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Lipoprotein(a) and Body Mass Compound the Risk of Calcific Aortic Valve Disease

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ABSTRACT

BACKGROUND High plasma lipoprotein(a) and high body mass index are both causal risk factors for calcific aortic valve disease.

OBJECTIVES This study sought to test the hypothesis that risk of calcific aortic valve disease is the highest when both plasma lipoprotein(a) and body mass index are extremely high.

METHODS From the Copenhagen General Population Study, we used information on 69,988 randomly selected individuals recruited from 2003 to 2015 (median follow-up 7.4 years) to evaluate the association between high lipoprotein(a) and high body mass index with risk of calcific aortic valve disease.

RESULTS Compared with individuals in the 1st to 49th percentiles for both lipoprotein(a) and body mass index, the multivariable adjusted HRs for calcific aortic valve disease were 1.6 (95% CI: 1.3-1.9) for the 50th to 89th percentiles of both (16% of all individuals) and 3.5 (95% CI: 2.5-5.1) for the 90th to 100th percentiles of both (1.1%) (*P* for interaction = 0.92). The 10-year absolute risk of calcific aortic valve disease increased with higher lipoprotein(a), body mass index, and age, and was higher in men than in women. For women and men 70-79 years of age with body mass index ≥30.0 kg/m^2, 10-year absolute risks were 5% and 8% for lipoprotein(a) ≤42 mg/dL (88 nmol/L), 7% and 11% for 42-79 mg/dL (89-169 nmol/L), and 9% and 14% for lipoprotein(a) ≥80 mg/dL (170 nmol/L), respectively.

CONCLUSIONS Extremely high lipoprotein(a) levels and extremely high body mass index together conferred a 3.5-fold risk of calcific aortic valve disease. Ten-year absolute risk of calcific aortic valve disease by categories of lipoprotein(a) levels, body mass index, age, and sex ranged from 0.4% to 14%. (J Am Coll Cardiol 2022;79:545-558) © 2022 by the American College of Cardiology Foundation.

Calcific aortic valve disease (CAVD) is a condition that in its first stage includes early cellular alterations of the aortic valve through aortic valve sclerosis to its last stage of aortic valve stenosis, and it is the most common heart valve disease in developed countries.[1,2] By 2013, 4.9 million elderly in Europe and 2.7 million elderly in North America had diagnosed aortic valve stenosis, and with increasing life expectancy the disease burden is expected to increase even further.[3]

High plasma lipoprotein(a) levels are a genetically determined, causal risk factor for aortic valve stenosis.[4-7] Lipoprotein(a) consists of a low-density lipoprotein (LDL)-like particle covalently bound to apolipoprotein(a). There are no approved pharmacological treatments to decrease levels of lipoprotein(a),

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAVD = calcific aortic valve disease

ICD = International Classification of Diseases

LDL = low-density lipoprotein

but randomized clinical trials with several different lipoprotein(a)-lowering agents are currently ongoing; however, these studies focus on preventing atherosclerotic cardiovascular disease, rather than preventing CAVD.[8-10]

High body mass index (BMI) has recently emerged as an additional causal risk factor for CAVD.[11-13] Thus, the increasing worldwide prevalence of high BMI[14] could contribute to an even higher burden of CAVD. Whether high BMI infers a similar, a lower, or higher risk of CAVD than high plasma lipoprotein(a) is unknown. It is also unknown whether a combination of extreme high plasma lipoprotein(a) and extreme high BMI can identify individuals at the very highest risk of CAVD. Finally, it is unknown how high the absolute risk of CAVD is in individuals in whom both plasma lipoprotein(a) and BMI are high.

We tested the hypothesis that risk of CAVD is the highest when both plasma lipoprotein(a) levels and BMI are extremely high. Further, we quantitated the 10-year absolute risk of CAVD by categories of lipoprotein(a), BMI, age, and sex.

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METHODS

The present study included 69,988 individuals from the Copenhagen General Population Study with information on both plasma lipoprotein(a) levels and BMI, and with no prior diagnosis of CAVD. From 2003 through 2015, White individuals of Danish descent were invited at random from the general population of the greater Copenhagen area, using the Danish Civil Registration System. The study was conducted in accordance with the Declaration of Helsinki, all individuals signed written informed consent, and local Institutional Review Boards and a Danish ethical committee (H-KF-01-144/01) approved the study. Participants provided information on health and lifestyle in a questionnaire, and physical examination and blood sampling were performed on site at the day of attendance. Participation rate was 43%. Individuals were followed until diagnosis of or death by incident CAVD (n = 1,226), death by other cause (n = 9,999), emigration (n = 241), or December 13, 2018, whichever occurred first.

The ability to predict and discriminate risk of CAVD of a model including age, sex, lipoprotein(a), and BMI derived in the present study was validated in the Copenhagen City Heart Study, from which 11,039 individuals were included.

CALCIFIC AORTIC VALVE DISEASE. Diagnoses of CAVD were obtained from the national Danish Patient Registry and the national Danish Causes of Death Registry, 2 nationwide registries in which individuals are identified by their unique Danish Civil Registration number. In these registries, medical doctors in Denmark register diagnoses based on the World Health Organization International Classification of Diseases (ICD). As done previously,[13,15,16] CAVD was defined as ICD-8th Revision codes 424.10, 424.12, 424.18, and 424.19 and as ICD-10th Revision codes I35.0 and I35.2, registered during hospital visits or on the death certificate; Denmark transferred directly from using ICD-8th Revision to ICD-10th Revision.

LIPOPROTEIN(a) AND OTHER LABORATORY ANALYSES. As endorsed in guidelines and consensus statements, blood samples were collected nonfasting.[17,18] Lipoprotein(a) was measured blinded to knowledge of CAVD and BMI, and vice versa. Lipoprotein(a) total mass (mg/dL) was measured using turbidimetric assays. Depending on time of attendance, either an assay from Denka or an assay from DiaSys (Diagnostic Systems) was used. As the assays uses polyclonal antibodies, they are not isoform independent, but they are the least isoform dependent of available commercial assays due to the use of 5-point calibration curves each with different isoforms of lipoprotein(a). All samples were standardized to concentrations of the Denka assay, in order to avoid bias as done previously.[19] Conversion of lipoprotein(a) from mg/dL to nmol/L was done using the equation 2.18 × lipoprotein(a), mg/dL – 3.83 based on previous calculations on 13,930 individuals with independent measurements using both units.[20]

In head-to-head analyses comparing lipoprotein(a) with BMI, lipoprotein(a) was categorized into groups of 1st to 49th, 50th to 89th, and 90th to 100th percentiles, as it is the extremely high lipoprotein(a) levels that are most associated with increased risk of CAVD,[5] and for comparison we used the same percentiles for BMI. For calculation of 10-year absolute risks, lipoprotein(a) was categorized into the following groups based on clinical cutpoints: ≤42 mg/dL (88 nmol/L), 43-79 mg/dL (89-169 nmol/L), and ≥80 mg/dL (170 nmol/L), as these cutpoints are of interest in a clinical setting; 42 mg/dL is the 80th percentile of lipoprotein(a) widely recommended as a clinical cutpoint,[21,22] and 80 mg/dL was chosen as a round number to illustrate risk for those with the highest lipoprotein(a) levels (top 6%).

BODY MASS INDEX. Height and weight were measured at the time of attendance. BMI was

calculated as measured weight divided by measured height squared. In head-to-head analyses comparing BMI with lipoprotein(a), BMI was categorized into the same percentiles as lipoprotein(a): 1st to 49th, 50th to 89th, and 90th to 100th. In analyses using clinical cutpoints, BMI was categorized into normal weight at 18.5 to 24.9 kg/m^2, overweight at 25.0 to 29.9 kg/m^2, and obesity at ≥30 kg/m^2, excluding underweight individuals with BMI below 18.5 kg/m^2, as this group typically contains a mixture of individuals intentionally underweight and those being underweight secondary to severe disease.

WAIST-HIP RATIO. Abdominal fat which can be measured by the waist-hip ratio has been linked to inflammation.[23] Thus, waist-hip ratio was also included as an exposure variable comparable to BMI. Waist and hip circumference were measured in centimeters at baseline, and the ratio between these measures was calculated as waist divided by hip circumference. Waist-hip ratio was categorized into the same percentiles as lipoprotein(a) and BMI; however, as waist-hip ratio differs between sexes, percentiles were made for each sex separately and then merged together, ensuring an equal distribution of women and men across categories, as done previously.[11,13] As there are no widely accepted clinical cutpoints for waist-hip ratio, such analyses were not conducted.

STATISTICAL ANALYSES. Stata 13.1 (StataCorp) was used. Cuzick's nonparametric test was used to estimate trend across categories. Information on covariates was 99.8% complete. Missing covariates were imputed using Stata's mi impute command; however, if only individuals with complete data were included, results were similar. All covariates were measured at baseline.

The associations of all covariates with CAVD were evaluated by a Cox proportional hazards model with time on study as underlying timescale and right censoring at end of study, emigration, or death by other cause than CAVD with results reported as cause-specific HRs with 95% CIs. The proportional hazard assumption was evaluated by Schoenfeld residuals. No major deviations were found. On continuous scales, results were presented using restricted cubic splines with 3 knots based on Akaike information criterion, and the reference value was the 2.5th percentile (1.5 mg/dL for lipoprotein(a), 19.5 kg/m^2 for BMI, and 0.73 for waist-hip ratio).

Analyses including plasma lipoprotein(a) levels were adjusted for baseline levels of age, sex, LDL cholesterol corrected for lipoprotein(a) cholesterol, triglycerides, systolic blood pressure, smoking status (current vs nonsmokers), diabetes, years of education, estimated glomerular filtration rate, and BMI. Analyses with BMI or waist-hip ratio as the investigated exposure were adjusted for the same confounders but for lipoprotein(a) instead of BMI. If age was used as underlying timescale, results were similar. When investigating combinations of lipoprotein(a) categories and BMI or waist-hip ratio categories, analyses were not adjusted for lipoprotein(a), BMI, or waist-hip ratio, as these measures were exposure variables. Otherwise, adjustment was as described previously. A model with age, sex, lipoprotein(a), and BMI on CAVD was used for validation in the Copenhagen City Heart Study.

To estimate 10-year absolute risk of CAVD, categories of baseline age, sex, lipoprotein(a), and BMI or waist-hip ratio were used as covariates in Fine and Gray's competing risks regression, taking the competing risks of death and emigration into account with time on study as the underlying timescale.[24] Ten-year risks were estimated with different combinations of values of these covariates.

Further information on materials and methods can be found in the Supplemental Appendix.

RESULTS

During follow-up (median 7.4 years, range up to 15 years), 1,226 of the included 69,988 individuals were diagnosed with CAVD. Baseline characteristics of individuals by categories of lipoprotein(a) levels, BMI, and waist-hip ratio are given in **Table 1**. BMI differed minimally by different lipoprotein(a) categories, and vice versa. The median age at study entry was 60 years (range 20-100 years), and 54% were women. Adjusted for age and sex, 1-kg/m^2 higher BMI was associated with a slightly higher lipoprotein(a) of 0.097 mg/dL (95% CI: 0.042-0.153 mg/dL) (Supplemental Figure 1). If lipoprotein(a) was further adjusted for high-sensitivity C-reactive protein, the association was slightly attenuated.

RISK FACTORS FOR CAVD. To compare the importance of the different risk factors for CAVD, continuous variables were categorized with focus on extreme phenotypes, while sex, diabetes, and smoking status were dichotomized. According to *P* values and HRs, male sex, top 10% lipoprotein(a), and top 10% BMI were the most important risk factors besides age (**Figure 1**). For age, the HR for CAVD was 38 (95% CI: 12-117; $P < 0.0001$) for the top 10% oldest individuals compared with the 50% youngest. If values for LDL cholesterol without correction for lipoprotein(a) cholesterol were used, the HR for CAVD

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TABLE 1 Baseline Characteristics by Plasma Lipoprotein(a), BMI, and Waist-Hip Ratio

	Lipoprotein(a)		
	1-49 Percentiles	50-89 Percentiles	90-100 Percentiles
	≤9 mg/dL	10-68 mg/dL	≥69 mg/dL
	≤16 nmol/L	17-144 nmol/L	≥145 nmol/L
Individuals	34,989	28,001	6,998
Age, y	59 (49-69)	60 (50-70)	61 (52-70)
Women	51.9	54.6	59.0
Current smokers	17.7	17.1	17.3
Systolic blood pressure, mm Hg	140 (127-156)	140 (127-155)	141 (128-157)
LDL cholesterol, noncorrected			
mmol/L	3.1 (2.5-3.7)	3.2 (2.6-3.9)	3.4 (2.8-4.1)
mg/dL	119 (95-143)	125 (100-151)	131 (108-158)
LDL cholesterol corrected for lipoprotein(a) cholesterol			
mmol/L	3.0 (2.4-3.7)	3.0 (2.4-3.7)	2.6 (2.0-3.3)
mg/dL	117 (94-142)	117 (93-143)	102 (77-127)
Triglycerides, mmol/L	1.4 (1.0-2.1)	1.4 (1.0-2.0)	1.4 (1.0-2.1)
Triglycerides, mg/dL	124 (85-186)	121 (85-179)	128 (89-185)
Diabetes mellitus	5.4	4.3	5.8
Education, y	10 (9-12)	10 (9-12)	10 (9-12)
eGFR, mL/min/1.73 m^2	83 (71-93)	81 (70-91)	79 (68-90)
BMI, kg/m^2	26 (23-29)	26 (23-28)	26 (24-29)
	BMI		
	1-49 Percentiles	50-89 Percentiles	90-100 Percentiles
	≤25 kg/m^2	26-31 kg/m^2	≥32 kg/m^2
Individuals	34,991	27,999	6,998
Age, y	58 (48-68)	62 (52-70)	62 (52-69)
Women	62.0	43.2	54.4
Current smokers	18.5	16.3	16.2
Systolic blood pressure, mm Hg	136 (122-152)	144 (130-159)	148 (135-162)
LDL cholesterol, noncorrected			
mmol/L	3.1 (2.5-3.7)	3.3 (2.7-4.0)	3.3 (2.6-4.0)
mg/dL	118 (97-143)	127 (103-154)	127 (100-154)
LDL cholesterol corrected for lipoprotein(a) cholesterol			
mmol/L	2.9 (2.3-3.5)	3.1 (2.5-3.8)	3.1 (2.4-3.8)
mg/dL	111 (89-135)	121 (95-146)	119 (92-146)
Triglycerides, mmol/L	1.1 (0.8-1.6)	1.7 (1.2-2.4)	2.0 (1.4-2.8)
Triglycerides, mg/dL	101 (74-144)	146 (102-211)	174 (124-247)
Diabetes mellitus	2.5	5.8	13.9
Education, y	12 (10-12)	10 (9-12)	10 (8-12)
eGFR, mL/min/1.73 m^2	83 (71-93)	81 (69-91)	80 (69-91)
Lipoprotein(a), mg/dL	10 (5-29)	10 (5-30)	9 (5-29)
Lipoprotein(a), nmol/L	17 (7-59)	18 (7-61)	17 (6-59)

Continued on the next page

was 1.02 (95% CI: 0.84-1.23; $P = 0.85$) for the 10% highest noncorrected LDL cholesterol compared with the lowest 50%. Similar results for a model with waist-hip ratio instead of BMI are also shown in **Figure 1**.

LIPOPROTEIN(a) VS BMI AND WAIST-HIP RATIO. On continuous scales, the multivariable adjusted HR for CAVD increased with both higher lipoprotein(a) levels, higher BMI, and higher waist-hip ratio (**Figure 2**). In analyses excluding individuals who had myocardial infarction before or during follow-up, results were similar (Supplemental Figure 2).

Compared with individuals with lipoprotein(a) levels in the 1st to 49th percentiles, the multivariable adjusted HR for CAVD was 1.28 (95% CI: 1.13-1.44) for individuals in the 50th to 89th percentiles and 1.86 (95% CI: 1.57-2.21) for individuals in the 90th to 100th percentiles (**Figure 3**). Compared with individuals with BMI in the 1st to 49th percentiles, the multivariable adjusted HR for CAVD was 1.26 (95% CI: 1.11-1.43) for individuals in the 50th to 89th percentiles and 1.79 (95% CI: 1.49-2.14) for individuals in the 90th to 100th percentiles. For waist-hip ratio, corresponding HRs were 1.29 (95% CI: 1.13-1.47) and 1.55 (95% CI: 1.30-1.85), respectively. Analyses examining lipoprotein(a) were adjusted for BMI, and analyses examining BMI and waist-hip ratio were adjusted for lipoprotein(a). On a subset comparing 666 cases with CAVD with 943 control subjects without heart disease, higher oxidized phospholipids on apolipoprotein B were associated with higher risk of CAVD, similar to higher lipoprotein(a) (Supplemental Figure 3), as shown previously.[16]

COMBINATION OF LIPOPROTEIN(a) AND BMI. Compared with individuals in the 1st to 49th percentiles for both lipoprotein(a) levels and BMI, the multivariable adjusted HRs for CAVD increased with both higher lipoprotein(a) levels and higher BMI (**Figure 4**), independent of each other (P for interaction = 0.92). With the same reference group, multivariable adjusted HRs for CAVD were 1.6 (95% CI: 1.3-1.9) for individuals with both lipoprotein(a) levels and BMI in the 50th to 89th percentiles (16% of all individuals) and 3.5 (95% CI: 2.5-5.1) for individuals with both lipoprotein(a) levels and BMI in the 90th to 100th percentiles (1.1%). For individuals with lipoprotein(a) in the 90th to 100th percentiles and BMI in the 50th to 89th percentiles (4.2%), the corresponding HR was 2.3 (95% CI: 1.7-2.9), and for those with BMI in the 90th to 100th percentiles and lipoprotein(a) in the 50th to 89th (3.8%), the HR was 2.2 (95% CI: 1.7-2.9). Corresponding HRs for categories using clinical cutpoints are provided in Supplemental Figure 4 with similar results. Results for combinations of oxidized phospholipids on apolipoprotein B and BMI on a case-control subset (N = 666+943) showed similar but attenuated results (Supplemental Figure 5). Results using aortic valve replacement as endpoint were similar to those for CAVD overall (Supplemental Figures 6 and 7).

COMBINATION OF LIPOPROTEIN(a) AND WAIST-HIP RATIO. Compared with individuals in the 1st to 49th

percentiles for both lipoprotein(a) levels and waist-hip ratio, the multivariable adjusted HRs for CAVD increased with both higher lipoprotein(a) levels and higher waist-hip ratio (**Figure 5**), independent of each other (*P* for interaction = 0.80). With the same reference group, multivariable adjusted HRs for CAVD were 1.7 (95% CI: 1.4-2.0) for individuals with both lipoprotein(a) levels and waist-hip ratio in the 50th to 89th percentiles (16% of all individuals) and 2.5 (95% CI: 1.7-3.8) for individuals with both lipoprotein(a) levels and waist-hip ratio in the 90th to 100th percentiles (1.1%). For individuals with lipoprotein(a) in the 90th to 100th percentiles and waist-hip ratio in the 50th to 89th percentiles (4.2%), the corresponding HR was 2.4 (95% CI: 1.9-3.1), and for those with waist-hip ratio in the 90th to 100th percentiles and lipoprotein(a) in the 50th to 89th (3.8%), the corresponding HR was 2.1 (95% CI: 1.6-2.8).

TABLE 1 Continued

	Waist-Hip Ratio		
	1-49 Percentiles	**50-89 Percentiles**	**90-100 Percentiles**
	≤0.82 Women	**0.83-0.92 Women**	**≥0.93 Women**
	≤0.93 Men	**0.94-1.02 Men**	**≥1.03 Men**
Individuals	34,694	27,707	6,969
Age, y	56 (47-67)	63 (53-71)	65 (57-73)
Women	53.7	53.8	53.5
Current smokers	15.9	18.2	21.1
Systolic blood pressure, mm Hg	136 (124-151)	144 (130-159)	148 (134-162)
LDL cholesterol, noncorrected			
mmol/L	3.1 (2.5-3.7)	3.3 (2.6-3.9)	3.2 (2.5-3.9)
mg/dL	120 (97-143)	127 (100-151)	124 (97-151)
LDL cholesterol corrected for lipoprotein(a) cholesterol			
mmol/L	2.9 (2.3-3.5)	3.1 (2.4-3.8)	3.0 (2.3-3.7)
mg/dL	113 (91-137)	119 (94-145)	117 (88-145)
Triglycerides, mmol/L	1.2 (0.9-1.7)	1.6 (1.1-2.3)	1.9 (1.3-2.7)
Triglycerides, mg/dL	104 (75-150)	142 (99-206)	168 (119-242)
Diabetes mellitus	2.2	5.9	14.7
Education, y	12 (10-12)	10 (9-12)	10 (8-12)
eGFR, mL/min/1.73 m^2	84 (73-94)	80 (69-90)	78 (67-89)
Lipoprotein(a), mg/dL	10 (5-29)	10 (5-30)	9 (4-30)
Lipoprotein(a), nmol/L	17 (7-59)	18 (7-61)	17 (6-62)

Values are n, median (IQR), or %. The number of individuals varies slightly according to availability of the variable (data are without imputation).

BMI = body mass index; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein.

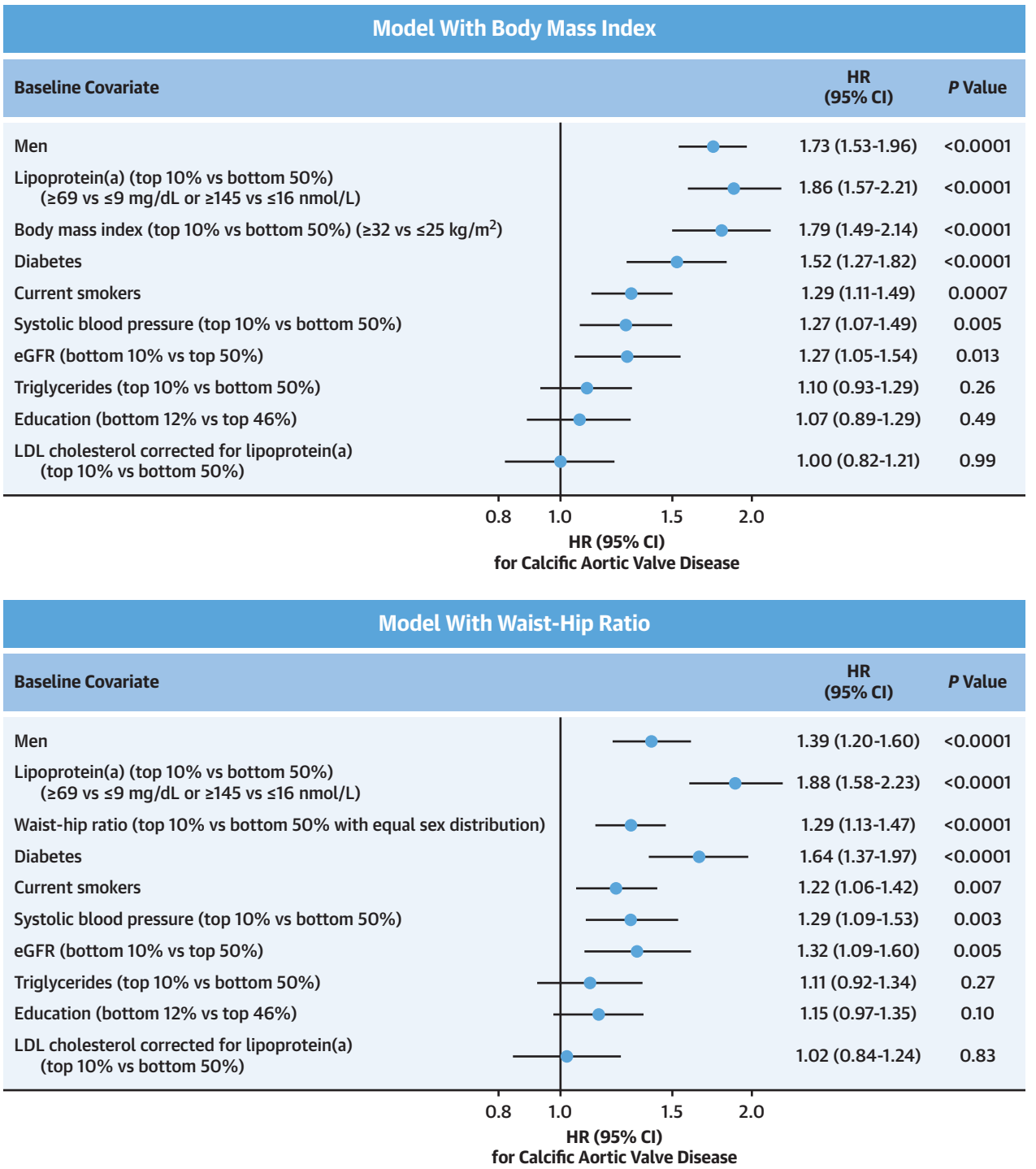
POPULATION ATTRIBUTABLE RISK. For individuals with BMI above the 50th percentile, the multivariable adjusted HR for CAVD was 1.35 (95% CI: 1.19-1.52) compared with individuals below the 50th percentile. Correspondingly, the population attributable risk was 14.7%, that is, the percentage of CAVD events attributed to BMI above the 50th percentile. For a comparable fraction of the population with lipoprotein(a) above the 50th percentile, the corresponding HR was 1.39 (95% CI: 1.24-1.56) with a population attributable risk of 16.3%, and for waist-hip ratio the corresponding HR was 1.19 (95% CI: 1.04-1.36) with a population attributable risk of 8.6%. A comparison of population attributable risks at other exposure levels is provided in Supplemental Table 1 with risks ranging from 9% to 16% for lipoprotein(a), from 7% to 18% for BMI, and from 3% to 12% for waist-hip ratio. For BMI and/or lipoprotein(a) above the median vs both below the median, the population attributable risk was 26%.

ABSOLUTE 10-YEAR RISK. To calculate absolute 10-year risk for individuals with information on the most important risk factors (**Figure 1**, see previous) of age, sex, plasma lipoprotein(a), and BMI, a chart of 10-year risk of CAVD was created using clinical cut-points for lipoprotein(a) and BMI (**Figure 6**). The 10-year risk increased with higher lipoprotein(a) levels, BMI, and age, and was higher in men than in women. Ten-year absolute risk of CAVD ranged from 0.4% to 2% for individuals 50 to 59 years of age, through 1% to 6% for individuals 60 to 69 years of age, to 3% to 14% for individuals 70 to 79 years of age.

For women and men 70 to 79 years of age and with BMI of 18.5-24.9 kg/m^2, 10-year risk of CAVD was 3% and 4% for lipoprotein(a) levels ≤42 mg/dL (88 nmol/L), 4% and 6% for 43 to 79 mg/dL (89-169 nmol/L), and 5% and 8% for lipoprotein(a) levels ≥80 mg/dL (170 nmol/L), respectively. For women and men 70 to 79 years of age with BMI of 25.0 to 29.9 kg/m^2, corresponding values were 4% and 6%, 5% and 8%, and 7% and 10%, respectively. Finally, for women and men 70 to 79 years of age with BMI ≥30.0 kg/m^2, corresponding values were 5% and 8%, 7% and 11%, and 9% and 14%, respectively. Corresponding 10-year absolute risks of CAVD using categories based on percentiles for both BMI and waist-hip ratio are provided in Supplemental Figure 8. For aortic valve replacement, corresponding 10-year absolute risk charts are shown in Supplemental Figure 9.

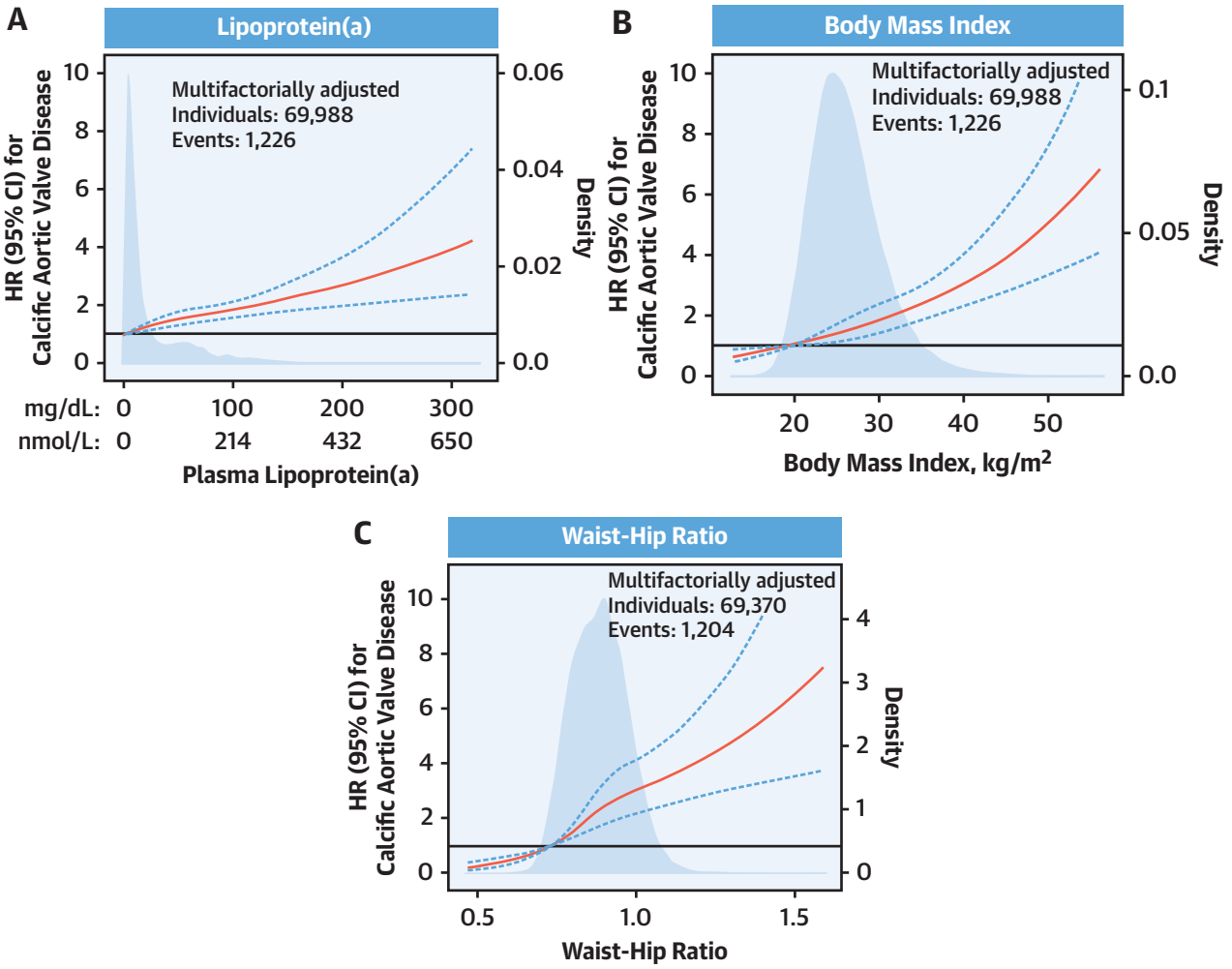
VALIDATION COHORT. A Cox proportional hazards model including age, sex, lipoprotein(a), and BMI categories derived from our derivation cohort (the Copenhagen General Population Study) was able to discriminate risk groups in a validation cohort consisting of 11,039 individuals with 342 incidences of CAVD from the Copenhagen City Heart Study recruited in 1991 to 1994 (Supplemental Table 2). The model was well calibrated for absolute risks up to 5%

FIGURE 1 Risk Factors for Calcific Aortic Valve Disease



Cause-specific HRs from Cox regression were adjusted for age and all baseline covariates shown in the figure and with censoring at time of death by another cause than calcific aortic valve disease, emigration, or end of study. For comparison, continuous variables were categorized with focus on extreme levels. eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein.

FIGURE 2 Risk of Calcific Aortic Valve Disease by Lipoprotein(a), BMI, and Waist-Hip Ratio



Cause-specific HRs **(solid lines)** and 95% CIs **(dashed lines)** are from Cox regression using restricted cubic splines on continuous scales. Censoring was at time of death by another cause than calcific aortic valve disease, emigration, or end of study. The 2.5th percentiles were used as references. Multifactorial adjustment was for age, sex, low-density lipoprotein cholesterol corrected for lipoprotein(a), plasma triglycerides, systolic blood pressure, current smoking, diabetes, years of education, estimated glomerular filtration rate, and body mass index (BMI) **(top left)** or lipoprotein(a) levels **(right and bottom)**. Graphs include lipoprotein(a) levels <325 mg/dL, BMI <56.5 kg/m^2, and waist-hip ratio <1.60 due to a limited number of individuals and events outside these cutpoints (99.99th percentile). Density plots of population distribution **(blue)** are made as kernel density estimation.

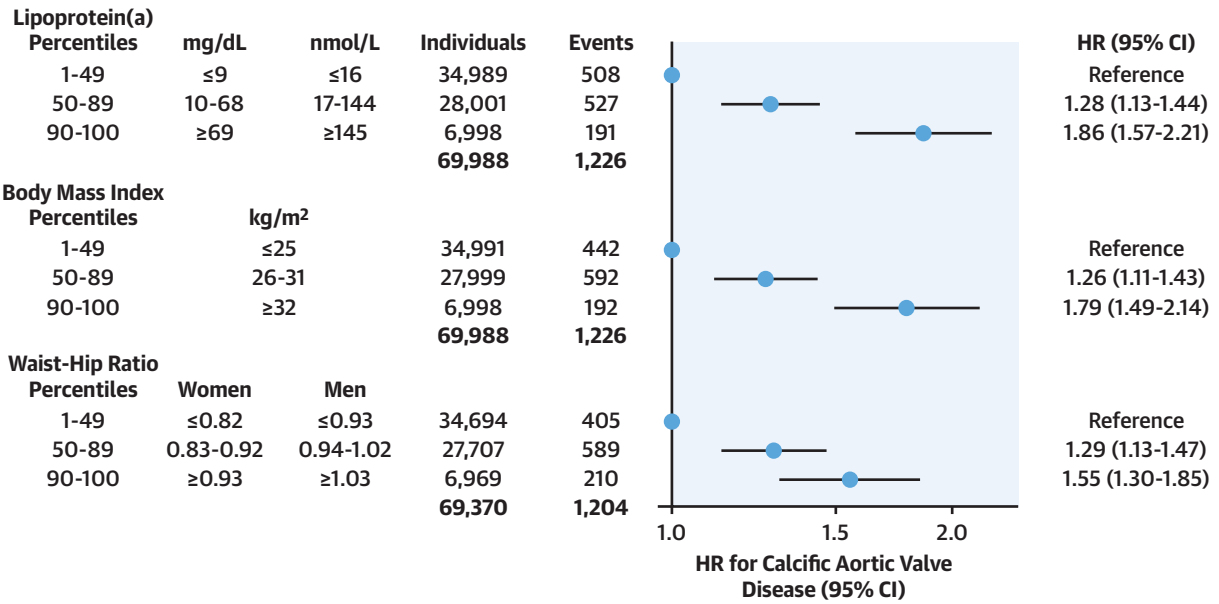
in the validation cohort, while the validation cohort had a low number of cases in groups with extreme phenotypes (Supplemental Figure 10).

DISCUSSION

In the Danish general population, extremely high lipoprotein(a) levels and extremely high BMI together conferred 3.5-fold risk of CAVD. Individual patients can be informed according to the provided 10-year absolute risk chart by categories of lipoprotein(a) levels, BMI, age, and sex, with risk of CAVD ranging up to 14% (Central Illustration). These findings are novel.

The mechanisms for lipoprotein(a) causing CAVD is probably through proatherosclerotic effects, influencing the initiation phase of the development of CAVD.[25] In the initiation phase, valve endothelial cells are injured, leading to local inflammation and increased infiltration of lipoprotein(a) into valve leaflets. Here, lipoprotein(a) could contribute to an inflammatory environment causing valve interstitial cells to differentiate into osteoblast-like cells, leading to calcification of the valve, that is, the

FIGURE 3 Risk of Calcific Aortic Valve Disease by Lipoprotein(a), BMI, and Waist-Hip Ratio



Cause-specific HRs are from Cox regression by categories of lipoprotein(a), body mass index (BMI), and waist-hip ratio with censoring at time of death by another cause than calcific aortic valve disease, emigration, or end of study. Adjustment was for age, sex, low-density lipoprotein cholesterol corrected for lipoprotein(a), triglycerides, systolic blood pressure, current smoking, diabetes, years of education, estimated glomerular filtration rate, and BMI **(top)** or lipoprotein(a) **(middle and bottom)**.

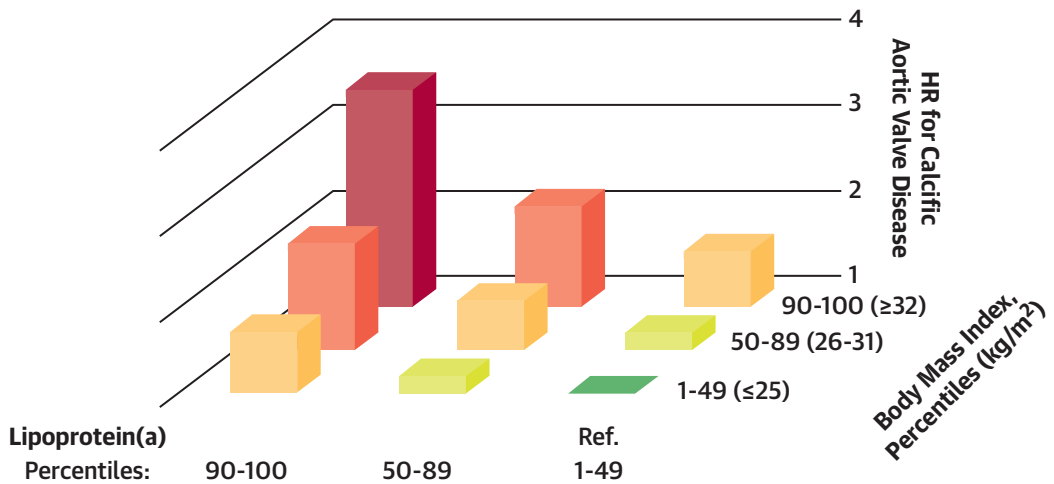
propagation phase of CAVD.[25-29] The pro-osteogenic effect of lipoprotein(a) is potentially mediated by oxidized phospholipids, which are abundant in lipoprotein(a).[26,28]

The mechanism from high BMI or obesity to CAVD is possibly more complex than for lipoprotein(a), as elevated BMI could affect numerous different pathways. High BMI increases blood pressure[30] and thereby the geometry of the left ventricle, causing turbulent flow and endothelial injury.[25,31] Obesity also leads to high levels of atherogenic lipoproteins[32] and proinflammatory processes,[33] affecting similar mechanisms as described for lipoprotein(a). However, our comparative analyses were adjusted for systolic blood pressure, plasma triglycerides, and LDL cholesterol, indicating that the association between BMI and CAVD is not solely driven through these mediators.

Previously, both high lipoprotein(a) levels and high BMI have been observationally and genetically associated with increased risk of CAVD, indicating that both are causal risk factors for the disease.[4-6,11-13] While previous studies investigated the associations of lipoprotein(a) and BMI separately with risk of CAVD,[5,11-13] direct comparison and joint association of these 2 exposures on risk of CAVD have never been examined before. Where previous studies found an association between elevated LDL cholesterol and CAVD,[34,35] we did not find such an association, irrespective of whether LDL cholesterol was corrected for the cholesterol content of lipoprotein(a) or not. A possible explanation is that our model included several other adjustments that could attenuate the association of elevated LDL cholesterol with CAVD.

Our study also illustrates that it is possible to estimate absolute 10-year risk of CAVD on a few easy identifiable risk factors, that is, age, sex, plasma lipoprotein(a), and BMI. Beside age and sex, lipoprotein(a) and BMI are each valuable in this model, as they both comprise high population attributable risks of up to 16% for lipoprotein(a) and up to 18% for BMI while being completely independent of each other. About 90% of plasma lipoprotein(a) levels are genetically determined,[36] minimizing the possibility that lipoprotein(a) is affected by any unmeasured variables. In contrast, high BMI is also a marker for high blood pressure, increased risk of diabetes, elevated plasma triglycerides, physical inactivity, unhealthy diet, and likely many unknown factors that could influence or mediate the risk from obesity to CAVD, which together could explain the substantial risk of CAVD associated with high BMI. Thus, our absolute risk chart, besides age and sex, combines

FIGURE 4 Calcific Aortic Valve Disease Risk by Combined Categories of Lipoprotein(a) and Body Mass Index



HR (95% CI) for Calcific Aortic Valve Disease

Body Mass Index		Lipoprotein(a)		
Percentiles	kg/m²	Percentiles: 90-100 / mg/dL: ≥69 / nmol/L: ≥145	50-89 / 10-68 / 17-144	1-49 / ≤9 / ≤16
90-100	≥32	3.5 (2.5-5.1)	2.2 (1.7-2.9)	1.7 (1.3-2.2)
50-89	26-31	2.3 (1.7-2.9)	1.6 (1.3-1.9)	1.2 (1.0-1.5)
1-49	≤25	1.7 (1.3-2.3)	1.2 (1.0-1.5)	1 (reference)

Number of Individuals/Events

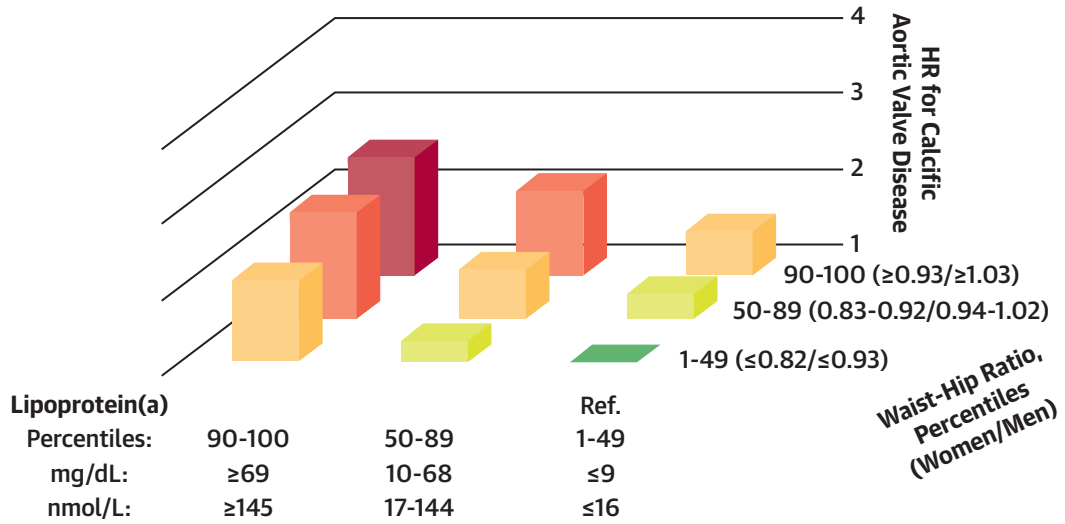
Body Mass Index		Lipoprotein(a)		
Percentiles	kg/m²	Percentiles: 90-100 / mg/dL: ≥69 / nmol/L: ≥145	50-89 / 10-68 / 17-144	1-49 / ≤9 / ≤16
90-100	≥32	754/36	2,687/79	3,557/77
50-89	26-31	2,954/90	11,164/258	13,881/244
1-49	≤25	3,290/65	14,150/190	17,551/187

Cause-specific HRs from Cox regression with censoring at time of death by another cause than calcific aortic valve disease, emigration, or end of study were adjusted for age, sex, low-density lipoprotein cholesterol corrected for lipoprotein(a), triglycerides, systolic blood pressure, current smoking, diabetes, years of education, and estimated glomerular filtration rate.

both genetically determined and lifestyle risk factors of CAVD. Our study did not find an interaction between lipoprotein(a) and BMI in their association with CAVD. Thus, the association between elevated lipoprotein(a) and CAVD is not affected by BMI and vice versa, indicating that the increased risks in individuals with both elevated lipoprotein(a) and high BMI are additive and not synergistic.

Strengths of our study include the large number of individuals studied. Furthermore, we were able to conduct a prospectively designed cohort study in an ethnically homologous population largely avoiding

FIGURE 5 Calcific Aortic Valve Disease Risk by Combined Categories of Lipoprotein(a) and Waist-Hip Ratio



HR (95% CI) for Aortic Valve Stenosis

Waist-Hip Ratio			Lipoprotein(a)		
		Percentiles:	90-100	50-89	1-49
Percentiles	Women	Men mg/dL:	≥69	10-68	≤9
		nmol/L:	≥145	17-144	≤16
90-100	≥0.93	≥1.03	2.5 (1.7-3.8)	2.1 (1.6-2.8)	1.6 (1.2-2.1)
50-89	0.83-0.92	0.94-1.02	2.4 (1.9-3.1)	1.7 (1.4-2.0)	1.3 (1.1-1.6)
1-49	≤0.82	≤0.93	2.1 (1.6-2.8)	1.3 (1.0-1.6)	1 (reference)

Number of Individuals/Events

Waist-Hip Ratio			Lipoprotein(a)		
		Percentiles:	90-100	50-89	1-49
Percentiles	Women	Men mg/dL:	≥69	10-68	≤9
		nmol/L:	≥145	17-144	≤16
90-100	≥0.93	≥1.03	757/29	2,660/91	3,552/90
50-89	0.83-0.92	0.94-1.02	2,946/90	11,107/251	13,654/248
1-49	≤0.82	≤0.93	3,241/68	13,987/174	17,466/163

Cause-specific HRs from Cox regression with censoring at time of death by another cause than calcific aortic valve disease, emigration, or end of study were adjusted for age, sex, low-density lipoprotein cholesterol corrected for lipoprotein(a), triglycerides, systolic blood pressure, current smoking, diabetes, years of education, and estimated glomerular filtration rate.

population stratification bias, which may otherwise be particularly relevant for genetically determined lipoprotein(a) levels. Also, BMI was based on measured weight and height at examination and was not based on self-reported values. Another strength is that we used nationwide Danish health registries for diagnoses of CAVD without losses to follow-up.

Finally, a model including only the 4 covariates of age, sex, lipoprotein(a), and BMI was able to discriminate risks in 2 different cohorts, indicating that the model could be used in other cohorts as well; however, there was some miscalibration at the highest risks estimated in the Copenhagen General Population Study recruited in 2003 to 3014, which could

FIGURE 6 Absolute 10-Year Risk of Calcific Aortic Valve Disease

Body mass index kg/m²	mg/dL: nmol/L:	Women Lipoprotein(a) ≤42 ≤88	Women Lipoprotein(a) 43-79 89-169	Women Lipoprotein(a) ≥80 ≥170	Age	Men Lipoprotein(a) ≤42 ≤88	Men Lipoprotein(a) 43-79 89-169	Men Lipoprotein(a) ≥80 ≥170
≥30.0		5	7	9	70-79	8	11	14
25.0-29.9		4	5	7		6	8	10
18.5-24.9		3	4	5		4	6	8
≥30.0		2	3	4	60-69	3	5	6
25.0-29.9		2	2	3		2	3	4
18.5-24.9		1	2	2		2	2	3
≥30.0		0.7	1	1	50-59	1	2	2
25.0-29.9		0.5	0.8	1		0.8	1	2
18.5-24.9		0.4	0.6	0.7		0.6	0.9	1

Risk estimates were based on Fine and Gray subdistribution cumulative incidence functions with death from another cause or emigration as competing risk event and with baseline age, sex, lipoprotein(a), and body mass index as categorized covariates using clinical cutpoints for lipoprotein(a) and body mass index. **Numbers in grids** are risk in percent.

be due to the low number of events in the extreme risk groups in the Copenhagen City Heart Study recruited in 1991 to 1994. In other words, the individuals in the Copenhagen City Heart Study were included earlier than in the Copenhagen General Population Study in a time with higher mortality from myocardial infarction, which could lower the number of diagnosed cases of CAVD. To address this issue, studies in other current cohorts validating the use of only these 4 risk factors are needed.

STUDY LIMITATIONS. Our study investigated observational measures, while previous studies focusing on genetic instruments have already indicated causality between elevated lipoprotein(a) levels and high BMI on risk of CAVD.[4-6,12,13,36,37] Thus, our study focused on risk estimates in an everyday clinical setting in which genetic risk scores are not used. Therefore, our results are theoretically prone to confounding and reverse causation. However, age, sex, and the largely genetically determined lipoprotein(a) levels are unlikely to be influenced by confounding or reverse causation. Though maybe partly confounded, BMI could still be a marker of risk.

Other potential limitations include that lipoprotein(a) and BMI were only measured once, and if these measures change over time, our results could be influenced. However, if nondifferential to diagnosis of CAVD, such changes over time in lipoprotein(a) and BMI would only drive our results toward the null hypothesis and cannot explain the findings. Further, possible underestimation of the number of individuals with CAVD could be a limitation, as many are undiagnosed when asymptomatic or when symptoms are mild. ICD codes probably miss some cases of CAVD unless echocardiography is performed. Also, we only excluded 50 individuals with congenital aortic valve malformations; however, more cases with bicuspid valves should be expected. It can be difficult to determine if bicuspid valves are due to heavy calcification or was present from birth. Therefore, we probably did not exclude all cases of congenital bicuspid aortic valves in our analyses.

Importantly, it cannot be concluded from our data that intervention to reduce lipoprotein(a) levels or BMI will reduce the risk of CAVD. Such effects need to be documented in randomized clinical trials before treatment advise can be given.

CONCLUSIONS

Extremely high lipoprotein(a) levels and extremely high BMI together conferred a 3.5-fold risk of CAVD. Ten-year absolute risk of CAVD by categories of lipoprotein(a) levels, BMI, age, and sex ranged from 0.4% to 14%.

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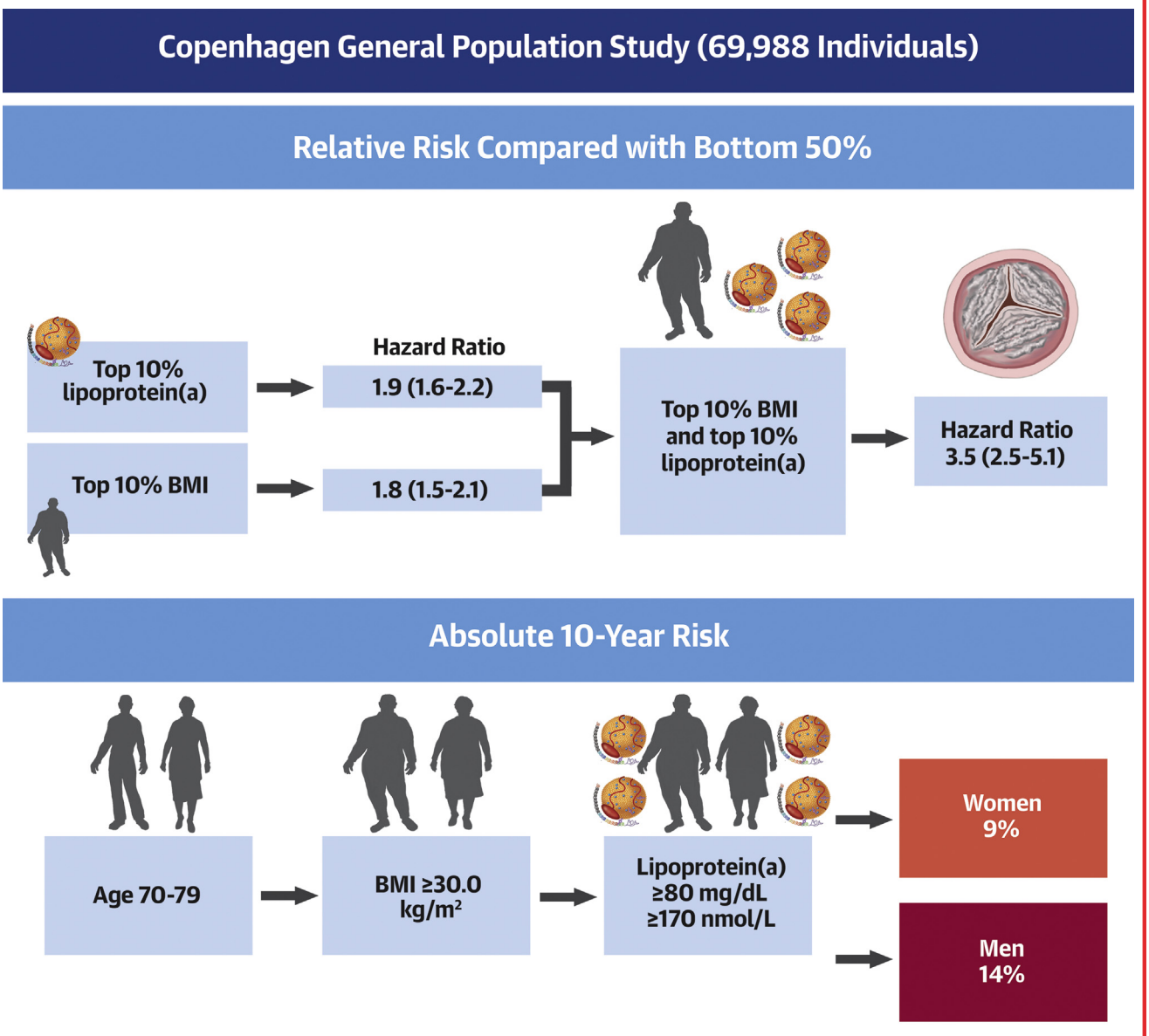
CENTRAL ILLUSTRATION Additive Risk of Calcific Aortic Valve Disease From High Lipoprotein(a) and High Body Mass Index



Hazard ratios (95% CI) for aortic valve stenosis are with multivariable adjustment

Kaltoft, M. et al. J Am Coll Cardiol. 2022;79(6):545–558.

Cause-specific HRs **(top)** from Cox regression with censoring at time of death by another cause than calcific aortic valve disease, emigration, or end of study were adjusted for age, sex, low-density lipoprotein cholesterol corrected for lipoprotein(a), triglycerides, systolic blood pressure, current smoking, diabetes, years of education, and estimated glomerular filtration rate. Absolute risk estimates **(bottom)** were based on Fine and Gray subdistribution cumulative incidence functions with death from another cause or emigration as competing risk event and with baseline age, sex, lipoprotein(a), and body mass index (BMI) as categorized covariates.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Along with age and male sex, high lipoprotein(a) and BMI are additive risk factors for development of CAVD.

TRANSLATIONAL OUTLOOK: Randomized trials should investigate the effect of interventions that lower lipoprotein(a) and BMI on risk of CAVD.

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KEY WORDS absolute risk, heart valve, lipoprotein, obesity, waist-hip ratio

APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.