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2004;25(11):982-985.
 151. Wang XL, McCredie RM, Wilcken DE. Polymorphisms of the apolipoprotein E gene and severity of coronary artery disease defined by angiography. *Arterioscler Thromb Vasc Biol*. 1995;15(8):1030-1034.
 152. Wu QP, Li PY, Wu SQ, et al. Study of apolipoprotein E gene polymorphism and coronary heart disease in the elderly. *Chin J Clin Rehabilitation (Chin)*. 2002;6:74-75.
 153. Wu QP, Li W, Li PY, Shen QL. Polymorphism of apolipoprotein E gene angiotensin-1 converting enzyme in the elderly with hypertension and coronary heart disease. *Chin J Clin Rehabilitation (Chin)*. 2005; 9:82-83.
 154. Wu XL, Long J. The relations between apolipoprotein E polymorphism and diseases. *J Navy Med (Chin)*. 2000;21:32-34.
 155. Yamamura T, Tajima S, Miyake Y, et al. Hyperlipoproteinemia as a risk factor for ischemic heart disease. *Jpn Circ J*. 1990;54(4):448-456.
 156. Yang SL, He BX, He ZY, Zhan H, Hong XF, Zou YC. Relation between extent of coronary heart disease and apolipoprotein E gene polymorphisms. *J Clin Cardiol (Chin)*. 2003;19:134-137.
 157. Yang SL, He BX, He ZY, Zhan H, Hong XF, Zou YC. Apolipoprotein E gene polymorphisms and risk of coronary heart disease in Chinese Xinjiang Uygur and Han populations. *Chin J Arterioscl (Chin)*. 2003; 11:429-433.
 158. Yang ZJ, Zhu TB, Yang B, et al. Study of apoE gene polymorphism in coronary heart disease. *Jiangsu Med J (Chin)*. 2000;26:269-270.
 159. Zhang GB, Chen HZ, Jiang ZW, Wen QZ, Lu YS, Zhuang WY. The relationship of apolipoprotein E gene polymorphism to coronary artery disease. *Chin J Arterioscl (Chin)*. 2001;9:310-312.
 160. Zhang HQ, Yu K, Huang WJ, Lin G, Shi CG. To explore the relativity of apolipoprotein B and E gene polymorphisms with coronary heart disease and hypertension. *Prev Treat Cardio-Cerebral-Vascular Dis (Chin)*. 2002;2:20-22.
 161. Zhang YL, You K, Zhang LH, et al. Effect of apolipoprotein E polymorphism on serum lipids, coronary heart disease and carotid artery atherosclerosis. *Chin J Cardiol (Chin)*. 1998;26:443-447.
 162. Zhu DM, Chen ZJ, Zeng WW, et al. Study on the relationship between apolipoprotein E gene polymorphism and coronary heart disease. *Chin Circ J (Chin)*. 1997;12:347-350.
 163. Zhu TB, Yang ZJ, Ma GS, et al. The study of apolipoprotein E gene polymorphism in patients with coronary heart disease. *Chin Circ J (Chin)*. 2000;15:221-222.
 164. Zou YC, Hong XF, Hu DY, et al. Relationship between apolipoprotein E gene polymorphisms and coronary heart disease. *Chin J Arterioscl (Chin)*. 2005; 13:355-358.
 165. Wilson PW, Schaefer EJ, Larson MG, Ordovas JM. Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. *Arterioscler Thromb Vasc Biol*. 1996;16(10):1250-1255.
 166. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005; 366(9493):1267-1278.
 167. Hatters DM, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. *Trends Biochem Sci*. 2006;31(8):445-454.
 168. Weisgraber KH, Innerarity TL, Mahley RW. Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site. *J Biol Chem*. 1982;257(5): 2518-2521.
 169. Weisgraber KH. Apolipoprotein E distribution among human plasma lipoproteins: role of the cysteine-arginine interchange at residue 112. *J Lipid Res*. 1990; 31(8):1503-1511.
 170. Mahley RW, Rall SC. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet*. 2000;1:507-537.
 171. Larson IA, Ordovas JM, DeLuca C, Barnard JR, Feussner G, Schaefer EJ. Association of apolipoprotein (Apo)E genotype with plasma apoE levels. *Atherosclerosis*. 2000;148(2):327-335.
 172. Frikke-Schmidt R, Nordestgaard BG, Gerholm-Larsen B, Schnohr P, Tybjaerg-Hansen A. Context-dependent and invariant associations between lipids, lipoproteins, and apolipoproteins and apolipoprotein E genotype. *J Lipid Res*. 2000;41(11):1812-1822.
 173. März W, Scharnagl H, Hoffmann MM, Boehm BO, Winkelmann BR. The apolipoprotein E polymorphism is associated with circulating C-reactive protein (the Ludwigshafen Risk and Cardiovascular Health Study). *Eur Heart J*. 2004;25(23):2109-2119.
 174. Bioletto S, Fontana P, Darioli R, James RW. Apolipoprotein E polymorphism and the distribution profile of very low density lipoproteins: an influence of the E4 allele on large (Sf > 60) particles. *Atherosclerosis*. 1998;138(1):207-215.
 175. Chasman DI, Kozlowski P, Zee RY, Kwiatkowski DJ, Ridker PM. Qualitative and quantitative effects of APOE genetic variation on plasma C-reactive protein, LDL-cholesterol, and apoE protein. *Genes Immun*. 2006;7(3):211-219.
 176. Colton CA, Brown CM, Vitek MP. Sex steroids, APOE genotype and the innate immune system. *Neurobiol Aging*. 2005;26(3):363-372.
 177. Brown CM, Wright E, Colton CA, Sullivan PM, Laskowitz DT, Vitek MP. Apolipoprotein E isoform mediated regulation of nitric oxide release. *Free Radic Biol Med*. 2002;32(11):1071-1075.
 178. Elosua R, Demissie S, Cupples LA, et al. Obesity modulates the association among APOE genotype, insulin, and glucose in men. *Obes Res*. 2003; 11(12):1502-1508.
 179. Ordovas JM, Schaefer EJ. Genes, variation of cholesterol, and fat intake and serum lipids. *Curr Opin Lipidol*. 1999;10(1):15-22.
 180. Weggemans RM, Zock PL, Ordovas JM, Pedro-Botet J, Katan MB. Apoprotein E genotype and the response of serum cholesterol to dietary fat, cholesterol and cafestol. *Atherosclerosis*. 2001;154(3): 547-555.
 181. Maitland-van der Zee AH, Jukema JW, Zwinderman AH, et al. Apolipoprotein-E polymorphism and response to pravastatin in men with coronary artery disease (REGRESS). *Acta Cardiol*. 2006;61(3):327-331.
 182. Keavney B, Parish S, Palmer A, et al. Large-scale evidence that the cardiotoxicity of smoking is not significantly modified by the apolipoprotein E epsilon2/epsilon3/epsilon4 genotype. *Lancet*. 2003;361(9355): 396-398.
 183. Ioannidis JP, Gwinn M, Little J, et al. A road map for efficient and reliable human genome epidemiology. *Nat Genet*. 2006;38(1):3-5.