REVIEW

Association of Apolipoprotein E Genotypes With Lipid Levels and Coronary Risk

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

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

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

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 ε*4* 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 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 ε3/ε3 individuals, ε*4* carriers have a much greater risk of coronary disease and that ε2 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 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

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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] criteria[10]) 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-analyses[11-14] who had published on variants other than apoE.

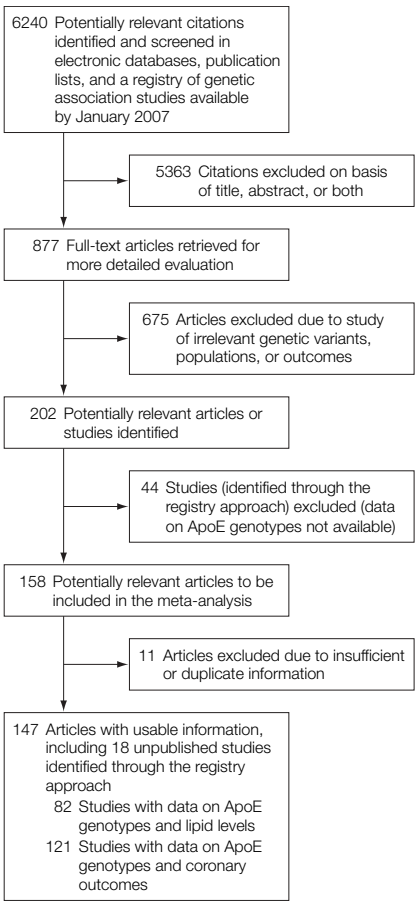
Statistical Analysis

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 ε3/ε3 genotype were defined as the reference group. Separate analyses were conducted for each genotype (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 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 funnel plots, Egger test[16] and the trim-and-fill[17] method. Heterogeneity was assessed using the Q statistic[18] and by examining prespecified groupings of studies characteristics. All analyses were performed using Stata Statistical Software, Release 9 (StataCorp LP, College Station, Texas).

Figure 1. Study Flow Diagram



RESULTS

ApoE Genotypes and Lipid Outcomes

Eighty-two studies[19-101] (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.
[a] Number of individuals with data on *ε2/ε2*, *ε2/ε3*, *ε2/ε4*, *ε3/ε3*, *ε3/ε4*, and *ε4/ε4* genotypes.
[b] Tabular data from the studies' principal investigators were provided for 51 studies (involving 79 929 noncases).
[c] Data on 50 907 of these participants were derived from previously unreported studies.
[d] Tabular data from the studies' principal investigators were provided for 42 studies (involving 24 626 cases and 55 305 controls).
[e] Data 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 study[51]). 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 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.
¶References 19-68, 88, 90-94, 96, 100-164.

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.

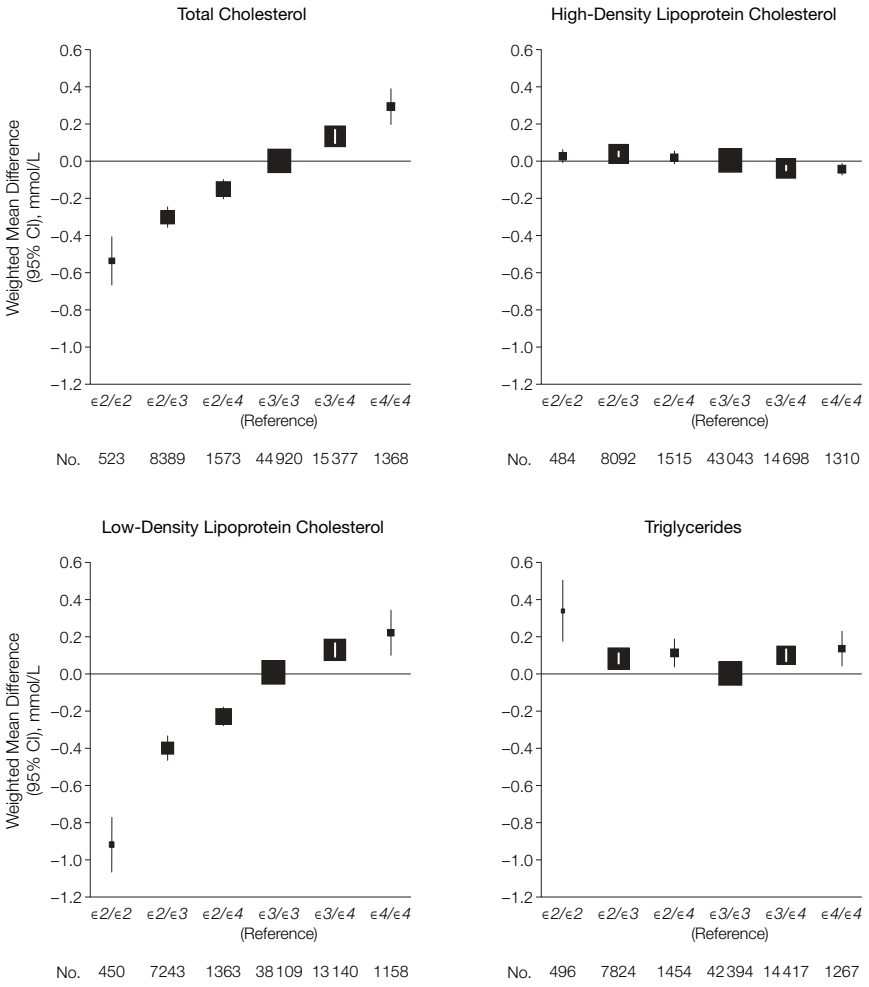
FIGURE 3 shows that the combined ORs for coronary disease in the studies with at least 500 cases were 0.80 (95% CI, 0.70-0.90) in ε2 carriers and 1.06 (95% CI, 0.99-1.13) in ε*4* carriers. With the ε3/ε3 genotype as the reference group, FIGURE 4 shows that the ORs increased progressively between ε2/ε2 (0.83; 95% CI, 0.55-1.25), ε2/ε3 (0.82; 95% CI, 0.72-0.92;), ε2/ε*4* (0.93; 95% CI, 0.81-1.07), ε3/ε*4* (1.05; 95% CI, 0.99-1.12;), and ε*4*/ε*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 survival 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 ε2 carriers and 1.66 (95% CI, 1.50-1.84) in ε*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 studies 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 ε2 carriers with ε3/ε3; or 1.06 (95% CI, 0.99-1.13) vs 1.66 (95% CI, 1.50-1.84), respectively, comparing ε*4* carriers with ε3/ε3). 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 ε*3*/ε*3* Genotype as the Reference Group



Sizes of data markers are proportional to the inverse of the variance of the weighted mean difference (ε*3*/ε*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.

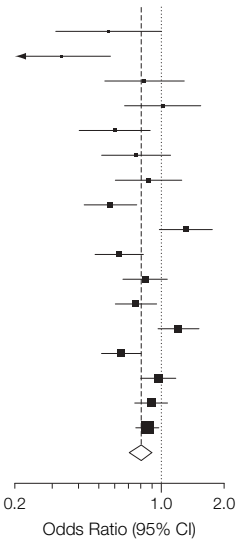
#References 25, 37, 39, 40, 44, 47, 48, 51, 62, 131, 148.
**References 27, 34, 35, 45, 59, 63, 92, 111.
††References 25, 27, 37, 39, 40, 44, 45, 47, 48, 51, 59, 62, 92, 148.
‡‡References 27, 37, 39, 40, 44, 45, 47, 48, 51, 59, 131, 148.

similar pattern of findings when cutoff 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 ε2 and 35 studies of ε4 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

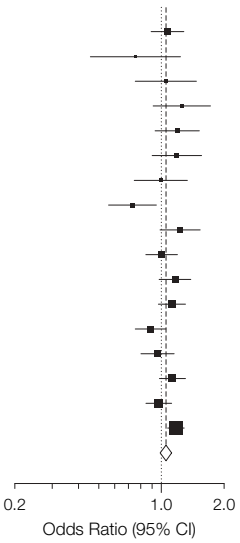
ε2 Carriers vs ε3/ε3 Genotype

Source	Cases: Total No.	Cases: ε2 Carrier, No. (%)	Cases: ε3/ε3 Genotype, No. (%)	Controls: Total No.	Controls: ε2 Carrier, No. (%)	Controls: ε3/ε3 Genotype, No. (%)	Odds Ratio (95% CI)
Kataoka et al,[35] 1996[a]	771	13 (1.7)	558 (72.4)	3370	102 (3.0)	2442 (72.5)	0.56 (0.31-1.00)
Kolovou et al,[39, 40] 2003	502	38 (7.6)	374 (74.5)	145	27 (18.6)	88 (60.7)	0.33 (0.19-0.57)
Marques-Vidal et al,[47] 2003	560	55 (9.8)	378 (67.5)	351	40 (11.4)	228 (65.0)	0.83 (0.53-1.29)
Girelli et al,[27] 2000[a]	987	86 (8.7)	693 (70.2)	380	34 (9.0)	278 (73.2)	1.04 (0.67-1.55)
Mamotte et al,[131] 2002	710	47 (6.6)	419 (59.0)	639	72 (11.3)	383 (59.9)	0.60 (0.40-0.88)
Lenzen et al,[118] 1986	570	52 (9.1)	360 (63.2)	624	75 (12.0)	393 (63.0)	0.76 (0.52-1.11)
Ye et al,[92] 2003[a]	1170	144 (12.3)	718 (61.4)	331	46 (13.9)	199 (60.1)	0.87 (0.60-1.25)
Utermann et al,[148] 1984	523	75 (14.3)	333 (63.7)	1141	244 (21.4)	617 (54.1)	0.57 (0.43-0.76)
Kardaun et al,[34] 2000[a]	661	68 (10.3)	456 (69.0)	2380	199 (8.4)	1749 (73.5)	1.31 (0.98-1.76)
Bennet et al,[59] 2006[a]	1172	95 (8.1)	707 (60.3)	1521	186 (12.2)	869 (57.1)	0.63 (0.48-0.82)
Luc et al,[44] 1994	1290	133 (10.3)	754 (58.5)	1406	178 (12.7)	844 (60.0)	0.84 (0.65-1.07)
Frikke-Schmidt et al,[25] 2000	940	93 (9.9)	528 (56.2)	9241	1216 (13.2)	5211 (56.4)	0.75 (0.60-0.95)
Orth et al,[51] 1999	2339	300 (12.8)	1490 (63.7)	1187	125 (10.5)	750 (63.2)	1.21 (0.96-1.51)
März et al,[45] 2004[a]	2230	244 (10.9)	1428 (64.0)	1033	165 (16.0)	620 (60.0)	0.64 (0.52-0.80)
Sturgeon et al,[63] 2005[a]	1037	137 (13.2)	558 (53.8)	12 947	1818 (14.0)	7157 (55.3)	0.97 (0.80-1.17)
Slooter et al,[62] 2004	1385	176 (12.7)	822 (59.4)	5014	696 (13.9)	2903 (57.9)	0.89 (0.74-1.07)
Keavney et al,[37] 2004	4484	474 (10.6)	2566 (57.2)	5757	730 (12.7)	3384 (58.8)	0.86 (0.75-0.97)
Total	21 331			47 467			0.80 (0.70-0.90)



ε4 Carriers vs ε3/ε3 Genotype

Source	Cases: Total No.	Cases: ε4 Carrier, No. (%)	Cases: ε3/ε3 Genotype, No. (%)	Controls: Total No.	Controls: ε4 Carrier, No. (%)	Controls: ε3/ε3 Genotype, No. (%)	Odds Ratio (95% CI)
Kataoka et al,[35] 1996[a]	771	198 (25.7)	558 (72.4)	3370	809 (24.0)	2442 (72.5)	1.07 (0.89-1.28)
Kolovou et al,[39, 40] 2003	502	83 (16.5)	374 (74.5)	145	26 (17.9)	88 (60.7)	0.75 (0.46-1.24)
Marques-Vidal et al,[47] 2003	560	122 (21.8)	378 (67.5)	351	70 (19.9)	228 (65.0)	1.05 (0.75-1.47)
Girell et al,[27] 2000[a]	987	197 (20.0)	693 (70.2)	380	63 (16.6)	278 (73.2)	1.25 (0.91-1.72)
Mamotte et al,[131] 2002	710	219 (30.9)	419 (59.0)	639	168 (26.3)	383 (59.9)	1.19 (0.93-1.52)
Lenzen et al,[118] 1986	570	148 (26.0)	360 (63.2)	624	136 (21.8)	393 (63.0)	1.19 (0.90-1.56)
Ye et al,[92] 2003[a]	1170	287 (24.5)	718 (61.4)	331	80 (24.2)	199 (60.1)	0.99 (0.74-1.33)
Utermann et al,[148] 1984	523	104 (19.9)	333 (63.7)	1141	265 (23.2)	617 (54.1)	0.73 (0.56-0.95)
Kardaun et al,[34] 2000	661	131 (19.8)	456 (69.0)	2380	408 (17.1)	1749 (73.5)	1.23 (0.99-1.54)
Bennet et al,[59] 2006[a]	1172	340 (29.0)	707 (60.3)	1521	416 (27.4)	869 (57.1)	1.00 (0.84-1.20)
Luc et al,[44] 1994	1290	371 (28.8)	754 (58.5)	1406	357 (25.4)	844 (60.0)	1.16 (0.98-1.39)
Frikke-Schmidt et al,[25] 2000	940	293 (31.2)	528 (56.2)	9241	2570 (27.8)	5211 (56.4)	1.13 (0.97-1.31)
Orth et al,[51] 1999	2339	504 (21.6)	1490 (63.7)	1187	286 (24.1)	750 (63.2)	0.89 (0.75-1.05)
März et al,[45] 2004[a]	2230	504 (22.6)	1428 (64.0)	1033	228 (22.1)	620 (60.0)	0.96 (0.80-1.15)
Sturgeon et al,[63] 2005[a]	1037	314 (30.3)	558 (53.8)	12 947	3561 (27.5)	7157 (55.3)	1.13 (0.98-1.31)
Slooter et al,[62] 2004	1385	351 (25.3)	822 (59.4)	5014	1275 (25.4)	2903 (57.9)	0.97 (0.84-1.12)
Keavney et al,[37] 2004	4484	1343 (29.9)	2566 (57.2)	5757	1506 (26.2)	3384 (58.8)	1.18 (1.08-1.29)
Total	21 331			47 467			1.06 (0.99-1.13)



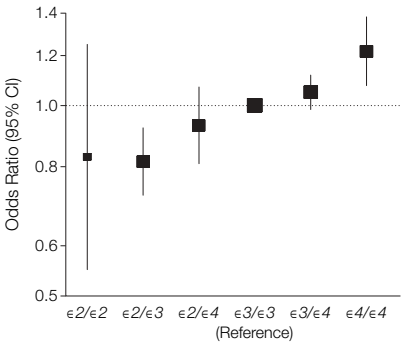
Assessment of heterogeneity: ε2 carriers vs ε3/ε3: I^2=72% (95% confidence interval [CI], 54%-83%; $P<.001$). ε4 carriers vs ε3/ε3: I^2=44% (95% CI, 2%-68%; $P=.03$). Size of data markers indicates the weight of each study in the analysis.
[a]Although these studies did not previously report on apolipoprotein 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,[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 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 comparble 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 ε2/ε2 genotype, with the latter about 2 times weaker than previously reported[4] (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.[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 ε2 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

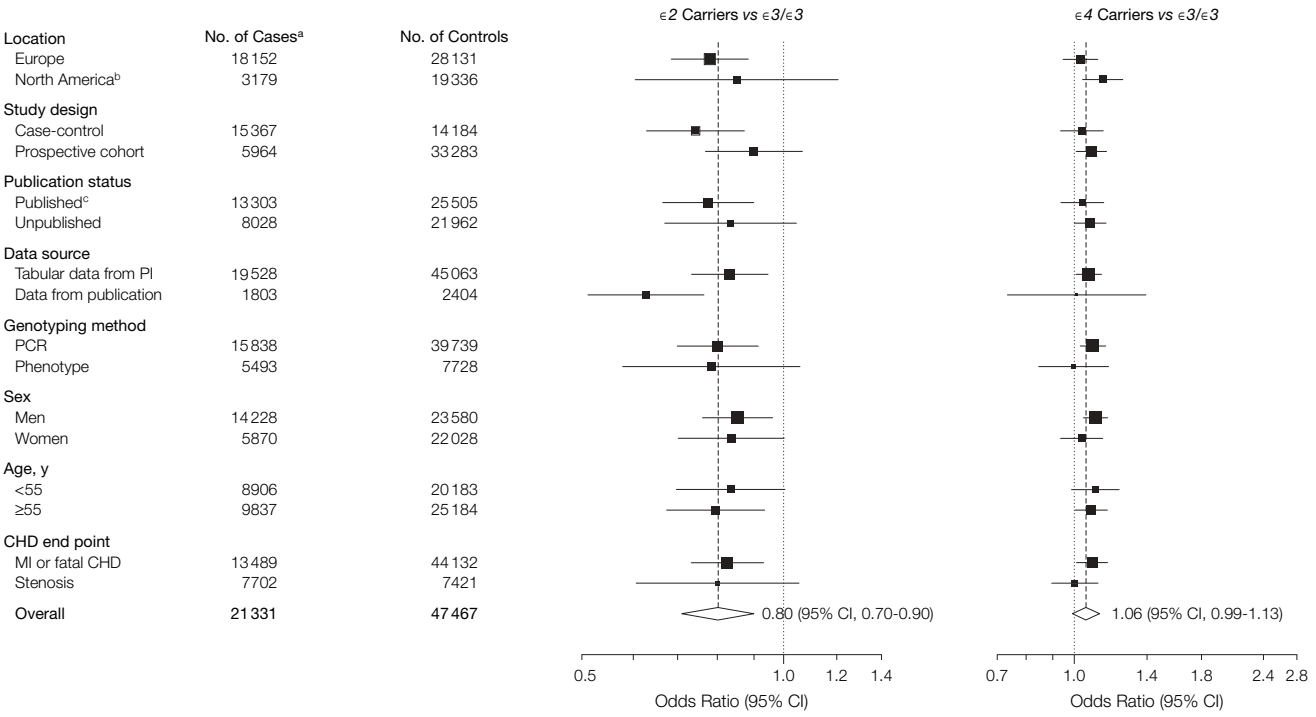
Figure 4. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes Using Individuals With the ε3/ε3 Genotype as the Reference Group, Based on Data From 21 331 Cases and 47 467 Controls in Studies With 500 or More Cases



No.	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
Cases	155	2075	450	13 142	5019	490
Controls	427	5526	1175	28 115	11 161	1063

Size of data markers is proportional to the inverse of the variance of the odds ratios (ε3/ε3 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 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.

[a] Total number for exposed and reference groups.

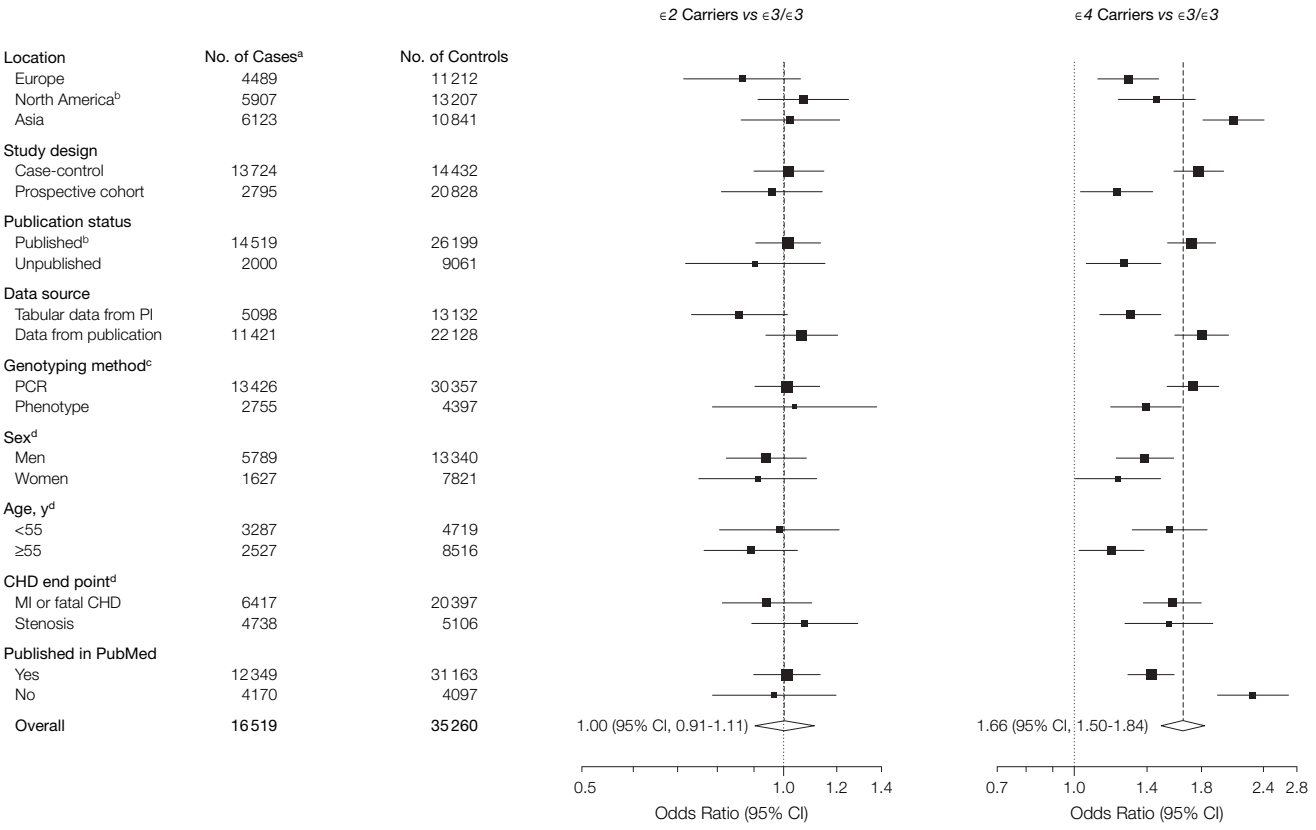
[b] Includes 1 Australian study.

[c] Refers 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 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 lipoprotein[174]) 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.[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.

[a]Total number for exposed and reference groups.

[b]Refers to status of the source study by January 2007.

[c]Genotype-specific data was not available from 3 studies.

[d]The 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 status[178]). 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 ε4 and coronary risk but underreported the unexpected inverse association between the uncommon ε2 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 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

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	
		ε2 Carriers vs ε3/ε3	ε4 Carriers vs ε3/ε3
≥1000	8	0.85 (0.74-0.97)	1.05 (0.97-1.13)
≥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.
[a]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/ε3 vs ε3/ε3				ε3/ε4 vs ε3/ε3			
	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
	ε2 Carriers vs ε3/ε3				ε4 Carriers vs ε3/ε3			
	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.
[a]Dallongeville et al.[4]
[b]Song 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 ε3/ε3 individuals, ε2 carriers have a 20% reduced risk of coronary disease whereas ε4 carriers have only a slightly increased risk.

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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, Ahlbom, Keavney, Collins, Wiman, de Faire, Danesh.
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Obtained funding: de Faire, Danesh.
Administrative, technical, or material support: Bennet, Di Angelantonio, Ye, Dahlin, Wiman, de Faire, Danesh.
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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 Genetica 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 Dijck-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 Dzimiri, 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; Aidil 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-Univesitat, Bochum, Germany; Dao-Quan Peng, MD, PhD, Central South University, Changsha, China; Daniel Petrovič, MD, PhD, University of Ljubljana, Ljubljana, Slovenja; 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 Tiret, 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.

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