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

The Emerging Risk Factors Collaboration*

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.

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LIPOPROTEIN(A) (LP[A]) IS A LOW-density lipoprotein (LDL)–like particle synthesized by the liver that consists of an apolipoprotein B100 (apo B_{100}) 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 humans[4]; 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 reviews[8-10] have been insufficiently detailed to enable reliable assessment of the nature of any independent association with CHD and have not addressed possible associations with ischemic stroke[11] 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-

CME available online at www.jamaarchivescme.com and questions on p 446.

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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.

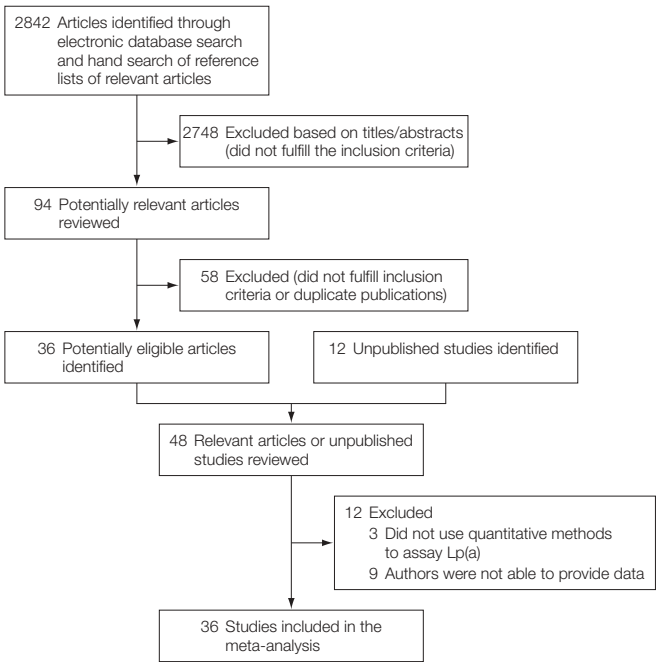
The objective of this report is to produce reliable estimates of associations of Lp(a) with CHD, stroke, and nonvascular mortality, incorporating adjustment for potential confounding by risk factors. The present study differs from previous reports on Lp(a) in several important ways that enhance its scientific 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 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*).

Figure 1. Literature Search and Study Selection



Lp(a) indicates lipoprotein(a).

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) examination. 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 studies[62-64] 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 1enzyme 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 Cardiovascular 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: Ischemic	Fatal/Nonfatal Stroke: Hemorrhagic	Fatal/Nonfatal Stroke: Unclassified	Non-CVD Death
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 (5.8-28.7)	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 (5.5-40.5)	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.
[a] eAppendix 3 lists the study acronyms.
[b] Numbers sum to less than the total of CHD events because 1 study[46] did not provide separate data on CHD death and nonfatal MI.
[c] Studies 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 µmol/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 B_{100}, 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 subanalyses 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 B_{100} (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 r (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	6223	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	7036	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).
[a] Pearson correlation coefficients between log_e Lp(a) and the row variables, pooled across studies using random-effects meta-analysis.
[b] Percentage 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.
[c] Median (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).
[d] Body mass index is calculated as weight in kilograms divided by height in meters squared.

jor 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).

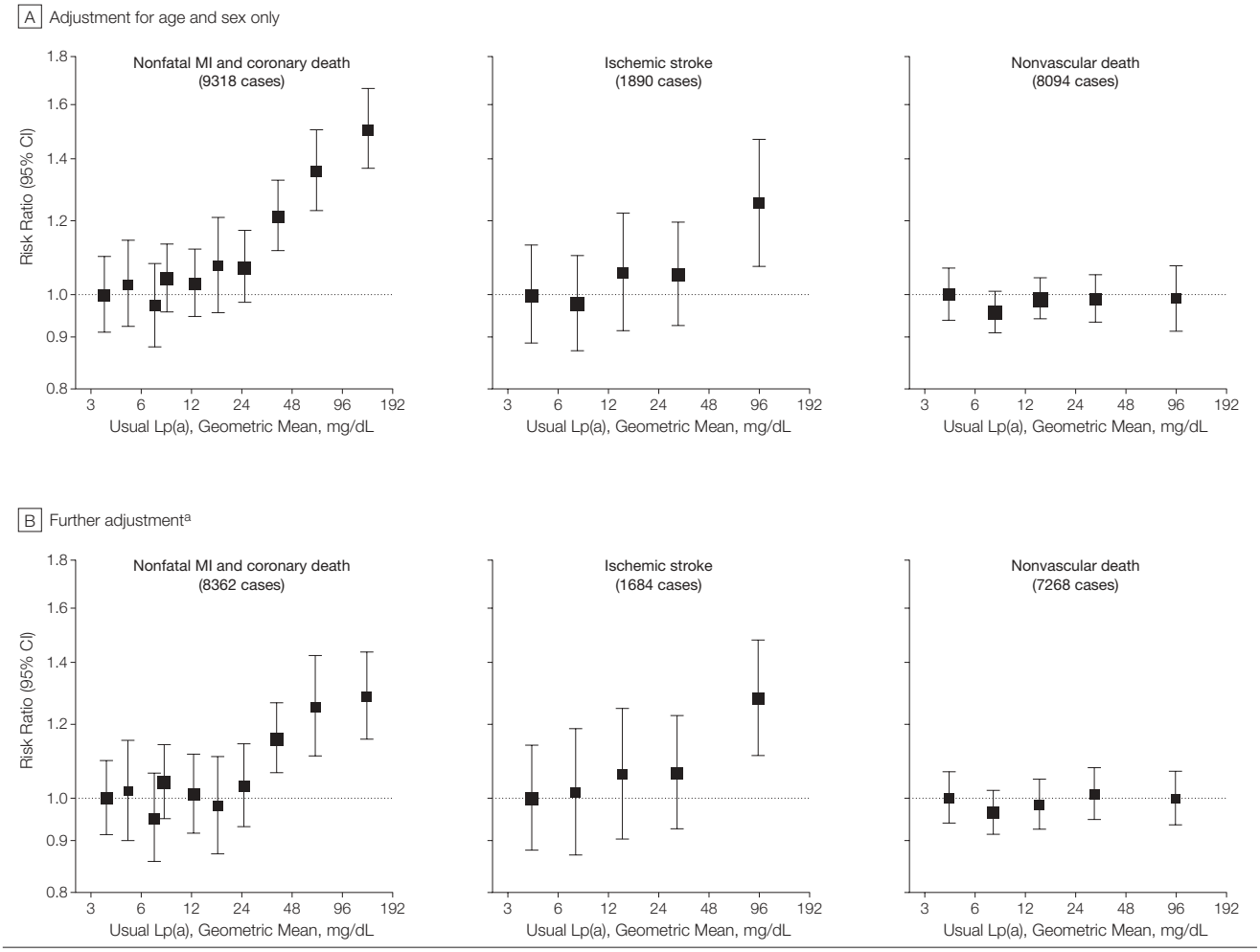
Associations With Stroke

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 pressure, smoking, history of diabetes, and total cholesterol (Table 3). There was no clear evidence of heterogeneity among studies contributing to ischemic stroke (I^2=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.
[a]Further 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	I^2, % (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.
[a] Analyses 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.
[b] For coronary heart disease, 106 645 individuals, 8362 cases, 30 studies.
[c] For 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 become 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).

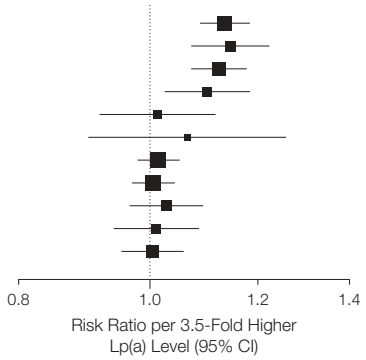
Whereas previous literature-based reviews of Lp(a) have focused only on CHD,[8-10] the current individual participant meta-analysis also investigated stroke subtypes and cause-specific mortality, including nonvascular deaths. Although current data in relation to Lp(a) concentration and stroke were somewhat 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 analyses 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 B_{100} 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 B_{100}, 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

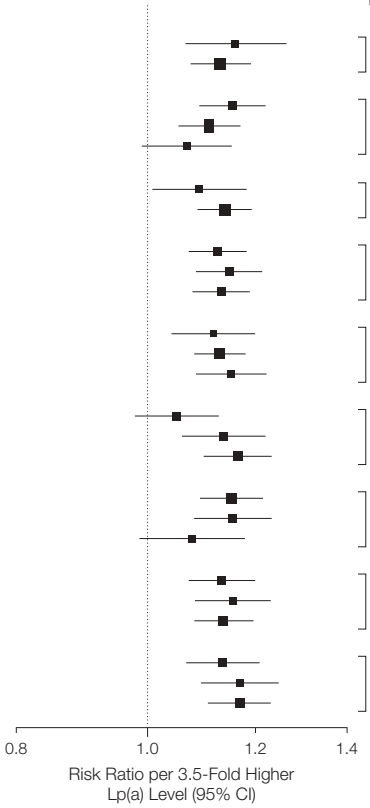
Outcome	No. of Studies	No. of Individuals	No. of Cases	Risk Ratio (95% CI)
Nonfatal MI and coronary death	30	106 645	8362	1.13 (1.09-1.18)
Coronary death[a]	24	72 683	2159	1.14 (1.07-1.22)
Nonfatal MI[a]	26	102 221	6045	1.12 (1.07-1.18)
Ischemic stroke	13	69 539	1684	1.10 (1.02-1.18)
Unclassified stroke	12	48 407	680	1.01 (0.92-1.12)
Hemorrhagic stroke	9	56 165	285	1.06 (0.90-1.26)
Nonvascular death	25	102 268	7268	1.01 (0.98-1.05)
All cancer death	20	91 424	3492	1.00 (0.97-1.04)
Smoking-related cancer death	16	63 555	1340	1.03 (0.97-1.09)
Other cancer death	19	91 307	2140	1.01 (0.94-1.08)
Other nonvascular death	22	100 378	3745	1.00 (0.95-1.06)



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.
[a]Subtotals 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

Characteristics	No. of Studies	No. of Individuals	No. of Cases	Risk Ratio (95% CI)	*P* Value for Interaction
Sex					
Female	16	50 016	2197	1.16 (1.07-1.26)	.45
Male	27	56 694	6255	1.13 (1.07-1.19)	
Age at survey, y					
40-59	26	74 315	5310	1.15 (1.09-1.22)	.23
60-69	24	19 359	1900	1.11 (1.05-1.17)	
≥70	15	7939	1010	1.07 (0.99-1.15)	
History of diabetes					
Yes	27	6372	941	1.09 (1.01-1.18)	.79
No	28	100 212	7495	1.14 (1.09-1.19)	
Systolic blood pressure, mm Hg					
<122	30	38 682	2212	1.12 (1.07-1.18)	.29
122-135	30	39 277	2848	1.15 (1.08-1.21)	
>135	30	29 653	3413	1.13 (1.08-1.19)	
Body mass index[a]					
<24	30	36 098	2338	1.12 (1.04-1.20)	.43
24-27	30	35 814	2883	1.13 (1.08-1.18)	
>27	30	35 700	3252	1.15 (1.08-1.22)	
Non–HDL-C, mg/dL					
<148	27	32 834	1307	1.05 (0.98-1.13)	.27
148-187	27	32 452	1983	1.14 (1.06-1.22)	
>187	27	32 438	2816	1.16 (1.10-1.23)	
HDL-C, mg/dL					
<43	26	33 944	2816	1.15 (1.09-1.21)	.17
43-55	26	32 335	1880	1.15 (1.08-1.23)	
>55	26	31 321	1389	1.08 (0.99-1.18)	
Triglycerides, mg/dL					
<97	29	35 792	1988	1.13 (1.07-1.20)	.35
97-150	29	35 220	2678	1.15 (1.08-1.23)	
>150	29	35 134	3365	1.14 (1.08-1.19)	
Corrected total cholesterol, mg/dL[b]					
<198	30	35 885	2053	1.13 (1.07-1.21)	.45
198-235	30	35 870	2757	1.17 (1.09-1.25)	
>235	30	35 857	3663	1.17 (1.11-1.23)	



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.
[a]Body mass index is calculated as weight in kilograms divided by height in meters squared.
[b]Correction 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 2000[91] 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 A_2).[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.

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