

Epidemiological and Bioinformatics Analyses of Air Pollution and Genetic Susceptibility in Aortic Stenosis Risk

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Text S1. Details of multiple imputation and data quality checks.

During the multiple imputation process, five imputed datasets were generated using Fully Conditional Specification. Specifically, linear and polytomous regression models were applied to continuous and categorical variables, respectively. Imputation quality and convergence were rigorously assessed using trace and density plots. Trace plots of the means and standard deviations confirmed that the imputation chains were well-mixed without distinct trends, indicating satisfactory convergence (**Fig. S3**). Additionally, distributional comparisons revealed that the proportions of categorical variables remained highly consistent between the observed and imputed datasets, confirming that the procedure preserved the original data structure without introducing significant bias (**Fig. S4**).

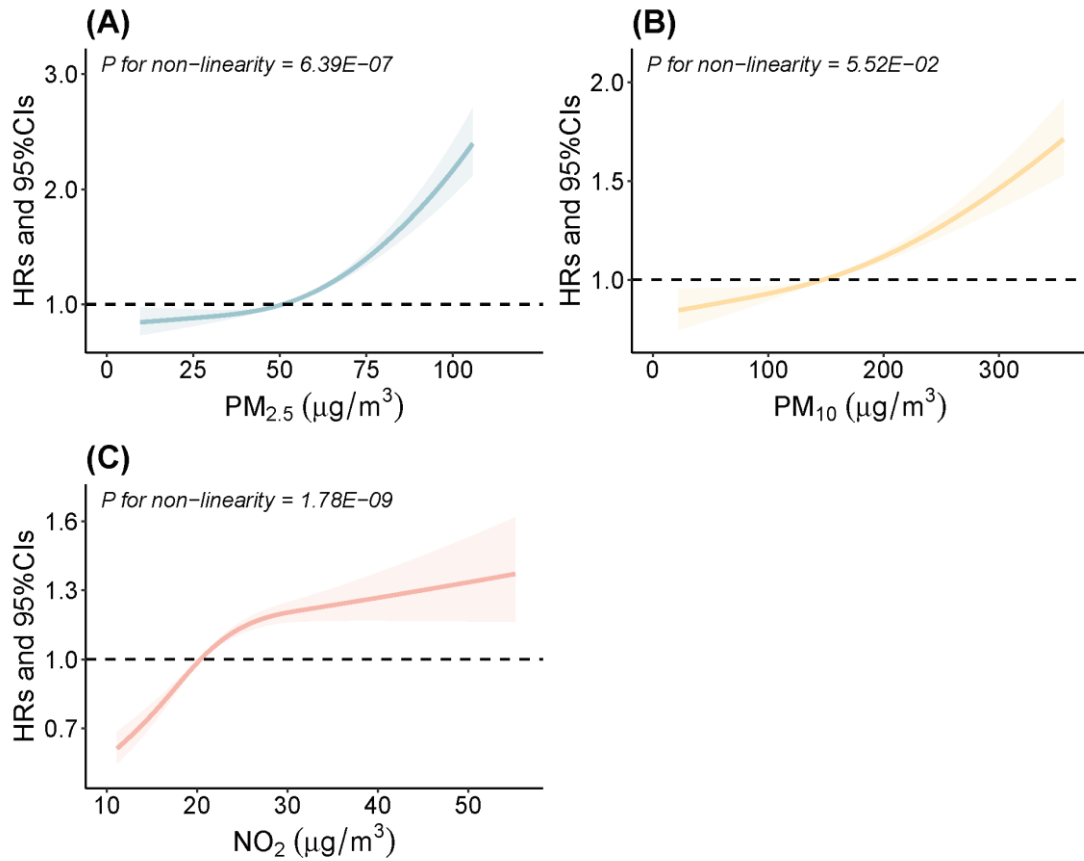


Fig. S1 Associations of long-term PM_{2.5} (A), PM₁₀ (B), and NO₂ (C) exposure with the risk of AS events based on the Tianshan Community Cohort.

A restricted cubic spline regression model with 3 knots (at the 10th, 50th, and 90th percentiles) was used to estimate the exposure-response relations between air pollutants and the risk of AS among participants.

The models are adjusted for age, sex, ethnic group, BMI, education level, occupation, smoking history, drinking status, dietary habits, fuel type, physical activity, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; PM_{2.5}, fine particulate matter with diameter <2.5 μm ; PM₁₀, particulate matter with diameter <10 μm ; NO₂, nitrogen dioxide; AS, aortic stenosis; BMI, body mass index.

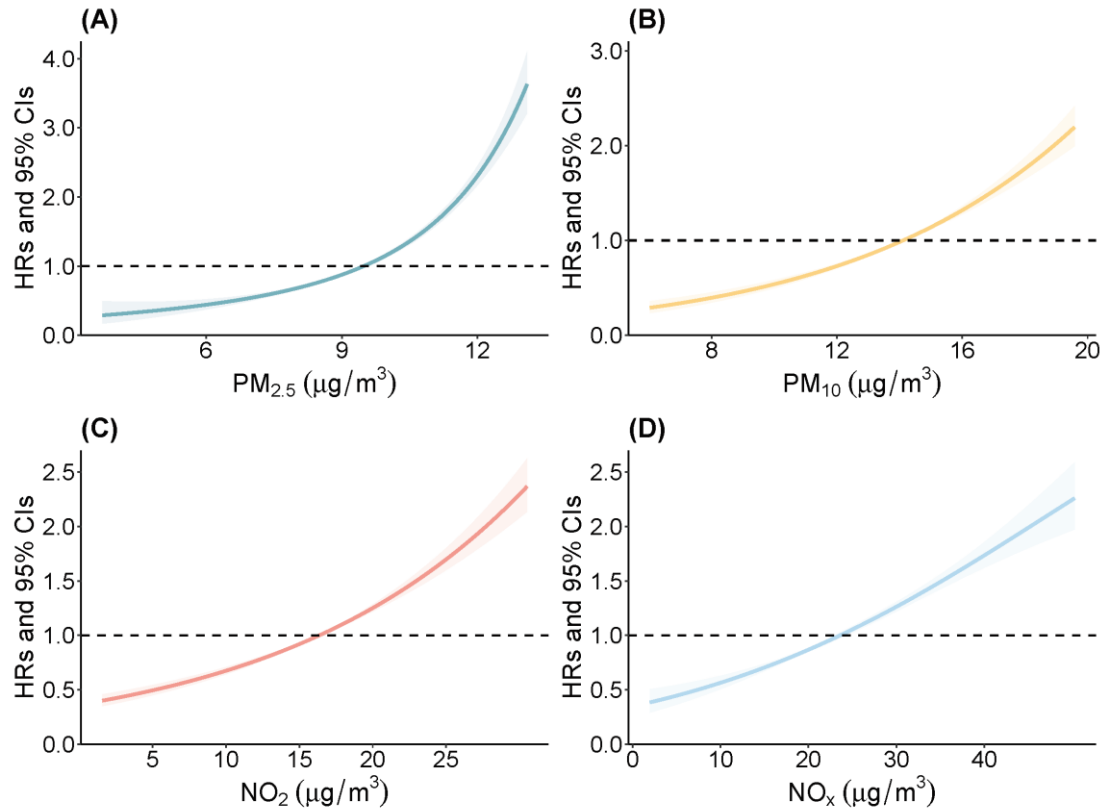


Fig. S3 Associations of long-term PM_{2.5} (A), PM₁₀ (B), NO₂ (C), and NO_x (D) exposure with the risk of AS events based on the shape constrained additive model. The models are adjusted for age, sex, ethnic groups, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; PM_{2.5}, fine particulate matter with diameter <2.5 μm ; PM₁₀, particulate matter with diameter <10 μm ; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index.

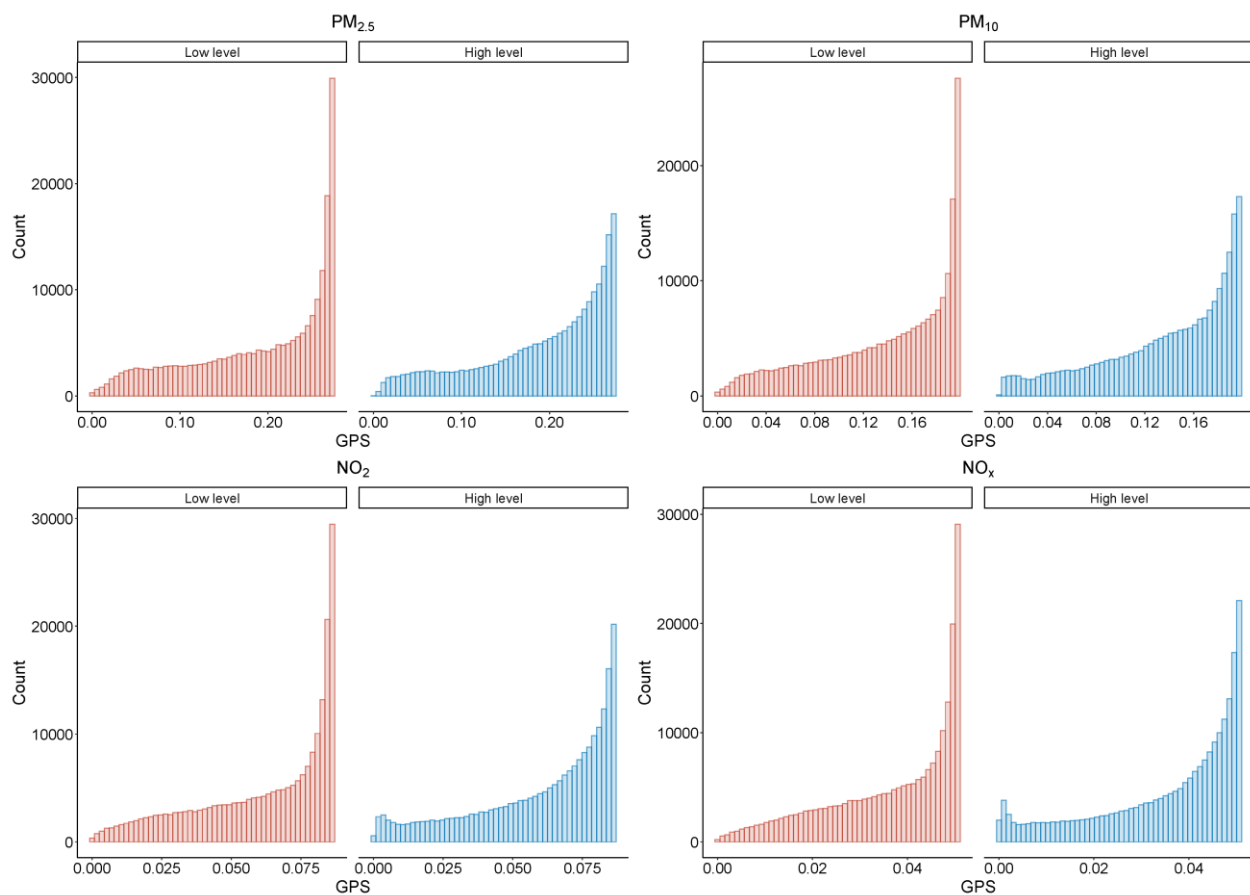


Fig. S4 Distribution of the GPS for the high and low air pollutants exposure groups.

Abbreviations: GPS, generalized propensity score; $PM_{2.5}$, fine particulate matter with diameter $<2.5 \mu m$; PM_{10} , particulate matter with diameter $<10 \mu m$; NO_2 , nitrogen dioxide; NO_x , nitrogen oxides.

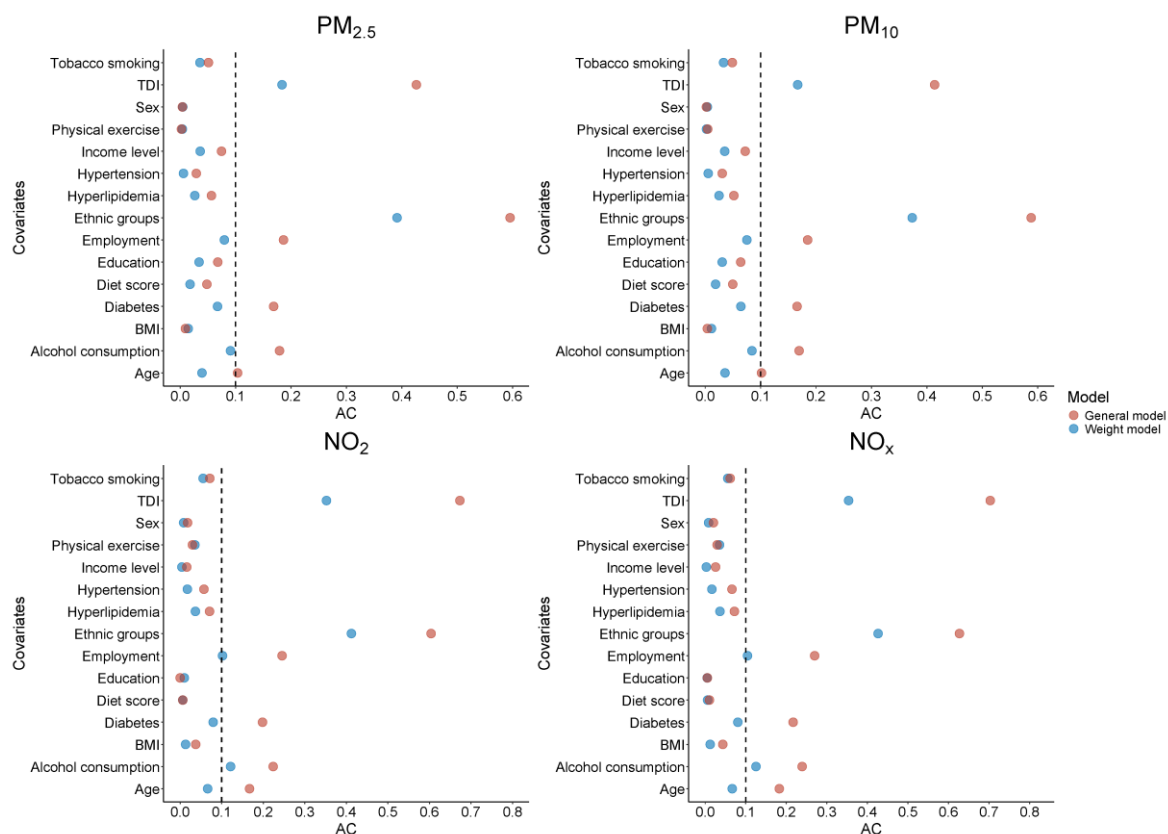


Fig. S5 Mean AC for Cox proportional hazards model and weighted Cox proportional hazards model.

Covariate balance was evaluated using mean AC, with AC < 0.1 indicating good balancing for covariates included in the analyses.

Abbreviations: AC, absolute correlation; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; BMI, body mass index; TDI, Townsend deprivation index.

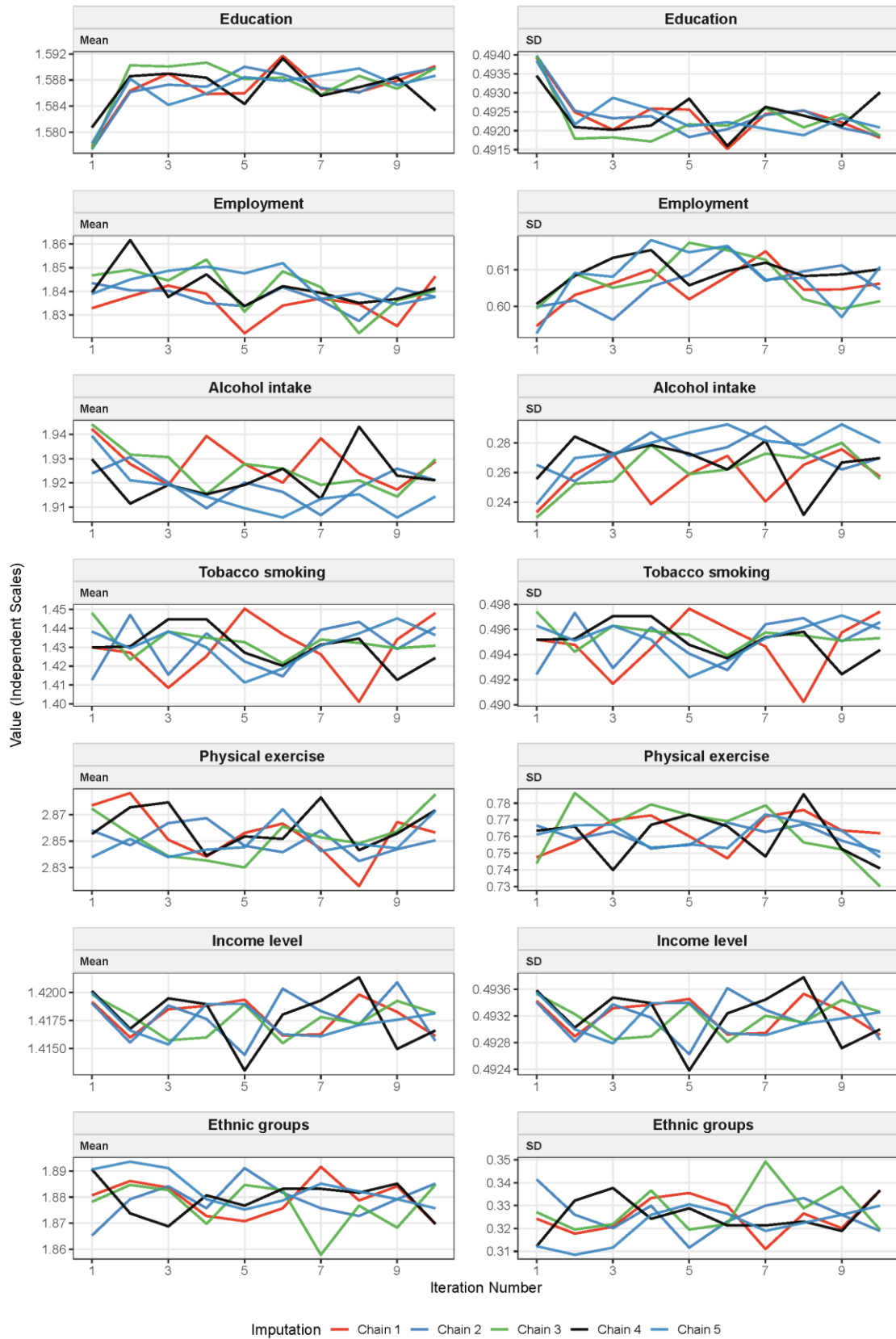


Fig. S6 Trace plots of mean and standard deviation for imputed covariates.

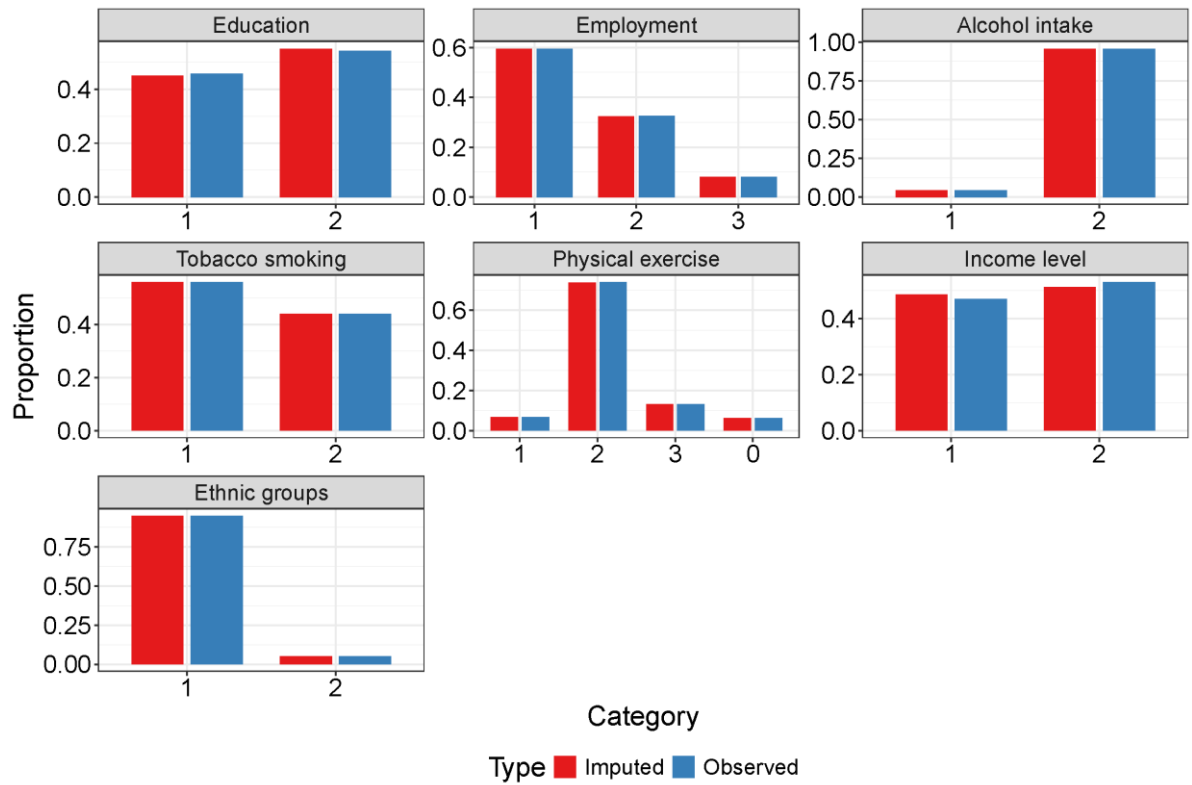


Fig. S7 Distributional balance of categorical covariates between observed and imputed datasets.

Table S1. Baseline characteristics of white European.

Baseline characteristics	Total participants (N = 422551)	Participants without AS (N= 418975)	Participants with AS (N = 3576)	P values
Age (mean (SD), year)	56.46 (8.02)	56.41 (8.02)	62.47 (5.75)	<2.20E-16
Sex (%)				<2.20E-16
Men	187115 (44.28)	184912 (44.13)	2203 (61.61)	
Women	235436 (55.72)	234063 (55.87)	1373 (38.39)	
BMI (mean (SD), kg/m ²)	27.30 (4.72)	27.28 (4.71)	29.42 (5.36)	<2.20E-16
Employment (%)				<2.20E-16
Employed	247676 (58.61)	246459 (58.82)	1217 (34.03)	
Retired	139990 (33.13)	137917 (32.92)	2073 (57.97)	
Unemployed	31605 (7.48)	31342 (7.48)	263 (7.35)	
Missing	3280 (0.78)	3257 (0.78)	23 (0.64)	
Education (%)				<2.20E-16
University degree	158183 (37.44)	157088 (37.49)	1095 (30.62)	
Non-university degree	191414 (45.30)	189985 (45.35)	1429 (39.96)	
Missing	72954 (17.27)	71902 (17.16)	1052 (29.42)	
Alcohol intake (%)				5.88E-04
Never	13286 (3.14)	13134 (3.13)	152 (4.25)	
Current or former alcohol intake	408914 (96.77)	405494 (96.78)	3420 (95.64)	
Missing	351 (0.08)	347 (0.08)	4 (0.11)	
Tobacco smoking (%)				<2.20E-16
Never	232455 (55.01)	230903 (55.11)	1552 (43.40)	
Current or former smoking	188670 (44.65)	186663 (44.55)	2007 (56.12)	
Missing	1426 (0.34)	1409 (0.34)	17 (0.48)	
Diet score (%)				7.64E-05
0-1	61540 (14.56)	60958 (14.55)	582 (16.28)	
2-3	227050 (53.73)	225095 (53.73)	1955 (54.67)	
4-5	133961 (31.70)	132922 (31.73)	1039 (29.05)	
Physical exercise (%)				<2.20E-16
Never	23850 (5.64)	23549 (5.62)	301 (8.42)	
Low activity	27957 (6.62)	27624 (6.59)	333 (9.31)	
Moderate activity	314403 (74.41)	311945 (74.45)	2458 (68.74)	
Vigorous activity	54554 (12.91)	54103 (12.91)	451 (12.61)	
Missing	1787 (0.42)	1754 (0.42)	33 (0.92)	
TDI (mean (SD))	-1.60 (2.88)	-1.60 (2.88)	-1.39 (3.02)	3.58E-05
Income level (%)				<2.20E-16
<£31000	169579 (40.13)	167685 (40.02)	1894 (52.96)	
≥£31000	194735 (46.09)	193653 (46.22)	1082 (30.26)	
Missing	58237 (13.78)	57637 (13.76)	600 (16.78)	
Hypertension (%)	107849 (25.52)	106017 (25.30)	1832 (51.23)	<2.20E-16
Diabetes (%)	17802 (4.21)	17298 (4.13)	504 (14.09)	<2.20E-16

Hyperlipidemia (%)	34954 (8.27)	34090 (8.14)	864 (24.16)	<2.20E-16
Genetic risk category (%)				<2.20E-16
Low genetic risk	140710 (33.30)	139919 (33.40)	791 (22.12)	
Intermediate genetic risk	141131 (33.40)	140002 (33.42)	1129 (31.57)	
High genetic risk	140710 (33.30)	139054 (33.19)	1656 (46.31)	

Differences between groups were evaluated using the χ^2 test, Wilcoxon-Mann-Whitney test, or Student's *t*-test, as appropriate for the variable type. All statistical tests were two-sided.

Abbreviations: AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index.

Table S2. Range of air pollutants exposure.

Air pollutants	Mean (SD), $\mu\text{g}/\text{m}^3$	T1, $\mu\text{g}/\text{m}^3$	T2, $\mu\text{g}/\text{m}^3$	T3, $\mu\text{g}/\text{m}^3$
PM _{2.5}	9.45 (1.53)	<8.73	8.73-10.09	≥ 10.09
PM ₁₀	14.11 (2.11)	<12.99	12.99-15.01	≥ 15.01
NO ₂	16.55 (5.09)	<14.05	14.05-18.47	≥ 18.47
NO _x	24.33 (8.72)	<19.84	19.84-27.12	≥ 27.12

Abbreviations: SD, standard deviation; PM_{2.5}, fine particulate matter with diameter <2.5 μm ; PM₁₀, particulate matter with diameter <10 μm ; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; T, tertile.

Table S3. Associations between air pollutants exposure and the risk of incident AS using the causal inference models.

Air pollutants (per SD increase)	HRs (95% CIs)	<i>P</i> values
Weighted Cox proportional hazards model (by IPW)		
PM _{2.5}	1.57 (1.50, 1.64)	<2.20E-16
PM ₁₀	1.31 (1.26, 1.36)	<2.20E-16
NO ₂	1.32 (1.27, 1.38)	<2.20E-16
NO _x	1.30 (1.24, 1.37)	<2.20E-16
Weighted Cox proportional hazards model (by trimmed IPW)		
PM _{2.5}	1.55 (1.49, 1.61)	<2.20E-16
PM ₁₀	1.31 (1.27, 1.36)	<2.20E-16
NO ₂	1.32 (1.27, 1.38)	<2.20E-16
NO _x	1.30 (1.25, 1.36)	<2.20E-16
Cox proportional hazards model adjusted for GPS (linear)		
PM _{2.5}	1.41 (1.37, 1.46)	<2.20E-16
PM ₁₀	1.27 (1.23, 1.32)	<2.20E-16
NO ₂	1.23 (1.20, 1.27)	<2.20E-16
NO _x	1.22 (1.18, 1.26)	<2.20E-16
Cox proportional hazards model adjusted for GPS (quintiles)		
PM _{2.5}	1.42 (1.38, 1.47)	<2.20E-16
PM ₁₀	1.28 (1.24, 1.32)	<2.20E-16
NO ₂	1.24 (1.20, 1.28)	<2.20E-16
NO _x	1.23 (1.19, 1.27)	<2.20E-16

HRs and 95% CIs are estimated using Cox proportional hazards models. The models are adjusted for age, sex, ethnic groups, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; IPW, inverse probability weighting; GPS, generalized propensity score; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index.

Table S4. Associations between air pollutants exposure at low levels and the risk of incident AS.

Air pollutants (per SD increase)	HRs (95% CIs)	<i>P</i> values
2005 WHO guidelines		
PM _{2.5}	1.19 (1.13, 1.25)	5.68E-12
PM ₁₀	1.38 (1.33, 1.43)	<2.20E-16
NO ₂	1.37 (1.32, 1.42)	<2.20E-16
NO _x	1.13 (1.07, 1.19)	5.10E-06

HRs and 95% CIs are estimated using Cox proportional hazards models. The models are adjusted for age, sex, ethnic groups, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; GRS, genetic risk score; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index; T, tertile.

Table S5. Associations between air pollutants and the risk of incident AS: external validation in the Tianshan Community Cohort.

Air pollutants	HRs (95% CIs)	<i>P</i> values	<i>P</i> for trend
PM _{2.5}			
PM _{2.5} -T1	1.00 (Ref.)	--	
PM _{2.5} -T2	1.14 (1.06, 1.23)	5.34E-04	<2.20E-16
PM _{2.5} -T3	1.60 (1.47, 1.75)	<2.20E-16	
PM _{2.5} , per SD ⁺ increase	1.30 (1.25, 1.34)	<2.20E-16	--
PM ₁₀			
PM ₁₀ -T1	1.00 (Ref.)	--	
PM ₁₀ -T2	1.14 (1.06, 1.23)	6.30E-04	<2.20E-16
PM ₁₀ -T3	1.45 (1.33, 1.58)	<2.20E-16	
PM ₁₀ , per SD ⁺ increase	1.22 (1.18, 1.27)	<2.20E-16	--
NO ₂			
NO ₂ -T1	1.00 (Ref.)	--	
NO ₂ -T2	1.23 (1.15, 1.31)	1.17E-09	<2.20E-16
NO ₂ -T3	1.41 (1.32, 1.51)	<2.20E-16	
NO ₂ , per SD ⁺ increase	1.15 (1.12, 1.18)	<2.20E-16	--

HRs and 95% CIs are estimated using Cox proportional hazards models. The models are adjusted for age, sex, ethnic group, BMI, education level, occupation, smoking history, drinking status, dietary habits, fuel type, physical activity, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

⁺Standard deviation of PM_{2.5}, PM₁₀, and NO₂ are 21.83, 90.88, and 7.77 µg/m³, respectively.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; AS, aortic stenosis; BMI, body mass index; T, tertile.

Table S6. Associations of GRS with the risk of incident AS.

GRS	HRs (95% CIs)	<i>P</i> values	<i>P</i> for trend
GRS categories			
Low genetic risk	1.00 (Ref.)	--	
Intermediate genetic risk	1.42 (1.30, 1.56)	2.57E-14	<2.20E-16
High genetic risk	2.11 (1.94, 2.30)	<2.20E-16	
GRS, per SD ⁺ increase	1.41 (1.36, 1.45)	<2.20E-16	--

⁺ Standard deviation of GRS is 4.41.

HRs and 95% CIs are estimated using Cox proportional hazards models. The models are adjusted for age, sex, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, hyperlipidemia, genotyping batch, and the first ten genetic principal components. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; GRS, genetic risk score; AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index.

Table S7. Additive interactions between air pollutants and GRS on the risk of incident AS.

Variables	RERIs (95% CIs)	APs (95% CIs)
PM_{2.5}		
Medium genetic risk		
PM _{2.5} -T2	0.27 (-0.07, 0.61)	0.14 (-0.03, 0.31)
PM _{2.5} -T3	0.83 (0.36, 1.30)	0.21 (0.10, 0.32)
High genetic risk		
PM _{2.5} -T2	0.49 (0.10, 0.87)	0.17 (0.04, 0.30)
PM _{2.5} -T3	2.03 (1.47, 2.59)	0.35 (0.27, 0.42)
PM₁₀		
Medium genetic risk		
PM ₁₀ -T2	0.29 (-0.04, 0.63)	0.14 (-0.02, 0.29)
PM ₁₀ -T3	0.36 (-0.05, 0.76)	0.12 (-0.01, 0.25)
High genetic risk		
PM ₁₀ -T2	0.65 (0.27, 1.02)	0.21 (0.09, 0.32)
PM ₁₀ -T3	1.30 (0.84, 1.77)	0.29 (0.20, 0.38)
NO₂		
Medium genetic risk		
NO ₂ -T2	0.31 (0.02, 0.61)	0.18 (0.01, 0.35)
NO ₂ -T3	0.53 (0.17, 0.90)	0.19 (0.06, 0.31)
High genetic risk		
NO ₂ -T2	0.29 (-0.05, 0.63)	0.11 (-0.02, 0.25)
NO ₂ -T3	0.97 (0.55, 1.39)	0.24 (0.14, 0.33)
NO_x		
Medium genetic risk		
NO _x -T2	0.31 (0.01, 0.61)	0.17 (0.01, 0.34)
NO _x -T3	0.53 (0.15, 0.90)	0.18 (0.06, 0.31)
High genetic risk		
NO _x -T2	0.33 (-0.02, 0.67)	0.13 (-0.01, 0.26)
NO _x -T3	1.02 (0.59, 1.45)	0.25 (0.15, 0.34)

If 0 is outside the CIs of RERIs and APs, it means that there is an additive interaction.

Cox regression models adjusted for age, sex, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, hyperlipidemia, genotyping batch, and the first 10 genetic principal components.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; GRS, genetic risk score; PM_{2.5}, fine particulate matter

with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis; BMI, body mass index TDI, Townsend deprivation index; T, tertile.

Table S8. Sensitivity analyses of associations between air pollution exposure and the risk of AS incidence.

Air pollutants (per SD increase)	HRs (95% CIs)	<i>P</i> values
Sensitivity analysis I		
PM _{2.5}	1.60 (1.54, 1.66)	<2.20E-16
PM ₁₀	1.35 (1.30, 1.40)	<2.20E-16
NO ₂	1.37 (1.32, 1.42)	<2.20E-16
NO _x	1.36 (1.31, 1.41)	<2.20E-16
Sensitivity analysis II		
PM _{2.5}	1.62 (1.56, 1.68)	<2.20E-16
PM ₁₀	1.38 (1.33, 1.43)	<2.20E-16
NO ₂	1.39 (1.34, 1.44)	<2.20E-16
NO _x	1.38 (1.33, 1.43)	<2.20E-16
Sensitivity analysis III		
PM _{2.5}	1.62 (1.57, 1.68)	<2.20E-16
PM ₁₀	1.38 (1.34, 1.43)	<2.20E-16
NO ₂	1.38 (1.33, 1.43)	<2.20E-16
NO _x	1.37 (1.32, 1.42)	<2.20E-16
Sensitivity analysis IV		
PM _{2.5}	1.63 (1.56, 1.69)	<2.20E-16
PM ₁₀	1.38 (1.33, 1.43)	<2.20E-16
NO ₂	1.38 (1.33, 1.43)	<2.20E-16
NO _x	1.37 (1.32, 1.42)	<2.20E-16
Sensitivity analysis V		
PM _{2.5}	1.61 (1.56, 1.67)	<2.20E-16
PM ₁₀	1.37 (1.33, 1.42)	<2.20E-16
NO ₂	1.38 (1.33, 1.43)	<2.20E-16
NO _x	1.37 (1.32, 1.42)	<2.20E-16
Sensitivity analysis VI		
PM _{2.5}	1.59 (1.54, 1.65)	<2.20E-16
PM ₁₀	1.36 (1.32, 1.41)	<2.20E-16
NO ₂	1.37 (1.32, 1.42)	<2.20E-16
NO _x	1.36 (1.31, 1.41)	<2.20E-16

Sensitivity analysis I: Exclusion of participants with incident AS within the first two years of follow-up.

Sensitivity analysis II: Exclusion of participants with <5 years of residential stability.

Sensitivity analysis III: Employing age as the underlying time scale in Cox regression.

Sensitivity analysis IV: Using continuous blood pressure, glucose, and lipid levels instead of binary disease diagnosis.

Sensitivity analysis V: Additional adjustment for occupational exposure, commuting exposure, and indoor air pollution.

Sensitivity analysis VI: Analysis based on the multiple-imputed dataset.

HRs and 95% CIs are estimated using Cox proportional hazards models. The models are adjusted for age, sex, ethnic groups, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, and hyperlipidemia. All statistical tests are two-sided.

Abbreviations: HRs, hazard ratios; CIs, confidence intervals; GRS, genetic risk score; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis; BMI, body mass index; TDI, Townsend deprivation index; T, tertile.

Table S9. Summary statistics for the 40 independent SNPs comprising the AS GRS.

RsID	Locus	Chr	RA	OR	<i>P</i> values	Reference
rs1016819	<i>PRRX1</i>	1	G	1.11	1.20E-14	Ref. 31
rs10770612	<i>PDE3A</i>	12	A	1.12	6.60E-13	Ref. 31
rs111825950	<i>ARHGEF26</i>	3	T	1.11	1.10E-10	Ref. 31
rs11570891	<i>LPL</i>	8	C	1.20	7.20E-09	Ref. 31
rs12270146	<i>MYEOV</i>	11	G	1.09	8.30E-10	Ref. 31
rs12429277	<i>SMAD9</i>	13	A	1.08	2.30E-08	Ref. 31
rs147558377	<i>PDGFRA</i>	4	G	1.10	2.40E-08	Ref. 31
rs150429885	<i>TMEM170A</i>	16	CT	1.08	1.90E-09	Ref. 31
rs1706003	<i>TMEM44</i>	3	G	1.09	3.10E-11	Ref. 31
rs174551	<i>FADS1</i>	11	T	1.09	3.10E-10	Ref. 31
rs17766960	<i>HMGA2</i>	12	G	1.10	1.60E-09	Ref. 31
rs17810852	<i>MYMK</i>	9	G	1.08	1.10E-08	Ref. 31
rs1965668	<i>NKX2-5</i>	5	G	1.08	1.60E-08	Ref. 31
rs2077522	<i>LMO4</i>	1	C	1.08	3.10E-10	Ref. 31
rs2286427	<i>SSC4D</i>	7	T	1.10	4.60E-08	Ref. 31
rs2869553	<i>ADAMTS7</i>	15	G	1.09	2.90E-08	Ref. 31
rs28744617	<i>STARD9</i>	15	A	1.09	2.20E-08	Ref. 31
rs3103933	<i>MUC4</i>	3	A	1.12	6.10E-09	Ref. 31
rs4646642	<i>ALDH1A2</i>	15	A	1.08	4.20E-09	Ref. 31
rs62139061	<i>ACTR2</i>	2	C	1.09	4.00E-10	Ref. 31
rs6511720	<i>LDLR</i>	19	G	1.12	2.50E-08	Ref. 31
rs682112	<i>NAV1</i>	1	A	1.11	3.20E-14	Ref. 31
rs72854462	<i>ZEB2</i>	2	A	1.15	1.70E-22	Ref. 31
rs771264	<i>RNF144A</i>	2	C	1.07	5.00E-08	Ref. 31
rs7804522	<i>FERD3L</i>	7	C	1.07	1.90E-08	Ref. 31
rs10455872	<i>LPA</i>	6	G	1.45	1.40E-75	Ref. 31, 32
rs11643207	<i>TMEM170A</i>	16	T	1.09	5.60E-13	Ref. 32
rs12740374	<i>CELSR2–SORT1</i>	1	G	1.09	2.40E-09	Ref. 32
rs17156153	<i>NLRP6</i>	11	T	1.16	2.60E-13	Ref. 32
rs174533	<i>FADS1/2</i>	11	G	1.09	2.00E-12	Ref. 32
rs1800797	<i>IL6</i>	7	A	1.13	1.90E-27	Ref. 31, 32
rs551520	<i>Intergenic (18q11.2)</i>	18	C	1.09	6.80E-11	Ref. 32
rs55909255	<i>SMC2</i>	9	C	1.07	5.10E-09	Ref. 32
rs61817383	<i>PRRX1</i>	1	T	1.09	3.70E-12	Ref. 32
rs62139062	<i>ACTR2</i>	2	T	1.08	4.40E-11	Ref. 32

rs631556	<i>NAVI</i>	1	A	1.09	4.10E-14	Ref. 32
rs6696066	<i>ALPL</i>	1	G	1.09	7.10E-14	Ref. 32
rs6702619	<i>PALMD</i>	1	G	1.16	8.70E-43	Ref. 31, 32
rs6794263	<i>ARHGEF26</i>	3	A	1.11	1.50E-09	Ref. 32
rs7593336	<i>TEX4I</i>	2	G	1.12	1.70E-25	Ref. 32

The ORs and *P* values are obtained from previously published genome-wide association studies. Ref. 31: Nature communications 15, 2407; Ref. 32: European heart journal 44, 1927-1939.

Abbreviations: AS, aortic stenosis; SNP, single nucleotide polymorphism; ORs, odds ratios; GRS, genetic risk score; Chr, chromosome; RA, risk allele.

Table S10. Definitions and sources of information for AS in the UK Biobank

Outcome	ICD-10 diagnosis	OPCS-4 procedure codes ^a
Aortic stenosis	I35.0, I35.2	K26.1, K26.2, K26.3, K26.4, K26.5

Abbreviations: ICD, International Classification of Disease; OPCS, the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures codes; AS, aortic stenosis.

K261-K264, aortic valve replacement.

K265, aortic balloon valvuloplasty.

Table S11. Associations between air pollutants exposure at low levels and the risk of incident AS.

Models	Bayesian Information Criterion			
	PM _{2.5}	PM ₁₀	NO ₂	NO _x
RCS model				
3 knots	90941.5	91338.65	91354.8	91360.4
4 knots	90955.9	91351.0	91361.0	91360.8

P values, HRs and 95% CIs in bold represent significance at *P* < 0.05.

Cox regression models adjusted for age, sex, ethnic groups, income level, TDI, education, employment, alcohol consumption, tobacco smoking, diet score, physical exercise, BMI, hypertension, diabetes, and hyperlipidemia.

Abbreviations: RCS, restricted cubic spline; SCAM, shape constrained additive model; PM_{2.5}, fine particulate matter with diameter <2.5 µm; PM₁₀, particulate matter with diameter <10 µm; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; AS, aortic stenosis.