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The Emerging Risk Factors Collaboration

JAMA. 2009;302(4):412-423 (doi:10.1001/jama.2009.1063)

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Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality

The Emerging Risk Factors Collaboration*

LIPOPROTEIN(A) (LP[A]) IS A LOW-density lipoprotein (LDL)-like particle synthesized by the liver that consists of an apolipoprotein B100 (apo B₁₀₀) molecule covalently linked to a very large glycoprotein known as apolipoprotein(a) (apo[a]).¹⁻³ The physiological and vascular effects of the particle remain uncertain, but Lp(a) has been shown to enter the arterial intima of humans⁴; in vitro and animal studies have reported that Lp(a) can promote thrombosis, inflammation, and foam cell formation.⁵⁻⁷

Many prospective epidemiological studies have reported positive associations of baseline Lp(a) concentration with coronary heart disease (CHD) risk.⁸⁻¹⁰ A literature-based meta-analysis of published data from 31 prospective studies reported a relative risk of 1.5 (95% confidence interval [CI], 1.3-1.6) in a comparison of people in the top third vs those in the bottom third of the Lp(a) distribution (corresponding to mean values in these categories of approximately 50 vs 5 mg/dL).¹⁰ However, such reviews⁸⁻¹⁰ have been insufficiently detailed to enable reliable assessment of the nature of any independent association with CHD and have not addressed possible

Context Circulating concentration of lipoprotein(a) (Lp[a]), a large glycoprotein attached to a low-density lipoprotein-like particle, may be associated with risk of coronary heart disease (CHD) and stroke.

Objective To assess the relationship of Lp(a) concentration with risk of major vascular and nonvascular outcomes.

Study Selection Long-term prospective studies that recorded Lp(a) concentration and subsequent major vascular morbidity and/or cause-specific mortality published between January 1970 and March 2009 were identified through electronic searches of MEDLINE and other databases, manual searches of reference lists, and discussion with collaborators.

Data Extraction Individual records were provided for each of 126 634 participants in 36 prospective studies. During 1.3 million person-years of follow-up, 22 076 first-ever fatal or nonfatal vascular disease outcomes or nonvascular deaths were recorded, including 9336 CHD outcomes, 1903 ischemic strokes, 338 hemorrhagic strokes, 751 unclassified strokes, 1091 other vascular deaths, 8114 nonvascular deaths, and 242 deaths of unknown cause. Within-study regression analyses were adjusted for within-person variation and combined using meta-analysis. Analyses excluded participants with known preexisting CHD or stroke at baseline.

Data Synthesis Lipoprotein(a) concentration was weakly correlated with several conventional vascular risk factors and it was highly consistent within individuals over several years. Associations of Lp(a) with CHD risk were broadly continuous in shape. In the 24 cohort studies, the rates of CHD in the top and bottom thirds of baseline Lp(a) distributions, respectively, were 5.6 (95% confidence interval [CI], 5.4-5.9) per 1000 person-years and 4.4 (95% CI, 4.2-4.6) per 1000 person-years. The risk ratio for CHD, adjusted for age and sex only, was 1.16 (95% CI, 1.11-1.22) per 3.5-fold higher usual Lp(a) concentration (ie, per 1 SD), and it was 1.13 (95% CI, 1.09-1.18) following further adjustment for lipids and other conventional risk factors. The corresponding adjusted risk ratios were 1.10 (95% CI, 1.02-1.18) for ischemic stroke, 1.01 (95% CI, 0.98-1.05) for the aggregate of nonvascular mortality, 1.00 (95% CI, 0.97-1.04) for cancer deaths, and 1.00 (95% CI, 0.95-1.06) for nonvascular deaths other than cancer.

Conclusion Under a wide range of circumstances, there are continuous, independent, and modest associations of Lp(a) concentration with risk of CHD and stroke that appear exclusive to vascular outcomes.

JAMA. 2009;302(4):412-423

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associations with ischemic stroke¹¹ and nonvascular outcomes. In particular, Lp(a) concentration is believed to be correlated with some lipid markers,^{12,13} but published studies have not adjusted for them in a consistent way. It has been suggested that Lp(a) is as-

*The authors/writing committee and investigators/contributors of the Emerging Risk Factors Collaboration are listed at the end of this article.

Corresponding Author: John Danesh, FRCP, Emerging Risk Factors Collaboration Coordinating Centre, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge CB1 8RN, England (erfc@phpc.cam.ac.uk).

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sociated with CHD only at very high concentrations,^{14,15} but this suggestion is controversial,¹⁶ indicating that studies with greater power than hitherto are needed to characterize the shape of any dose-response relationship reliably.

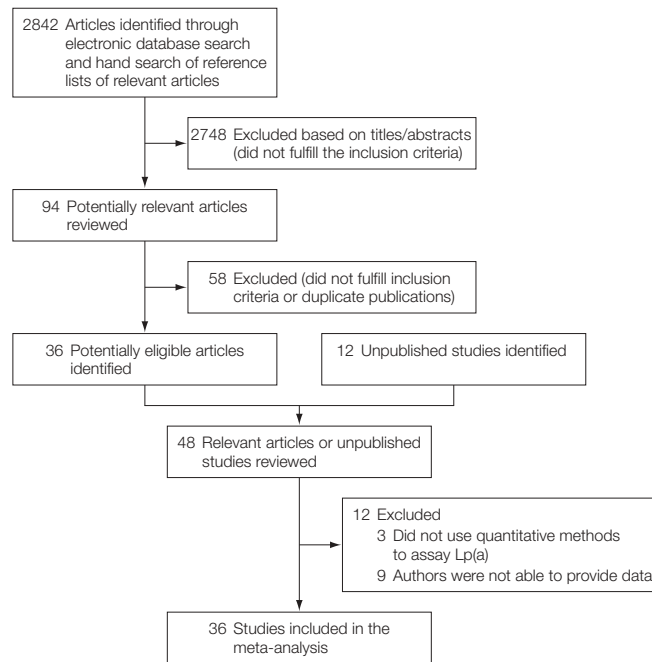
The objective of this report is to produce reliable estimates of associations of Lp(a) with CHD, stroke, and non-vascular mortality, incorporating adjustment for potential confounding by risk factors. The present study differs from previous reports on Lp(a) in several important ways that enhance its scientific value and reliability. First, it is large and comprehensive. Second, harmonization of individual records allows a consistent approach to adjustment for lipids and other potential confounders. Third, correction for within-person variation (regression dilution)^{17,18} in Lp(a) concentration and in potential confounders has been made by use of serial measurements in a subset of participants. Fourth, individual records are available for each participant, allowing detailed analyses under different circumstances (such as by age or at different lipid levels). Fifth, individuals with known preexisting CHD and stroke are excluded, limiting any effects of clinically evident disease on Lp(a) concentration (ie, reverse causality). Given the substantial variations in average Lp(a) levels across available studies, we emphasize that the current analyses compare participants only within each contributing study.

METHODS

Study Design

Details of study selection, data collection, and harmonization procedures in the Emerging Risk Factors Collaboration (ERFC) have been described previously.¹⁹ Studies were identified through electronic searches of databases, scanning of the reference lists of relevant articles (including previously published reviews), and discussion with collaborators of the ERFC (FIGURE 1). Electronic searches, not limited to the English language, were performed in MEDLINE and EMBASE for studies

Figure 1. Literature Search and Study Selection



Lp(a) indicates lipoprotein(a).

published between January 1970 and March 2009 using terms related to Lp(a) (eg, *lipoprotein[a]*, *Lp[a]*, *apo[a]*, *apolipoprotein[a]*) and cardiovascular disease outcomes (eg, *cardiovascular disease*, *coronary heart disease*, *myocardial infarction*, *stroke*).

Studies were considered for inclusion if they had baseline information on age, sex, Lp(a), and several conventional vascular risk factors; if they did not select participants on the basis of having previous cardiovascular disease; used quantitative Lp(a) assay methods; recorded cause-specific mortality and/or major vascular morbidity using accepted criteria; and had accrued more than 1 year of follow-up.

Thirty-six eligible prospective studies,^{10,15,16,20-52} including 12 that had not previously published their findings,* were included. These studies involved a total of 126 634 individuals who had no known prior history of CHD (ie, myocardial infarction [MI] or angina, which was defined in each study) or stroke at the initial (baseline) exami-

nation. The contributing studies comprise about 90% of relevant incident CHD cases identified in known Western studies (TABLE 1); several smaller studies (collectively comprising about 10% of relevant known incident CHD cases) could not supply data.⁵³⁻⁶¹ A few studies⁶²⁻⁶⁴ could not be included because they did not use quantitative assay methods.

Concomitant information was available on Lp(a), age, sex, systolic blood pressure, smoking habits, history of diabetes, body mass index, triglycerides, and total cholesterol in 106 645 participants from 30 studies. A total of 96 113 participants from 26 studies had concomitant data on all the preceding characteristics plus high-density lipoprotein (HDL) cholesterol. To measure Lp(a), 2 studies used in-house assays, 32 used commercially available assays, and 2 did not specify the assay used. Twenty-one studies used enzyme-linked immunosorbent assay methods, 9 immunoturbimetry or nephelometry, 3 immunoradiometry, and 1 enzyme immunodiffusion (eTable 1; available at <http://www.jama.com>).

*References 21, 24, 29, 31, 32, 38-42, 47, 50.

Twenty-four studies used assays insensitive to apo(a) isoforms.

In registering fatal outcomes, all contributing studies used *International Classification of Diseases* coding to at least 3 digits and ascertainment was based on death certificates. Twenty-

eight of the 36 contributing studies also involved medical records, autopsy findings, and other supplementary sources to help classify deaths (eTable 2). Twenty-nine studies used standard definitions of MI based on Monitoring Trends and Determinants in Cardio-

vascular Disease (MONICA) or World Health Organization criteria. Twenty-five studies reported diagnosis of strokes on the basis of typical clinical features and characteristic changes on brain imaging, and most attempted to provide attribution of stroke subtype.

Table 1. Characteristics of 36 Prospective Studies Contributing Data to the Current Analysis

Source ^a	Participants, No./Male, No.	Age at Survey, Mean (SD), y	Lp(a), Median (IQR), mg/dL	Median Follow-up (5th-95th Percentile)	No. of Events							
					Nonfatal MI/CHD Death	CHD Death	Nonfatal MI	Fatal MI	Fatal/Nonfatal Stroke			Non-CVD Death
					Ischemic	Hemorrhagic	Unclassified					
Cohort Studies												
AFTCAPS ^{42C}	902/745	59 (7.1)	7.6 (3.3-17.9)	5.7 (4.5-6.8)	21	1	20	1	3	0	0	7
ARIC, ²⁰ 2001	14 033/6087	54 (5.7)	18.3 (6.9-43.8)	14.1 (5.0-15.7)	850	190	660	114	431	52	16	947
ATTICA ^{21C}	1508/777	51 (11.1)	11.4 (4.9-25.2)	5.0 (5.0-5.0)	0	0	0	0	0	0	0	16
BRUN, ²² 1999	798/385	58 (11.4)	8.8 (4.4-21.6)	15.3 (3.9-15.5)	53	31	22	19	24	14	0	120
CHARL ^{24C}	165/165	70 (7.5)	10.4 (3.4-22.3)	6.8 (1.2-7.5)	19	3	16	2	0	2	7	15
CHS 1, ²³ 2003	3860/1480	72 (5.2)	12.6 (4.8-22.2)	12.1 (2.0-12.9)	592	212	380	212	367	62	36	797
COPEN, ¹⁶ 2008	7487/3144	59 (13.6)	19.1 (6.9-42.6)	7.4 (2.4-8.9)	283	36	247	0	184	39	94	525
DUBBO, ²⁵ 2002	2008/842	68 (6.7)	11.0 (5.0-27.8)	14.1 (1.8-14.9)	273	56	217	0	73	19	81	315
EAS, ²⁶ 2001	637/323	64 (5.6)	9.2 (3.7-25.4)	15.1 (2.3-15.6)	54	25	29	18	0	2	34	123
FINRISK 92, ²⁷ 2005	2201/1022	54 (6.2)	12.2 (4.5-31.7)	11.8 (4.4-11.9)	92	21	71	10	45	18	0	114
FRAMOFF, ²⁸ 1996	2850/1316	54 (9.8)	16.7 (7.1-36.6)	12.0 (5.7-14.4)	109	12	97	0	52	6	0	182
GOH ^{29C}	638/307	71 (6.7)	17.5 (10.0-37.0)	3.9 (0.3-6.9)	0	0	0	0	0	0	0	0
GRIPS, ³⁰ 1997	5784/5784	48 (5.1)	9.0 (4.0-25.0)	9.8 (4.8-10.0)	299	0	299	0	0	0	103	158
KIHD ^{31C}	1996/1996	53 (5.3)	9.6 (3.8-22.1)	19.2 (2.9-23.1)	386	11	375	6	104	34	3	239
NHANES 3 ^{32C}	4496/1923	54 (15.7)	23.0 (9.0-46.0)	7.5 (3.9-9.0)	107	107	0	38	0	0	46	321
NPHS II, ³³ 2001	2375/2375	57 (3.4)	10.9 (4.3-29.3)	8.3 (3.5-10.4)	157	18	139	16	28	7	17	97
PRIME, ³⁴ 2002	7441/7441	55 (2.9)	10.0 (5.0-30.0)	5.2 (5.0-7.3)	115	13	102	10	24	3	3	92
PROCAM, ³⁵ 1996	3198/2255	43 (10.4)	4.0 (2.0-13.0)	17.4 (5.3-18.6)	94	23	71	8	12	4	2	98
QUEBEC, ³⁶ 1998	2012/2012	56 (6.9)	19.0 (7.8-47.3)	5.3 (4.3-5.6)	53	5	48	4	0	0	9	45
SHS, ³⁷ 2002	3837/1515	56 (8.0)	3.0 (1.1-6.7)	12.5 (2.1-14.3)	416	133	283	62	8	8	177	750
TARFS ^{38C}	1400/667	54 (10.5)	10.1 (4.2-21.6)	2.2 (1.2-4.5)	3	3	0	3	0	0	3	12
ULSAM ^{39C}	1866/1866	51 (4.5)	8.3 (3.4-22.3)	27.1 (5.9-35.8)	485	124	361	60	164	42	30	457
WHITE 2 ^{40C}	7903/5467	49 (6.0)	21.0 (12.0-46.0)	7.6 (3.8-8.2)	170	23	147	18	1	0	3	86
WHS, ¹⁵ 2006	27 791/0	55 (7.1)	10.6 (4.4-32.8)	10.2 (8.4-10.8)	227	10	217	4	229	25	1	540
WOSCOPS, ⁴³ 2000	4617/4617	55 (5.6)	17.0 (7.0-50.0)	5.0 (2.8-6.0)	299	60	239	0	0	0	61	83
ZUTE ^{41C}	305/305	75 (4.5)	12.3 (6.8-28.7)	9.1 (1.1-10.1)	42	13	29	9	1	1	25	65
Subtotal	112 108/54 816	55 (9.5)	12.9 (5.0-32.7)	9.7 (3.6-15.7)	5199	1130	4069	614	1750	338	751	6204
Nested Case-Control Studies (Individually Matched)												
BUPA, ⁴⁴ 1994	1505/1505	53 (7.2)	19.2 (8.7-47.7)	23.7 (4.5-26.9)	208	208	0	170	0	0	0	173
FIA, ⁴⁵ 1998	1492/1073	55 (7.6)	26.5 (11.8-45.0)	3.7 (0.5-8.6)	519	118	401	118	0	0	0	0
FLETCHER, ⁴⁶ 2007	689/541	57 (14.3)	20.7 (7.2-59.5)	5.6 (2.2-6.4)	140	NA	NA	0	0	0	0	0
HPFS ^{47C}	726/726	63 (8.3)	13.0 (5.6-37.3)	7.7 (3.0-8.5)	220	35	185	9	0	0	0	18
MRFIT, ⁴⁸ 2001	736/736	47 (5.6)	3.4 (1.2-9.3)	7.1 (6.0-7.8)	246	19	227	13	0	0	0	5
NHS, ⁴⁹ 2005	705/0	60 (6.5)	9.5 (4.8-28.2)	8.0 (1.4-8.8)	234	27	207	27	0	0	0	10
Subtotal	5853/4581	55 (9.6)	16.0 (6.5-40.5)	7.0 (1.3-25.9)	1567	407 ^b	1020 ^b	337	0	0	0	206
Nested Case-Control Studies (Frequency-Matched)												
BRHS ^{50C}	1561/1561	52 (5.3)	6.5 (3.4-16.6)	20.3 (3.7-23.6)	461	169	292	122	0	0	0	221
GOTO 33, ⁵¹ 1993	128/128	51 (0.2)	10.2 (4.2-32.0)	12.8 (1.7-13.1)	16	7	9	4	0	0	0	7
REYK, ¹⁰ 2008	6179/4359	55 (9.0)	9.3 (2.9-22.8)	20.3 (3.3-33.5)	1850	810	1040	228	0	0	0	1476
USPHS, ⁵² 1993	805/805	60 (9.0)	9.5 (3.8-24.1)	NA	243	22	221	22	153	0	0	0
Subtotal	8673/6853	55 (8.6)	8.7 (3.2-21.8)	20.1 (3.4-32.9)	2570	1008	1562	376	153	0	0	1704
Total	126 634/65 755	55 (9.4)	12.6 (4.9-32.1)	9.8 (3.5-21.3)	9336	2545 ^b	6651 ^b	1327	1903	338	751	8114

Abbreviations: CHD, coronary heart disease; IQR, interquartile range; Lp(a), lipoprotein(a); MI, myocardial infarction; NA, data not available; non-CVD, nonvascular.

^aAppendix 3 lists the study acronyms.

^bNumbers sum to less than the total of CHD events because 1 study⁴⁶ did not provide separate data on CHD death and nonfatal MI.

^cStudies that had not previously published their findings on LP(a) and vascular risk.

Statistical Analyses

Details of the statistical methods are provided in eAppendixes 1 and 2. Normal distributions were achieved by taking natural logarithms (\log_e) of Lp(a). The pooled standard deviation across studies in baseline \log_e Lp(a) concentration was 1.25, which corresponds to about a 3.5-fold difference (ie, $e^{1.25}$) on the original scale of Lp(a) measurement in milligrams per deciliter. The primary disease outcome was CHD (ie, first-ever MI or fatal CHD), with subsidiary analyses of stroke by subtype and all cardiovascular deaths. Analyses involved a 2-stage approach with estimates of association calculated separately within each study before pooling across studies by random-effects meta-analysis. Parallel analyses using fixed-effect models yielded very similar results (eFigure 1).

For the 26 studies analyzed as prospective cohort studies, hazard ratios were calculated using Cox proportional hazard regression models stratified by sex (and, where appropriate, by study group). The assumptions of the proportionality of hazards for \log_e Lp(a) levels were satisfied. Each participant contributed only either the first nonfatal outcome or death recorded at age 20 years or older (ie, deaths preceded by nonfatal CHD or stroke were not included in the analyses).

For the 10 "nested" case-control studies within prospective cohorts, odds ratios were calculated using either conditional or unconditional logistic regression models, as appropriate. Hazard ratios and odds ratios were assumed to approximate the same relative risk and are collectively described as risk ratios (RRs).

To assess the shape of association, study-specific RRs calculated within overall quantiles (eg, tenths) of baseline Lp(a) levels were combined by multivariate random-effects meta-analysis and plotted against mean usual \log_e Lp(a) levels within each quantile. Ninety-five percent CIs were estimated from the floated variances that reflect the amount of information underlying each group (including the reference group).⁶⁵ When associations were approximately log-linear, regression coefficients were calculated to estimate the RR associated

with a 3.5-fold (ie, 1-SD) higher Lp(a). Risk ratios were adjusted progressively for age, sex, and several other conventional risk factors, with evidence of association indicated by the Wald χ^2 statistic.⁶⁶ Heterogeneity between studies was assessed by the I^2 statistic.^{67,68} (I^2 is a measure of consistency across studies: the percentage of variance in estimated \log_e RRs that is attributable to between study variation as opposed to sampling variation. Values of I^2 close to 0 indicate lack of evidence of heterogeneity.) Diversity at the study level (such as differences by study design or laboratory methods) was investigated by grouping studies by recorded characteristics and by meta-regression. Non-HDL cholesterol (calculated by subtraction of HDL cholesterol from total cholesterol) was used as the principal marker of cholesterol content in proatherogenic lipoproteins (eAppendix 2).

Because most characteristics in epidemiological studies are measured with some error and are subject to fluctuations within individuals over time, correction for such regression dilution—ideally, both in levels of Lp(a) and in potential confounding factors—can help avoid biases that may exaggerate or obscure associations.^{18,69} Regression dilution ratios for each characteristic were calculated by regressing serial measurements, taken from participants in the ERFC, on the established baseline vascular risk factors listed above plus baseline levels of Lp(a) and duration of follow-up (eAppendix 1).^{18,69}

Correction for within-person variation in Lp(a) and in potential confounders was achieved by use of conditional expectations of long-term average (ie, "usual") levels of Lp(a) and error-prone confounders predicted from these regression calibration models, and used in assessments of associations with disease risk, as previously described.⁷⁰⁻⁷² Regression calibration models allowed variability in Lp(a) to vary by its baseline levels. Analyses were performed using Stata software, release 10 (StataCorp, College Station, Texas), involving 2-sided statistical tests, a significance level of $P < .05$, and 95% CIs.

This study was approved by the Cambridgeshire Ethics Review Committee and was conducted and analyzed independently from its funders.

RESULTS

Mean age at entry of participants was 57 (SD, 8) years and 48% were women; 47% were European and 50% North American. During 1.3 million person-years at risk (mean, 10.2 years to first outcome), there were 9336 CHD outcomes, 1903 ischemic strokes, 338 hemorrhagic strokes, 751 unclassified strokes, 1091 other vascular deaths, 8114 nonvascular deaths, and 242 deaths of unknown cause (Table 1).

As expected, mean Lp(a) concentration varied across studies, but values were as diverse within groups of studies that used similar assay methods as across studies that used different methods (eFigure 2). The overall median of Lp(a) at baseline was 12.6 (interquartile range, 4.9-32.1) mg/dL. (To convert to $\mu\text{mol/L}$, multiply by 0.0357.) Blacks had more than a 100% higher Lp(a) concentration than whites (TABLE 2). Racial groups were examined separately in subanalyses.

Correlates and Within-Person Variation Over Time

Lp(a) concentration was weakly correlated with several known or suspected risk factors: positively with total and non-HDL cholesterol, apo B₁₀₀, and fibrinogen and inversely with \log_e triglycerides. Lp(a) levels were 12% (95% CI, 8%-16%) higher in women and 11% (95% CI, 4%-17%) lower in people with diabetes (Table 2). Repeat information on Lp(a) was available in 6597 participants from 7 studies (mean interval, 8.3 years) (eFigure 3). The regression dilution ratio of \log_e Lp(a), adjusted for age and sex, was 0.87 (95% CI, 0.81-0.93), which was considerably higher in these studies than those for total cholesterol (0.65; 95% CI, 0.62-0.65), HDL cholesterol (0.72; 95% CI, 0.70-0.75), \log_e triglycerides (0.63; 95% CI, 0.61-0.65), or systolic blood pressure (0.52; 95% CI, 0.49-0.55).

Associations With CHD

In analyses adjusted for age and sex only, there were continuous associations of Lp(a) with the risk of CHD, potentially consistent with either a curvilinear or a log-linear shape (FIGURE 2). Statistical tests of the compatibility of the data with a linear vs a quadratic model suggested a better fit with a curvilinear shape ($P=.003$) (eAppendix 1 and eTable 3). In analyses restricted to participants with complete information on relevant covariates, the RR for CHD per 3.5-fold higher Lp(a) level, adjusted for age and sex only, was 1.16 (95% CI, 1.11-1.22), and it was 1.13 (95% CI, 1.09-1.18) following further adjustment for systolic blood pressure, smoking, history of diabetes, and total cholesterol (TABLE 3). There was moderate heterogeneity among studies

contributing to the fully adjusted CHD result ($I^2=49%$; 95% CI, 22%-66%) (Table 3).

Findings were broadly similar in sub-analyses of coronary death and nonfatal MI (FIGURE 3 and eFigure 4), adjusted for non-HDL and HDL cholesterol (instead of total cholesterol) and adjusted for fibrinogen, C-reactive protein, or apo AI and apo B₁₀₀ (eTable 4). Because adjustment for total cholesterol may obscure associations of Lp(a) with disease risk because total cholesterol includes the cholesterol contained in Lp(a) particles, we conducted sensitivity analyses that corrected also for estimated Lp(a) cholesterol concentration,⁷³ which gave a higher RR than without such correction (eTable 4).

The findings were qualitatively similar in analyses that excluded the first 5 years of follow-up (eFigure 5), ignored regression dilution (eTable 5), and used fixed-effect models (eFigure 1). The RR, adjusted for several conventional risk factors, was 1.27 (95% CI, 1.17-1.38) in a comparison of those in the top third with those in the bottom third of baseline Lp(a) concentration (eTable 5). In the cohort studies, the rates of CHD in the top and bottom thirds of baseline Lp(a) distributions, respectively, were 5.6 (95% CI, 5.4-5.9) per 1000 person-years and 4.4 (95% CI, 4.2-4.6) per 1000 person-years.

The RRs for CHD did not vary importantly by sex, non-HDL or HDL cholesterol, triglycerides, blood pressure, diabetes, or body mass index (FIGURE 4). There was no convincing evidence of ma-

Table 2. Summary of Available Data and Correlates of Lp(a) Levels

	Summary of Available Data			Correlates of Lp(a)	
	No. of Studies	No. of Participants	Mean (SD) or %	Pearson Correlation <i>r</i> (95% CI) ^a	Percentage Difference (95% CI) in Lp(a) Levels per 1 SD Higher or Compared With Reference Category of Correlate ^b
Log _e Lp(a), mg/dL ^c	36	126 634	2.37 (1.25)		
Age at survey, y	36	126 634	57 (8)	0.01 (0.00 to 0.02)	2 (0 to 3)
Sex	36	126 634			
Male	34	66 250	52		Reference
Female	21	60 384	48		12 (8 to 16)
Race	26	91 706			
White	26	85 046	93		Reference
Black	11	6 223	7		119 (84 to 161)
Smoking status	35	122 994			
Never/former	35	89 658	73		Reference
Current	34	33 336	27		0 (-2 to 3)
History of diabetes	36	121 027			
No	35	113 991	94		Reference
Yes	34	7 036	6		-11 (-17 to -4)
Systolic blood pressure, mm Hg	35	120 643	134 (18)	0.01 (-0.01 to 0.02)	1 (0 to 2)
Body mass index ^d	35	123 740	26 (5)	-0.02 (-0.04 to 0.00)	-4 (-6 to -1)
Lipid markers, mg/dL					
Total cholesterol	36	126 128	228 (42)	0.12 (0.10 to 0.13)	16 (14 to 18)
HDL-C	33	114 889	49 (15)	0.03 (0.02 to 0.04)	4 (2 to 6)
Non-HDL-C	33	114 876	178 (42)	0.11 (0.09 to 0.13)	14 (12 to 17)
Log _e triglycerides ^c	35	124 232	4.85 (0.51)	-0.05 (-0.07 to -0.02)	-6 (-9 to -3)
Apolipoprotein AI	21	91 480	151 (29)	0.02 (0.00 to 0.04)	1 (-1 to 4)
Apolipoprotein B	23	93 058	108 (28)	0.11 (0.09 to 0.13)	15 (11 to 18)
Inflammatory markers					
Log _e C-reactive protein, mg/L ^c	27	78 153	0.62 (1.12)	0.03 (0.01 to 0.05)	4 (2 to 6)
Fibrinogen, mg/dL	25	101 346	326 (78)	0.08 (0.06 to 0.10)	11 (8 to 15)

SI conversions: To convert total cholesterol, HDL-C, and non-HDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; apolipoproteins to g/L, multiply by 0.01; C-reactive protein to nmol/L, multiply by 9.524; and fibrinogen to μmol/L, multiply by 0.0294.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

^aPearson correlation coefficients between log_e Lp(a) and the row variables, pooled across studies using random-effects meta-analysis.

^bPercentage change in Lp(a) levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean Lp[a] levels for the category vs the reference), adjusted for age and sex and allowing for random effects across studies.

^cMedian (interquartile range) values were for Lp(a), 12.6 mg/dL (4.9-32.1 mg/dL); triglycerides, 120 mg/dL (86-173 mg/dL); and C-reactive protein, 1.75 mg/L (0.82-3.87 mg/L).

^dBody mass index is calculated as weight in kilograms divided by height in meters squared.

major variations in RRs of studies using isoform-sensitive vs isoform-insensitive assays or with other features of study design recorded (eFigure 6). Subsidiary analyses restricted to people of European continental ancestry (>90% of the participants) yielded very similar findings to the overall findings described herein (data available from the authors on request), but comparisons of RRs between racial groups lacked power because data were limited on other races/ethnicities (eFigure 6). In a common set of participants, the adjusted RR for CHD per 1-SD higher Lp(a) concentration was considerably weaker than the corresponding

RR with non-HDL cholesterol (1.14 vs 1.66, respectively) (eFigure 7).

Associations With Stroke

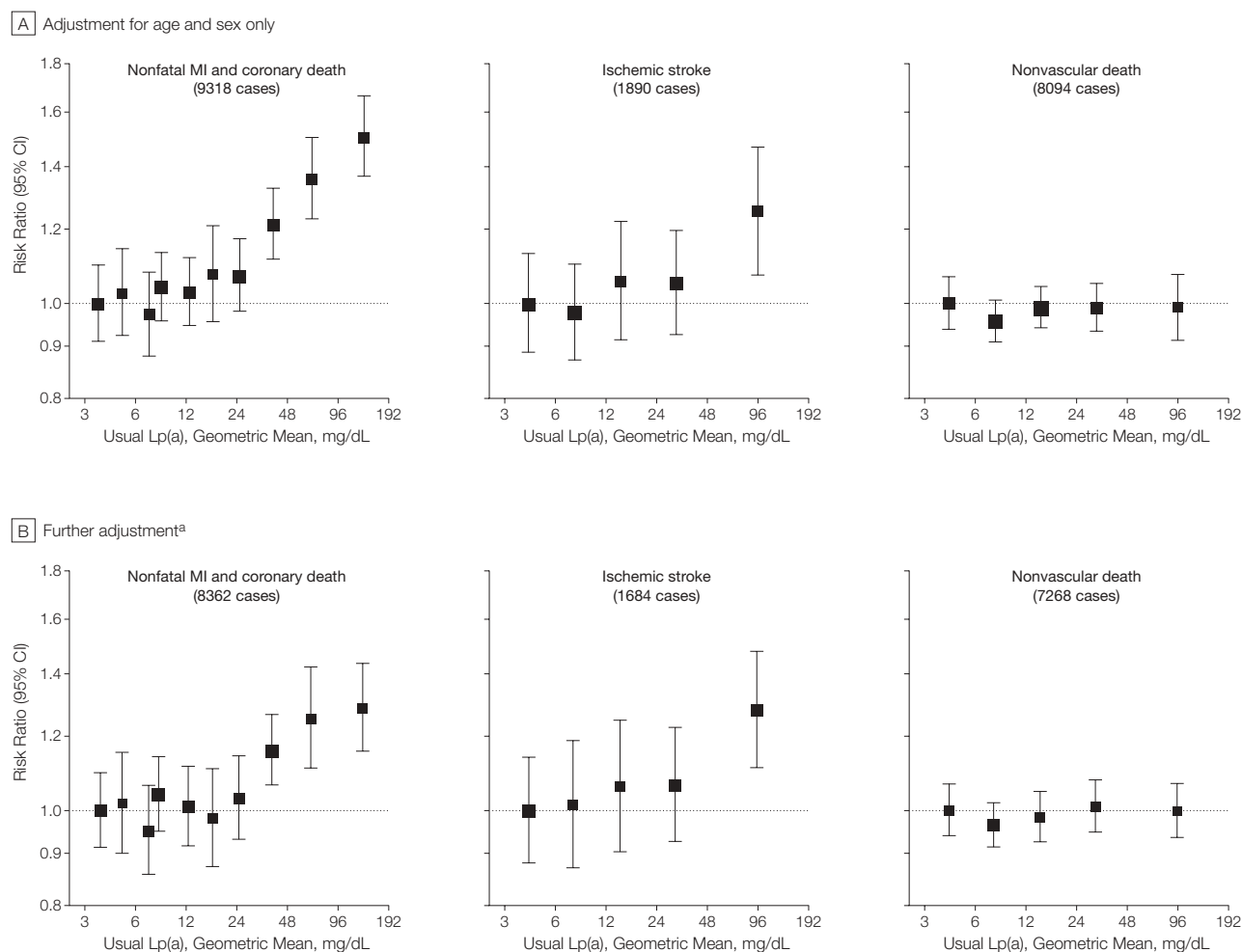
In analyses adjusted for age and sex only, the shape of association of Lp(a) with the risk of ischemic stroke was indistinct (Figure 2). Assuming a log-linear association with risk, the age-and-sex-only-adjusted RR for ischemic stroke was 1.11 (95% CI, 1.02-1.20) per 3.5-fold higher usual Lp(a) levels in analyses restricted to participants with complete information on relevant covariates (Table 3). The RR was 1.10 (95% CI, 1.02-1.18) following further adjustment for systolic blood pres-

sure, smoking, history of diabetes, and total cholesterol (Table 3). There was no clear evidence of heterogeneity among studies contributing to ischemic stroke ($P=30\%$; 95% CI, 0%-64%). The adjusted RRs per 3.5-fold higher usual Lp(a) levels were 1.01 (95% CI, 0.92-1.12) for unclassified stroke and 1.06 (95% CI, 0.90-1.26) for hemorrhagic stroke (Figure 3).

Associations With Nonvascular Mortality

The adjusted RR for the aggregate of nonvascular mortality was 1.01 (95% CI, 0.98-1.05) (Figure 3). The adjusted RRs were 1.00 (95% CI, 0.97-

Figure 2. Risk Ratios for Coronary Heart Disease, Ischemic Stroke, or Nonvascular Death by Quantile of Usual Lp(a) Level



Lp(a) indicates lipoprotein(a); MI, myocardial infarction. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Confidence intervals (CIs) were calculated using a floating absolute risk technique. Studies involving fewer than 10 cases of any outcome were excluded from the analysis of that outcome.

^aFurther adjustment for usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol. The x- and y-axes are shown on a log scale. Lowest quantiles are referents.

Table 3. Risk Ratios for Coronary Heart Disease and Ischemic Stroke per 3.5-Fold (1-SD) Higher Usual Lipoprotein(a) Levels With Progressive Adjustment for Usual Levels of Confounders^a

Adjustments	Risk Ratio (95%CI)	Wald χ^2	P, % (95% CI)
Coronary heart disease ^b			
Age and sex only	1.16 (1.11-1.22)	46	57 (36-72)
Age and sex plus			
Systolic blood pressure	1.16 (1.11-1.21)	43	57 (36-71)
Smoking status	1.16 (1.11-1.21)	42	57 (36-72)
History of diabetes	1.17 (1.12-1.22)	47	58 (37-72)
Body mass index	1.17 (1.12-1.23)	51	57 (36-71)
Total cholesterol	1.13 (1.09-1.18)	36	49 (22-66)
Ischemic stroke ^c			
Age and sex only	1.11 (1.02-1.20)	6	46 (0-72)
Age and sex plus			
Systolic blood pressure	1.09 (1.01-1.17)	6	31 (0-64)
Smoking status	1.09 (1.01-1.17)	6	30 (0-64)
History of diabetes	1.10 (1.02-1.17)	7	26 (0-62)
Body mass index	1.10 (1.03-1.18)	8	25 (0-61)
Total cholesterol	1.10 (1.02-1.18)	7	30 (0-64)

Abbreviation: CI, confidence interval.

^aAnalyses were restricted to participants with complete information on sex and all confounding variables. Risk ratios are stratified by sex and study group where appropriate. Studies with fewer than 10 cases of coronary heart disease or ischemic stroke outcomes were excluded from the analyses of that outcome.

^bFor coronary heart disease, 106 645 individuals, 8362 cases, 30 studies.

^cFor ischemic stroke, 69 539 individuals, 1684 cases, 13 studies.

1.04) for all cancer deaths and 1.03 (95% CI, 0.97-1.09) for smoking-related cancer deaths. The adjusted RR for nonvascular deaths other than cancer was 1.00 (95% CI, 0.95-1.06). There were too few cases of particular types of cancer (or other nonvascular outcomes) to enable reliable analyses by subtype. Adjusted RRs for major vascular and nonvascular outcomes were qualitatively similar in analyses that included fatal outcomes without censoring previous nonfatal outcomes (eFigure 8).

COMMENT

Contrary to previous suggestions of steep threshold effects, the current analysis of 126 634 individuals has demonstrated broadly continuous associations of Lp(a) concentration with the risk of CHD. Because these associations were only slightly reduced after adjustment for long-term average levels of lipids and other established risk factors, it increases the likelihood that Lp(a) is an independent risk factor for CHD. Lipoprotein(a) concentration is, however, a relatively modest coronary risk factor, being only about one-quarter as strong overall as non-HDL cholesterol, although Lp(a) may be-

come proportionally more important to CHD at very high concentrations owing to its potentially curvilinear risk relationship. Because associations of higher Lp(a) concentration with CHD are similar at different levels of non-HDL cholesterol, the absolute benefits of cholesterol lowering should be greater if Lp(a) concentration is high (or when absolute risk is high for some other reason).

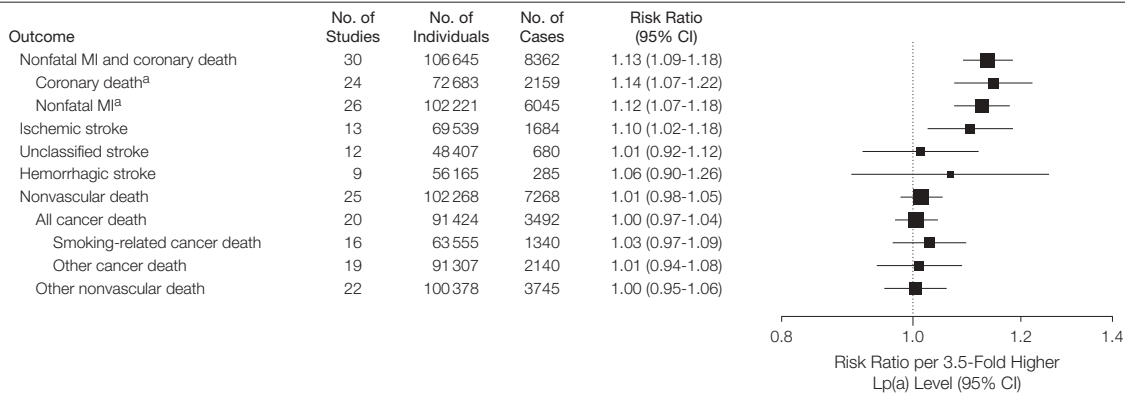
Whereas previous literature-based reviews of Lp(a) have focused only on CHD,⁸⁻¹⁰ the current individual participant meta-analysis also investigated stroke subtypes and cause-specific mortality, including nonvascular deaths. Although current data in relation to Lp(a) concentration and stroke were somewhat sparser and less distinct than those for CHD, findings were broadly similar to those for CHD. In contrast, Lp(a) concentration was unrelated to the aggregate of nonvascular mortality, including cancer and noncancer deaths. Hence, Lp(a) appears to be more specifically associated with vascular outcomes than are a number of systemic markers of inflammation that have been strongly associated with both vascular and nonvascular outcomes.^{66,74,75} As a subsidiary finding, the current analy-

ses convincingly demonstrate that Lp(a) concentration is more consistent within individuals over several years than are levels of total cholesterol, HDL cholesterol, or systolic blood pressure.

Recent large studies have reported highly significant associations of variants in or near the *LPA* gene (a locus known to strongly influence circulating Lp[a] concentration)⁷⁶⁻⁷⁸ with CHD risk.^{79,80} Together with the current findings of continuous, independent, and specific associations of Lp(a) concentration with vascular outcomes, available data are consistent with the existence of a causal relationship and increase priority for investigation of Lp(a) as a potential therapeutic target. Because the current findings show that Lp(a) concentration is a relatively modest risk factor for CHD, however, interventions capable of much more powerful and specific Lp(a) lowering than currently available may be required to demonstrate any vascular benefits in randomized trials.

Substantial modification of Lp(a) concentration has been difficult to achieve without pharmacological agents.⁸¹ Niacin and certain inhibitors of cholesteryl ester transfer protein can reduce Lp(a) by about 20% and about 40%, respectively.⁸² Contradictory findings have been reported about the effect of statins on Lp(a) concentration,^{83,84} and it remains uncertain whether statin use attenuates the CHD risk associated with Lp(a) concentration.^{2,85,86} Large randomized trials of niacin and cholesteryl ester transfer protein inhibitors in the secondary prevention of CHD are in progress.⁸⁷ Such studies may not, however, enable causal inferences because, in addition to Lp(a) lowering, these agents increase HDL cholesterol and decrease LDL cholesterol and triglyceride concentrations. Similar considerations may apply to mipomersen, an antisense oligonucleotide directed at human apo B₁₀₀ now in phase 2 clinical trials that has been shown to reduce circulating Lp(a) concentration by 70% in transgenic mice, as well as reducing LDL cholesterol, apo B₁₀₀, and oxidized phospholipids.^{88,89}

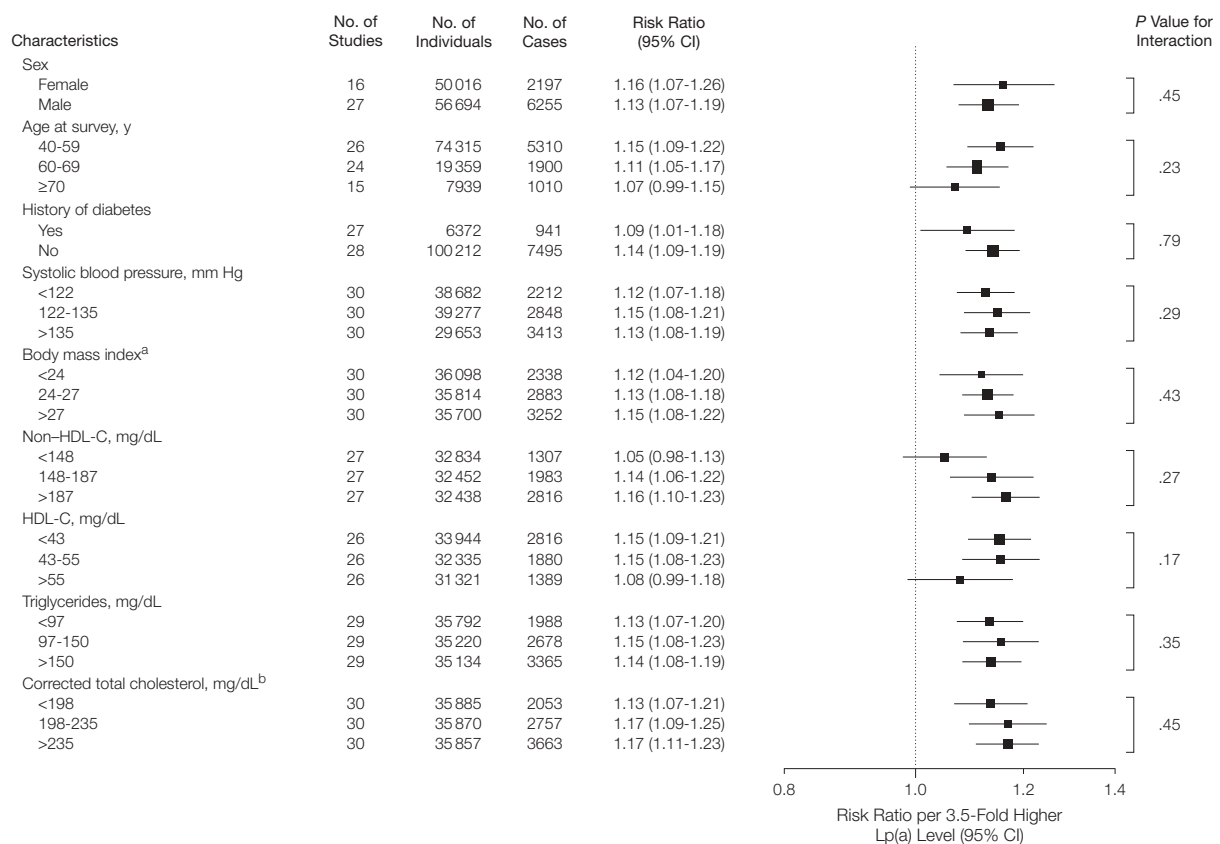
Figure 3. Risk Ratios for Vascular and Nonvascular Outcomes per 3.5-Fold (1-SD) Higher Usual Lp(a) Level, Adjusted for Cardiovascular Risk Factors



Lp(a) indicates lipoprotein(a); MI, myocardial infarction; CI, confidence interval. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Risk ratios are adjusted for age, usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol and are stratified, where appropriate, by sex and study group. Studies involving fewer than 10 cases of any outcome were excluded from the analysis of that outcome.

^aSubtotals do not add to the total number of coronary heart disease outcomes because some nested case-control studies did not subdivide outcomes into coronary death or nonfatal MI.

Figure 4. Risk Ratios for Coronary Heart Disease per 3.5-Fold (1-SD) Higher Usual Lp(a) Level, by Age and Thirds of Individual Characteristics



Lp(a) indicates lipoprotein(a); HDL-C, high-density lipoprotein cholesterol; CI, confidence interval. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Risk ratios are adjusted for age, usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol and are stratified, where appropriate, by sex and study group. Studies with fewer than 3 cases per stratum were excluded from analyses.

^aBody mass index is calculated as weight in kilograms divided by height in meters squared.

^bCorrection for the cholesterol content of Lp(a) was made by subtracting estimated Lp(a) cholesterol values from total cholesterol; Lp(a) cholesterol was estimated from Lp(a) total mass using the following equation: Lp(a)–cholesterol (mg/dL)=0.15 × Lp(a) (mg/dL) + 1.24.⁷³

Even though the first epidemiological study of Lp(a) and CHD was reported in 1972,⁹⁰ the investigation of this lipoprotein as a potential cardiovascular risk factor has been hampered by the lack of consistent approaches to its measurement. International reference material for Lp(a) laboratory standardization emerged only in 2000⁹¹ and was accepted by the World Health Organization in 2003.⁹² Even with methods that use the same standard, however, there is significant variability in measured Lp(a) concentration if assays are sensitive to variation in numbers of repeat domains in apo(a).^{93,94} Hence, in 2003 an expert panel recommended use of assay systems not sensitive to apo(a) isoforms (eFigure 2B).⁸³ Population differences can also contribute to variation in Lp(a) concentration, particularly since values differ substantially between individuals and are highly heritable.^{1,78,95} Nevertheless, pooled analyses of individual data from prospective studies should remain informative, provided that, as in the current study, analyses compare cases and noncases only within each study and explore potential diversity across groups of studies using similar assay methods.

Despite considerable scope for such diversity, it is notable that there is relatively moderate heterogeneity in RRs among the studies based in 15 different Western countries contributing to the current findings, an observation that supports the ability to generalize these data to such populations. Because more than 90% of the participants in the current study were of European continental ancestry, however, further studies are needed in nonwhite racial groups, particularly in black and South Asian populations, which have different Lp(a) concentrations.^{96,97} The RRs in the current analysis were not strongly different between studies using assays sensitive and insensitive to apo(a) isoforms (although there was, of course, some heterogeneity within each of these groups of studies). Although the findings did not differ appreciably in subgroups defined by the laboratory and population features recorded, further studies are needed that can explore in greater depth such potential sources of heterogeneity and joint effects

with other lipid markers. For example, large studies are needed to assess whether Lp(a) particles with smaller-sized apo(a) isoforms confer even higher RRs for CHD^{55,98} (such assessment was not possible in the current study because it lacked concomitant data on apo[a] isoforms). Similarly, larger studies are needed to assess proposed synergy in the promotion of vascular disease through oxidative damage (again, this was not possible in the current study because the data set lacked concomitant information on oxidized LDL and lipoprotein-associated phospholipase A₂).⁹⁹⁻¹⁰¹

CONCLUSION

Under a wide range of circumstances, there are continuous, independent, and modest associations of Lp(a) concentration with the risk of CHD and stroke that appear exclusive to vascular outcomes.

Authors/Writing Committee: The following members of the Emerging Risk Factors Collaboration take authorship responsibility for the study results: Sebat Erqou, MD, Stephen Kaptoge, PhD, Philip L. Perry, MBChB, Emanuele Di Angelantonio, MD, University of Cambridge, Cambridge, England; Alexander Thompson, PhD, University of Cambridge; Ian R. White, MSc, MRC Biostatistics Unit, Cambridge, England; Santica M. Marcovina, PhD, University of Washington, Seattle; Rory Collins, FMedSci, University of Oxford, Oxford, England; Simon G. Thompson, DSc, MRC Biostatistics Unit; John Danesh, FRCP, University of Cambridge.

Author Contributions: Drs Erqou and Danesh had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analyses. *Study concept and design:* Erqou, Kaptoge, Di Angelantonio, Thompson, White, Marcovina, Thompson, Danesh.

Acquisition of data: Erqou, Kaptoge, Perry, Di Angelantonio, Thompson, White, Collins, Thompson, Danesh.

Analysis and interpretation of data: Erqou, Kaptoge, Perry, Di Angelantonio, Thompson, White, Marcovina, Collins, Thompson, Danesh.

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

Critical revision of the manuscript for important intellectual content: Erqou, Kaptoge, Perry, Di Angelantonio, Thompson, White, Marcovina, Collins, Thompson, Danesh.

Statistical analysis: Erqou, Kaptoge, Perry, Di Angelantonio, Thompson.

Obtained funding: Danesh.

Administrative, technical, or material support: Kaptoge, Thompson, White, Marcovina, Collins, Thompson, Danesh.

Study supervision: Thompson, Danesh.

Financial Disclosures: Dr Collins reports having received research funding from AstraZeneca, Bayer, British Heart Foundation, Cancer Research UK, European Union, Kadoorie Trust, Medical Research Council, Merck, Schering, Solvay, and UK Biobank. Dr Danesh reports having received research funding from the British Heart Foundation, BUPA Foundation, diaDexus, European Union, Evelyn Trust, GlaxoSmithKline, Medical Research Council, Merck Sharp and Dohme, Roche, and Wellcome Trust. No other disclosures were reported.

Investigators/Contributors: (Appendix 1 in Danesh et al¹⁹ lists the study acronyms.) **AFTCAPS:** Robert W. Tipping, MS, Merck Research Laboratories, United States; **ALLHAT:** Charles E. Ford, PhD, University of Texas School of Public Health, United States; Lara M. Simpson, PhD, University of Texas School of Public Health, United States; **AMORIS:** Göran Walldius, MD, Karolinska Institutet, Sweden; Ingmar Jungner, MD, Karolinska Institutet, Sweden; **ARIC:** Aaron R. Folsom, MD, University of Minnesota, United States; Lloyd Chambless, PhD, University of North Carolina, United States; **ATTICA:** Demosthenes Panagiotakos, MD, Harokopio University, Greece; Christos Pitsavos, MD, University of Athens, Greece; Christina Chrysohou, MD, University of Athens, Greece; Christodoulos Stefanadis, MD, University of Athens, Greece; **BIP:** Uri Goldbourt, PhD, Sheba Medical Center, Israel; Michal Benderly, PhD, Sheba Medical Center, Israel; David Tanne, MD, Sheba Medical Center, Israel; **BRHS:** Peter Whincup, FRCP, University of London, England; S. Goya Wannamethee, PhD, University College London, England; Richard W. Morris, PhD, University College London, England; **BRUN:** Stefan Kiechl, MD, Medical University Innsbruck, Austria; Johann Willeit, MD, Medical University Innsbruck, Austria; Peter Santer, MD, Bruneck Hospital, Italy; Agnes Mayr, MD, Bruneck Hospital, Italy; **BUPA:** Nicholas Wald, FRS, Wolfson Institute of Preventive Medicine, England; **BWHHS:** Shah Ebrahim, DM, London School of Hygiene & Tropical Medicine, England; Debbie Lawlor, PhD, University of Bristol, England; **CAPS:** John Yarnell, MD, Queen's University of Belfast, Northern Ireland; John Gallacher, PhD, Cardiff University, Wales; **CASTEL:** Edoardo Casiglia, MD, University of Padova, Italy; Valérie Tikhonoff, MD, University of Padova, Italy; **CHARL:** Paul J. Nietert, PhD, Medical University of South Carolina, United States; Susan E. Sutherland, PhD, Medical University of South Carolina, United States; David L. Bachman, MD, Medical University of South Carolina, United States; **CHS:** Mary Cushman, MD, University of Vermont, United States; Bruce M. Psaty, MD, University of Washington, United States; Russ Tracy, PhD, University of Vermont, United States (see <http://chs-nhlbi.org> for acknowledgments); **COPEN:** Anne Tybjaerg-Hansen, MD, University of Copenhagen, Denmark; Børge G. Nordestgaard, MD, University of Copenhagen, Denmark; Ruth Frikke-Schmidt, MD, University of Copenhagen, Denmark; Pia R. Kamstrup, MD, University of Copenhagen, Denmark; **CUORE:** Simona Giampaoli, MD, Istituto Superiore di Sanità, Italy; Luigi Palmieri, DrStat, Istituto Superiore di Sanità, Italy; Salvatore Panico, MD, Federico II University, Italy; Diego Vanuzzo, MD, Centre for Cardiovascular Prevention, Italy; Lorenza Pilotto, MD, Centre for Cardiovascular Prevention, Italy; **DRECE:** Agustín Gómez de la Cámara, MD, Hospital 12 de Octubre, Spain; Juan A. Gómez Gerique, PhD, Hospital Marqués de Valdecilla, Spain; **DUBBO:** Leon Simons, MD, University of New South Wales, Australia; John McCallum, DPhil, Victoria University, Australia; Yecheiel Friedlander, PhD, Hebrew University, Israel; **EAS:** F. Gerry R. Fowkes, MBChB, University of Edinburgh, Scotland; Amanda Lee, PhD, University of Edinburgh, Scotland; Felicity B. Smith, PhD, University of Edinburgh, Scotland; **EPESEBOS:** James Taylor, MD, East Boston Neighborhood Health Center, United States; Jack M. Guralnik, MD, US National Institute on Aging, United States; Caroline L. Phillips, MS, US National Institute on Aging, United States; **EPESEIOW:** Robert B. Wallace, MD, University of Iowa, United States; Jack M. Guralnik, MD, US National Institute on Aging, United States; Caroline L. Phillips, MS, US National Institute on Aging, United States; **EPESENCA:** Dan G. Blazer, MD, Duke University Medical Centre, United States; Jack M. Guralnik, MD, US National Institute on Aging, United States; Caroline L. Phillips, MS, US National Institute on Aging, United States; **EPESENHA:** Caroline L. Phillips, MS, US National Institute on Aging, United States; Jack M. Guralnik, MD, US National Institute on Aging, United States; **ESTHER:** Hermann Brenner, MD, German Cancer Research Center, Germany; Elke Raum, MD, German Cancer Research Center, Germany; Heiko Müller, DrScHum, Ger-

man Cancer Research Center, Germany; Dietrich Rothenbacher, MD, German Cancer Research Center, Germany; **FA:** Jan-Håkan Jansson, MD, Umeå University, Sweden; Patrik Wennberg, MD, Umeå University, Sweden; **FINE FIN:** Aulikki Nissinen, MD, National Institute for Health and Welfare, Finland; **FINE IT:** Chiara Donfrancesco, DrStat, Istituto Superiore di Sanità, Italy; Simona Giampaoli, MD, Istituto Superiore di Sanità, Italy; **FINRISK92, FINRISK97:** Veikko Salomaa, MD, National Institute for Health and Welfare, Finland; Kennet Harald, MA, National Institute for Health and Welfare, Finland; Pekka Jousilahti, MD, National Institute for Health and Welfare, Finland; Erkki Vartiainen, MD, National Institute for Health and Welfare, Finland; **FLETCHER:** Mark Woodward, PhD, Mount Sinai School of Medicine, United States; **FRAMOFF:** Ralph B. D'Agostino, PhD, Boston University, United States; Philip A. Wolf, MD, Boston University School of Medicine, United States; Ramachandran S. Vasan, MD, Boston University School of Medicine, United States; Michael J. Pencina, PhD, Boston University, United States; **GLOSTRUP:** Else-Marie Bladbjerg, PhD, University of Southern Denmark, Denmark; Torben Jørgensen, MD, University of Copenhagen, Denmark; Lars Møller, MD, World Health Organization; Jørgen Jespersen DSc, University of Southern Denmark, Denmark; **GOH:** Rachel Dankner, MD, Gertner Institute for Epidemiology and Health Policy Research, Israel; Angela Chetrit, MSc, Gertner Institute for Epidemiology and Health Policy Research, Israel; Flora Lubin, RD, Gertner Institute for Epidemiology and Health Policy Research, Israel; **GOTO33, GOTO43:** Annika Rosengren, MD, Göteborg University, Sweden; Lars Wilhelmsen, MD, Göteborg University, Sweden; Georgios Lappas, Göteborg University, Sweden; Henry Eriksson, MD, Göteborg University, Sweden; **GOTOW:** Cecilia Björkelund, MD, Göteborg University, Sweden; Lauren Lissner, PhD, Göteborg University, Sweden; Calle Bengtsson, MD, Göteborg University, Sweden; **GRIPS:** Peter Cremer, MD, Klinikum der Universität München LMU, Germany; Dorothea Nagel, PhD, University of Munich, Germany; **HELSINAG:** Reijo S. Tilvis, MD, Helsinki University Hospital, Finland; Timo E. Strandberg, MD, Oulu University Hospital, Finland; **HONOL:** Beatriz Rodriguez, MD, University of Hawaii, United States; **HOORN:** Jacqueline Dekker, PhD, VU University Medical Center, the Netherlands; G. Nijpels, MD, Vrije Universiteit Medical Center, the Netherlands; Coen D. A. Stehouwer, MD, Maastricht University Medical Centre, the Netherlands; **HPFS:** Eric Rimm, ScD, Harvard University, United States; Jennifer K. Pai, ScD, Brigham and Women's Hospital, United States; **IKNS:** Shinichi Sato, MD, Osaka Medical Center for Health Science and Promotion, Japan; Hiroyasu Iso, MD, Osaka University, Japan; Akihiko Kitamura, MD, Osaka Medical Center for Health Science and Promotion, Japan; Hiroyuki Noda, MD, Osaka University, Japan; **ISRAEL:** Uri Goldbourt, PhD, Sheba Medical Center, Israel; **KIHD:** Jukka T. Salonen, MD, University of Kuopio, Finland; Kristiina Nyyssönen, PhD, University of Kuopio, Finland; Tomi-Pekka Tuomainen, MD, University of Kuopio, Finland; **LASA:** Dorly J. H. Deeg, PhD, VU University Medical Centre, the Netherlands; Jan L. Poppelars, MA, VU University Medical Centre, the Netherlands; **MALMO:** Bo Hedblad, MD, Lund University, Sweden; Göran Berglund, MD, Lund University, Sweden; Gunnar Engström, MD, Lund University, Sweden; **MCVDRFP:** W. M. M. Verschuren, PhD, National Institute of Public Health and the Environment, the Netherlands; Anneke Blokstra, MSc, National Institute for Public Health and the Environment, the Netherlands; **MOGERAUG1, MOGERAUG2, MOGERAUG3:** Angela Döring, MD, German Research Center for Environmental Health, Germany; Wolfgang Koenig, MD, University of Ulm Medical Center, Germany; Christa Meisinger, MD, German Research Center for Environmental Health, Germany; Wilfried Mraz, PhD, University of Munich, Germany; **MORGEN:** W. M. M. Verschuren, PhD, National Institute of Public Health and the Environment, the Netherlands; Anneke Blokstra, MSc, National Institute for Public Health and the Environment, the Netherlands; H. Bas

Bueno-de-Mesquita, PhD, National Institute for Public Health and the Environment, the Netherlands; **MOSWEGOT:** Lars Wilhelmsen, MD, Göteborg University, Sweden; Annika Rosengren, MD, Göteborg University, Sweden; Georgios Lappas, Göteborg University, Sweden; **MRFIT:** Lewis H. Kuller, MD, University of Pittsburgh, United States; Greg Grandits, MS, University of Minnesota, United States; **NCS:** Randi Selmer, PhD, Norwegian Institute of Public Health, Norway; Aage Tverdal, PhD, Norwegian Institute of Public Health, Norway; Wenche Nystad, PhD, Norwegian Institute of Public Health, Norway; **NHANES I, NHANES II, NHANES III:** R. F. Gillum, MD, Centers for Disease Control and Prevention, United States; Michael Mussolino, PhD, National Institutes of Health, United States; **NHS:** Eric Rimm, ScD, Harvard University, United States; Sue Hankinson, ScD, Harvard School of Public Health, United States; JoAnn E Manson, MD, Harvard Medical School, United States; Jennifer K. Pai, ScD, Brigham and Women's Hospital, United States; **NORTH KARELIA:** Veikko Salomaa, MD, National Institute for Health and Welfare, Finland; Kennet Harald, MA, National Institute for Health and Welfare, Finland; Pekka Jousilahti, MD, National Institute for Health and Welfare, Finland; Erkki Vartiainen, MD, National Institute for Health and Welfare, Finland; **NPHS II:** Jackie A. Cooper, MSc, University College London, England; Kenneth A Bauer, MD, Harvard Medical School, United States; **OSAKA:** Shinichi Sato, MD, Osaka Medical Center for Health Science and Promotion, Japan; Akihiko Kitamura, MD, Osaka Medical Center for Health Science and Promotion, Japan; Yoshihiko Naito, MD, Mukogawa Women's University, Japan; Hiroyasu Iso, MD, Osaka University, Japan; **OSLO:** Ingar Holme, PhD, Oslo University Hospital, Norway; Randi Selmer, PhD, Norwegian Institute of Public Health, Norway; Aage Tverdal, PhD, Norwegian Institute of Public Health, Norway; Wenche Nystad, PhD, Norwegian Institute of Public Health, Norway; **OYABE:** Hideaki Nakagawa, MD, Kanazawa Medical University, Japan; Katsuyuki Miura, MD, Shiga University of Medical Science, Japan; **PARIS1:** Pierre Ducimetiere, PhD, INSERM, France; Xavier Jouven, MD, INSERM, France; Gérard Luc, MD, University of Lille, France; **PRHP:** Carlos J. Crespo, DrPH, Portland State University, United States; Mario R. Garcia Palmieri, MD, University of Puerto Rico, United States; **PRIME:** Philippe Amouyel, MD, Institut Pasteur de Lille, France; Dominique Arveiler, MD, Université de Strasbourg, France; Alun Evans, MD, The Queens University of Belfast, Northern Ireland; Jean Ferrières, MD, University of Toulouse, France; **PROCAM:** Helmut Schulte, PhD, Assmann-Stiftung für Prävention, Germany; Gerd Assmann FRCP, Assmann-Stiftung für Prävention, Germany; **PROSPER:** James Shepherd, MD, Glasgow Royal Infirmary, Scotland; Chris J. Packard, DSc, University of Glasgow, Scotland; Naveed Sattar, FRCP, University of Glasgow, Scotland; Ian Ford, PhD, University of Glasgow, Scotland; **QUEBEC:** Bernard Cantin, MD, Institut de Cardiologie de Québec, Hôpital Laval, Canada; Benoît Lamarche, PhD, Laval University, Canada; Jean-Pierre Després, PhD, Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec, Canada; Gilles R. Dagenais, MD, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Canada; **RANCHO:** Elizabeth Barrett-Connor, MD, University of California, United States; Lori B. Daniels, MD, University of California, United States; Gail A. Laughlin, PhD, University of California, United States; **REYK:** Vilundur Gudnason, MD, University of Iceland, Iceland; Thor Aspelund, PhD, University of Iceland, Iceland; Gunnar Sigurdsson, MD, University of Iceland, Iceland; Bolli Thorsson, MD, Icelandic Heart Association, Iceland; **RIFLE:** Maurizio Trevisan, MD, Nevada System of Higher Education, United States; **ROTT:** Jacqueline Witteman, PhD, Erasmus MC, the Netherlands; Isabella Kardys, MD, Erasmus MC, the Netherlands; Monique M. B. Breteler, MD, Erasmus MC, the Netherlands; Albert Hofman, MD, Erasmus MC, the Netherlands; **SHHEC:** Hugh Tunstall-Pedoe, MD, University of Dundee, Scotland; Roger Tavendale, PhD, University of Dundee, Scotland; Gordon Lowe, DSc,

University of Glasgow, Scotland; Mark Woodward, PhD, Mount Sinai School of Medicine, United States; **SPEED:** Yoav Ben-Shlomo, PhD, University of Bristol, England; George Davey-Smith, MD, University of Bristol, England; **SHS:** Barbara V. Howard, PhD, Medstar Research Institute, United States; Ying Zhang, MD, University of Oklahoma Health Sciences Center, United States; Lyle Best, MD, Missouri Breaks Industries Research Inc, United States; Jason Umans, MD, Georgetown University Medical Center, United States; **TARFS:** Altan Onat, MD, Istanbul University, Turkey; **TROMSØ:** Inger Njølstad, MD, University of Tromsø, Norway; Ellisiv B. Mathiesen, MD, University of Tromsø, Norway; Maja-Lisa Løchen, PhD, University of Tromsø, Norway; Tom Wilsgaard, PhD, University of Tromsø, Norway; **ULSAM:** Erik Ingelsson, MD, Karolinska Institutet, Sweden; Johan Sundström, MD, Uppsala University, Sweden; Lars Lind, MD, Uppsala University Hospital, Sweden; Lars Lannfelt, MD, Uppsala University, Sweden; **USPHS:** J. Michael Gaziano, MD, Brigham and Women's Hospital, United States; Meir Stampfer, MD, Harvard School of Public Health, United States; Paul M Ridker, MD, Brigham and Women's Hospital, United States; **USPHS2:** J. Michael Gaziano, MD, Brigham and Women's Hospital, United States; Paul M Ridker, MD, Brigham and Women's Hospital, United States; **VHMPP:** Hanno Ulmer, PhD, Innsbruck Medical University, Austria; Günter Diem, MD, Agency for Preventive and Social Medicine, Austria; Hans Concin, MD, Agency for Preventive and Social Medicine, Austria; **VITA:** Alberto Tosetto, MD, San Bartolo Hospital, Italy; Francesco Rodeghiero, MD, San Bartolo Hospital, Italy; **WHITE:** Michael Marmot, FMedSci, University College London, England; Robert Clarke, MD, University of Oxford, England; Rory Collins, FMedSci, University of Oxford, England; Astrid Fletcher, PhD, London School of Hygiene and Tropical Medicine, England; **WHITEII:** Eric Brunner, PhD, University College London, England; Martin Shipley, MSc, University College London, England; **WHS:** Paul M Ridker, MD, Brigham and Women's Hospital, United States; Julie Buring, ScD, Brigham and Women's Hospital, United States; **WOSCOPS:** James Shepherd, MD, Glasgow Royal Infirmary, Scotland; Stuart Cobbe, FMedSci, BHF Glasgow Cardiovascular Research Centre, Scotland; Ian Ford, PhD, University of Glasgow, Scotland; Michele Robertson, BSc, University of Glasgow, Scotland; **XIAN:** Yao He, MD, Chinese PLA General Hospital, China; **ZARAGOZA:** Alejandro Marin Ibañez, MD, San Jose Norte Health Centre, Spain; **ZUTE:** Edith Feskens, PhD, Wageningen University, the Netherlands; Daan Kromhout, PhD, Wageningen University, the Netherlands.

Investigators/Data Management Team: Matthew Walker, PhD, University of Cambridge, England; Sarah Watson, MMath, University of Cambridge, England. **Investigators/Coordinating Center:** Rory Collins, FMedSci, University of Oxford, England; Emanuele Di Angelantonio, MD, University of Cambridge, England; Sebat Erqou, MD, University of Cambridge, England; Stephen Kaptoge, PhD, University of Cambridge, England; Sarah Lewington, DPhil, University of Oxford, England; Lia Orfei, MSc, University of Cambridge, England; Lisa Pennells, MSc, University of Cambridge, England; Philip L. Perry, MBChB, University of Cambridge, England; Kausik K. Ray, MD, University of Cambridge, England; Nadeem Sarwar, PhD, University of Cambridge, England; Myriam Alexander, MPhil, University of Cambridge, England; Alexander Thompson, PhD, University of Cambridge, England; Simon G. Thompson, DSc, MRC Biostatistics Unit, England; Matthew Walker, PhD, University of Cambridge, England; Sarah Watson, MMath, University of Cambridge, England; Frances Wensley, MSc, University of Cambridge, England; Ian R. White, MSc, MRC Biostatistics Unit, England; Angela M. Wood, PhD, University of Cambridge, England; John Danesh, FRCP, University of Cambridge, England (principal investigator). **Funding/Support:** The ERFC Coordinating Centre is supported by a program grant from the British Heart Foundation (RG/08/014) and supported by grants from

the UK Medical Research Council and the BUPA Foundation. Aspects of this work have been supported by unrestricted educational grants from GlaxoSmithKline and a grant from Merck Sharp and Dohme in relation to Lp(a). A variety of sources have supported recruitment, follow-up, and laboratory measurements in the 116 cohorts contributing to the ERFC. Investigators of several of these studies have contributed to a list naming some of these funding sources, available at <http://www.phpc.cam.ac.uk/MEU/>. Dr Erqou is supported by a Gates Cambridge Trust and Overseas Studentship Award. Drs Di Angelantonio and Thompson have been supported by UK Medical Research Council PhD studentships.

Role of the Sponsor: None of the sponsors had any 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 Information: eAppendixes 1 through 3, eTables 1 through 5, and eFigures 1 through 8 are available online at <http://www.jama.com>.

Additional Contributions: Hannah Sneath and Angela Harper, University of Cambridge, provided secretarial support.

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