

# Thirty-Year Risk of Cardiovascular Disease Among Healthy Women According to Clinical Thresholds of Lipoprotein(a)

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 Supplemental content

**IMPORTANCE** Elevated lipoprotein(a) predicts high risk of cardiovascular disease among a modest proportion of healthy individuals, an issue that complicates screening guidelines.

**OBJECTIVE** To examine spline models, clinical thresholds, and percentiles of baseline lipoprotein(a) levels as 30-year determinants of cardiovascular risk.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study was conducted among female health professionals participating in the Women's Health Study, who were followed up prospectively from 1993 to 2023. Women without cardiovascular disease, cancer, and other major chronic illnesses had blood samples taken at baseline. All individuals with lipoprotein(a) measurements and/or of European ancestry with genotype information for the *LPA* rs3798220 variation were included. Data analyses were performed from January through April 2025.

**EXPOSURES** Continuously valued baseline lipoprotein(a), lipoprotein(a) clinical thresholds and percentiles, and *LPA* rs3798220 genotypes known to predict lipoprotein(a) levels among individuals of European ancestry.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were incident major cardiovascular events, coronary heart disease, ischemic stroke, and cardiovascular death. Age- and multivariable-adjusted cause-specific Cox models were used to calculate hazard ratios for the cardiovascular outcomes. The hypothesis was formulated after collection of the data.

**RESULTS** A total of 27 748 women with baseline lipoprotein(a) measurements and 23 279 women of European ancestry with rs3798220 genotype information were included (median [IQR] age, 53 [49-60] years), among whom 3707 and 3165 major cardiovascular events, respectively, accrued during a median (IQR) follow-up period of 27.8 (22.8-29.4) years. Among women with lipoprotein(a) measurements, lipoprotein(a) levels above 30 mg/dL or the 75th percentile (31 mg/dL) were associated with increased 30-year risk of major cardiovascular events and coronary heart disease. Levels above 120 mg/dL or the 99th percentile (131 mg/dL) were associated with increased risk of ischemic stroke and cardiovascular death. Multivariable adjusted hazard ratios for levels above 120 mg/dL vs below 10 mg/dL or above the 99th percentile vs below the 50th percentile (11 mg/dL) were 1.54 (95% CI, 1.24-1.92) and 1.74 (95% CI, 1.35-2.25) for major cardiovascular events, 1.80 (95% CI, 1.36-2.37) and 2.06 (95% CI, 1.49-2.84) for coronary heart disease, 1.41 (95% CI, 0.93-2.15) and 1.85 (95% CI, 1.17-2.93) for ischemic stroke, and 1.63 (95% CI, 1.16-2.28) and 1.86 (95% CI, 1.26-2.72) for cardiovascular death, respectively. Among women with genotype information, rs3798220 minor allele carriers had a higher risk of major cardiovascular events.

**CONCLUSIONS AND RELEVANCE** Per the results of this cohort study, very high lipoprotein(a) levels correlated with increased 30-year risk of cardiovascular disease among healthy women. Screening for elevated lipoprotein(a) in the general population may be warranted.

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Elevated plasma lipoprotein(a) is a strong risk factor for cardiovascular disease.<sup>1-3</sup> Importantly, lipoprotein(a) levels are predominantly determined genetically and stabilize within the first 2 years of life,<sup>4</sup> indicating that elevated lipoprotein(a) is a lifelong independent risk factor for cardiovascular disease. Lifestyle intervention and currently available pharmacological treatment only modestly impact plasma lipoprotein(a) levels,<sup>2,3</sup> and it remains to be demonstrated that isolated effective lipoprotein(a) lowering reduces risk of cardiovascular disease.<sup>5-9</sup> Consequently, contemporary guidelines do not consistently recommend lipoprotein(a) screening among individuals free from cardiovascular disease.<sup>10,11</sup>

Nevertheless, in primary prevention and/or general population cohorts, elevated lipoprotein(a) is a significant risk factor for future atherosclerotic cardiovascular disease,<sup>12-24</sup> aortic valve stenosis,<sup>25,26</sup> and cardiovascular death.<sup>14,27</sup> However, unlike other commonly measured cardiovascular risk markers, the proportion of individuals for whom lipoprotein(a) determines clinically important levels of risk may be modest in most populations,<sup>21</sup> an issue that complicates screening guidelines. In line with these observations, we have recently shown that 30-year cardiovascular risk increases gradually across quintiles of baseline high-sensitivity C-reactive protein (hsCRP) and low-density lipoprotein (LDL) cholesterol, while in contrast, only lipoprotein(a) levels in the highest quintile predict 30-year cardiovascular risk in healthy women.<sup>28</sup> Importantly, risk estimates for lipoprotein(a) may be primarily driven by those with even more extreme levels. Therefore, these findings may be less suitable for establishing thresholds for prediction and preventive interventions for lipoprotein(a).

As a follow-up study to further examine the clinical utility of lipoprotein(a) as a predictor of long-term cardiovascular risk, we here present data on the overall association of continuously modeled and clinically relevant cut points of baseline lipoprotein(a) with risk of cardiovascular disease for these same individuals across 30 years of follow-up. We hypothesized that high lipoprotein(a) levels would strongly predict long-term cardiovascular risk, while mild to moderately elevated lipoprotein(a) would not confer additional risk. To examine this hypothesis, we estimated risk of major cardiovascular events, coronary heart disease, ischemic stroke, and cardiovascular death across spline models, clinical thresholds, and percentiles of baseline lipoprotein(a) levels among 27 748 healthy women participating in the Women's Health Study and prospectively followed up since 1993. In addition, we examined the corresponding associations for genotypes of the *LPA* rs3798220 single-nucleotide variation (formerly known as single-nucleotide polymorphism) known to predict plasma levels of lipoprotein(a) and 10-year cardiovascular risk in the majority subset of women with European ancestry from the same cohort.<sup>29</sup>

## Methods

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

## Key Points

**Question** Do elevated lipoprotein(a) levels according to clinical thresholds and percentiles predict long-term risk of cardiovascular disease among healthy women?

**Findings** In this cohort study among 27 748 healthy women followed up for nearly 30 years, lipoprotein(a) levels greater than 30 mg/dL or above the 75th percentile were associated with increasing risk of major cardiovascular events and coronary heart disease. Only levels greater than 120 mg/dL or above the 99th percentile were associated with increased risk of ischemic stroke and cardiovascular death.

**Meaning** In this study, very high lipoprotein(a) levels were associated with 30-year risk of cardiovascular disease among healthy women; clinicians may consider lipoprotein(a) screening in the general population.

## Population

The Women's Health Study is an ongoing cohort study of initially healthy women recruited between 1992 and 1995 and followed up prospectively since 1993. The study was originally designed as a randomized clinical trial of aspirin and vitamin E for cardiovascular disease prevention in women aged 45 years and older with no history of cardiovascular disease, cancer, or other major chronic illness.<sup>30,31</sup> Since the trial ended in 2004, participants have been followed up continuously through January 2023 for up to 30 years, with virtually complete follow-up for vital status during this period. At baseline, participants provided information on lifestyle and demographic risk factors for disease via questionnaires and had blood samples drawn for biochemical analyses and DNA extraction.<sup>32</sup> Race was self-reported in the baseline questionnaire and verified by genome-wide genetic data. All women with available baseline lipoprotein(a) measurements and/or rs3798220 genotype information were included. However, only women with genetically verified European ancestry were included in the analyses of rs3798220 to limit known ancestry-related genotype-phenotype heterogeneity at the *LPA* locus. All participants provided written informed consent, and the study protocol was approved by the institutional review board of Brigham and Women's Hospital.

## Lipoprotein(a)

Plasma lipoprotein(a) levels were measured in all baseline samples at once using the Denka Seiken assay (Denka).<sup>12</sup> Participants were grouped according to the following lipoprotein(a) clinical thresholds and percentiles: less than 10 mg/dL, 10 to less than 30 mg/dL, 30 to less than 60 mg/dL, 60 to less than 90 mg/dL, 90 to less than 120 mg/dL, and above or equal to 120 mg/dL. Percentiles were grouped in the following categories: below or equal to the 50th percentile (<11 mg/dL), 51st to the 75th (11-33 mg/dL), 75th to the 90th (33-66 mg/dL), 91st to the 95th (66-83 mg/dL), 96th to the 99th (83-131 mg/dL), and above the 99th percentile ( $\geq 131$  mg/dL). The cut points were chosen to examine risk differences across individuals with moderately to extremely elevated lipoprotein(a) levels, as done previously by us and others.<sup>12,13,19</sup>

### LPA rs3798220 Genotyping

Women's Health Study participants had previously been genotyped for approximately 360 000 genome-wide single-nucleotide variations, including rs3798220.<sup>32</sup>

### Outcomes

The primary outcome was the first occurrence of a major cardiovascular event, encompassing incident myocardial infarctions, coronary revascularizations, incident ischemic stroke, and death from cardiovascular causes. Secondary outcomes were coronary heart disease, including fatal and nonfatal myocardial infarctions and coronary revascularization, fatal and nonfatal ischemic stroke, and death from cardiovascular causes. Information on each event was obtained from medical records, death certificates, and autopsy reports and adjudicated by an end point committee consisting of study-affiliated physicians.

### Statistical Analysis

First, to accurately assess the association between continuously modeled lipoprotein(a) and risk of cardiovascular disease, restricted cubic and penalized smoothing spline curves of hazard ratios for major cardiovascular events, coronary heart disease, ischemic stroke, and cardiovascular death were constructed across baseline lipoprotein(a) levels from Cox proportional hazards regressions multivariably adjusted for age, blood pressure, smoking status, alcohol intake, history of diabetes, hormone therapy, LDL cholesterol, and hsCRP at baseline. All analyses, including the subsequent estimates, were further adjusted for randomized treatment group assignment in the original trial. We used 3 knots at the Harrell recommended percentiles for the restricted cubic splines, since curves from 4 knots showed signs of overfitting upon visual inspection.<sup>33</sup> For the penalized splines, the number of degrees of freedom was chosen automatically based on the Akaike information criterion.

Second, we constructed age-adjusted cumulative incidence curves and calculated the corresponding age- and multivariable-adjusted (as previously described) hazard ratios for major cardiovascular events, coronary heart disease, ischemic stroke, and cardiovascular death across the lipoprotein(a) clinical threshold and percentile groups. For these analyses, we used cause-specific Cox proportional hazards regression models accounting for noncardiovascular, noncoronary, or noncerebrovascular deaths as competing risks when examining associations with risk of major cardiovascular events or cardiovascular deaths, coronary heart disease, or ischemic stroke. The cumulative incidence curves were constructed by stratifying the underlying Cox models according to the lipoprotein(a) exposure groups. To test for a trend, each participant was assigned the median lipoprotein(a) value for the respective group, and these median values were treated as independent continuous predictors in the regression models. We evaluated the proportional hazards assumption by visual inspection of the cumulative incidence curves and formally tested the independence of the Schoenfeld residuals over time.

Third, the corresponding age-adjusted hazard ratios for major cardiovascular events were calculated for individuals who were heterozygous for the lipoprotein(a)-increasing minor

allele of the rs3798220 variant vs homozygotes for the major allele. Due to the small sample of minor allele homozygotes ( $n = 13$ ), the risk estimate in this group could not be defined.

Finally, we calculated the concordance index (C index) for 30-year risk of total cardiovascular disease (referred to as CVD: coronary heart disease, stroke, and heart failure) and atherosclerotic CVD (ASCVD: coronary heart disease and stroke) in the Women's Health Study using the American Heart Association (AHA) Predicting Risk of Cardiovascular Disease Events (PREVENT) equation with and without the addition of baseline lipoprotein(a) levels.<sup>34,35</sup>

Two-sided  $\alpha = .05$  was considered significant. All analyses were performed using R version 4.4.2 (R Foundation) at the Division of Preventive Medicine at Brigham and Women's Hospital in Boston, Massachusetts.

### Sensitivity Analyses

As sensitivity analyses, we (1) constructed restricted cubic splines with 4 knots at the Harrell recommended percentiles, 3 knots at 40 mg/dL lipoprotein(a) intervals, and with lipoprotein(a) levels winsorized at the 99th percentile (131 mg/dL), and calculated hazard ratios for major cardiovascular events (2) for aspirin treatment vs placebo assignment in the original trial in strata of lipoprotein(a) thresholds, since aspirin interacts with the effect of the rs3798220 variations on risk of cardiovascular disease,<sup>29,36</sup> (3) for individuals with baseline lipoprotein(a) above 50 and 70 mg/dL vs below 10 mg/dL, and (4) across lipoprotein(a) clinical thresholds stratified by LDL cholesterol levels at baseline. To formally test for an interaction between LDL cholesterol and lipoprotein(a), we (5) included an interaction term between baseline lipoprotein(a) and LDL cholesterol to the multivariable-adjusted Cox model described previously.

## Results

Among 28 345 women who had blood samples taken at study enrollment, 27 748 individuals had baseline lipoprotein(a) measurements, and 23 179 women of European ancestry had rs3798220 genotype information (median [IQR] age, 53 [49-60] years). During a median (IQR) follow-up duration of 27.8 (22.8-29.4) years, there were 3707 and 3165 incident major cardiovascular events, 1985 and 1696 fatal or nonfatal coronary events, 1041 and 807 fatal or nonfatal ischemic stroke events, and 1543 and 1325 cardiovascular deaths among the women with baseline lipoprotein(a) measurements and women with rs3798220 genotype information, respectively. Baseline characteristics are presented in the **Table**. The distribution of lipoprotein(a) levels according to clinical thresholds and percentiles are presented in eFigure 1 in **Supplement 1**. Less than 1.5% of the participants had missing information on at least 1 covariable (**Table**) and were not included in the multivariable regression analyses.

### Cardiovascular Risk Across Continuously Modeled Lipoprotein(a)

Restricted cubic spline-modeled hazard ratios for major cardiovascular events increased gradually with increasing baseline lipoprotein(a) levels up to a hazard ratio of approxi-

Table. Baseline Characteristics of the Women's Health Study Participants by Clinical Threshold and Percentile Groups

Characteristic <sup>a</sup>	Lipoprotein(a) clinical threshold in mg/dL, No. (%)					
	<10	10-<30	30-<60	60-<90	90-<120	≥120
Percentile	<48th	48th-<74th	74th-<88th	88th-<97th	97th-<98th	≥98th
Individuals, No.	13 355	7054	3913	2374	625	427
Age, median (IQR), y	53 (49-59)	53 (49-59)	53 (49-59)	54 (50-60)	53 (49-60)	54 (50-60)
Current smokers	1559 (12)	807 (11)	439 (11)	270 (11)	84 (13)	54 (13)
Daily alcohol intake	1401 (10)	731 (10)	367 (9)	256 (11)	71 (11)	43 (10)
Hypertension	3304 (25)	1775 (25)	943 (24)	645 (27)	171 (27)	125 (29)
History of diabetes	350 (3)	157 (2)	83 (2)	50 (2)	22 (4)	17 (4)
Hormone therapy	6224 (47)	2793 (40)	1622 (42)	993 (42)	252 (41)	176 (41)
LDL cholesterol, median (IQR), mg/dL	116 (96-139)	124 (103-146)	123 (103-145)	131 (111-154)	138 (117-159)	143 (122-163)
hsCRP, median (IQR), mg/dL	0.21 (0.08-0.44)	0.19 (0.08-0.41)	0.19 (0.08-0.43)	0.22 (0.09-0.47)	0.23 (0.10-0.44)	0.21 (0.09-0.45)
Characteristic	Lipoprotein(a) percentile groups, No. (%)					
	≤50th	51st-75th	76th-90th	91st-95th	96th-99th	>99th
Range, mg/dL	<11	11-<33	33-<66	66-<83	83-<131	≥131
Individuals, No.	13 892	6921	4163	1386	1109	277
Age, median (IQR), y	53 (49-59)	53 (49-59)	53 (49-59)	54 (50-60)	53 (49-59)	54 (50-61)
Current smokers	1622 (12)	796 (12)	464 (11)	160 (12)	133 (12)	38 (14)
Daily alcohol intake	1456 (10)	721 (10)	401 (10)	143 (10)	118 (11)	30 (11)
Hypertension	3432 (25)	1748 (25)	1002 (24)	391 (28)	308 (28)	82 (30)
History of diabetes	360 (3)	152 (2)	94 (2)	21 (2)	42 (4)	10 (4)
Hormone therapy	6442 (46)	2742 (40)	1719 (41)	589 (43)	458 (41)	110 (40)
LDL cholesterol, median (IQR), mg/dL	117 (96-139)	124 (104-147)	124 (103-146)	133 (112-155)	136 (116-158)	146 (128-168)
hsCRP, median (IQR), mg/dL	0.20 (0.08-0.44)	0.19 (0.08-0.41)	0.20 (0.08-0.43)	0.23 (0.09-0.49)	0.22 (0.09-0.45)	0.20 (0.09-0.45)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

SI conversion notes: To convert LDL cholesterol from mg/dL to mmol/L, multiply by 0.0259; hsCRP, from mg/dL to mg/L, multiply by 10.

<sup>a</sup> Information on smoking status, alcohol intake, blood pressure, history of diabetes, and hormone therapy could not be obtained for 24, 6, 318, 15, and 55 participants, respectively.

mately 1.8 for a lipoprotein(a) level of 175 mg/dL vs the median (11 mg/dL) (Figure 1; see eFigure 2 in Supplement 1 for hazard ratios on a natural logarithmic scale). The increase in risk was similar but more pronounced for coronary heart disease, reaching a hazard ratio of approximately 2.5, while elevated lipoprotein(a) from low to high levels was associated with a less pronounced increase in risk of ischemic stroke and cardiovascular death, with corresponding hazard ratios of approximately 1.6 and 1.3, respectively (Figure 1). Results were similar when penalized smoothing splines were used (Figure 2); however, lipoprotein(a) levels below approximately 125 mg/dL showed a less consistent association with risk of ischemic stroke.

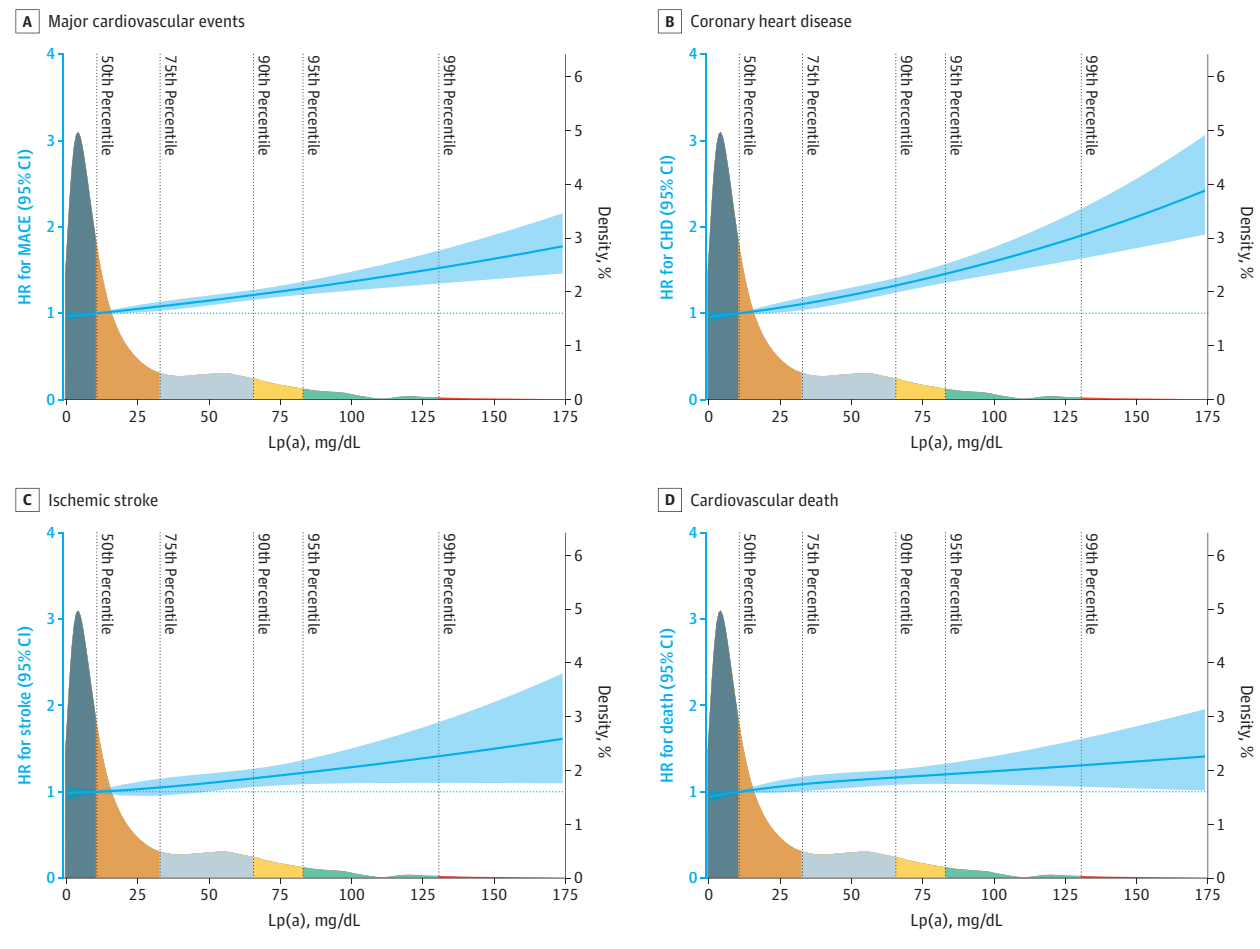
### Major Cardiovascular Events Across Clinical Thresholds and Percentiles

Individuals with lipoprotein(a) levels above or equal to 30 mg/dL had a higher 30-year cumulative incidence of major cardiovascular events compared to individuals with lower levels (Figure 3). The cumulative incidence increased in a stepwise fashion from individuals with lipoprotein(a)

levels between 30 and 60 mg/dL to individuals with lipoprotein(a) levels above or equal to 120 mg/dL (test for trend:  $P < .001$ ). There was a similar increase in cumulative risk across percentile groups from individuals with lipoprotein(a) below the 75th percentile ( $\geq 33$  mg/dL) to individuals with levels above the 99th percentile ( $\geq 131$  mg/dL) (test for trend:  $P < .001$ ) (eFigure 3 in Supplement 1). Corresponding age- and multivariable-adjusted hazard ratios were 1.75 (95% CI, 1.42-2.17) and 1.54 (95% CI, 1.24-1.92) for individuals with lipoprotein(a) levels above or equal to 120 vs below 10 mg/dL and 1.98 (95% CI, 1.54-2.53) and 1.74 (95% CI, 1.35-2.25) for individuals with lipoprotein(a) levels above the 99th percentile vs below or equal to the 50th percentile ( $< 11$  mg/dL), respectively (Figure 4).

The proportional hazards assumption appeared to be violated for both clinical threshold and percentile groups for the primary outcome (test for nonindependence of the scaled Schoenfeld residuals over time:  $P = .02$ ), likely due to an abrupt increase in the cumulative incidence of coronary heart disease ( $P = .02$ ) among individuals with very high lipoprotein(a) levels at 5 years of follow-up (Figure 3).

**Figure 1. Restricted Cubic Spline Curves of 30-Year Hazard Ratios (HRs) for Major Cardiovascular Events (A), Coronary Heart Disease (B), Ischemic Stroke (C), and Cardiovascular Death (D)**



The analyses included all 27 748 individuals from the Women's Health Study with available lipoprotein(a) (Lp[a]) measurements, among whom there were 3707 incident major cardiovascular events (MACE), 1985 coronary events, 1041 ischemic stroke events, and 1543 cardiovascular deaths. The curves were constructed from Cox proportional hazards regressions adjusted for age, blood pressure, smoking status, alcohol intake, history of diabetes, hormone therapy,

low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein, and with 3 knots at the Harrell recommended percentiles. Density plots illustrate the distribution of baseline Lp(a) levels in the population and are colored in accordance with the corresponding percentile groups. CHD indicates coronary heart disease.

### Coronary Heart Disease and Ischemic Stroke Across Clinical Thresholds and Percentiles

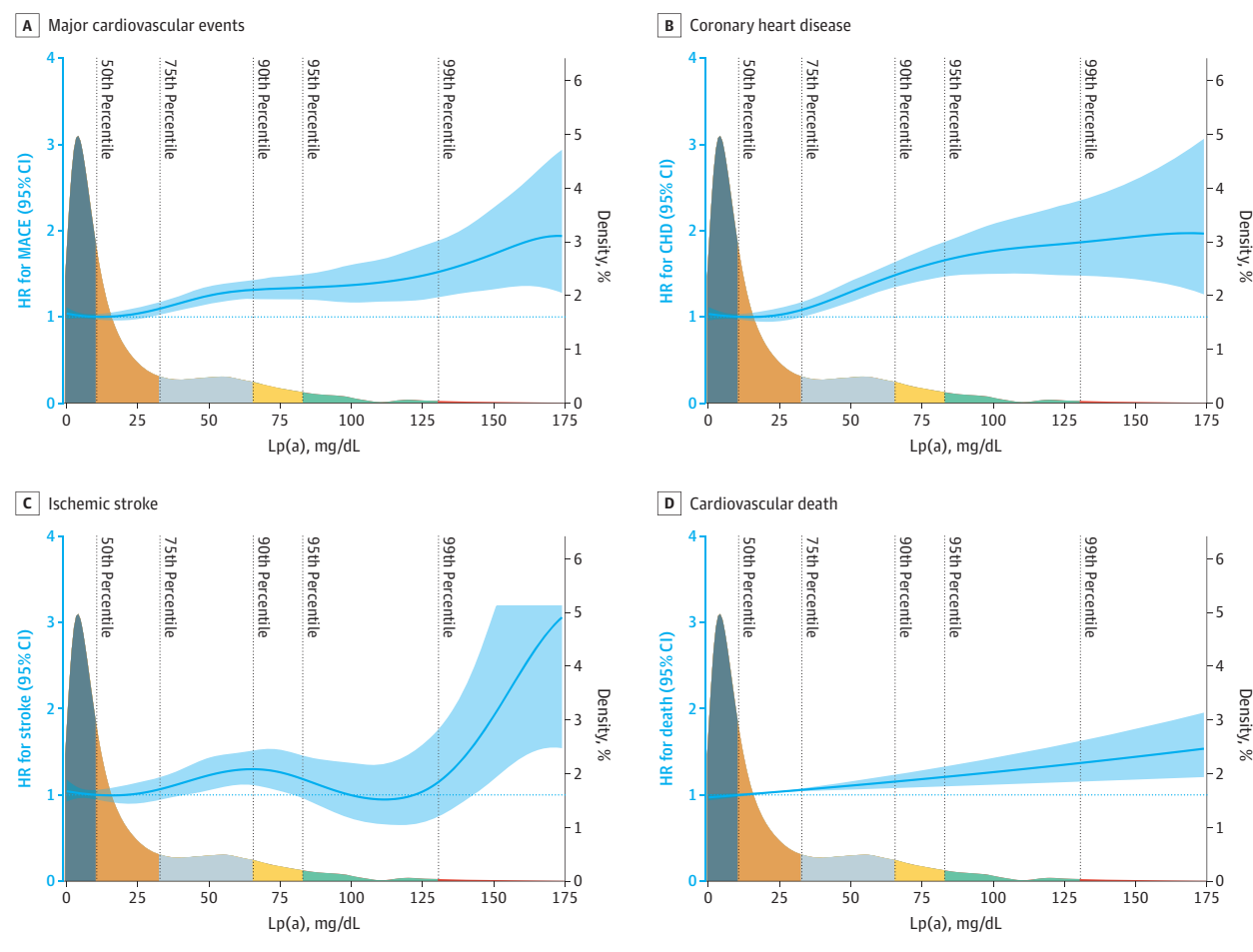
There was a stepwise increase in cumulative incidence of coronary heart disease across lipoprotein(a) clinical thresholds and percentiles from above 30 mg/dL (Figure 3) or above the 75th percentile ( $\geq 33$  mg/dL) (eFigure 3 in Supplement 1) (test for trend:  $P < .001$ ). Individuals with very high lipoprotein(a) ( $>120$  mg/dL or  $>99$ th percentile [ $\geq 131$  mg/dL]) had a higher cumulative incidence of ischemic stroke (Figure 3; eFigure 3 in Supplement 1) compared to individuals with lower levels (test for trend across clinical thresholds:  $P = .006$ ; test for trend across percentiles:  $P = .005$ ); however, individuals with lipoprotein(a) between 90 and 120 mg/dL or in the 96th to 99th percentile (83- $<131$  mg/dL) did not appear to be at increased risk. Multivariable adjusted hazard ratios for coronary heart disease for individuals with lipoprotein(a) levels above 120 vs below 10 mg/dL or above the 99th vs below or equal to the 50th

percentile ( $<11$  mg/dL) were 1.80 (95% CI, 1.36-2.37) and 2.06 (95% CI, 1.49-2.84) (Figure 4). Corresponding hazard ratios for ischemic stroke were 1.41 (95% CI, 0.93-2.15) and 1.85 (95% CI, 1.17-2.93), respectively.

### Cardiovascular Death Across Clinical Thresholds and Percentiles

Individuals with lipoprotein(a) above 120 mg/dL or above the 99th percentile ( $\geq 131$  mg/dL) had a higher cumulative incidence of cardiovascular death compared to individuals with lower lipoprotein(a) levels (Figure 3; eFigure 3 in Supplement 1) (test for trend:  $P < .001$ ). Corresponding multivariable-adjusted hazard ratios were 1.63 (95% CI, 1.16-2.28) for individuals with lipoprotein(a) levels above or equal to 120 vs below 10 mg/dL and 1.86 (95% CI, 1.26-2.75) for individuals above the 99th vs below or equal to the 50th percentile ( $<11$  mg/dL) (eFigure 4 in Supplement 1). Individuals with less extreme

Figure 2. Penalized Smoothing Spline Curves of 30-Year Hazard Ratios (HRs) for Major Cardiovascular Events (A), Coronary Heart Disease (B), Ischemic Stroke (C), and Cardiovascular Death (D)



The analyses included all 27 748 individuals from the Women's Health Study with available lipoprotein(a) [Lp(a)] measurements, among whom there were 3707 incident major cardiovascular events (MACE), 1985 coronary events, 1041 ischemic stroke events, and 1543 cardiovascular deaths. The curves were constructed from Cox proportional hazards regressions adjusted for age, blood pressure, smoking status, alcohol intake, history of diabetes, hormone therapy,

low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein, and with the number of degrees of freedom chosen for optimized smoothing based on the Akaike information criterion. Density plots illustrate the distribution of baseline Lp(a) levels in the population and are colored in accordance with the corresponding percentile groups. CHD indicates coronary heart disease.

lipoprotein(a) elevations were not at increased risk of cardiovascular death.

### Cardiovascular Risk Across rs3798220 Genotypes

Of the 23 179 women of European ancestry who were genotyped for the rs3798220 variations, 22 349 were homozygotes for the major allele and 817 were heterozygotes for the lipoprotein(a)-increasing minor allele. As previously shown, median (IQR) baseline lipoprotein(a) levels were 10 (4-29) mg/dL and 82 (21-104) mg/dL, respectively.<sup>29</sup> The 30-year age-adjusted hazard ratio for major cardiovascular events for minor allele heterozygotes vs major allele homozygotes was 1.27 (95% CI, 1.07-1.51).

### Predictive Strength of the AHA PREVENT Equation Including Lipoprotein(a)

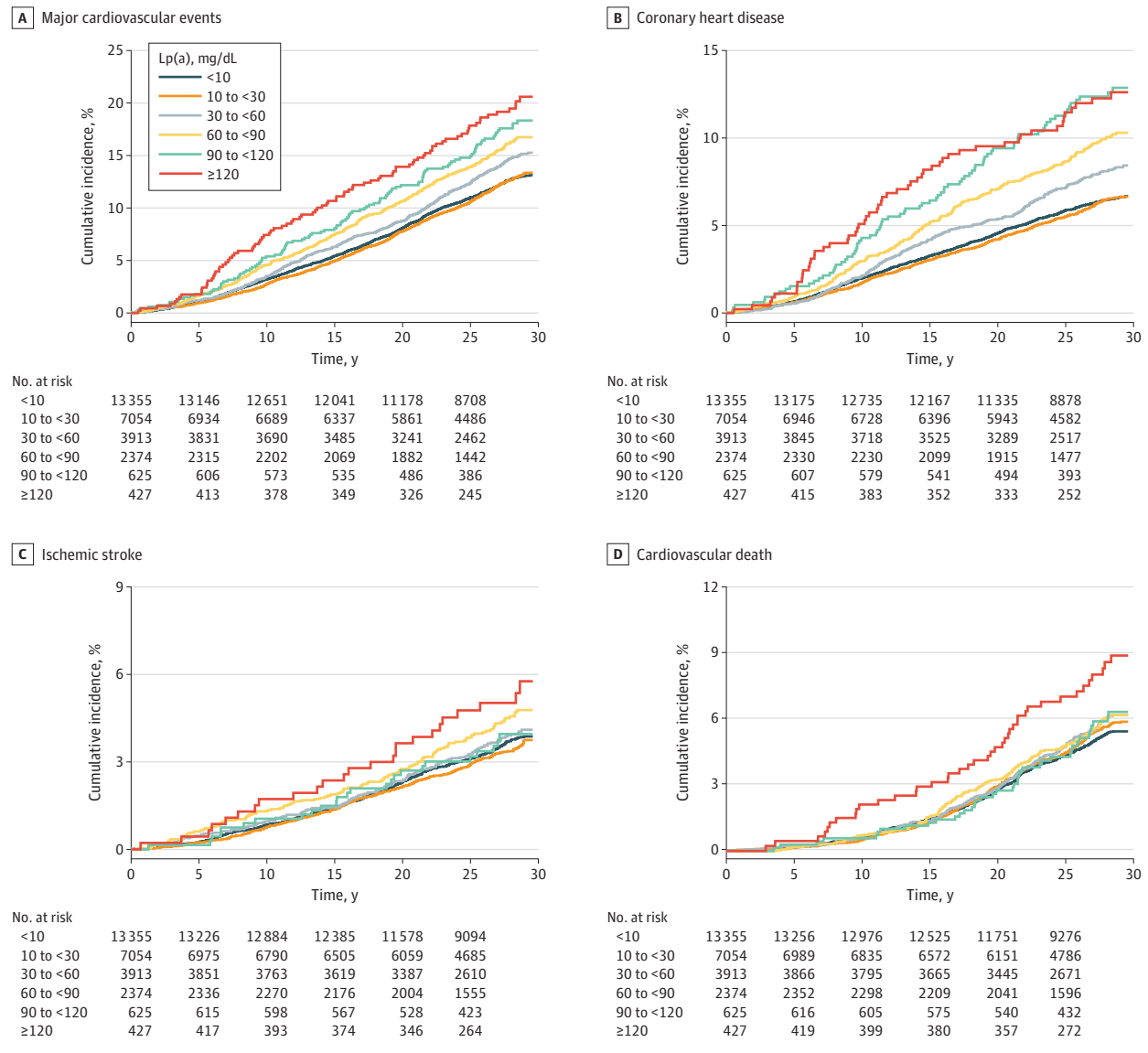
C indices for total CVD for the AHA PREVENT equation with and without the inclusion of baseline lipoprotein(a) levels were

0.71 and 0.70, respectively. The corresponding estimates for ASCVD were both 0.67, irrespective of the inclusion of lipoprotein(a).

### Sensitivity Analyses

Restricted cubic spline curves were similar to those presented in Figure 1 when (1) the number or location of knots were varied and when lipoprotein(a) levels were winsorized at the 99th percentile (eFigure 5 in Supplement 1). (2) Lipoprotein(a) levels did not appear to interact with the effect of aspirin treatment in the original trial on risk of major cardiovascular events (data not shown). (3) Multivariable adjusted hazard ratios for major cardiovascular events for individuals with lipoprotein(a) levels above 50 or 70 mg/dL vs below 10 mg/dL were 1.32 (95% CI, 1.21-1.44) and 1.36 (95% CI, 1.22-1.52), respectively. (5) Finally, among women with LDL cholesterol levels below the median (121 mg/dL [to convert LDL cholesterol from mg/dL to mmol/L, multiply by 0.0259]), very high

**Figure 3. Cumulative Incidence Curves for Major Cardiovascular Events (A), Coronary Heart Disease (B), Ischemic Stroke (C), and Cardiovascular Death (D)**



The analyses included 27 748 women with available baseline lipoprotein(a) (Lp[a]) measurements, among whom there were 3707 incident major cardiovascular events, 1985 coronary events, 1041 ischemic stroke events, and 1543 cardiovascular deaths accrued. The curves were constructed from age-adjusted cause-specific Cox regressions models accounting for

noncardiovascular deaths as competing risk for the analyses of major cardiovascular events and cardiovascular death, and for noncoronary or noncerebrovascular deaths for the analyses of coronary heart disease and ischemic stroke.

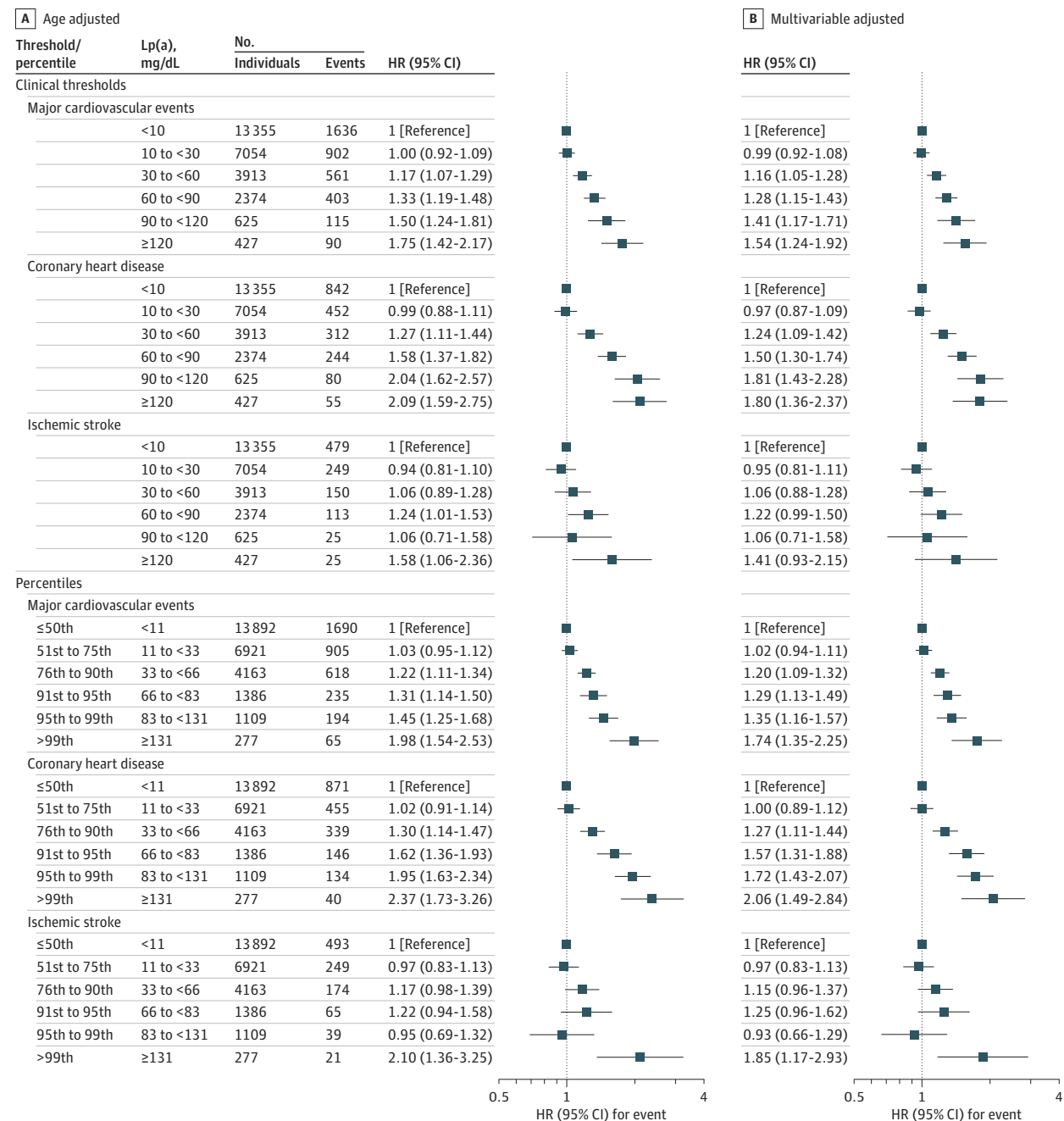
lipoprotein(a) levels were not significantly associated with higher risk of major cardiovascular events (eFigure 6 in Supplement 1). However, baseline LDL cholesterol levels did not appear to significantly interact with the association between the lipoprotein(a) clinical threshold groups and risk of major cardiovascular events (test for interaction:  $P \geq .06$ ).

## Discussion

In this study of 27 748 healthy women participating in the Women's Health Study and prospectively followed up for up

to 30 years, increasing baseline lipoprotein(a) levels were associated with an increased long-term risk of major cardiovascular events. Importantly, only lipoprotein(a) levels above 30 mg/dL or above the 75th percentile were associated with a significant increase in risk, with women in the most extreme percentile having an approximately 74% higher risk of future cardiovascular disease compared to individuals with low levels. The association of baseline lipoprotein(a) to risk of coronary heart disease showed a similar pattern. However, the increases in risks of ischemic stroke and cardiovascular death were modest across lipoprotein(a) levels, and only women with extremely elevated lipoprotein(a) were at increased risk of

Figure 4. Hazard Ratios (HRs) for Major Cardiovascular Events, Coronary Heart Disease, and Ischemic Stroke



The analyses included 27 748 women with available baseline lipoprotein(a) (Lp[a]) measurements. HRs were calculated using cause-specific Cox proportional hazards regressions adjusted for age (A) and multivariable-adjusted for age, blood pressure, smoking status, alcohol intake, history of

diabetes, hormone therapy, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein (B) and accounting for noncardiovascular, noncoronary, or noncerebrovascular deaths as competing risk.

death from cardiovascular causes. Finally, compared to noncarriers, women of European ancestry carrying the *LPA* rs3798220 lipoprotein(a)-increasing allele had a corresponding elevated risk of future cardiovascular events.

Plasma levels of lipoprotein(a) are only modestly affected by lifestyle intervention and available pharmacological treatment,<sup>2,3</sup> and our results thus likely give a reliable

estimate of the cardiovascular risk associated with elevated lipoprotein(a) levels across 30 years of follow-up. In support of this statement, an increase in median baseline lipoprotein(a) levels from 10 to 82 mg/dL due to variation in *LPA* rs3798220 was associated with a 27% higher risk of major cardiovascular events, in line with the observational estimate of a 28% increase for women with lipoprotein(a) levels between

60 and 90 mg/dL vs below 10 mg/dL. Interestingly, the age-adjusted hazard ratios for the cardiovascular outcomes were consistently higher than the corresponding multivariable-adjusted estimates in our study, suggesting that a minor proportion of the increase in cardiovascular risk among women with elevated lipoprotein(a) levels may be explained by confounding. That said, the 95% confidence intervals for the multivariable-adjusted estimates included the age-adjusted hazard ratios and vice versa, indicating that the additional covariables did not considerably alter the observed associations with long-term cardiovascular risk. In addition, our findings of a 54% to 74% higher risk of major cardiovascular events among individuals with very high baseline lipoprotein(a) levels are consistent with the results from other primary prevention and/or general population cohorts with shorter follow-up<sup>13,14,16,17</sup> and with the results for 10-year follow-up in the Women's Health Study.<sup>12</sup> Importantly, across 30 years of follow-up, this relative risk difference amounts to an approximately 10% higher absolute risk of cardiovascular disease compared to individuals with low lipoprotein(a) levels (Figure 3).

As seen elsewhere,<sup>13-15,17</sup> the increase in cardiovascular risk among individuals with high lipoprotein(a) levels was mainly driven by a high rate of coronary events. Nevertheless, individuals with very high lipoprotein(a) levels had an increased long-term risk of ischemic stroke and cardiovascular death as well. We observed some indication of an increase in risk of stroke with increasing lipoprotein(a) levels above 30 mg/dL, in line with the findings for coronary heart disease. Lipoprotein(a) levels between 90 and 120 mg/dL were notably not associated with increased risk of stroke. However, the wide confidence intervals were still consistent with a monotonic increase in risk of stroke across baseline lipoprotein(a) levels.

We are still waiting for the results from large cardiovascular outcome trials of lipoprotein(a)-lowering drugs (NCT04023552, NCT05581303, NCT06292013, and NCT07157774). Given the robust epidemiological and genetic evidence supporting a causal association across various populations<sup>13,14,17,19,20,27,29,37-39</sup> and the pronounced lipoprotein(a)-lowering effects of these drugs (80%-98% reductions),<sup>5-7</sup> these trials are well positioned to provide definitive evidence of clinical benefit. Even so, the skewed distribution of lipoprotein(a) in most populations requires thoughtful consideration when the results from these high-risk trials are applied to a primary prevention setting.<sup>3</sup> Importantly, our data and those of others<sup>13-21,24</sup> show that among healthy individuals, only a fraction will be at very high risk of cardiovascular disease due to elevated lipoprotein(a). That said, the cardiovascular risk among individuals with severely elevated lipoprotein(a) is comparable to that associated with familial

hypercholesterolemia, emphasizing the importance of early identification of these individuals.<sup>40</sup> In addition, the proportion of individuals at risk due to elevated lipoprotein(a) is likely higher in some non-European populations (eg, in some African and South American populations), and thus screening in these populations may yield greater benefits.<sup>21,41</sup>

In light of these considerations, we believe our findings for 30-year cardiovascular risk support the case for screening for elevated lipoprotein(a) among healthy individuals, as recommended in some guidelines.<sup>42,43</sup> Most importantly, such screening could help identify individuals with very high lipoprotein(a) levels, as these individuals may benefit from primary preventive efforts, including possible future lipoprotein(a)-lowering therapies.

### Strengths and Limitations

Strengths of our study include the large sample size of 27 748 healthy women with baseline lipoprotein(a) measurements. Plasma lipoprotein(a) levels were assessed in baseline samples all at once to limit analytical variability and using an assay, which is largely insensitive to apolipoprotein(a) isoform size.<sup>44-46</sup> Importantly, a one-time baseline measure of lipoprotein(a) is likely a reliable marker of future lipoprotein(a) levels, since plasma lipoprotein(a) levels are predominantly genetically determined and remain stable over time.<sup>47</sup>

Several limitations should be considered. First, some indication of a violation of the proportional hazards assumption was observed for the associations between lipoprotein(a) percentile and clinical threshold groups and risk of major cardiovascular disease. Second, results may have been influenced by menopausal changes in lipoprotein(a).<sup>48</sup> Third, lipoprotein(a) measurements were not available in molar units. Fourth, results may not be applicable to populations of non-European ancestry—that said, estimates of risk conferred by lipoprotein(a) levels are concordant across populations of different ancestry.<sup>21</sup> Finally, our results should be confirmed in men as well; we note, however, that elevated lipoprotein(a) correlated with similar increases in cardiovascular risk among men and women in cohort studies of shorter follow-up.<sup>15,16,48</sup>

### Conclusions

In conclusion, according to the results of this cohort study, very high lipoprotein(a) levels correlated with increased risk of future cardiovascular disease among healthy women across 30 years of follow-up. Screening for elevated lipoprotein(a) in the general population may be considered.

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