Journal of the American Heart Association

ORIGINAL RESEARCH

Association Between Inflammatory Arthritis, Genetic Risk, and the Long-Term Risk of Degenerative Aortic Stenosis: A Prospective Cohort Study

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BACKGROUND: Inflammatory arthritis is recognized to increase cardiovascular disease risk, but its association with degenerative aortic stenosis is not well understood.

METHODS: This prospective cohort study used participants from the UK Biobank, focusing on 4 major types of inflammatory arthritis, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout. The primary outcome was the incidence of degenerative aortic stenosis. The primary analysis used Cox proportional hazards models to evaluate the association between inflammatory arthritis and the long-term risk of degenerative aortic stenosis, as well as to explore potential effect modifiers. Genetic risk was evaluated using polygenic risk scores and self-reported family history of cardiovascular diseases.

RESULTS: The study included 497 567 participants, with 271 129 women (54.5%) and 468 015 White individuals (94.1%). The median age was 58 years. Over a median follow-up of 12.58 years, 4571 cases (0.9%) of degenerative aortic stenosis were identified. Compared with the control group, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout were associated with increased risks of degenerative aortic stenosis by 54% (hazard ratio [HR], 1.54 [95% CI, 1.28–1.85]), 72% (HR, 1.72 [95% CI, 1.19–2.50]), 176% (HR, 2.76 [95% CI, 1.43–5.32]), and 36% (HR, 1.36 [95% CI, 1.20–1.54]), respectively. These associations were independent of genetic risk (*P* for interaction>0.05). Additionally, we identified significant interactions between sex (*P* for interaction=0.036), age (*P* for interaction<0.001), and socioeconomic status (*P* for interaction=0.014) with rheumatoid arthritis, ankylosing spondylitis, and gout on the incidence of degenerative aortic stenosis, respectively.

CONCLUSIONS: Inflammatory arthritis is significantly associated with an increased long-term risk of degenerative aortic stenosis, underscoring the need for enhanced risk assessment for degenerative aortic stenosis in these populations.

Key Words: aortic stenosis ■ degenerative ■ genetic risk ■ inflammatory arthritis ■ prospective cohort study ■ UK Biobank

Aortic stenosis is the most common valvular heart disease in developed countries, with a prevalence as high as 9.8% in individuals aged ≥80 years.[1] More importantly, aortic stenosis is often asymptomatic in its early stages, but once clinical symptoms appear, the mortality rate can reach up to 50% within 2 years if not treated promptly.[2] This condition imposes a considerable global public health burden. Along with improvements in socioeconomic conditions and increasing life expectancy, the pathogenesis of aortic stenosis has undergone a marked shift, and degenerative changes are currently the

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This manuscript was sent to Suha Bachir, MD, MS, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.038815

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this large prospective cohort study (n=497 567), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout are significantly associated with an increased long-term risk of degenerative aortic stenosis.
- Rheumatoid arthritis is associated with a higher risk of degenerative aortic stenosis in women only, while ankylosing spondylitis tends to elevate this risk in younger populations; additionally, gout is more likely to increase the risk of degenerative aortic stenosis in individuals with high socioeconomic status.

What Are the Clinical Implications?

- Our findings indicate that special attention should be given to the prevention and screening of degenerative aortic stenosis in individuals with inflammatory arthritis, along with timely interventions as necessary.

Nonstandard Abbreviation and Acronym

PRS	polygenic risk score

leading causes.[3] A cross-sectional study in Europe showed that aortic stenosis accounts for ≈43.1% of all valvular heart diseases, 81.9% of which are classified as degenerative aortic stenosis.[4] Therefore, identifying risk factors associated with degenerative aortic stenosis and determining high-risk populations are crucial for the prevention and treatment of the disease.

Inflammatory arthritis is a group of chronic inflammatory diseases characterized primarily by synovial hyperplasia and inflammation,[5] including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout. The global prevalence of inflammatory arthritis is 3%.[6] In addition to causing joint stiffness, deformity, and limited mobility, these diseases can affect extra-articular organs such as the heart, lungs, and eyes, imposing considerable social and economic burden. Cardiovascular diseases are the severe complications of inflammatory arthritis, and cardiovascular death is the leading cause of death in patients with inflammatory arthritis, accounting for 40% of all deaths.[7] Unfortunately, existing research on the relationship between inflammatory arthritis and cardiovascular diseases is limited, primarily focuses on atherosclerotic cardiovascular disease, and lacks high-quality prospective cohort studies, limiting our comprehensive understanding and hindering the effective management of cardiovascular diseases in the context of inflammatory arthritis. Inflammation is an important mechanism in the development of degenerative aortic stenosis, and known risk factors, such as obesity, hyperlipidemia, and diabetes, are the common comorbidities of inflammatory arthritis.[8] These findings suggest a link between inflammatory arthritis and degenerative aortic stenosis, but more evidence is needed to confirm this association. Additionally, genome-wide association studies have successfully identified genetic variants associated with degenerative aortic stenosis.[9] Exploring the potential interactions between inflammatory arthritis and genetic risk in the development of degenerative aortic stenosis is crucial.

Therefore, in this study, we used high-quality clinical and genetic data from the UK Biobank prospective cohort to systematically investigate the longitudinal association between inflammatory arthritis (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout) and the long-term risk of degenerative aortic stenosis, and explore potential effect modifiers. Additionally, we aimed to elucidate the role of genetic factors in this association.

METHODS

The data supporting the findings of this study are available from the UK Biobank project site, subject to the registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

Research Objective

The UK Biobank is a renowned prospective cohort study in the United Kingdom (Application ID: 107175) and recruited >500 000 participants aged 40 to 69 years.[10] Accessing and obtaining data from the UK Biobank requires the submission and approval of a research proposal, the signing of a material transfer agreement, and the payment of associated access fees. Baseline assessments were conducted from 2006 to 2010, during which sociodemographic, lifestyle, and self-reported health information were collected using a touchscreen questionnaire. Additionally, physical measurements, clinical biochemical analyses, and genetic testing were performed. Before data collection, informed consent was obtained from each participant, and ethical approval was granted by the North West Multi-Centre Research Ethics Committee (Approval No. 11/NW/0382). This study excluded participants who were diagnosed with various valvular heart diseases at baseline (N=3911), who developed degenerative aortic stenosis (N=257) within 2 years after recruitment, and who had multiple types of inflammatory arthritis (N=428). Consequently, a total of 497 567 participants were included in subsequent

analyses (Figure S1). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Diagnosis of Inflammatory Arthritis and Degenerative Aortic Stenosis

Considering the accessibility of data in the UK Biobank, this study focused on inflammatory arthritis, specifically rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout. The diagnosis of inflammatory arthritis was determined according to the diagnostic codes from the *International Classification of Diseases, Tenth Revision* (*ICD-10*; Table S1): rheumatoid arthritis (M5 and M6), ankylosing spondylitis (M45), psoriatic arthritis (L40.5, M07, M07.0, M07.0*, M07.1, M07.1*, M07.2, M07.2*, M07.3, M07.3*, M09.0, M09.0*), and gout (M10). Similarly, degenerative aortic stenosis was defined using the *ICD-10* codes I35.0 and I35.2, which was used in the previous study.[11,12]

Covariates

The covariates considered in this study included the following aspects: (1) demographic characteristics: age, sex, ethnicity, education level, and Townsend deprivation index; (2) lifestyle habits: smoking status, drinking status, physical activity, dietary patterns, and sleep patterns (Table S2); (3) personal medical history: hypertension, diabetes, and hyperlipidemia; and (4) physical and laboratory examinations: body mass index (BMI), CRP (C-reactive protein), and estimated glomerular filtration rate. The detailed descriptions of the covariates are shown in Data S1.

Assessment of Genetic Risk

Two methods were used in assessing participants' genetic risk: constructing a polygenic risk score (PRS) and self-reported family history of cardiovascular diseases. The summary statistics of Iceland's genome-wide association study from deCODE were used in identifying genetic variants strongly associated with degenerative aortic stenosis.[13] After quality control (Data S2), 12 independent single-nucleotide polymorphisms were selected for PRS construction. Each single-nucleotide polymorphism was weighted according to its effect on the risk of degenerative aortic stenosis, and the weighted single-nucleotide polymorphism values were summed. The total score was then standardized using *Z* scores. For family history of cardiovascular diseases, participants were asked whether their first-degree relatives (including parents and siblings) had cardiovascular diseases.

Statistical Analysis

We conducted statistical analyses using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and a 2-sided *P* value of <0.05 indicated statistical significance. Continuous variables were assessed for normal distribution with quantile-quantile plots. For nonnormally distributed variables, median and interquartile range were used for description, and comparisons between groups were performed using the Mann–Whitney *U* test. Categorical variables were reported as frequencies (percentages), and group comparisons were conducted using the χ^2 test. Missing data are detailed in Table S3. Variables with <10% missing data were imputed with the median, whereas variables with >10% missing data were treated as a separate category and labeled as "Missing."[14]

The follow-up time for this study was the period between the date when participants attended the assessment center and the date when degenerative aortic stenosis was first diagnosed, date when the participant was lost to follow-up, death, or the end of the current follow-up period (September 30, 2021, for England and Wales; and October 31, 2021, for Scotland), whichever occurred first. Kaplan–Meier curves were used in estimating the cumulative incidence of degenerative aortic stenosis in the study population, and the log-rank test was used in comparing the cumulative incidence curves between participants with and without inflammatory arthritis. Moreover, the association between inflammatory arthritis and the incidence of degenerative aortic stenosis was examined using Cox proportional hazards regression models, and participants without inflammatory arthritis were included in the control group. The results were presented as hazard ratios (HRs) with 95% CIs. The proportional hazards assumption was tested using Schoenfeld residuals, and no violations were detected. Model 1 was adjusted for demographic characteristics, including age, sex, ethnicity, education level, and Townsend deprivation index. Model 2 was adjusted for the variables in model 1 in addition to lifestyle factors (smoking, drinking, physical activity, diet, and sleep), personal medical history (hypertension, diabetes, and hyperlipidemia), BMI, CRP, and estimated glomerular filtration rate. We divided inflammatory arthritis into short- and long-disease-duration groups according to the median disease duration and examined their relationship with the occurrence of degenerative aortic stenosis.

To assess the role of genetic risk in the association between inflammatory arthritis and degenerative aortic stenosis, we performed adjustments for PRS and family history of cardiovascular disease on the basis of model 2. Next, we categorized participants into low- (quantile 1), intermediate- (quantiles 2–4), and high-genetic-predisposition groups (quantile 5) according to their PRS scores, and investigated the effect of inflammatory arthritis on degenerative aortic stenosis across different genetic predisposition strata and participants with or without a family history of cardiovascular

disease. We assessed the interaction between genetic risk and inflammatory arthritis with likelihood ratio tests.

To explore potential effect modifiers, we conducted subgroup analyses stratified by demographic characteristics, hypertension, BMI, and CRP levels. Interactions between these stratification variables and inflammatory arthritis was tested using likelihood ratio tests. To enhance the robustness of the results, we reassessed the association between inflammatory arthritis and degenerative aortic stenosis with a competing risk model, and death was considered as a competing event. Besides, we conducted a propensity score matching analysis based on covariates included in the multivariable Cox proportional hazards model to balance the baseline characteristics between the 2 groups. A nearest-neighbor algorithm was used with a 1:4 matching ratio and 0.2 caliper width. The balance between the groups before and after matching was assessed with the standardized mean difference (SMD), and SMD of <0.1 indicated good matching quality. We further performed adjustments for treatment measures on the basis of model 2, including the use of nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, urate-lowering medications, and glucocorticoids, to analyze the association between inflammatory arthritis and degenerative aortic stenosis.

RESULTS

Baseline Characteristics

A total of 497 567 participants were included, with a median age of 58 (interquartile range, 50–63) years. Among them, 271 129 (54.5%) were women, and 468 015 (94.1%) were White individuals. At baseline, gout had the highest prevalence among the 4 types of inflammatory arthritis (10 179 cases [2.0%]), followed by rheumatoid arthritis (6287 cases [1.3%]), ankylosing spondylitis (1397 cases [0.3%]), and psoriatic arthritis (265 cases [0.1%]). Compared with the control group, the inflammatory arthritis group exhibited lower education levels, higher CRP levels, and lower estimated glomerular filtration rate. Additionally, traditional cardiovascular risk factors were more prevalent in the inflammatory arthritis group, which showed higher proportions of poor physical activity and sleep patterns and a higher prevalence of hypertension (Table 1).

Over a median follow-up period of 12.58 years (interquartile range, 11.84–13.30), a total of 4571 cases (0.9%) of degenerative aortic stenosis were observed. Compared with the control group (4135 cases [0.9%]), all inflammatory arthritis groups had higher incidences of degenerative aortic stenosis (rheumatoid arthritis, 118 cases [1.9%]; ankylosing spondylitis, 28 cases [2.0%]; psoriatic arthritis, 9 cases [3.4%]; gout, 281 cases [2.8%]). Similarly, compared with the nondegenerative aortic stenosis group, the degenerative aortic stenosis group had older subjects, a higher proportion of male subjects, lower socioeconomic status and education levels, and a higher prevalence of unhealthy lifestyle habits (smoking, insufficient physical activity, unhealthy sleep and diet patterns). Additionally, the degenerative aortic stenosis group had a higher prevalence of chronic diseases such as hypertension and diabetes, lower estimated glomerular filtration rate, and higher BMI and CRP levels (Table S4).

Association Between Inflammatory Arthritis and the Long-Term Risk of Degenerative Aortic Stenosis

The Kaplan–Meier curve analysis results showed that the cumulative incidence of degenerative aortic stenosis was significantly higher in rheumatoid arthritis (Figure 1A), ankylosing spondylitis (Figure 1B), psoriatic arthritis (Figure 1C), and gout groups (Figure 1D) compared with the control group. These differences were statistically significant (log-rank $P<0.05$). In the fully adjusted Cox proportional hazards model (Table 2), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout were positively associated with the long-term risk of degenerative aortic stenosis, with 54% (adjusted HR, 1.54 [95% CI, 1.28–1.85]), 72% (adjusted HR, 1.72 [95% CI, 1.19–2.50]), 176% (adjusted HR, 2.76 [95% CI, 1.43–5.32]), and 36% (adjusted HR, 1.36 [95% CI, 1.20–1.54]) increases in risk, respectively. Short- and long-disease-duration inflammatory arthritis increased the risk of degenerative aortic stenosis, and the risk of degenerative aortic stenosis increased with the duration of the disease (P for trend<0.05; Table S5).

Interaction Between Inflammatory Arthritis and Genetic Risk on the Risk of Degenerative Aortic Stenosis

The PRS score we constructed (HR, 1.20 [95% CI, 1.16–1.23]) and family history of cardiovascular diseases (HR, 1.23 [95% CI, 1.16–1.31]) can effectively predict the long-term risk of degenerative aortic stenosis (Figure S2). After further adjustment for PRS and family history of cardiovascular diseases, the association between inflammatory arthritis and the incidence of degenerative aortic stenosis remained significant (HR >1; $P<0.05$; Figure S3). The association between rheumatoid arthritis and degenerative aortic stenosis was significant across all genetic risk strata (Figures 2 and 3A), but no interaction between them was observed (P for interaction with PRS=0.842; P for interaction with family history of cardiovascular diseases=0.465). Ankylosing spondylitis increased the risk of degenerative aortic stenosis only in individuals

Table 1. Baseline Characteristics of the Study Population

Variables	Control	Rheumatoid arthritis	*P* value	Ankylosing spondylitis	*P* value	Psoriatic arthritis	*P* value	Gout	*P* value
No.	479 439	6287		1397		265		10 179	
Age, y	58.00 (50.00 to 63.00)	61.00 (55.00 to 65.00)	<0.001	59.00 (53.00 to 63.00)	<0.001	58.00 (52.00 to 63.00)	0.400	61.00 (56.00 to 65.00)	<0.001
Female sex, n (%)	265 019 (55.3)	4430 (70.5)	<0.001	525 (37.6)	<0.001	133 (50.2)	0.109	1022 (10.0)	<0.001
White race, n (%)	450 840 (94.0)	5911 (94.0)	0.980	1349 (96.6)	<0.001	253 (95.5)	0.391	9662 (94.9)	<0.001
Townsend deprivation index	−2.14 (−3.65 to 0.52)	−1.67 (−3.45 to 1.43)	<0.001	−2.14 (−3.68 to 0.92)	0.242	−2.12 (−3.46 to 1.61)	0.119	−2.00 (−3.58 to 0.74)	<0.001
Education, n (%)			<0.001		0.002		<0.001		<0.001
College	155 364 (32.4)	1365 (21.7)		425 (30.4)		58 (21.9)		2595 (25.5)	
High school	53 077 (11.1)	629 (10.0)		123 (8.8)		27 (10.2)		1004 (9.9)	
Middle school	100 560 (21.0)	1260 (20.0)		293 (21.0)		56 (21.1)		2055 (20.2)	
Others	170 438 (35.5)	3033 (48.2)		556 (39.8)		124 (46.8)		4525 (44.5)	
BMI, kg/m^2	26.70 (24.10 to 29.78)	27.44 (24.51 to 31.13)	<0.001	26.77 (24.50 to 29.76)	0.076	28.57 (25.63 to 32.26)	<0.001	29.54 (27.02 to 32.74)	<0.001
CRP, mg/L	1.33 (0.68 to 2.54)	2.34 (1.31 to 5.68)	<0.001	2.29 (1.19 to 5.52)	<0.001	2.86 (1.35 to 6.53)	<0.001	1.80 (1.08 to 3.64)	<0.001
eGFR, mL/min·per 1.73 m^2	97.13 (87.89 to 106.09)	91.19 (81.10 to 100.87)	<0.001	96.61 (86.16 to 105.36)	0.021	94.99 (83.47 to 104.89)	0.003	89.19 (78.02 to 99.15)	<0.001
Drinking status, n (%)			<0.001		<0.001		<0.001		<0.001
Never	21 377 (4.5)	470 (7.5)		49 (3.5)		7 (2.6)		202 (2.0)	
Previous	16 827 (3.5)	483 (7.7)		75 (5.4)		27 (10.2)		367 (3.6)	
Current	441 235 (92.0)	5334 (84.8)		1273 (91.1)		231 (87.2)		9610 (94.4)	
Smoking status, n (%)			<0.001		<0.001		0.144		<0.001
Never	265 927 (55.5)	3014 (47.9)		627 (44.9)		136 (51.3)		4376 (43.0)	
Previous	162 900 (34.0)	2495 (39.7)		577 (41.3)		105 (39.6)		4883 (48.0)	
Current	50 612 (10.6)	778 (12.4)		193 (13.8)		24 (9.1)		920 (9.0)	
Physical activity, n (%)			<0.001		<0.001		0.002		<0.001
Regular	186 967 (39.0)	1997 (31.8)		500 (35.8)		94 (35.5)		3901 (38.3)	
Excessive	114 144 (23.8)	1157 (18.4)		302 (21.6)		44 (16.6)		2392 (23.5)	
Poor	66 911 (14.0)	1224 (19.5)		256 (18.3)		50 (18.9)		1751 (17.2)	
Sleep pattern, n (%)			<0.001		<0.001		<0.001		<0.001
Healthy	229 348 (47.8)	2457 (39.1)		548 (39.2)		99 (37.4)		4143 (40.7)	
Intermediate	153 481 (32.0)	2331 (37.1)		536 (38.4)		109 (41.1)		3842 (37.7)	
Poor	9221 (1.9)	241 (3.8)		44 (3.1)		12 (4.5)		317 (3.1)	
Diet pattern, n (%)			<0.001		<0.001		0.177		<0.001
Healthy	180 827 (37.7)	2389 (38.0)		460 (32.9)		86 (32.5)		2908 (28.6)	
Intermediate	222 712 (46.5)	2893 (46.0)		674 (48.2)		126 (47.5)		5063 (49.7)	
Poor	54 702 (11.4)	631 (10.0)		198 (14.2)		38 (14.3)		1681 (16.5)	
Medical history, n (%)									
Hyperlipidemia	213 128 (44.5)	3153 (50.2)	<0.001	643 (46.0)	0.248	140 (52.8)	0.007	6375 (62.6)	<0.001
Hypertension	254 507 (53.1)	3901 (62.0)	<0.001	870 (62.3)	<0.001	181 (68.3)	<0.001	8339 (81.9)	<0.001
Diabetes	27 671 (5.8)	588 (9.4)	<0.001	89 (6.4)	0.367	34 (12.8)	<0.001	1579 (15.5)	<0.001
Aortic stenosis, n (%)	4135 (0.9)	118 (1.9)	<0.001	28 (2.0)	<0.001	9 (3.4)	<0.001	281 (2.8)	<0.001

BMI indicates body mass index; CRP, C-reactive protein; and eGFR, estimated glomerular filtration rate.

with low genetic predisposition or no family history of cardiovascular diseases (Figures 2 and 3B). Psoriatic arthritis was significantly associated with the incidence of degenerative aortic stenosis only in participants with intermediate genetic predisposition or no family history (Figures 2 and 3C). The association between gout and degenerative aortic stenosis was evident in individuals with or without a family history of cardiovascular

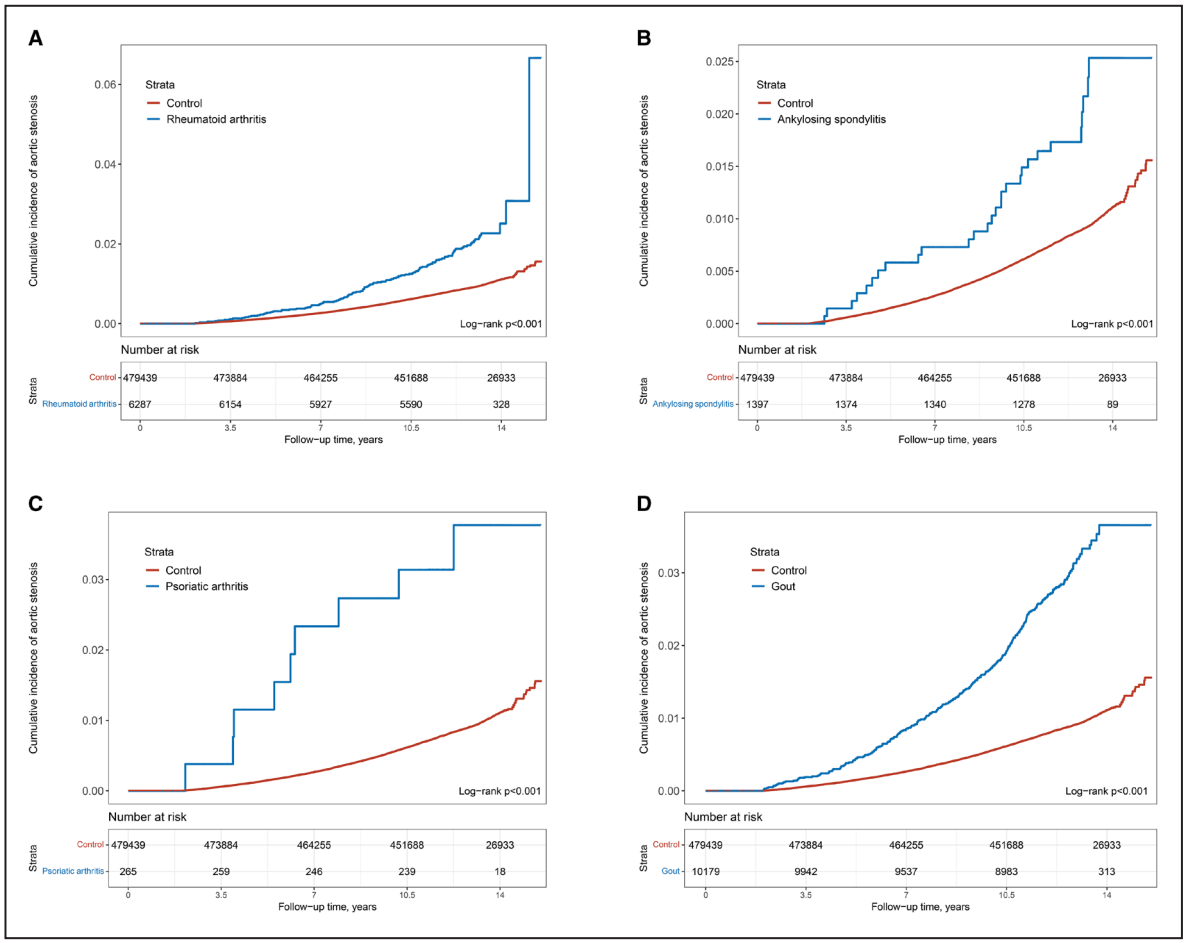

Figure 1. Cumulative hazard of degenerative aortic stenosis among participants with or without rheumatoid arthritis (A), ankylosing spondylitis (B), psoriatic arthritis (C), and gout (D).
Group comparisons were conducted using log-rank test.

diseases but was significant only in those with low or intermediate genetic predisposition (Figures 2 and 3D). Moreover, no interaction was found between ankylosing spondylitis (*P* for interaction with PRS=0.195; *P* for interaction with family history=0.255), psoriatic arthritis (*P* for interaction with PRS=0.533; *P* for interaction with family history=0.319), or gout (*P* for interaction with PRS=0.511; *P* for interaction with family history=0.730) and genetic risk in the occurrence of degenerative aortic stenosis.

Subgroup and Sensitivity Analyses

Subgroup analysis (Table 3) revealed no statistically significant interactions between inflammatory arthritis and stratification variables such as ethnicity, education level, hypertension, BMI, and CRP level (*P* for interaction>0.05). However, rheumatoid arthritis was significantly associated with the incidence of degenerative aortic stenosis in women only (*P* for interaction=0.036). Ankylosing spondylitis was associated with the elevated risk of degenerative aortic stenosis in participants aged ≤60 years, but no significant difference was observed in participants aged >60 years (*P* for interaction<0.001). Additionally, the association between gout and the risk of degenerative aortic stenosis was more pronounced in individuals with high socioeconomic status (*P* for interaction between Townsend deprivation index and gout=0.014). In the competing risks model, when death was considered a competing event, inflammatory arthritis remained significantly associated with the long-term risk of degenerative aortic stenosis (Figure S4). After propensity score matching, differences in baseline characteristics between the 2 groups were significantly reduced, achieving satisfactory balance (SMD <0.1; Tables S6 through S9). The association between inflammatory arthritis and degenerative aortic stenosis remained significant (Table S10). After further adjustments for treatment status based on model 2, inflammatory arthritis significantly increased the risk of aortic stenosis (Table S11).

Table 2. Association Between Inflammatory Arthritis and the Risk of Degenerative Aortic Stenosis

Inflammatory arthritis	Cases/N	Crude		Model 1		Model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Rheumatoid arthritis							
Control	4135/479 439	1 (ref)		1 (ref)		1 (ref)	
Rheumatoid arthritis	118/6287	2.25 (1.87–2.70)	<0.001	1.86 (1.54–2.23)	<0.001	1.54 (1.28–1.85)	<0.001
Ankylosing spondylitis							
Control	4135/479 439	1 (ref)		1 (ref)		1 (ref)	
Ankylosing spondylitis	28/1397	2.33 (1.60–3.37)	<0.001	1.87 (1.29–2.72)	0.001	1.72 (1.19–2.50)	0.004
Psoriatic arthritis							
Control	4135/479 439	1 (ref)		1 (ref)		1 (ref)	
Psoriatic arthritis	9/265	4.07 (2.12–7.83)	<0.001	3.90 (2.03–7.51)	<0.001	2.76 (1.43–5.32)	0.002
Gout							
Control	4135/479 439	1 (ref)		1 (ref)		1 (ref)	
Gout	281/10 179	3.41 (3.02–3.85)	<0.001	1.89 (1.67–2.14)	<0.001	1.36 (1.20–1.54)	<0.001

Crude adjusted for none. Model 1 adjusted for age, sex, ethnicity, Townsend deprivation index, education levels. Model 2 adjusted for model 1 plus body mass index, C-reactive protein, estimated glomerular filtration rate, smoking and drinking status, physical activity, sleep and diet patterns, hypertension, diabetes, and hyperlipemia. HR indicates hazard ratio.

DISCUSSION

The results of this study indicated that inflammatory arthritis was significantly associated with the long-term risk of degenerative aortic stenosis in the prospective cohort of the UK Biobank, independent of genetic risk. Sex, age, and socioeconomic status interacted with rheumatoid arthritis, ankylosing spondylitis, and gout on the incidence of degenerative aortic stenosis, respectively.

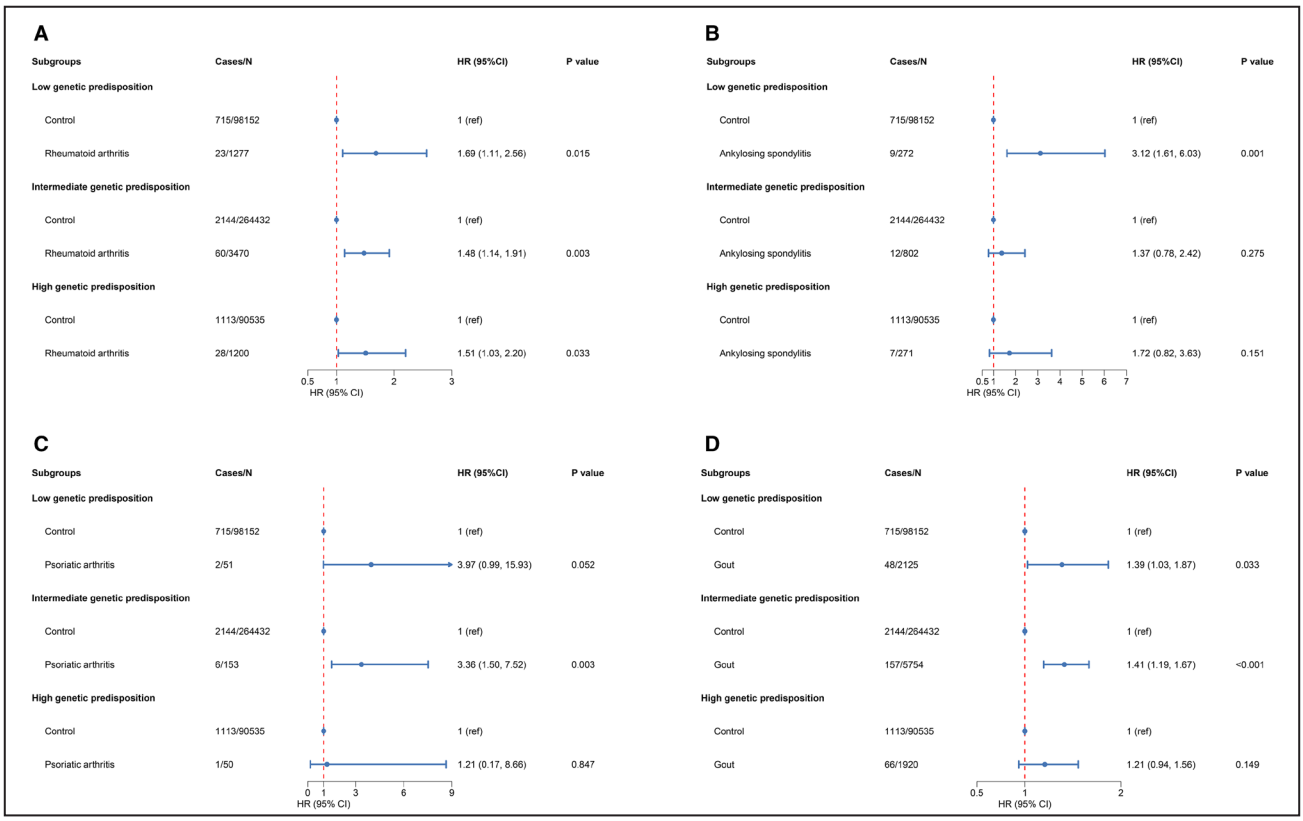

Figure 2. Associations between rheumatoid arthritis (A), ankylosing spondylitis (B), psoriatic arthritis (C), and gout (D), with degenerative aortic stenosis in individuals with different genetic predispositions for degenerative aortic stenosis.
HR indicates hazard ratio.

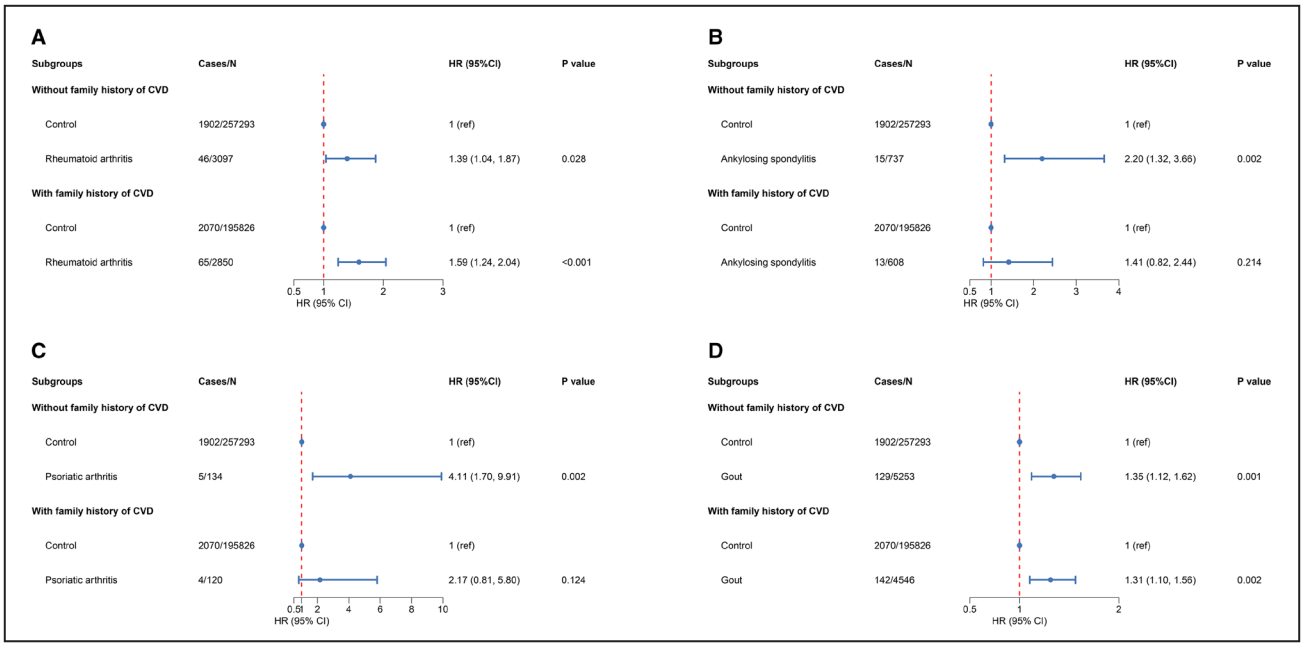

Figure 3. Associations between rheumatoid arthritis (A), ankylosing spondylitis (B), psoriatic arthritis (C), and gout (D), with degenerative aortic stenosis in individuals with or without a family history of cardiovascular disease.
Results are presented as HR with 95% CI using a Cox proportional hazards model, adjusted for age, sex, ethnicity, Townsend deprivation index, education levels, body mass index, C-reactive protein, estimated glomerular filtration rate, smoking and drinking status, physical activity, sleep and diet patterns, hypertension, diabetes, hyperlipemia. CVD indicates cardiovascular disease; and HR, hazard ratio.

Inflammation is an important mechanism in the development of degenerative aortic stenosis.[15] Diseased tissues in aortic stenosis are infiltrated by various immune–inflammatory cells, predominantly T lymphocytes and mononuclear macrophages.[16] These cells secrete inflammatory factors, including tumor necrosis factor-α, interleukin-1β, and interleukin-6, which promote the osteogenic differentiation of valve interstitial cells and the remodeling of the extracellular matrix, thereby contributing to the pathological progression of aortic stenosis.[17] In patients with inflammatory arthritis, including rheumatoid arthritis and gout, elevated levels of inflammatory factors, such as tumor necrosis factor-α and interleukin-1β, are commonly observed in the circulation.[18] A chronic systemic inflammatory state over the long term may partially explain the positive association between inflammatory arthritis and the long-term risk of degenerative aortic stenosis in this study. Additionally, as observed in this study and previous research, the prevalence of "traditional" cardiovascular risk factors, such as hypertension and diabetes, is increased in patients with inflammatory arthritis. This effect may be an important reason for this association.[6] Inflammation can induce oxidative stress and endothelial dysfunction, contributing to the development of hypertension and other conditions.[19] In addition, patients with inflammatory arthritis often experience joint pain that restricts physical activity, which in turn causes obesity and subsequently a higher incidence of metabolic disorders.[6]

Inflammatory arthritis is a heterogeneous group of chronic inflammatory diseases, and epidemiological characteristics, pathogenesis, and pathological features vary among the types of arthritis. Rheumatoid arthritis is a chronic autoimmune disease characterized by synovitis, pannus formation, and cartilage erosion. An association between rheumatoid arthritis and aortic stenosis has been found.[20] Consistent with the findings of this study, a retrospective cohort study by Johnson et al[21] found that rheumatoid arthritis increased the risk of aortic stenosis by 48% (adjusted HR, 1.48 [95% CI, 1.41–1.55]); however, this cohort included predominantly male subjects; that is, male subjects constituted 87.6% of the rheumatoid arthritis group, whereas women constituted 12.4%. This difference limited the generalizability of the findings given that rheumatoid arthritis is more common in women. In our study cohort, the rheumatoid arthritis group consisted of mostly women (70.5%) versus men (29.5%), closely aligning with the epidemiologically reported male-to-female ratio of 1:2 to 4 for rheumatoid arthritis.[22] Therefore, our study results served as an important supplement and further validated existing research. We found that sex modified this association, and the association between rheumatoid arthritis and degenerative aortic stenosis was significant only in women. Compared with male patients, female patients

Table 3. Subgroup Analysis for the Association Between Inflammatory Arthritis and the Risk of Degenerative Aortic Stenosis

Subgroup	Rheumatoid arthritis		Ankylosing spondylitis		Psoriatic arthritis		Gout	
	Control	Rheumatoid arthritis	Control	Ankylosing spondylitis	Control	Psoriatic arthritis	Control	Gout
Age, y								
<60	1 (ref)	1.86 (1.24–2.78)	1 (ref)	4.71 (2.86–7.75)	1 (ref)	1.87 (0.46–7.52)	1 (ref)	1.45 (1.08–1.94)
≥60	1 (ref)	1.51 (1.23–1.86)	1 (ref)	0.88 (0.50–1.55)	1 (ref)	2.96 (1.41–6.23)	1 (ref)	1.35 (1.18–1.55)
P for interaction		0.150		<0.001*		0.733		0.119
Sex								
Female	1 (ref)	1.78 (1.41–2.26)	1 (ref)	1.82 (0.91–3.64)	1 (ref)	4.65 (2.07–10.45)	1 (ref)	1.71 (1.17–2.50)
Male	1 (ref)	1.24 (0.92–1.67)	1 (ref)	1.69 (1.09–2.62)	1 (ref)	1.53 (0.49–4.75)	1 (ref)	1.34 (1.17–1.53)
P for interaction		0.036*		0.842		0.109		0.191
Race or ethnicity								
White	1 (ref)	1.53 (1.27–1.85)	1 (ref)	1.69 (1.16–2.47)	1 (ref)	2.82 (1.46–5.43)	1 (ref)	1.38 (1.21–1.56)
Non-White	1 (ref)	1.87 (0.69–5.10)	1 (ref)	3.36 (0.46–24.53)	1 (ref)	0.00 (0.00–Inf)	1 (ref)	0.88 (0.38–2.03)
P for interaction		0.907		0.564		0.516		0.37
Townsend deprivation index								
Low	1 (ref)	1.98 (1.42–2.75)	1 (ref)	2.40 (1.33–4.36)	1 (ref)	1.27 (0.18–9.00)	1 (ref)	1.67 (1.35–2.06)
Intermediate	1 (ref)	1.55 (1.11–2.16)	1 (ref)	1.45 (0.72–2.92)	1 (ref)	3.97 (1.28–12.34)	1 (ref)	1.41 (1.14–1.74)
High	1 (ref)	1.29 (0.96–1.74)	1 (ref)	1.43 (0.74–2.75)	1 (ref)	3.06 (1.26–7.40)	1 (ref)	1.09 (0.88–1.36)
P for interaction		0.192		0.422		0.537		0.014*
Education								
College	1 (ref)	1.80 (1.17–2.79)	1 (ref)	2.65 (1.37–5.12)	1 (ref)	2.23 (0.31–15.86)	1 (ref)	1.27 (0.96–1.69)
High school	1 (ref)	0.87 (0.36–2.11)	1 (ref)	3.09 (0.99–9.68)	1 (ref)	5.89 (0.81–42.75)	1 (ref)	1.72 (1.12–2.64)
Middel school	1 (ref)	1.67 (1.09–2.56)	1 (ref)	1.72 (0.71–4.16)	1 (ref)	3.47 (0.86–14.01)	1 (ref)	1.39 (1.05–1.84)
Others	1 (ref)	1.50 (1.18–1.91)	1 (ref)	1.21 (0.67–2.19)	1 (ref)	2.38 (0.99–5.75)	1 (ref)	1.33 (1.12–1.58)
P for interaction		0.481		0.298		0.875		0.813
BMI								
<25 kg/m^2	1 (ref)	1.51 (0.95–2.40)	1 (ref)	2.19 (0.98–4.92)	1 (ref)	5.89 (1.46–23.72)	1 (ref)	1.62 (1.03–2.54)
≥25 kg/m^2	1 (ref)	1.52 (1.24–1.86)	1 (ref)	1.57 (1.03–2.38)	1 (ref)	2.48 (1.18–5.21)	1 (ref)	1.41 (1.24–1.60)
P for interaction		0.94		0.496		0.344		0.437
CRP								
Low	1 (ref)	1.55 (1.01–2.39)	1 (ref)	2.15 (1.02–4.52)	1 (ref)	2.14 (0.30–15.20)	1 (ref)	1.28 (1.00–1.65)
High	1 (ref)	1.57 (1.28–1.92)	1 (ref)	1.65 (1.07–2.53)	1 (ref)	3.08 (1.54–6.17)	1 (ref)	1.38 (1.20–1.60)
P for interaction		0.886		0.561		0.708		0.616
Hypertension								
No	1 (ref)	1.50 (0.93–2.40)	1 (ref)	2.38 (1.06–5.32)	1 (ref)	4.27 (1.06–17.30)	1 (ref)	1.66 (1.09–2.53)
Yes	1 (ref)	1.54 (1.26–1.88)	1 (ref)	1.60 (1.05–2.43)	1 (ref)	2.49 (1.18–5.24)	1 (ref)	1.33 (1.17–1.52)
P for interaction		0.858		0.435		0.533		0.298

Adjusted for age, sex, ethnicity, Townsend deprivation index, education levels, body mass index, C-reactive protein, estimated glomerular filtration rate, smoking and drinking status, physical activity, sleep and diet patterns, hypertension, diabetes, hyperlipemia.

*Indicates a significant interaction between inflammatory arthritis and stratified variables.

with rheumatoid arthritis generally have higher disease activity scores, experience more pain and fatigue, and have worse functional status.[23] These characteristics may lead to social isolation and reduced physical activity, thereby increasing traditional cardiovascular risk factors. This finding may explain why female patients with rheumatoid arthritis are more prone to developing degenerative aortic stenosis.

Ankylosing spondylitis primarily affects the sacroiliac joints and axial skeleton, and its characteristic

pathological changes are inflammation in ligaments and tendon attachment points.[24] Approximately 2% to 10% of patients with ankylosing spondylitis experienced cardiac involvement, including atrioventricular block and aortitis.[25–27] A cross-sectional study preliminarily found that ankylosing spondylitis was associated with an increased risk of aortic stenosis (odds ratio, 2.25 [95% CI, 1.57–3.23]).[28] This association was further confirmed in this prospective cohort. Interestingly, we found that the association between ankylosing spondylitis and degenerative aortic stenosis was statistically significant only in younger participants. Ankylosing spondylitis primarily affects young adults. Specifically, ≈80% of patients experience initial symptoms before the age of 30 years, <5% develop symptoms after the age of 45 years, and younger patients are more likely to present with extra-articular manifestations.[29] A small-sample study[30] found that, compared with patients with early-onset ankylosing spondylitis, patients with late-onset ankylosing spondylitis had lower levels of inflammation (lower CRP and erythrocyte sedimentation rate), which may explain our observed results. However, more evidence is needed to support this finding.

Psoriatic arthritis is a chronic progressive inflammatory arthritis that primarily affects the spine or peripheral joints or both and is associated with psoriasis.[31] Currently, studies on the association between psoriatic arthritis and valvular heart disease is limited. To the best of our knowledge, this study is the first to elucidate the long-term risk association between psoriatic arthritis and degenerative aortic stenosis. However, the number of psoriatic arthritis cases in this study is relatively small, and thus the observed association between psoriatic arthritis and degenerative aortic stenosis should be interpreted with caution. Studies with larger sample size may be necessary to provide more meaningful insights.

Gout is a painful inflammatory arthritis caused by the deposition of uric acid crystals in joints and surrounding soft tissues.[32] Although many studies have evaluated the relationship between gout and atherosclerotic cardiovascular diseases, few have assessed its association with other cardiovascular diseases, especially prospective cohort studies. In a case–control study by Chang et al, the prevalence of gout in patients with aortic stenosis was significantly higher than that in age-matched controls, and gout was associated with aortic stenosis (odds ratio, 2.08 [95% CI, 1.00–4.32]). However, the sample size of this study is limited, and the multivariate adjustment did not consider demographic characteristics such as age and sex, and lifestyle factors such as alcohol consumption and diet, which are important influencing factors for gout and aortic stenosis.[1] This study partially addressed these shortcomings. Nevertheless, our study found that socioeconomic status can modify the association between gout and degenerative aortic stenosis, and this association is more pronounced in participants with high socioeconomic status. This result may be attributed to differences in dietary habits and lifestyle. Individuals with high socioeconomic status are likely to have access to high-energy and processed foods, which are significant factors for the onset and exacerbation of gout.[33] According to the data from the Global Burden of Disease, a high sociodemographic index is closely associated with high age-standardized prevalence, incidence, and years lived with gout-related disability.[34]

This study had several strengths. First, to the best of our knowledge, this prospective cohort study is the first to systematically explore the association between inflammatory arthritis and the long-term risk of degenerative aortic stenosis. The large sample size, standardized data, and long-term follow-up of the UK Biobank enhanced the reliability of the findings. In clinical management, monitoring and preventive strategies for heart valves should be proactive for patients with inflammatory arthritis, especially those with a long-standing condition. These strategies will help to prevent the occurrence of degenerative aortic stenosis or enable the early detection of its onset, allowing for timely intervention. Second, this study thoroughly accounted for the impact of various confounding factors, including demographic characteristics, lifestyle, personal medical history, and treatment status, which were overlooked in previous studies. Third, we further assessed the effect of genetic risk on the association between inflammatory arthritis and degenerative aortic stenosis, using genetic data from the UK Biobank. Finally, the study conducted subgroup and sensitivity analyses to test the robustness of the findings and to examine whether the association between inflammatory arthritis and degenerative aortic stenosis differs across subgroups on the basis of age and sex, thereby identifying specific populations at risk. The findings suggested that clinicians should consider differences in disease progression and risk among patients of different age groups and sex when developing treatment and monitoring plans. Early screening and intervention for specific high-risk subgroups may considerably reduce the incidence of aortic stenosis.

This study also has some limitations. First, as an observational study, our findings cannot infer a causal relationship between inflammatory arthritis and degenerative aortic stenosis. Second, although we performed adjustments for relevant confounding factors, completely ruling out interference by some important unmeasured confounding factors was impossible. Third, owing to the “healthy volunteer” selection bias, the prevalence and incidence of

diseases in the UK Biobank cohort are lower than those in the general population. Fourth, given that the UK Biobank is predominantly composed of White individuals, more evidence is needed to support the association between inflammatory arthritis and degenerative aortic stenosis in other racial and ethnic groups. Additionally, further research is needed to explore and elucidate the mechanisms underlying the association between inflammatory arthritis and degenerative aortic stenosis.

CONCLUSIONS

Our study indicated that rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and gout were significantly associated with an increased long-term risk of degenerative aortic stenosis. These findings underscore the importance of screening for degenerative aortic stenosis in individuals with inflammatory arthritis.

ARTICLE INFORMATION

Received September 11, 2024; accepted January 10, 2025.

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Acknowledgments

This research made use of resources from the UK Biobank (Application ID: 107175). The authors extend their sincere gratitude to all contributors—funders, staff, and participants of the UK Biobank project—for their invaluable contributions to this study.

Sources of Funding

This work was funded by National Natural Science Foundation of China (82470054 and 82300081), Natural Science Foundation of Hunan Province (2023JJ40963, 2024JJ6620, and 2024JJ6673), Changsha Natural Science Foundation (kq2403050), and the Project Program of National Clinical Research Center for Geriatric Disorders (Xiangya Hospital, 2023LNJJ18).

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S11
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