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Obesity as a Causal Risk Factor for Aortic Valve Stenosis

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ABSTRACT

BACKGROUND Causal risk factors for aortic valve stenosis are poorly understood, limiting the possibility of preventing the most common heart valve disease.

OBJECTIVES The hypothesis was tested that genetically based obesity measured by body mass index is causally associated with risk of aortic valve stenosis and replacement.

METHODS The authors included 108,211 individuals from the Copenhagen General Population Study. Participants had measurements of body mass index, waist-hip ratio, and waist circumference, and information on 5 genetic variants associated with obesity. A Mendelian randomization design was used to investigate genetic and observational associations of obesity with incident aortic valve stenosis (n = 1,215) and replacement (n = 467) for a median follow-up time of 8.7 years.

RESULTS Genetically increased body mass index was causally associated with increased risk of aortic valve stenosis. Compared with an unweighted allele score of 0 to 3, individuals with an allele score 7 to 10 had a mean increase in body mass index of 0.87 kg/m^2, and the age and sex-adjusted hazard ratio for aortic valve stenosis was 1.3 (95% confidence interval [CI]: 1.0 to 1.7) for allele score 4, 1.4 (95% CI: 1.1 to 1.8) for allele score 5 to 6, and 1.6 (95% CI: 1.3 to 2.1) for allele score 7 to 10 (p for trend: 9×10^{-5}). A 1-kg/m^2 increase in body mass index was associated with causal risk ratios for aortic valve stenosis and replacement, respectively, of 1.52 (95% CI: 1.23 to 1.87) and 1.49 (95% CI: 1.07 to 2.08) genetically, and with corresponding hazard ratios of 1.06 (95% CI: 1.05 to 1.08) and 1.06 (95% CI: 1.03 to 1.08) observationally.

CONCLUSIONS Obesity from human genetics was causally associated with higher risk of aortic valve stenosis and replacement. (J Am Coll Cardiol 2020;75:163–76) © 2020 by the American College of Cardiology Foundation.

Aortic valve stenosis is the most common heart valve disease, where the prevalence increases from 0.2% in those 50 to 59 years of age to 9.8% in those 80 to 89 years of age (1). With aging populations worldwide, the disease is expected to be an increasing burden on public health (2). In untreated individuals with symptomatic aortic valve stenosis, the survival is only a couple of years from onset of heart failure symptoms. The only available treatment is aortic valve replacement or transcatheter aortic valve implantation (3). These procedures are comprehensive and expensive (4), which emphasizes the need for identifying modifiable causal risk factors.

Aortic valve stenosis shares some risk factors with atherosclerotic cardiovascular disease, including age, smoking, cholesterol levels, lipoprotein(a), and diabetes mellitus (5–12), but the pathogenesis and causal pathways are not entirely understood. Obesity is another factor that could possibly increase the risk of aortic valve stenosis; however, previous smaller studies have shown conflicting results (1,9,13–15). Nevertheless, a recent study with 71,817 individuals

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ABBREVIATIONS AND ACRONYMS

ICD = International Classification of Diseases

SNP = single nucleotide polymorphism

showed a clear observational association between both high body mass index and waist circumference and risk of aortic valve stenosis (16).

We tested the hypothesis that genetically based obesity measured by body mass index is causally associated with risk of aortic valve stenosis and replacement. For genetic analyses, we used the top 5 single nucleotide polymorphisms (SNPs) causally associated with increased body mass index (17), that is, the best genetic instruments available rather than using all SNPs associated with body mass index, thereby minimizing weak instrument bias (18).

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METHODS

For an expanded Methods section, see the Online Appendix.

STUDY COHORT. We used data from the Copenhagen General Population Study, which is a prospective cohort study that recruited from 2003 through 2015. White individuals of Danish descent 20 to 100 years of age were invited randomly from the general population of the greater Copenhagen area. The study was conducted in accordance with the Declaration of Helsinki and approved by local institutional reviews and a Danish ethical committee (H-KF-01-144/01). Information on health and lifestyle was obtained from questionnaires and from physical examinations. Blood samples were drawn for biochemical measurements, including DNA analyses. The participation rate was 43%, and 108,304 individuals were included.

OBESITY FROM HUMAN GENETICS. The following 5 SNPs were chosen for individual genotyping because these are known to have the largest effect on body mass index (19): *FTO* (rs9939609), *MC4R* (rs17782313), *TMEM18* (rs6548238), *BDNF* (rs10767664), and *GNPDA2* (rs10938397). An unweighted allele score of 0 to 10 was created by counting the number of alleles associated with increase in body mass index (20). The unweighted allele score was categorized as 0 to 3 (9% of population), 4 (19%), 5 to 6 (52%), and 7 to 10 alleles (20%) to improve statistical power.

Furthermore, internally and externally weighted allele score groups were created on the basis of the specific polymorphisms' effect on body mass index (21), using the magnitude of individual beta-coefficients for the individual genotypes (Online Tables 1 and 2).

To identify genetic instruments for waist-hip ratio adjusted for body mass index, we found SNPs with a known association in the GIANT (Genetic Investigation of Anthropometric Traits) consortium ($p < 1 \times 10^{-6}$) (22). Of these, 30 SNPs were available on a subset of the present population (Online Table 3).

OBESITY. Weight, height, hip circumference, and waist circumference were all measured at the time of attendance. Body mass index was calculated as weight (in kg) divided by height squared (in m^2). Individuals were grouped into 5 World Health Organization categories of body mass index (kg/m^2): <18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, and ≥35.0 (23).

AORTIC VALVE STENOSIS AND REPLACEMENT. Diagnoses were obtained from the nationwide Danish Causes of Death Registry and the nationwide Danish Patient Registry, using the individuals' unique Danish Civil Registration Number. Aortic valve stenosis was defined as International Classification of Diseases (ICD) 10th edition (ICD-10) codes I35.0 and I35.2 either registered during hospital visits or on the death certificate; individuals with these codes or corresponding ICD-8 codes before study entry were excluded in statistical analyses. Aortic valve replacement was defined as surgery on the aortic valve, thereby including open aortic valve replacement and transcatheter aortic valve replacement. Codes used for aortic valve replacement are shown in Online Table 4.

Individuals were enrolled from 2003 to 2015 and followed until event (n = 1,215 for incident aortic valve stenosis and n = 467 for aortic valve replacement), emigration (n = 459), death (n = 10,236), or April 2018, whichever occurred first.

COVARIATES. For multivariable adjustment in observational analyses, risk factors for aortic valve stenosis were included: age (underlying time-scale), sex, smoking status (current, previous, never), pack-years smoked, systolic blood pressure (mm Hg), years of education, low-density lipoprotein cholesterol (mmol/l), lipoprotein(a) (mg/dl), and diabetes mellitus.

STATISTICAL ANALYSES. We used Stata version 13.1 software (StataCorp, College Station, Texas). Cuzick's nonparametric test for trend assessed trend across genetic and observational categories.

Genetic allele score associations were calculated using Cox regression with sex as a covariate and age as timescale (=age adjustment) and left truncation at examination. As done previously (20), causal, genetic associations were assessed for body mass index using instrumental variable analysis; the effect size was normalized to a 1-kg/m^2 genetic increase in body mass index to allow direct comparison with a 1-kg/m^2 body mass index increase in observational analyses.

Restricted cubic splines were used to evaluate the relationships of body mass index, waist-hip ratio, and waist circumference with aortic valve stenosis. Observational associations of body mass index, waist-hip ratio, and waist circumference with aortic valve stenosis were calculated adjusted for age and sex or multivariable, using Cox regression as for genetic analyses. Cumulative incidences excluding other death and emigration as competing risks were calculated with Fine and Gray regression (24).

RESULTS

We included 108,304 individuals from the white Danish general population. During a median follow-up of 8.7 years (range 0 to 14 years), 1,215 individuals were diagnosed with aortic valve stenosis, and 467 with aortic valve replacement. Baseline characteristics are shown in **Table 1**. For allele score groups by body mass index, systolic blood pressure, diabetes, and status as current smoker differed slightly between groups. For individuals with obesity (body mass index ≥30), 92% had >3 obesity-associated alleles compared with 90% of nonobese individuals (Online Table 5).

OBESITY AND AORTIC VALVE STENOSIS: GENETIC ANALYSES. We calculated an unweighted allele score by counting the number of body mass index-increasing alleles, that is, each allele had the same weight (Online Table 1). Further, we also calculated a weighted allele score where each allele was weighted on the basis of the influence on body mass index, that is, by multiplying the number of alleles with the beta-coefficient from linear regression for each genotype separately, and then adding all individual contributions into a single score.

Individuals with an unweighted allele score of 7 to 10, compared with an allele score of 0 to 3, had a mean increase in body mass index of 0.87 kg/m^2 (**Figure 1**). Compared with individuals with unweighted body mass index allele score of 0 to 3, the age and sex-adjusted hazard ratio for aortic valve stenosis was 1.3 (95% confidence interval [CI]: 1.0 to 1.7) for allele score 4, 1.4 (95% CI: 1.1 to 1.8) for allele score 5 to 6, and 1.6 (95% CI: 1.3 to 2.1) for allele score 7 to 10 (p for trend = 9×10^{-5}).

Using the internally weighted allele score categories, individuals in group 4, the group with the highest allele score, had a mean increase in body mass index of 0.93 kg/m^2 compared with group 1, the group with the lowest allele score (**Figure 1**). Compared with individuals in internally weighted allele score group 1, the age and sex-adjusted hazard ratio for aortic valve stenosis was 1.3 (95% CI: 1.0 to 1.7) for group 2, 1.4 (95% CI: 1.1 to 1.9) for group 3, and 1.6 (95% CI: 1.2 to 2.0) for group 4 (p for trend = 2×10^{-4}). When adjusting analyses for systolic blood pressure, smoking status, pack-years, and diabetes, results were similar (Online Figure 1). Results for aortic valve replacement are shown in Online Figure 2. In analyses including genetic variants associated with waist-hip ratio adjusted for body mass index on a subset of the population including 11,226 individuals, the age and sex-adjusted hazard ratio for aortic valve stenosis was 1.5 (95% CI: 0.8 to 2.6) for weighted allele score group 4 compared with group 1 (p for trend = 0.27) (Online Figure 3). For the combined weighted allele score (both body mass index and waist-hip ratio adjusted for body mass index), the age and sex-adjusted hazard ratio for aortic valve stenosis was 1.7 (95% CI: 0.9 to 3.2) for group 4 compared with group 1 (p for trend = 0.28) (Online Figure 4).

OBSERVATIONAL AND GENETIC ANALYSES. In instrumental variable analysis, the age and sex-adjusted causal risk ratio for aortic valve stenosis based on the unweighted allele score was 1.52 (95% CI: 1.23 to 1.87) per 1-kg/m^2 increase in body mass index (**Figure 2**). For aortic valve replacement, the corresponding causal risk ratio was 1.49 (95% CI: 1.07 to 2.08). These results were similar in models whether allele scores were weighted internally or externally.

Observational hazard ratio for aortic valve stenosis per 1-kg/m^2 increase in body mass index was 1.07 (95% CI: 1.06 to 1.09) in the age and sex-adjusted model and 1.06 (95% CI: 1.05 to 1.08) in the multivariable-adjusted model (**Figure 2**). The corresponding hazard ratios for aortic valve replacement were 1.07 (95% CI: 1.04 to 1.09) in the age and sex-adjusted model and 1.06 (95% CI: 1.03 to 1.08) in the multivariable-adjusted model. Observational results without correction for regression dilution bias are shown in Online Figure 5.

OBESITY AND AORTIC VALVE STENOSIS: OBSERVATIONAL ANALYSES. On continuous scales in multivariable-adjusted analyses, higher body mass index, waist-hip ratio, and waist circumference were associated with increased risk of aortic valve stenosis (**Figure 3**). These results were similar for both sexes separately (Online Figure 6). Results for aortic valve replacement are shown in Online Figure 7. Taking competing risk of death and emigration into account, the cumulative incidence of aortic valve stenosis was stepwise higher in groups with higher body mass index (p for trend = 3×10^{-20}), waist-hip ratio (p for trend = 9×10^{-16}), and waist circumference (p for trend = 7×10^{-13}) (**Figure 4**). Results were similar for aortic valve replacement.

TABLE 1 Baseline Characteristics

	Genetic, Causal Analyses				
	Internally Weighted Allele Score Group for Body Mass Index				
	1	2	3	4	p Value
Individuals, n	8,518	17,791	57,833	21,277	
Age, yrs	58 (48–67)	58 (48–68)	58 (48–67)	58 (48–68)	0.57
Women	55	55	55	55	0.40
Smoking status					
Never	43	43	42	42	0.03
Previous	41	40	41	41	0.94
Current	16	17	17	18	0.001
Cumulative smoking, current and previous smokers only, pack-yrs	15 (6–30)	16 (6–30)	15 (6–30)	16 (6–30)	0.03
Systolic blood pressure, mm Hg	139 (126–154)	140 (126–155)	140 (126–155)	140 (127–155)	9×10^{-5}
LDL cholesterol, mmol/l	3.2 (2.6–3.8)	3.2 (2.6–3.8)	3.2 (2.6–3.8)	3.2 (2.6–3.8)	0.03
Lipoprotein(a), mg/dl	9.7 (4.6–29)	9.9 (4.8–30)	9.7 (4.8–29)	9.6 (4.7–28)	0.41
Education, yrs	11 (10–12)	11 (9–12)	11 (10–12)	11 (9–12)	0.43
Diabetes	4.0	3.9	4.1	4.8	2×10^{-5}
	Observational Analyses				
	Body Mass Index, kg/m^2				
	18.5–24.9	**25.0–29.9**	**30.0–34.9**	**≥35.0**	**p Value**
Individuals, n	46,698	43,059	13,472	3,886	
Age, yrs	56 (46–66)	60 (50–68)	61 (51–68)	58 (49–66)	1×10^{-204}
Women	66	44	48	64	$<1 \times 10^{-300}$
Smoking status					
Never	45	40	39	41	7×10^{-41}
Previous	37	44	45	43	1×10^{-77}
Current	18	16	16	16	3×10^{-12}
Cumulative smoking, current and previous smokers only, pack-yrs	13 (5–26)	17 (7–31)	20 (10–36)	20 (9–36)	3×10^{-277}
Systolic blood pressure, mm Hg	134 (121–150)	142 (130–156)	147 (134–160)	150 (137–164)	$<1 \times 10^{-300}$
LDL cholesterol, mmol/l	3.0 (2.5–3.7)	3.3 (2.7–4.0)	3.3 (2.7–4.0)	3.3 (2.6–4.0)	8×10^{-296}
Lipoprotein(a), mg/dl	9.6 (4.8–29)	10 (4.8–30)	9.5 (4.6–30)	9.3 (4.3–27)	0.81
Education, yrs	12 (10–12)	10 (9–12)	10 (9–12)	10 (9–12)	$<1 \times 10^{-300}$
Diabetes	1.9	4.4	8.7	15.4	$<1 \times 10^{-300}$

Continued on the next page

Compared with individuals with body mass index of 18.5 to 24.9 kg/m^2, the multivariable-adjusted hazard ratio for aortic valve stenosis was 1.3 (95% CI: 1.1 to 1.5) for individuals with a body mass index of 25.0 to 29.9 kg/m^2, 1.8 (95% CI: 1.5 to 2.2) for 30.0 to 34.9 kg/m^2, and 2.6 (95% CI: 2.0 to 3.5) for individuals with body mass index ≥35.0 kg/m^2 (Figure 5). Corresponding hazard ratios for aortic valve replacement were 1.3 (95% CI: 1.0 to 1.7), 1.8 (95% CI: 1.3 to 2.4), and 2.1 (95% CI: 1.3 to 3.5), respectively.

Compared with individuals with waist-hip ratio ≤0.80 for women and ≤0.91 for men, the multivariable-adjusted hazard ratio for aortic valve stenosis was 1.5 (95% CI: 1.2 to 1.9) for women/men with a waist-hip ratio of 0.81 to 0.89/0.92 to 0.99, 2.0 (95% CI: 1.5 to 2.6) for 0.90 to 0.96/1.00 to 1.06, and 3.2 (95% CI: 2.2 to 4.6) for women/men with waist-hip ratio ≥0.97/≥1.07 (Figure 5). Corresponding hazard ratios for aortic valve replacement were 1.0 (95% CI: 0.7 to 1.4), 1.4 (95% CI: 0.9 to 2.2), and 1.9 (95% CI: 1.0 to 3.5), respectively.

Compared with individuals with waist circumference ≤81 cm for women and ≤94 cm for men, the multivariable-adjusted hazard ratio for aortic valve stenosis was 1.3 (95% CI: 1.1 to 1.5) for women/men with waist circumference 82 to 96/95 to 106 cm, 1.5 (95% CI: 1.2 to 1.8) for 97 to 109/107 to 117 cm, and 2.4 (95% CI: 1.8 to 3.2) for women/men with waist circumference ≥110/≥118 cm (Figure 5). Corresponding hazard ratios for aortic valve replacement were 1.1 (95% CI: 0.8 to 1.4), 1.4 (95% CI: 1.0 to 1.9), and 1.8 (95% CI: 1.1 to 2.8), respectively. Results without correction for regression dilution bias are shown in Online Figure 8.

INCREMENTAL VALUE OF WAIST-HIP RATIO AND WAIST CIRCUMFERENCE. In observational analyses

TABLE 1 Continued

	Waist-Hip Ratio				
Women **Men**	**≤0.80** **≤0.91**	**0.81–0.89** **0.92–0.99**	**0.90–0.96** **1.00–1.06**	**≥0.97** **≥1.07**	**p Value**
Individuals, n	46,498	42,093	14,337	3,893	
Age, yrs	53 (45–64)	60 (51–69)	63 (55–71)	65 (57–72)	$<1 \times 10^{-300}$
Women	55	56	51	55	8×10^{-5}
Smoking status					
Never	48	39	34	31	$<1 \times 10^{-300}$
Previous	37	43	47	46	2×10^{-132}
Current	15	18	20	23	2×10^{-73}
Cumulative smoking, current and previous smokers only, pack-yrs	12 (5–24)	17 (7–30)	23 (10–39)	28 (13–45)	$<1 \times 10^{-300}$
Systolic blood pressure, mm Hg	135 (123–150)	141 (128–156)	146 (133–160)	149 (135–164)	$<1 \times 10^{-300}$
LDL cholesterol, mmol/l	3.1 (2.5–3.7)	3.3 (2.6–3.9)	3.3 (2.6–4.0)	3.2 (2.5–3.9)	8×10^{-138}
Lipoprotein(a), mg/dl	9.6 (4.8–28)	10.0 (4.8–30)	9.7 (4.6–30)	9.3 (4.3–28)	0.96
Education, yrs	12 (10–12)	10 (9–12)	10 (9–12)	10 (8–12)	$<1 \times 10^{-300}$
Diabetes	1.7	4.1	9.4	16.5	$<1 \times 10^{-300}$
	Waist Circumference, cm				
Women **Men**	**≤81** **≤94**	**82–96** **95–106**	**97–109** **107–117**	**≥110** **≥118**	**p Value**
Individuals, n	47,902	41,235	13,651	4,068	
Age, yrs	54 (45–65)	60 (50–69)	63 (54–70)	62 (53–69)	$<1 \times 10^{-300}$
Women	55	55	54	54	0.22
Smoking status					
Never	46	39	37	36	5×10^{-127}
Previous	37	44	46	46	7×10^{-122}
Current	17	17	17	18	0.27
Cumulative smoking, current and previous smokers only, pack-yrs	12 (5–25)	17 (7–30)	22 (10–38)	24 (11–40)	$<1 \times 10^{-300}$
Systolic blood pressure, mm Hg	135 (122–150)	142 (130–157)	147 (134–160)	150 (137–164)	$<1 \times 10^{-300}$
LDL cholesterol, mmol/l	3.0 (2.5–3.7)	3.3 (2.7–4.0)	3.3 (2.7–4.0)	3.2 (2.5–3.9)	3×10^{-225}
Lipoprotein(a), mg/dl	9.4 (4.7–28)	10 (4.9–31)	9.6 (4.6–29)	9.3 (4.4–29)	0.06
Education, yrs	12 (10–12)	10 (9–12)	10 (9–12)	10 (8–12)	$<1 \times 10^{-300}$
Diabetes	1.7	4.2	8.8	18.3	$<1 \times 10^{-300}$

Values are median (interquartile range) or %, unless otherwise indicated. If corrected using the Bonferroni method, a p value of 0.05 = 0.001 (0.05/44). The number of individuals varies slightly according to availability of the variable (data are without imputation).

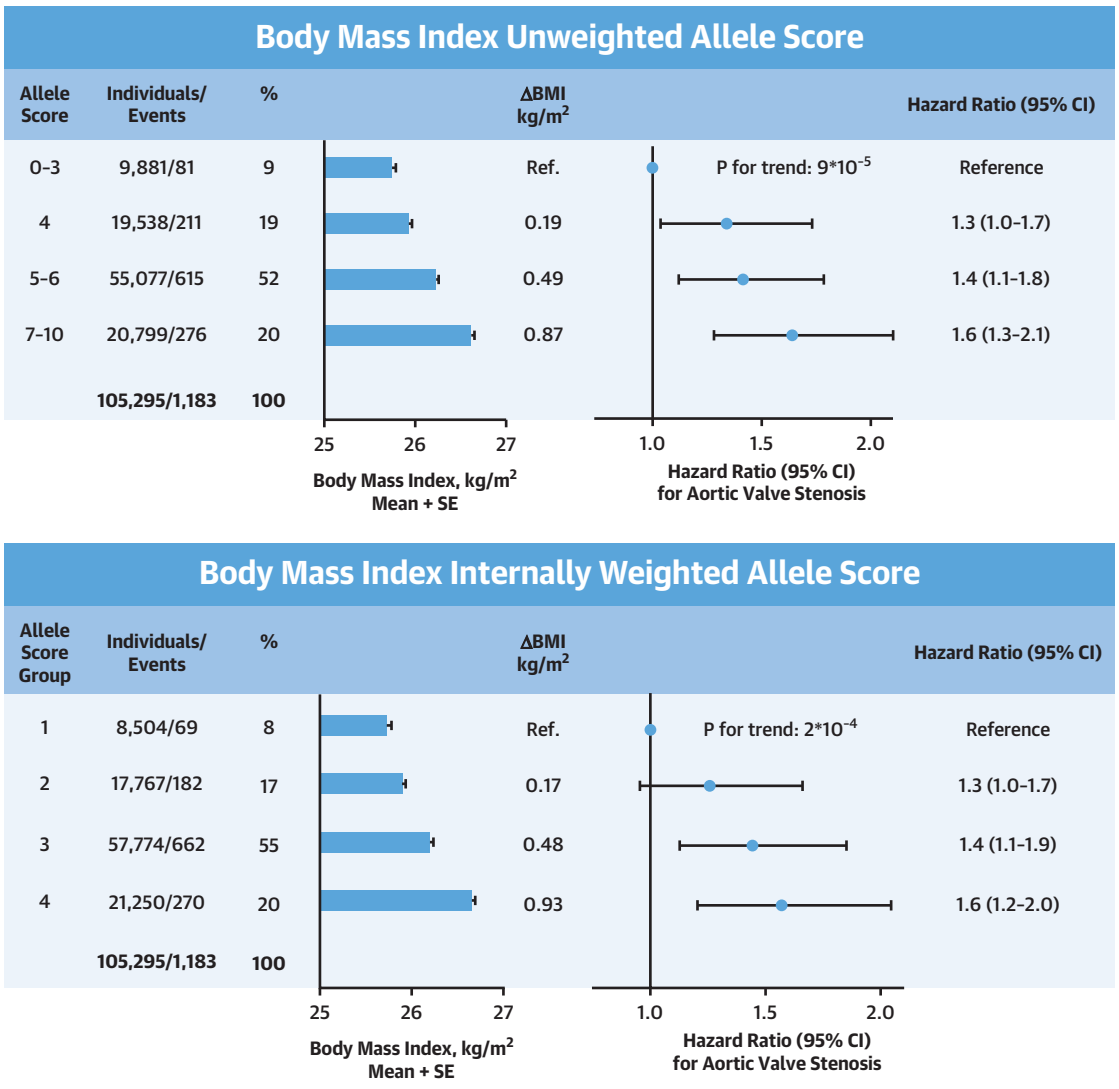
LDL = low-density lipoprotein.

where individuals are categorized by both body mass index and waist-hip ratio, individuals with both increasing body mass index and waist-hip ratio had increased risk of aortic valve stenosis (**Figure 6**). Compared with individuals with body mass index 18.5 to 24.9 kg/m^2 and waist-hip ratio (women/men) ≤0.80/≤0.91, multivariable-adjusted hazard ratio for aortic valve stenosis was 4.5 (95% CI: 2.8 to 7.1) for individuals with body mass index ≥35.0 and waist-hip ratio (women/men) ≥0.97/≥1.07. Results for waist circumference are shown in Online Figure 9. Furthermore, when adding waist-hip ratio to a multivariable-adjusted model including body mass index, the net reclassification index was 0.084 (95% CI: 0.051 to 0.11; $p < 0.001$). Analyses of C-statistics, integrated discrimination index, and net reclassification index are provided in Online Table 6.

The percentage of aortic valve stenosis events attributed to weighted allele score groups 3 and 4 compared with 1 and 2, that is, the population-attributable fraction, was 16% (Online Figure 10). The corresponding population-attributable fraction of combined body mass index ≥30 or weighted allele score groups 3 and 4 was 17%.

SENSITIVITY ANALYSES. In the observational analyses, results were also similar when excluding individuals with <2 years of follow-up, or age <60 years (Online Figures 11 and 12). The association between higher body mass index and higher risk of aortic valve stenosis was found in individuals with the highest waist circumference (men ≥101 cm, women ≥88 cm), but not in those with the lowest waist circumference (p for interaction = 0.07)

FIGURE 1 Genetic Association of BMI in Allele Score Categories With Risk of Aortic Valve Stenosis



Hazard ratios from Cox regression were adjusted for age and sex. Internally weighted allele score groups were created to follow approximately the distribution of individuals in the different unweighted allele score groups. ΔBMI = difference in mean body mass index (BMI) compared with reference; CI = confidence interval; Ref = reference; SE = standard error.

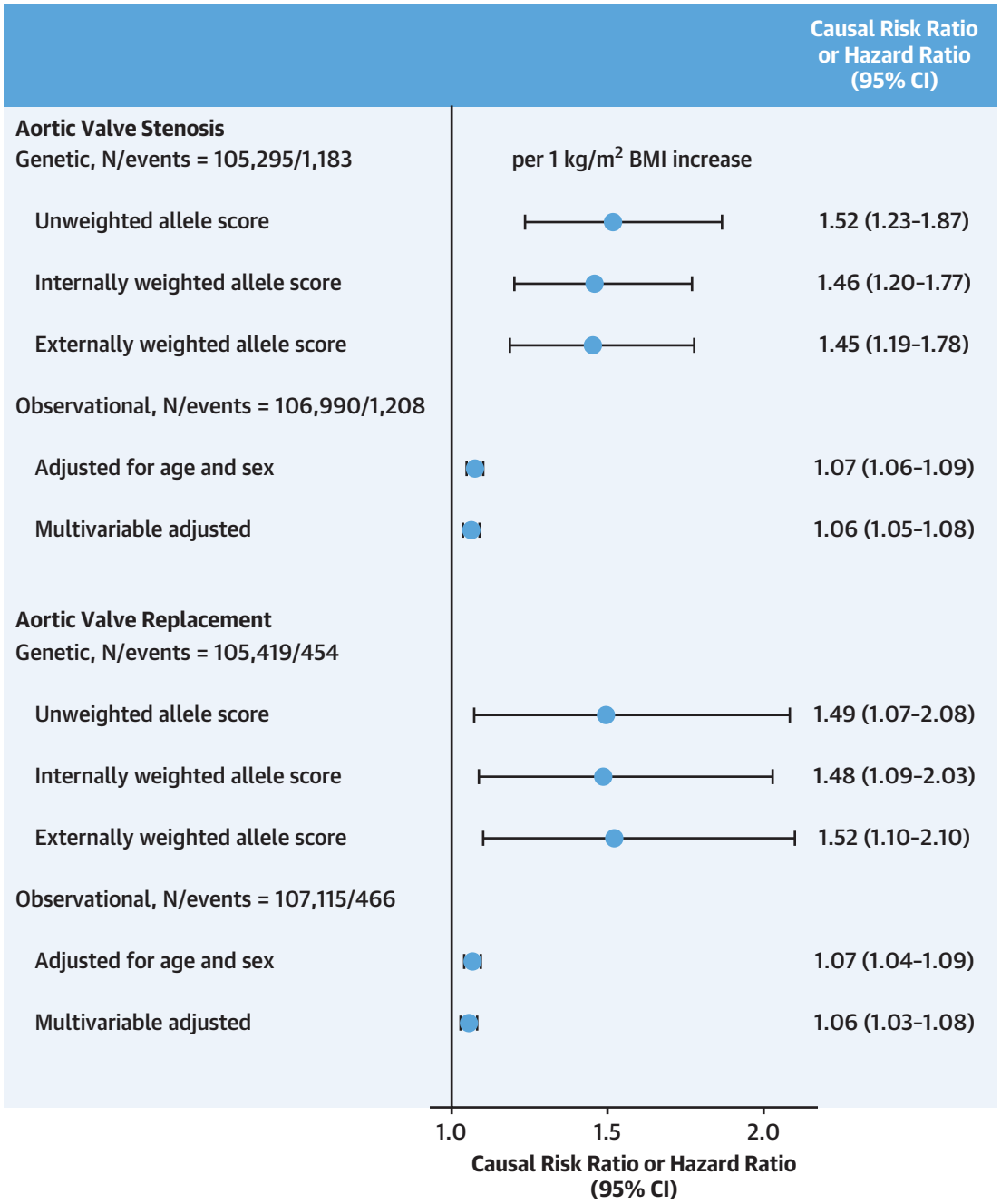
(Online Figure 13). If underweight individuals were included, results were similar to those shown (compare **Figures 2 and 5** with Online Figures 14 and 15).

Further stratifications on covariates are shown in Online Figure 16. For a 1-kg/m^2 increase in body mass index, the multivariable-adjusted hazard ratios for aortic valve stenosis were 1.07 (95% CI: 1.05 to 1.09) for women and 1.04 (95% CI: 1.02 to 1.06) for men (p for interaction = 0.02; p value is larger than the Bonferroni-corrected significance level at 0.003). Corresponding values for aortic valve replacement were 1.07 (95% CI: 1.04 to 1.10) for women and 1.03 (95% CI: 0.99 to 1.06) for men (p for interaction = 0.06) (Online Figures 6 and 16).

DISCUSSION

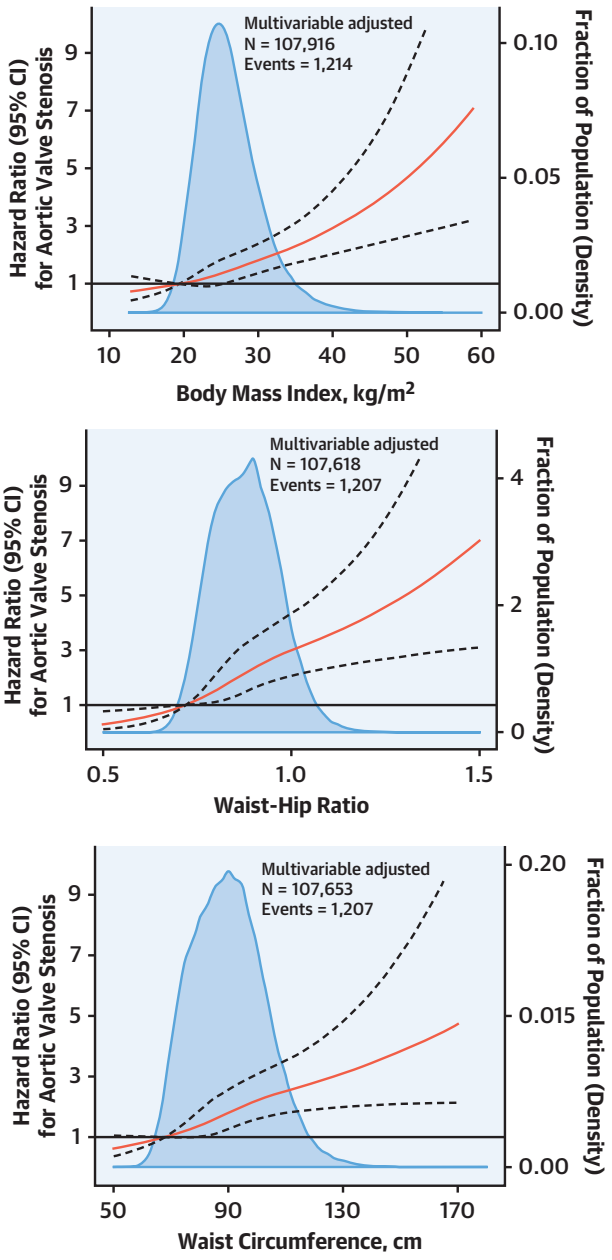
In this Mendelian randomization study of the Danish general population, obesity estimated through body mass index was causally from human genetics and observationally associated with higher risk of aortic

FIGURE 2 **Risk of Aortic Valve Stenosis and Replacement With Increasing BMI in Causal, Genetic Instrumental Variable and Observational Analyses**



In observational analyses, hazard ratios from Cox regression were age and sex adjusted or multivariable adjusted for age, sex, smoking status (current, previous, never), pack-years, low-density lipoprotein cholesterol, lipoprotein(a), systolic blood pressure, years of education, and diabetes, and were corrected for regression dilution bias. Internal weighting used genotype-body mass index beta-coefficients from the Copenhagen General Population Study, whereas external weighting used corresponding published values (21). Number of individuals varies slightly in different analyses depending on availability of data. Abbreviations as in Figure 1.

FIGURE 3 Risk of Aortic Valve Stenosis by BMI, Waist-Hip Ratio, and Waist Circumference on Continuous Scales



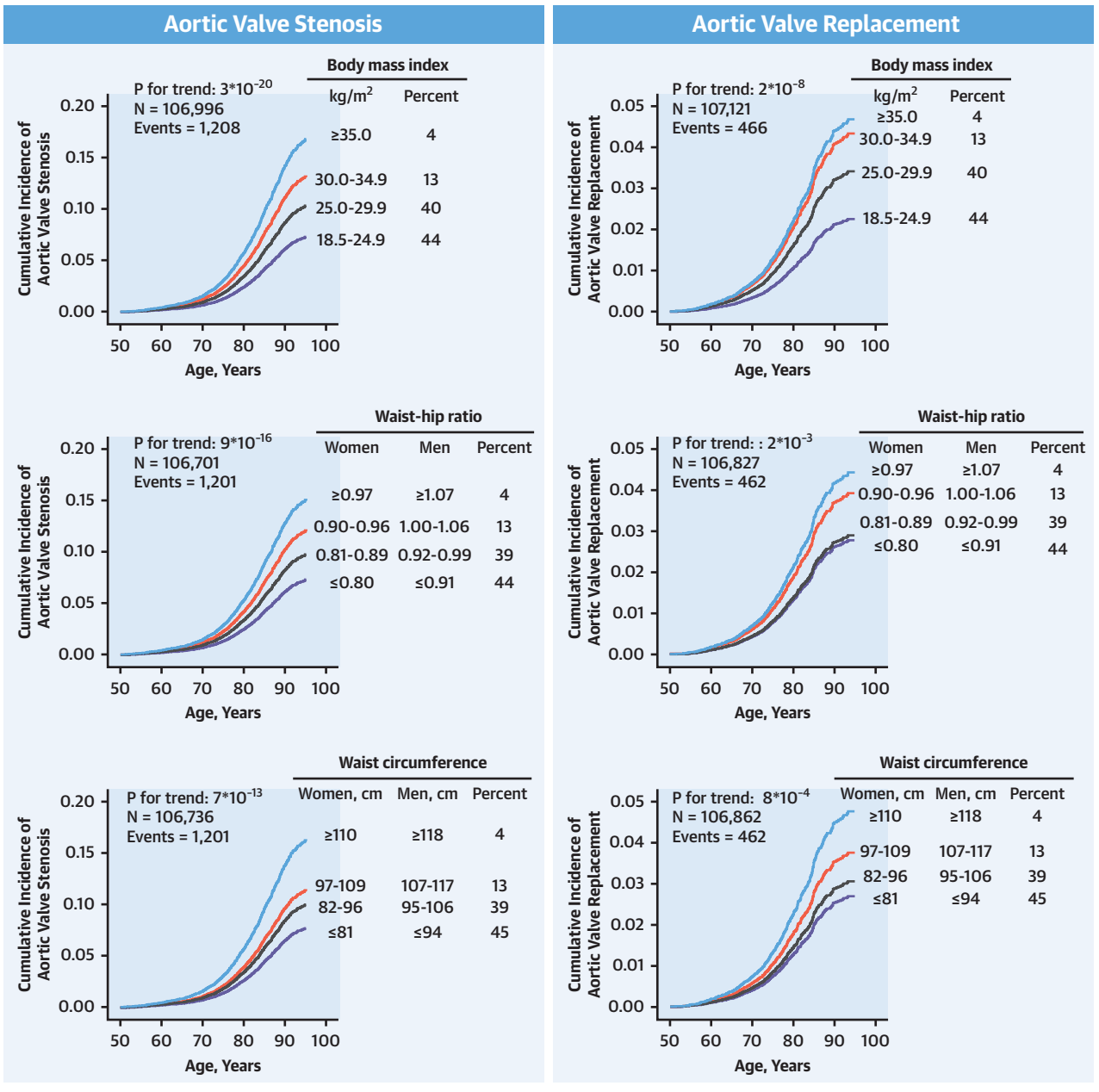
Hazard ratios **(solid lines)** and 95% CIs **(dashed lines)** are from Cox regression using restricted cubic splines. The 2.5 percentiles for BMI, waist-hip ratio, and waist circumference were used as reference in the 3 graphs, respectively. Multivariable adjustment was for age, sex, smoking status (current, previous, never), pack-years, low-density lipoprotein cholesterol, lipoprotein(a), systolic blood pressure, years of education, and diabetes. **Graphs** were truncated at body mass index >60 kg/m^2, waist-hip ratio <0.5 and >1.5, and waist circumference <50 cm and >180 cm due to limited number of individuals and events outside these cutpoints. Density plots of population distribution **(blue)** are made as kernel density estimation, in which the area under the curve is fixed to 1, resulting in different y-axes when the x-axes are numerically different. Number of individuals varies slightly depending on availability of data. Abbreviations as in Figure 1.

valve stenosis and replacement (Central Illustration). Our causal, genetic findings are novel.

The mechanism behind obesity causing aortic valve stenosis may be due to either structural changes of the heart or metabolic changes of the obese body. Structurally, obesity causes higher blood pressure, increasing stress on the heart, which could lead to geometric changes of the left ventricle (25) and aortic valve, and high blood pressure could initiate atherosclerosis through endothelial injury (26). Metabolically, obesity causes increased levels of atherogenic lipoproteins (27) that are deposited on the leaflet wall of the aortic valve (26). Ongoing injury and lipid deposition lead to an inflammatory response and infiltration of macrophages, T-lymphocytes, and mast cells (28). Inflammatory mediators cause valve interstitial cells to differentiate into osteoblasts, thus leading to calcification of valve leaflets (26). However, risk remains when adjusting for systolic blood pressure and low-density lipoprotein cholesterol in our study. Thus, other mediating causal factors from obesity to aortic valve stenosis are yet to be discovered, but may be found within metabolic changes of the obese. Obesity has been linked to proinflammatory processes (29) that triglyceride-rich remnant lipoproteins also facilitate (30–32), and it has been indicated that high triglycerides could be a genetic risk factor for aortic valve stenosis (33); however, the precise role of triglycerides and inflammation in aortic valve stenosis is unclear.

Previous studies of the association between body mass index and aortic valve stenosis have shown conflicting results (5,14,15,34), but the majority of these have been small, cross-sectional studies, some of which focus on aortic valve calcification rather than on actual stenosis. One study has shown that weight loss did not decrease progression of aortic valve stenosis in individuals who already had the diagnosis (35), but it may be important to distinguish between disease incidence and progression as they follow 2 different pathways (26). In support of our observational findings, a recent Swedish study (16) including 71,817 individuals showed robust evidence that body mass index is observationally associated with aortic valve stenosis when body mass index is above 27.5 kg/m^2, with a multivariable-adjusted hazard ratio of 1.34 (95% CI: 1.09 to 1.64) when compared with individuals with a body mass index of 18.5 to 22.4 kg/m^2. That study further proposed that abdominal fat measured in waist circumference could enhance the risk of aortic valve stenosis in overall obese individuals estimated by body mass index, which emphasizes the need to study the metabolic

FIGURE 4 Cumulative Incidence of Aortic Valve Stenosis and Replacement by Categories of BMI, Waist-Hip Ratio, and Waist Circumference



Waist-hip ratio and waist circumference categories were created to approximately follow the fraction of individuals in the World Health Organization BMI categories used, and to keep sex distribution equal between categories. Number of individuals varies slightly depending on availability of data. BMI = body mass index.

state in such individuals because aortic valve stenosis has previously been linked to the metabolic syndrome (36,37). Similarly, our study showed that risk of aortic valve stenosis is higher in individuals with both high body mass index and high waist-hip ratio or waist circumference. However, whether the waist-hip ratio-associated SNPs have an effect on the incidence of aortic valve stenosis and replacement is unclear from our data, as is the question of whether overall and abdominal obesity would differentially influence aortic valve stenosis and replacement.

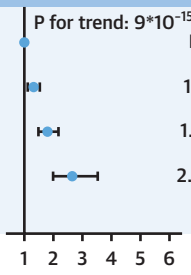
Strengths of our study include the large number of individuals, well-established genetic instruments for obesity (38), and the ethnic homogeneity of the study

FIGURE 5 Observational Association of BMI, Waist-Hip Ratio, and Waist Circumference With Risk of Aortic Valve Stenosis and Replacement

Aortic Valve Stenosis

Body Mass Index kg/m^2	Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
18.5–24.9	46,646/340	8	Reference
25.0–29.9	43,009/557	15	1.3 (1.1–1.5)
30.0–34.9	13,458/235	20	1.8 (1.5–2.2)
≥35.0	3,877/76	23	2.6 (2.0–3.5)
	106,990/1,208	**13**	

P for trend: $9*10^{-15}$

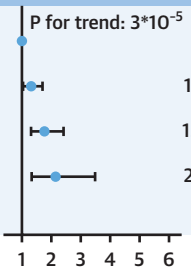


Hazard Ratio (95% CI) for Aortic Valve Stenosis

Aortic Valve Replacement

Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
46,698/127	3	Reference
43,059/220	6	1.3 (1.0–1.7)
13,472/93	8	1.8 (1.3–2.4)
3,886/26	8	2.1 (1.3–3.5)
107,115/466	**5**	

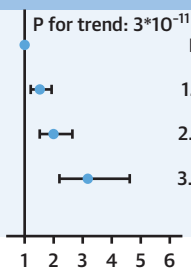
P for trend: $3*10^{-5}$



Hazard Ratio (95% CI) for Aortic Valve Replacement

Waist-hip Ratio		Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
Women	Men			
≤0.80	≤0.91	46,455/294	7	Reference
0.81–0.89	0.92–0.99	41,983/531	15	1.5 (1.2–1.9)
0.90–0.96	1.00–1.06	14,375/269	23	2.0 (1.5–2.6)
≥0.97	≥1.07	3,882/107	35	3.2 (2.2–4.6)
		106,695/1,201	**13**	

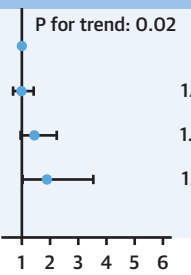
P for trend: $3*10^{-11}$



Hazard Ratio (95% CI) for Aortic Valve Stenosis

Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
46,498/139	3	Reference
42,093/187	5	1.0 (0.7–1.4)
14,337/101	9	1.4 (0.9–2.2)
3,893/35	11	1.9 (1.0–3.5)
106,821/462	**5**	

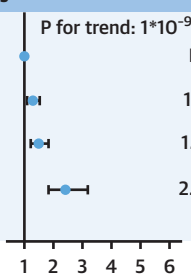
P for trend: 0.02



Hazard Ratio (95% CI) for Aortic Valve Replacement

Waist Circumference cm		Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
Women	Men			
≤81	≤94	47,856/331	8	Reference
82–96	95–106	41,179/539	15	1.3 (1.1–1.5)
97–109	107–117	13,639/236	21	1.5 (1.2–1.8)
≥110	≥118	4,056/95	28	2.4 (1.8–3.2)
		106,730/1,201	**13**	

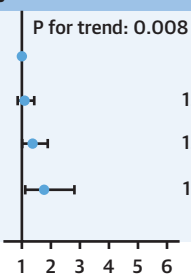
P for trend: $1*10^{-9}$



Hazard Ratio (95% CI) for Aortic Valve Stenosis

Individuals/ Events	Events per 10,000 Person Years	Hazard Ratio (95% CI)
47,902/143	3	Reference
41,235/195	5	1.1 (0.8–1.4)
13,651/91	8	1.4 (1.0–1.9)
4,068/33	10	1.8 (1.1–2.8)
106,856/462	**5**	

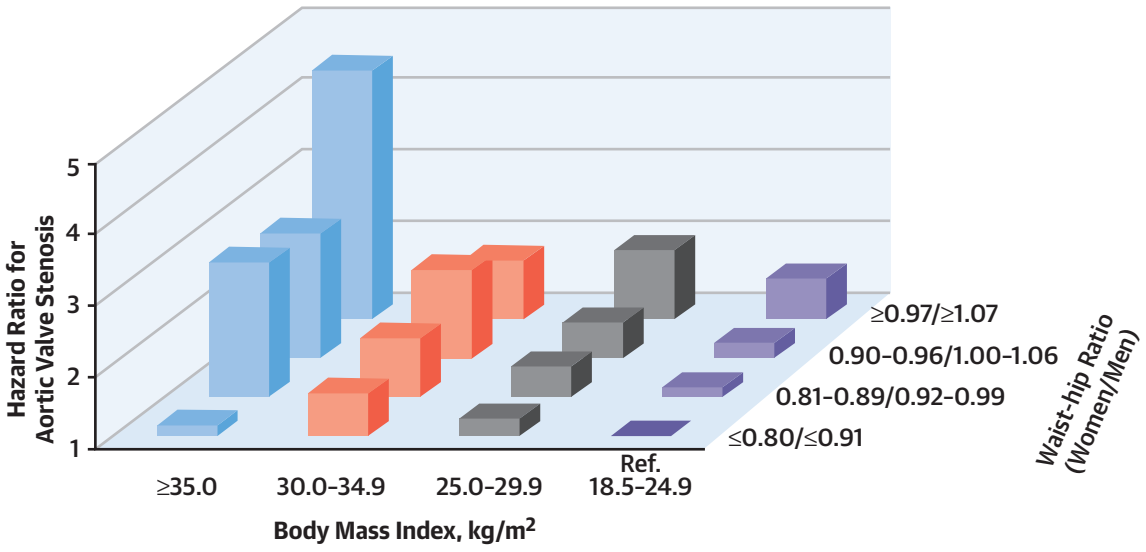
P for trend: 0.008



Hazard Ratio (95% CI) for Aortic Valve Replacement

Hazard ratios from Cox regression were multivariable adjusted for age, sex, smoking status (current, previous, never), pack-years, low-density lipoprotein cholesterol, lipoprotein(a), systolic blood pressure, years of education, and diabetes, and were corrected for regression dilution bias. Number of individuals varies slightly depending on availability of data. Waist-hip ratio and waist circumference groups were created to approximately follow the fraction of individuals in the World Health Organization BMI categories used, and to keep sex distribution equal between categories. Abbreviations as in Figure 1.

FIGURE 6 Risk of Aortic Valve Stenosis With BMI Categories Stratified by Waist-Hip Ratio



Hazard Ratio (95% Confidence Interval) for Aortic Valve Stenosis

Waist-hip Ratio		Body Mass Index, kg/m²			
Women	Men	≥35.0	30.0–34.9	25.0–29.9	18.5–24.9
≥0.97	≥1.07	4.5 (2.8–7.1)	1.8 (1.2–2.8)	2.0 (1.3–2.9)	1.6 (0.7–3.4)
0.90–0.96	1.00–1.06	2.8 (1.8–4.3)	2.2 (1.7–2.9)	1.5 (1.2–2.0)	1.2 (0.8–1.9)
0.81–0.89	0.92–0.99	2.9 (1.8–4.6)	1.8 (1.4–2.4)	1.4 (1.2–1.8)	1.1 (0.9–1.5)
≤0.80	≤0.91	1.1 (0.3–4.6)	1.6 (0.9–2.8)	1.2 (1.0–1.6)	1 (reference)

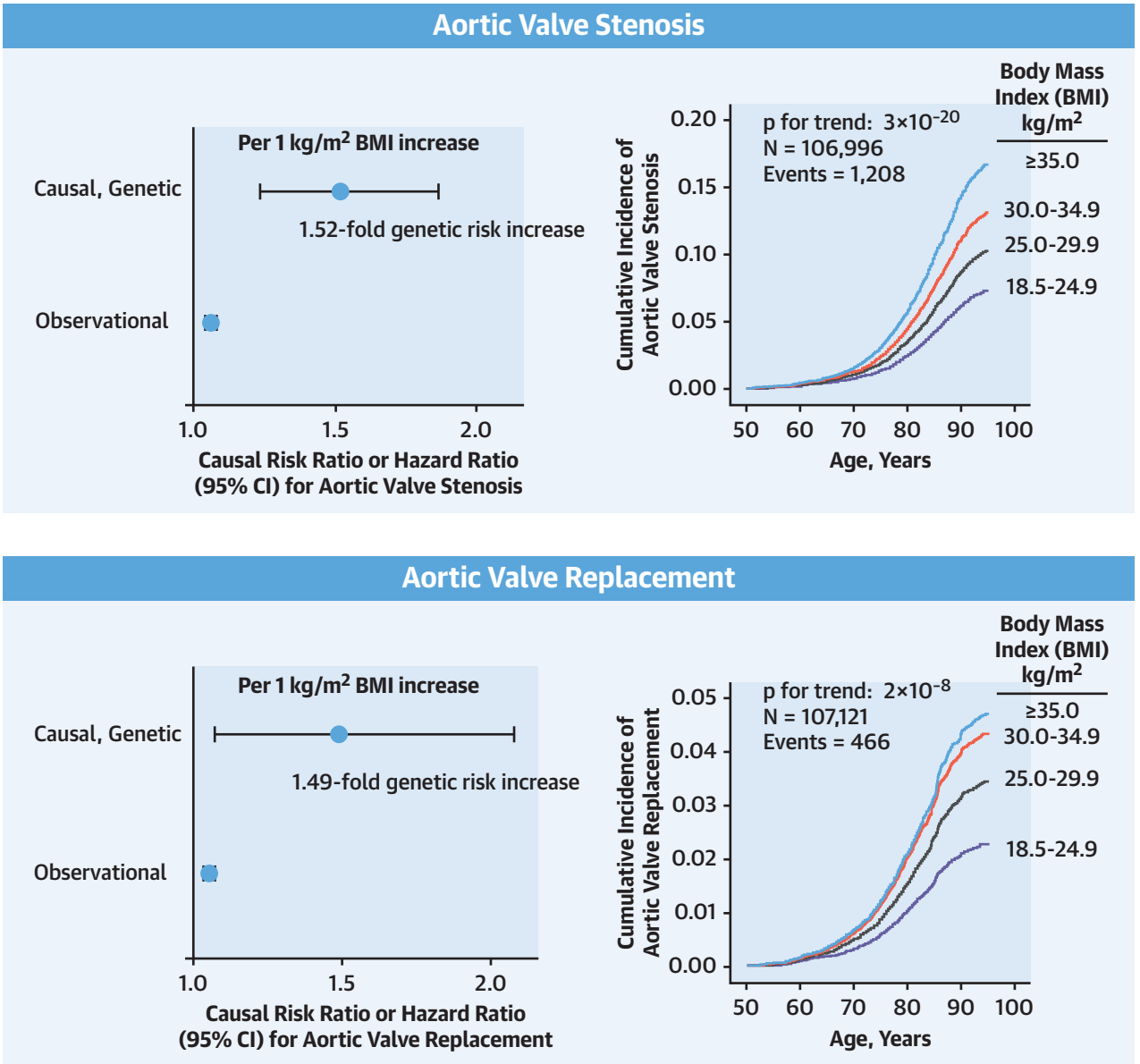
Number of Individuals/Events

Waist-hip Ratio		Body Mass Index, kg/m²			
Women	Men	≥35.0	30.0–34.9	25.0–29.9	18.5–24.9
≥0.97	≥1.07	765/22	1,338/27	1,225/30	408/7
0.90–0.96	1.00–1.06	1,305/24	4,135/85	6,472/103	2,138/23
0.81–0.89	0.92–0.99	1,375/22	5,932/78	19,987/243	14,159/110
≤0.80	≤0.91	355/2	1,805/14	14,649/96	29,209/138

Hazard ratios from Cox regression were multivariable adjusted for age, sex, smoking status (current, previous, never), pack-years, low-density lipoprotein cholesterol, lipoprotein(a), systolic blood pressure, years of education, and diabetes. Number of individuals varies slightly depending on availability of data. Waist-hip ratio groups were created to approximately follow the fraction of individuals in the World Health Organization BMI categories used, and to keep sex distribution equal between categories. BMI = body mass index; Ref. = reference.

population to avoid effects of population stratification. Additionally, measurements of body mass index, waist-hip ratio, and waist circumference were objectively conducted by an examiner at the day of attendance, in contrast to using self-reported values (16). It is also a strength that we used both hospital visits and death certificate diagnoses of aortic valve stenosis from nationwide Danish registries, and that

CENTRAL ILLUSTRATION **Risk of Aortic Valve Stenosis and Replacement in 107,000 Individuals From the Copenhagen General Population Study**



Kaltoft, M. et al. J Am Coll Cardiol. 2020;75(2):163–76.

Causal, genetic risk ratios are from instrumental variable analyses based on the unweighted allele score. Cumulative incidence curves are from Fine and Gray regression. BMI = body mass index; CI = confidence interval.

sensitivity analysis only including the endpoint of aortic valve replacement gave similar results. Last, no individual was lost to follow-up.

STUDY LIMITATIONS. Mendelian randomization studies are potentially limited by genetic pleiotropy, and it has been described that the 5 genetic variants used in this study are also associated with smoking, as individuals with genetic propensity to obesity are less likely to quit smoking, possibly due to the risk of gaining weight (39). The distribution of systolic blood pressure was also slightly different over the allele

score groups, which is a likely effect of obesity causing hypertension and, thus, being part of the causal pathway (40,41), which likely is also the case for diabetes (17). Adjusting genetic analyses for smoking, systolic blood pressure, and diabetes did not, however, change the study conclusions. Nevertheless, we cannot totally exclude that allele scores are confounded by yet unidentified pleiotropic effects.

Because we only measured body mass index, waist-hip ratio, and waist circumference once, changes in these measures over time could bias our results. If such bias was nondifferential, it would bias the results toward the null hypothesis and, therefore, likely cannot explain our findings. The higher effect size for risk of aortic valve stenosis for genetically higher body mass index compared with observationally higher body mass index likely is explained by the fact that genetic estimates typically capture lifelong effects. Some diagnoses of aortic valve stenosis may be caused by a congenitally abnormal bicuspid aortic valve and should not be considered part of the calcific etiology. However, congenital aortic valve malformations were excluded from all analyses, and further exclusion of individuals age <60 years showed similar results; most cases of aortic valve stenosis before age 60 years are due to bicuspid aortic valves. Another limitation is the relatively short median follow-up time of 8.7 years for a slowly progressing disease. Further, a limitation could be possible underestimation of the number of individuals with aortic valve stenosis, because many are undiagnosed in the beginning of the disease progression. ICD codes probably miss some cases of aortic valve stenosis unless echocardiography is performed. Also, we have no information on aortic valve stenosis severity, which is a slowly progressive disease, although the number of aortic valve replacements relative to the diagnosis of aortic valve stenosis (467 of 1,215, 38%) suggests that many included individuals had severe aortic valve stenosis. If such underdiagnosis is nondifferential to obesity determined genetically and observationally, this would bias the results toward the null hypothesis and thus cannot explain our results. However, it could be argued that individuals with obesity present earlier with symptoms of aortic valve stenosis due to already present wheezing or dyspnea due to obesity (38), and thereby are diagnosed earlier. Conversely, doctors could be more likely to blame obesity for the symptoms and thus halt diagnostic procedures.

CONCLUSIONS

Obesity estimated through body mass index was causally based on human genetics and observationally associated with higher risk of aortic valve stenosis and replacement. Further investigation of metabolic and atherogenic alterations in the obese body could reveal unknown causal pathways, potentially leading to a treatable trait in this complex disease, with the long-term goal of preventing aortic valve stenosis. Although most of the obesity impact on aortic valve stenosis that can be explained is accounted for by the genetic score, this does not preclude potential benefit of intervention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Genetically based obesity, as assessed by body mass index, is a risk factor for development of aortic valve stenosis.

TRANSLATIONAL OUTLOOK: Metabolic studies of obese patients are needed to reveal the biological pathways underlying the development and progression of aortic stenosis and identify genetic targets amenable to therapeutic intervention.

REFERENCES

1. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromsø Study. Heart 2013;99:396–400.

2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

3. Chakos A, Wilson-Smith A, Arora S, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. Ann Cardiothorac Surg 2017;6:432–43.

4. Osnabrugge RLJ, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002–12.

5. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. J Am Coll Cardiol 1997;29:630–4.

6. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the

Multi-Ethnic Study of Atherosclerosis. Circulation 2006;113:2113–9.

7. Stritzke J, Linsel-Nitschke P, Markus MRP, et al. Association between degenerative aortic valve disease and long-term exposure to cardiovascular risk factors: results of the longitudinal population-based KORA/MONICA survey. Eur Heart J 2009; 30:2044–53.

8. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD. Incidence and progression of aortic valve calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Cardiol 2010;105: 701–8.

9. Thanassoulis G, Massaro JM, Cury R, et al. Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. J Am Coll Cardiol 2010;55:2491–8.

10. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J 2015;36: 2425–37.

11. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol 2014;63:470–7.

12. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013;368: 503–12.

13. Dumesnil JG, Pibarot P. The obesity paradox in aortic stenosis: to be or not to be. J Am Coll Cardiol 2013;62:1691–3.

14. Lindroos M, Kupari M, Valvanne J, et al. Factors associated with calcific aortic valve degeneration in the elderly. Eur Heart J 1994;15: 865–70.

15. Messika-Zeitoun D, Bielak LF, Peyser PA, et al. Aortic valve calcification: determinants and progression in the population. Arterioscler Thromb Vasc Biol 2007;27:642–8.

16. Larsson SC, Wolk A, Hakansson N, Back M. Overall and abdominal obesity and incident aortic valve stenosis: two prospective cohort studies. Eur Heart J 2017;38:2192–7.

17. Afzal S, Brondum-Jacobsen P, Bojesen SE, Nordestgaard BG. Vitamin D concentration, obesity, and risk of diabetes: a Mendelian randomisation study. Lancet Diabetes Endocrinol 2014;2:298–306.

18. Benn M, Nordestgaard BG. From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment. Cardiovasc Res 2018;114: 1192–208.

19. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206.

20. Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. PLoS Med 2012;9:e1001212.

21. Turcot V, Lu Y, Highland HM, et al. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. Nat Genet 2018;50:26–41.

22. Justice AE, Karaderi T, Highland HM, et al. Protein-coding variants implicate novel genes related to lipid homeostasis contributing to body-fat distribution. Nat Genet 2019;51:452–69.

23. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i–xii:1–253.

24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

25. Otto CM, Prendergast B. Aortic-valve stenosis–from patients at risk to severe valve obstruction. N Engl J Med 2014;371:744–56.

26. Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. J Am Coll Cardiol 2015;66:561–77.

27. Varbo A, Benn M, Smith GD, Timpson NJ, Tybjaerg-Hansen A, Nordestgaard BG. Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease. Circ Res 2015;116:665–73.

28. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844–53.

29. Mathieu P, Lemieux I, Despres JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther 2010;87:407–16.

30. Varbo A, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation 2013;128: 1298–309.

31. Varbo A, Freiberg JJ, Nordestgaard BG. Remnant cholesterol and myocardial infarction in normal weight, overweight, and obese individuals from the Copenhagen General Population Study. Clin Chem 2018;64:219–30.

32. Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BG. Low-grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115,000 individuals from the general population. Clin Chem 2019;65:321–32.

33. Smith JG, Luk K, Schulz CA, et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. JAMA 2014;312:1764–71.

34. Agmon Y, Khandheria BK, Meissner I, et al. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population-based study. J Am Coll Cardiol 2001;38:827–34.

35. Rogge BP, Cramariuc D, Lonnebakken MT, et al. Effect of overweight and obesity on cardiovascular events in asymptomatic aortic stenosis: a SEAS substudy (Simvastatin Ezetimibe in Aortic Stenosis). J Am Coll Cardiol 2013;62:1683–90.

36. Briand M, Lemieux I, Dumesnil JG, et al. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. J Am Coll Cardiol 2006;47:2229–36.

37. Capoulade R, Clavel MA, Dumesnil JG, et al. Impact of metabolic syndrome on progression of aortic stenosis: influence of age and statin therapy. J Am Coll Cardiol 2012;60:216–23.

38. Colak Y, Afzal S, Lange P, Nordestgaard BG. Obese individuals experience wheezing without asthma but not asthma without wheezing: a Mendelian randomisation study of 85,437 adults from the Copenhagen General Population Study. Thorax 2016;71:247–54.

39. Winslow UC, Rode L, Nordestgaard BG. High tobacco consumption lowers body weight: a Mendelian randomization study of the Copenhagen General Population Study. Int J Epidemiol 2015;44:540–50.

40. Timpson NJ, Harbord R, Davey Smith G, Zacho J, Tybjaerg-Hansen A, Nordestgaard BG. Does greater adiposity increase blood pressure and hypertension risk?: Mendelian randomization using the FTO/MC4R genotype. Hypertension 2009;54:84–90.

41. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71–82.

KEY WORDS aortic stenosis, cardiovascular disease, general population, Mendelian randomization, overweight, waist

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