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Original Report

Physical Frailty and the Risk of Degenerative Valvular Heart Disease

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Abstract

Background and Objectives: The relationship between physical frailty, age-related conditions, and the incidence of degenerative valvular heart disease (VHD) remains unclear. This study aimed to investigate the potential association between physical frailty and the development of degenerative VHD.

Research Design and Methods: Participants from the UK Biobank who were initially free of VHD and heart failure were categorized into 3 groups based on the frailty phenotype: non-frailty, pre-frailty, and frailty. The frailty phenotype was determined by evaluating the following 5 components: weight loss, exhaustion, reduced physical activity, slow gait speed, and low grip strength. The incidence of degenerative VHD, including mitral valve regurgitation (MR), aortic valve regurgitation (AR), and aortic valve stenosis (AS), was assessed using hospital admission or death registries.

Results: Among the 331 642 participants, 11 885 (3.6%) exhibited frailty and 143 379 (43.2%) were categorized as pre-frailty. During a median follow-up of 13.8 years, there were 3 684 MR, 1 205 AR, and 3 166 AS events. Compared to non-frailty participants, those with pre-frailty and frailty showed significantly increased risks for MR (hazard ratio [HR], $HR_{pre\text{-}frailty}$:1.19, 95% confidence interval [CI]: 1.11–1.28; $HR_{frailty}$: 1.50, 95% CI: 1.30–1.74), AR ($HR_{pre\text{-}frailty}$:1.19, 95% CI: 1.05–1.34; $HR_{frailty}$: 1.58, 95% CI: 1.22–2.04), and AS ($HR_{pre\text{-}frailty}$:1.19, 95% CI: 1.11–1.29; $HR_{frailty}$: 1.74, 95% CI: 1.51–2.00). Among the 5 components, slow gait speed showed the strongest association with the risk of various types of VHD (HR_{MR}: 1.50, 95% CI: 1.34–1.65; HR_{AR}: 1.50, 95% CI: 1.24–1.80; HR_{AS}: 1.46, 95% CI: 1.32–1.62), followed by exhaustion, low grip strength, and weight loss.

Discussion and Implications: Pre-frailty and frailty were associated with a higher risk of all 3 types of degenerative VHD. Early detection and intervention for pre-frailty and frailty in middle-aged and older individuals may assist in preventing or delaying the onset of degenerative VHD.

Keywords: Aortic valve regurgitation, Aortic valve stenosis, Mitral valve regurgitation

Translational Significance: Little is known about physical frailty and its association with the incidence of degenerative valvular heart disease (VHD) in middle-aged and older adults. Our study found that pre-frailty and frailty were associated with a higher risk of the 3 types of degenerative VHD. Among the 5 frailty components, slow gait speed showed the strongest association with increased VHD risk. Physical interventions targeting frailty, especially pre-frailty, may have the potential to improve overall physical function and prevent adverse cardiovascular outcomes. Therefore, routine detection and early-stage physical intervention for pre-frailty and frailty could help prevent and delay the onset of degenerative VHD.

With an aging global population, the incidence and prevalence of degenerative valvular heart disease (VHD) have increased, particularly in high-income countries (1). A gross estimate suggests that the total population prevalence of clinically significant VHD in the United Kingdom is approximately 11.3% among patients aged 65 years and older, and it is expected to potentially double before 2050 (2). Underlying the long-term clinical impact of degenerative VHD, patients may experience a range of adverse outcomes including heart failure, cardiac arrhythmias, and cardiac death, all of which are associated with an unfavorable prognosis (3–5). This condition imposes a substantial burden owing to the high rates of comorbidities and increased risks associated with invasive interventions. The absence of effective pharmacological interventions

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highlights the urgent need to identify modifiable risk factors that can impede or delay the progression of degenerative VHD.

Frailty, characterized by declining physical function and reduced resistance to stressors, is becoming increasingly prevalent in the aging population (6–8). A recent meta-analysis involving over 60 000 participants aged 65 and older from 21 community-based studies found that 10.7% experienced physical frailty (9). In the Hertfordshire cohort study, the overall prevalence of frailty was 6.3% among community-dwelling participants aged 64–74 years (10). Another study involving nearly 0.5 million people in the United Kingdom, with a median follow-up of 7 years, reported that 38% were in the pre-frailty state and 3% were in the frailty state. Both states were significantly associated with increased mortality (11).

Frailty can trigger inflammatory responses, metabolic imbalances, lean tissue loss, and fat tissue accumulation, thereby accelerating the aging process in older patients (12). Recent evidence suggests that nearly half of the patients with severe VHD have an intermediate or higher risk of frailty (13). Frailty not only accelerates VHD progression but is also associated with poorer prognosis (14). Given the shared pathophysiological mechanisms of degenerative VHD and frailty (15), it is reasonable to hypothesize that frailty is a key risk factor for the development of degenerative VHD. Understanding the interplay between frailty and VHD can guide tailored interventions in at-risk individuals.

Therefore, we conducted a prospective cohort study involving 331 642 middle-aged and older participants from the UK Biobank to investigate whether the physical frailty status and its features were independently associated with the development of degenerative VHD.

Method

Study Population

Data for this study were drawn from the UK Biobank, a prospective biomedical database that recruited over 500 000 participants aged 37–73 years across the United Kingdom from 2006 to 2010. Comprehensive information was gathered, including sociodemographic details, lifestyle, physical examination data, and other pertinent information at baseline and during follow-up (16). The UK Biobank study was approved by the Northwest Multi-Center Research Ethics Committee (REC reference 11/NW/0382), and all participants provided written informed consent. The number of applications used in this study was 91 035.

Of the 502 394 accessible participants, we excluded 108 who withdrew from the UK Biobank and 4 198 who had VHD at baseline (rheumatic, nonrheumatic, congenital, endocarditis, or Marfan syndrome). Participants with missing frailty assessment data (n = 117 519) and covariate data (n = 48 927) were further excluded, resulting in a final analysis of 331 642 adults (Figure 1). Complete case analysis was employed for the main analyses. Multiple imputations for missing covariate data were conducted for sensitivity analysis.

Frailty Phenotype Assessment

The frailty phenotype, initially described by Fried et al. in the Cardiovascular Health Study (17), was assessed based on the following 5 features: unintentional weight loss, exhaustion, low physical activity, slow gait speed, and low grip strength. We adjusted the frailty definitions to align with the UK Biobank data set (11,18). Detailed definitions and field IDs are provided in Supplementary Table 1. Participants were stratified into 3 groups based on the number of features fulfilled: non-frailty (0 scores), pre-frailty (1–2 scores), or frailty (≥3 scores).

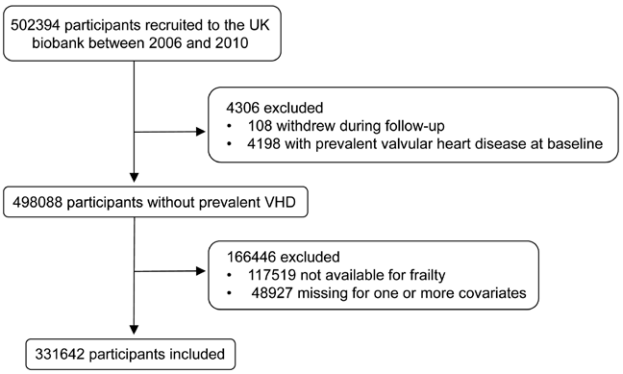

Figure 1. Flowchart of participants in the current study. VHD = valvular heart disease.

Outcomes

Degenerative VHD includes mitral valve regurgitation (MR), mitral valve stenosis (MS), aortic valve regurgitation (AR), and aortic valve stenosis (AS). Incidence data were sourced from hospital admission electronic health records and the death registers, aligning with the World Health Organization International Classification of Diseases (ICD-10). Detailed definitions are provided in Supplementary Table 2.

Covariates

Information on age, sex, ethnicity, Townsend Deprivation Index (TDI), educational attainment, smoking status, alcohol consumption, diet score, and sleep score were collected using a touchscreen questionnaire. Body mass index (BMI) was derived from height and weight measurements conducted by skilled researchers at baseline. The diet score evaluated the participants' adherence to their regular dietary habits, including the consumption of fruits, vegetables, fish, red meat, and processed meat. The scores range from 0 to 3 (Supplementary Table 3). Sleep scores assessed the sleep quality by considering 5 sleep-related factors: morning chronotype, sleep duration, insomnia, snoring, and daytime sleepiness (Supplementary Table 4). The comorbidities included hypertension, obesity, type 2 diabetes, dyslipidemia, ischemic heart disease, stroke, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, end-stage renal disease, and cancer. These conditions were identified based on self-reports and primary care and hospital admission records.

Statistical Analyses

The participants were categorized based on their baseline frailty status. Categorical variables are presented as counts (percentage, %), whereas continuous variables are expressed as means or medians (standard deviation [*SD*], interquartile range [IQR]). The frailty phenotype was assessed as a categorical variable (non-frailty, pre-frailty, or frailty), with the non-frailty group serving as the reference group in each model. Frailty scores ranging from 0 to 5 were treated as continuous variables in the multivariate models when assessing the linear trend (per increase in the frailty phenotype score). Time to

events was calculated from the date of baseline recruitment to the date of the first diagnosis of degenerative VHD, death, or censoring (December 31, 2022), whichever occurred first.

Cox proportional hazard regression models were used to assess hazard ratios (HRs) with 95% confidence intervals (CIs) to examine the association between frailty phenotype and VHD. Potential confounding factors included age, sex, ethnicity, educational attainment, TDI, smoking status, alcohol consumption, diet score, sleep score, systolic blood pressure, BMI, and clinical comorbidities including type 2 diabetes, dyslipidemia, ischemic heart disease, stroke, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, end-stage renal disease, and cancer. The dose–response shape of the association between the frailty phenotype score and incident degenerative VHD events was illustrated using a restricted cubic spline model. Furthermore, we examined the relationships between the 5 frailty components and the risk of VHD events, individually and mutually (considering other frailty components).

Several sensitivity analyses were conducted to test the robustness of the results. First, we compared the characteristics of the total sample (n = 498 088), the available frailty sample (n = 380 569), and the complete sample (n = 331,642). Second, to address the influence of missing data on our results (Supplementary Table 5), we multiple-imputed the missing covariates using chained equations under the assumption of missing data at random. Third, we repeated the main analyses after excluding participants with less than 2 years of follow-up to mitigate the potential influence of reverse causality. Moreover, we reanalyzed the association between frailty and incident VHD diseases across strata of age (<60, ≥60), sex (male, female), ethnicity (White, others), TDI (high deprivation, low deprivation), education level (college or university, below college), smoking status (never, former and current), alcohol consumption status (never, former and current), and population with underlying conditions consisting of obesity, hypertension, type 2 diabetes and dyslipidemia. Finally, to account for the competing risk of mortality, we validated the robustness of our results using Fine and Gray competing risk regression models. p Values <.05 were considered statistically significant. All analyses were performed using the R software (version 4.1.1).

Results

Baseline Characteristics

The baseline characteristics of the participants categorized by frailty phenotype are summarized in Table 1. Among the 331 642 participants (mean age: 55.9 years; 48.9% male), 11 885 (3.6%) exhibited frailty, 143 379 (43.2%) were categorized as pre-frailty, and 176 738 (53.2%) were classified as non-frailty. Participants with pre-frailty and frailty, compared to those without frailty, tended to be older, female, non-White, current smokers, living in areas of higher deprivation, having lower educational attainment, higher body weight, and lower alcohol consumption. Moreover, individuals in the frail category were more likely to have a higher burden of long-term morbidities, including hypertension, type 2 diabetes, dyslipidemia, cardiovascular disease, chronic obstructive pulmonary disease, renal dysfunction, and cancer. During a median follow-up of 13.8 years (IQR: 13.0–14.5 years), a total of 8 110 degenerative VHD cases were documented, including 3 684 events of MR, 55 events of MS, 1 205 events of AR, and 3 166 events of AS. Notably, the study did not evaluate the impact of frailty phenotype on MS incidence due to the limited number of MS events.

Association Between Frailty Phenotype and Incident Degenerative VHD

In the restricted cubic spline analyses, we observed positive linear relationships between the frailty phenotype score and the incidence of degenerative VHD (all $p_{\text{nonlinear}} > .05$, $p_{\text{overall}} < .001$) (Figure 2). Each 1-point increase in frailty phenotype score corresponded to a 14% increase in MR risk (HR: 1.14, 95% CI: 1.10–1.19), a 16% increase in AR risk (HR: 1.16, 95% CI: 1.09–1.24), and an 18% increase in AS risk (HR: 1.18, 95% CI: 1.14–1.23; Supplementary Table 6). The incidence of MR per 10 000 person-years was 7.1 for non-frailty, 9.2 for pre-frailty, and 15.5 for frailty. For AR, the rates were 2.3, 3.0, and 5.0, and for AS, they were 5.6, 8.0, and 19.0, respectively. Compared to non-frailty, both pre-frailty and frailty were significantly associated with an increased MR risk, even after adjusting for covariates (Figure 3, Supplementary Table 6). The HRs were 1.19 (95% CI: 1.11–1.28) for pre-frailty and 1.50 (95% CI: 1.30–1.74) for frailty ($p < .001$). Similarly, individuals categorized as pre-frailty or frailty displayed significantly higher risks of AR and AS. The risk for AR was 19% higher for those with pre-frailty (HR: 1.19, 95% CI: 1.05–1.34) and 58% higher for those with frailty (HR: 1.58, 95% CI: 1.22–2.04). For AS, the risk was 19% higher for pre-frail individuals (HR: 1.19, 95% CI: 1.11–1.29) and 74% higher for those with frailty (HR: 1.74, 95% CI: 1.51–2.00).

Association Between Frailty Components and Risk Degenerative VHD

We further investigated each component of frailty and its association with incident degenerative VHD after full adjustment for covariates (Figure 4) and other frailty components (Supplementary Table 7). All 5 frailty components, except for low physical activity, were independently associated with the risk of degenerative MR after adjusting for covariates. After further adjusting for the other frailty components, the HRs for MR incidence gradually attenuated (HR weight loss: 1.12, 95% CI: 1.03–1.23; HR exhaustion: 1.18, 95% CI: 1.06–1.30; HR slow gait speed: 1.43, 95% CI: 1.28–1.60; HRlow grip strength: 1.12, 95% CI: 1.02–1.22). Similarly, for AS incidence, the same associations and trends were observed in both individual and mutual adjustment models ($HR_{\text{weight loss}}$: 1.30, 95% CI: 1.19–1.43; $HR_{\text{exhaustion}}$: 1.18, 95% CI: 1.06–1.32; $HR_{\text{slow gait speed}}$: 1.39, 95% CI: 1.25–1.55; $HR_{\text{low grip strength}}$: 1.16, 95% CI: 1.06–1.27). Additionally, for incident AR, exhaustion (HR: 1.26, 95% CI: 1.06–1.51), slow gait speed (HR: 1.50, 95% CI: 1.24–1.80), and low grip strength (HR: 1.25, 95% CI: 1.08–1.45) exhibited a risk association after adjusting for covariates. However, after adjusting for other frailty components, only slow gait speed (HR: 1.42, 95% CI: 1.18–1.72) and low grip strength (HR: 1.20, 95% CI: 1.04–1.40) showed independent risk associations.

Sensitivity Analyses

The characteristics of the total sample, the available frailty sample, and the complete sample in Supplementary Table 8 were similar. After multiple imputations, the main results exhibited associations similar to those in previous findings. (Supplementary Tables 9 and 10). The results remained

Table 1. Baseline Characteristics by Frailty Category

Baseline Characteristics	Overall	Frailty Phenotype, *N* (%)		
		Non-frailty	Pre-frailty	Frailty
No. of participants	331 642	176 738 (53.2)	143 379 (43.2)	11 885 (3.6)
Age in years, mean (*SD*)	55.9 (8.1)	55.7 (8.1)	56.0 (8.1)	57.7 (7.7)
Sex, *n* (%)				
Male	162 241 (48.9)	88 892 (50.4)	68 445 (47.7)	4 894 (41.2)
Female	169 401 (51.1)	68 455 (49.6)	74 924 (52.3)	6 991 (58.8)
White ethnicity, *n* (%)	317 430 (95.7)	170 639 (96.7)	135 924 (94.8)	10 867 (91.4)
Townsend deprivation index, median [IQR]	-2.3 [-3.7, 0.3]	-2.4 [-3.8, -0.1]	-2.1 [-3.6, 0.5]	-0.8 [-3.0, 2.3]
University education, *n* (%)	124 258 (37.5)	70 367 (39.9)	51 035 (35.6)	2 855 (24.0)
Smoking status, *n* (%)				
Never	181 360 (54.7)	98 853 (56.0)	76 951 (53.7)	5 556 (46.7)
Former	11 6726 (35.2)	61 699 (35.0)	50 646 (35.3)	4 381 (36.9)
Current	33 556 (10.1)	15 826 (9.0)	15 782 (11.0)	1 948 (16.4)
Alcohol consumption, *n* (%)				
Never	11 366 (3.4)	4 654 (2.6)	5 754 (4.0)	958 (8.1)
Previous	10 595 (3.2)	4 220 (2.4)	5 305 (3.7)	1 070 (9.0)
Current	309 681 (93.4)	167 504 (95.0)	132 320 (92.3)	9 857 (82.9)
Alcohol intake, grams/day, median [IQR]	13.1 [1.8, 27.1]	14.9 [4.3, 28.9]	11.3 [0.4, 26.1]	3.1 [0.0, 17.7]
Diet score, *n* (%)				
0	1 652 (0.5)	609 (0.4)	866 (0.6)	177 (1.5)
1	54 579 (16.5)	27 176 (15.4)	25 070 (17.5)	2 333 (19.6)
2	155 309 (46.8)	81 844 (46.4)	67 619 (47.2)	5 846 (49.2)
3	120 102 (36.2)	66 749 (37.8)	49 824 (34.7)	3 529 (29.7)
Sleep duration, hours/day, median [IQR]	7.0 [7.0, 8.0]	7.0 [7.0, 8.0]	7.0 [6.0, 8.0]	7.0 [6.0, 8.0]
Sitting time, hours/day, median [IQR]	3.5 [2.5, 5.0]	3.0 [2.0, 4.5]	4.0 [2.5, 5.0]	3.0 [4.5, 6.0]
Biomarkers				
SBP, mean (*SD*), mmHg	137.2 (18.5)	137.5 (18.5)	136.9 (18.4)	136.6 (18.4)
DBP, mean (*SD*), mmHg	82.2 (10.1)	82.2 (10.1)	82.2 (10.2)	82.0 (10.3)
BMI, mean (*SD*), kg/m^2	27.3 (4.7)	26.4 (4.0)	28.0 (4.9)	31.0 (6.5)
eGFR, mL/min/1.73m^2, median [IQR])	97.6 [87.7, 104.2]	97.6 [87.9, 104.1]	97.7 [87.6, 104.3]	97.2 [84.7, 104.2]
LDL direct, mmol/L, mean (SD)	3.6 (0.9)	3.6 (0.8)	3.5 (0.9)	3.4 (1.0)
HDL, mmol/L, mean (*SD*)	1.4 (0.4)	1.5 (0.4)	1.4 (0.4)	1.3 (0.4)
Lipoprotein(a), nmol/L, median [IQR]	20.6 [9.4, 61.5]	20.3 [9.4, 61.0]	20.9 [9.5, 62.1]	21.3 [9.4, 63.4]
HbA1c, mmol/mol, mean (*SD*)	36.0 (6.5)	35.2 (5.3)	36.3 (7.2)	39.3 (10.6)
Comorbidities, *n* (%)				
Hypertension	84 774 (25.6)	37 692 (21.4)	41 568 (29.0)	5 514 (46.4)
Obesity	8 084 (2.4)	2 711 (1.5)	4 390 (3.1)	983 (8.3)
Type 2 diabetes	7 797 (2.4)	2 010 (1.1)	4 470 (3.1)	1 317 (11.1)
Dyslipidemia	46 706 (14.1)	20 689 (11.7)	22 788 (15.9)	3 229 (27.2)
Ischemic heart disease	15 658 (4.7)	6 116 (3.5)	7 822 (5.5)	1 720 (14.5)
Stroke	4 483 (1.4)	1 651 (0.9)	2 263 (1.6)	569 (4.8)
Atrial fibrillation	4 804 (1.4)	2 129 (1.2)	2 279 (1.6)	396 (3.3)
Cardiomyopathy	520 (0.2)	183 (0.1)	276 (0.2)	61 (0.5)
Chronic obstructive pulmonary disease	5 532 (1.7)	1 800 (1.0)	2 836 (2.0)	896 (7.5)
End-stage renal disease	355 (0.1)	105 (0.1)	191 (0.1)	59 (0.5)
Cancer	29 609 (8.9)	14 918 (8.5)	13 195 (9.2)	1 496 (12.6)
Frailty features, *n* (%)				
Weight loss	50 896 (15.3)	0 (0.0)	45 609 (44.5)	5 287 (31.8)
Exhaustion	37 307 (11.2)	0 (0.0)	29 556 (65.6)	7 751 (20.6)
Low physical activity	65 555 (19.8)	0 (0.0)	56 320 (39.3)	9 235 (77.7)
Slow gait speed	21 231 (6.4)	0 (0.0)	12 867 (9.0)	8 364 (70.4)
Low grip strength	40 538 (12.2)	0 (0.0)	32 664 (22.8)	7 874 (66.3)

Table 1. Continued

Baseline Characteristics	Overall	Frailty Phenotype, *N* (%)		
		Non-frailty	Pre-frailty	Frailty
Valvular heart diseases, *n* (%)				
Mitral regurgitation	3 684 (1.1)	1 692 (1.0)	1 760 (1.2)	232 (2.0)
Mitral stenosis	55 (0.0)	22 (1.2)	23 (1.6)	10 (8.4)
Aortic regurgitation	1 205 (0.4)	557 (0.3)	572 (0.4)	76 (0.6)
Aortic stenosis	3 166 (1.0)	1339 (0.8)	1542 (1.1)	285 (2.4)

Notes: BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; SBP = systolic blood pressure; *SD* = standard deviation.

consistent with the main analyses after excluding 1 859 individuals diagnosed with degenerative VHD or who died within a 2-year follow-up period, mitigating the potential influence of reverse causation (Supplementary Table 11). In the stratified analyses, the associations between frailty and the incidence of degenerative VHD were not significantly altered by any of the subgroup factors (all p for interaction >.05; Supplementary Tables 12–14). Furthermore, the study results remained robust when the Fine and Gray models were applied to account for competing risks (Supplementary Table 15).

Discussion

In this large-scale cohort of 331 642 middle-aged and older adults from the UK Biobank, we discovered a significant association between physical frailty and subsequent degenerative VHD risk, even after accounting for potential confounding factors. Individuals classified as pre-frailty or frailty had a 19%–50% higher risk of MR, a 19%–58% higher risk of AR, and a 19%–74% higher risk of AS than those without frailty. Each 1-point increase in the frailty phenotype score corresponded to a 14%, 16%, and 18% increase in the risks of MR, AR, and AS events, respectively. Further investigations revealed that specific frailty components, including exhaustion, slow gait speed, and low grip strength, were adversely associated with VHD incidence.

This study is the first large-scale, prospective, population-based cohort investigation to explore the relationship between frailty and incident degenerative VHD. Existing research consistently indicates a high prevalence of frailty among patients with degenerative VHD, correlating with an increased risk of adverse prognosis and mortality (19–22). In a prospective study involving 606 patients with severe symptomatic AS, nearly half (49.3%) exhibited frailty (23). Another prospective cohort study of older adults, with a median age of 82 years, who underwent aortic valve replacement, found that frailty significantly increased the risk of mortality and worsening disability, with odds ratios of 3.27 and 2.13, respectively (14). However, limited longitudinal prospective evidence exists regarding the association between physical frailty and the risk of degenerative VHD. Our findings found that participants classified as pre-frailty or frailty had a moderate risk of degenerative VHD, even after accounting for sociodemographic factors, lifestyle variables, and multiple comorbidities.

Our study found that 43.2% of middle-aged and older individuals were in the pre-frailty stage, highlighting the importance of recognizing this category in public health. The prevalence of pre-frailty in middle-aged and older populations in cohorts from China and the United Kingdom is approximately 40% (11,24), which is consistent with our findings. Early intervention in pre-frail individuals could potentially reverse the progression of biological aging. A recent systematic review and meta-analysis of 16 studies revealed that 23.1% of pre-frail older adults can transition to a healthy state, whereas only 3% of frail older adults can achieve this (25). Given the high prevalence and potential for improvement of pre-frailty among middle-aged and older individuals, early screening and intervention for those in the pre-frailty stage may have profound public health implications for preventing VHD.

Among the 5 components, slow gait speed demonstrated the most significant association with VHD risk, with an approximate HR of 1.5. Multiple studies have linked slow gait speed to an increased risk of cardiovascular disease and adverse outcomes (26–28), particularly cardiovascular mortality, among older adults (29). Additionally, slow gait speed reflects insufficient energy and decreased function in various organ systems, including the heart, blood vessels, nervous system, and musculoskeletal systems (30). Therefore, identifying older individuals with slow gait speed could be crucial for proactively preventing or delaying the onset of VHD. Encouraging appropriate physical activity tailored to their capabilities may significantly reduce the risk of VHD in this population.

The underlying mechanism by which frailty contributes to the incidence of degenerative VHD involves a complex interplay of factors. Frailty may trigger inflammation (31,32), leading to mitochondria dysfunction and elevated oxidative stress (33). This molecular interplay can induce pathological changes in heart valves over time. Among older adults, frailty often coexists with chronic inflammation within the immune system (31,34,35), adversely impacting heart valve function and promoting valve calcification. The combined effects of inflammation and calcification may result in structural changes that compromise the overall valve integrity. Frailty, characterized by reduced physical activity and an imbalanced diet (36), poses additional risks. This lifestyle pattern is associated with factors implicated in degenerative VHD, such as metabolic dysregulation (37), heightened platelet activity (38), and arteriosclerosis (39). Population-based studies have also shown that frail older adults are at increased risk of various cardiovascular risk factors, including obesity, high-density lipoprotein cholesterol, hypertension, and decreased lung function (40). The cumulative effects of these factors

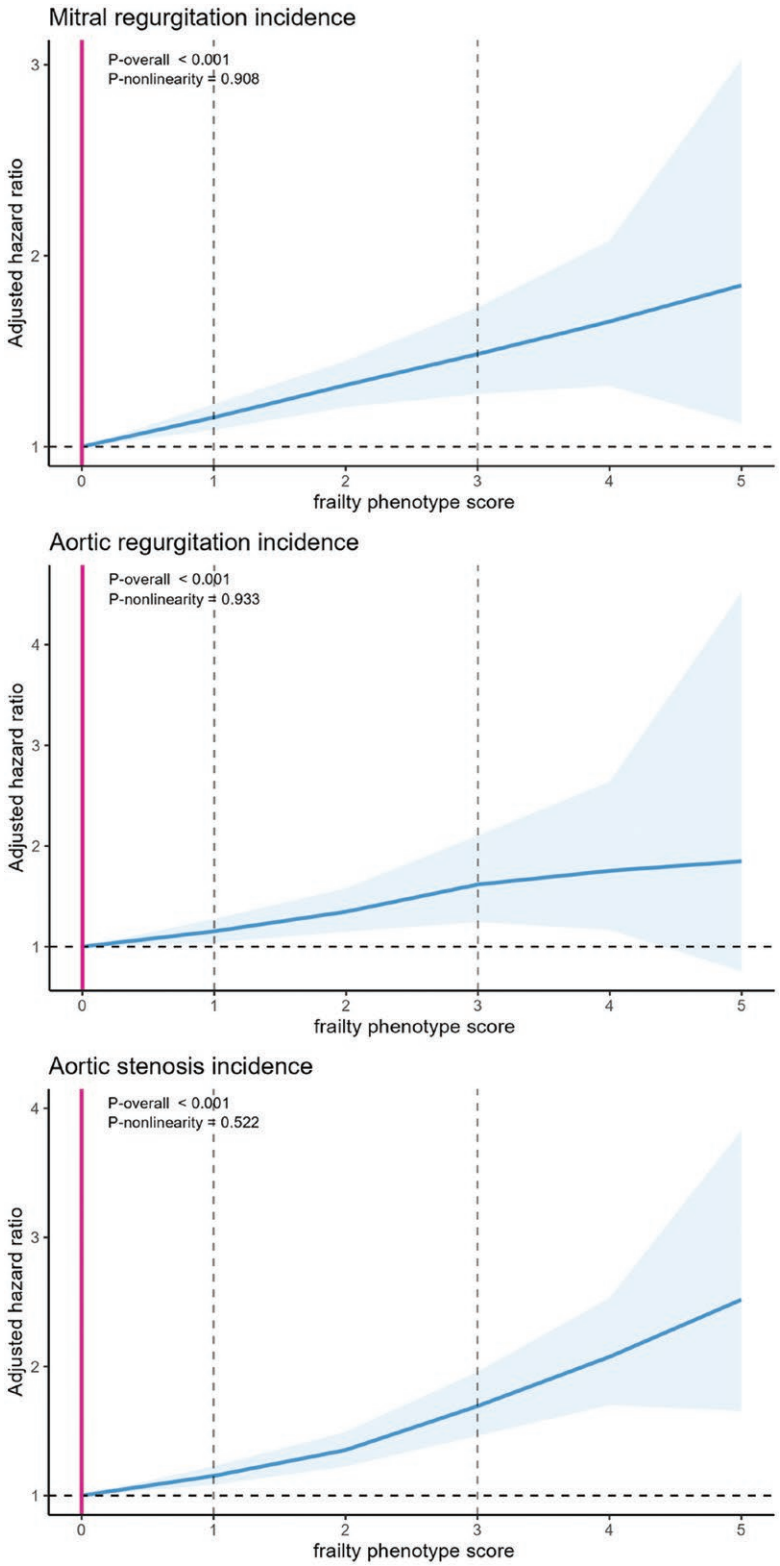

Figure 2. Dose–response curves for frailty phenotype scores and the incidence of valvular heart disease, including mitral regurgitation, aortic regurgitation, and aortic stenosis. Data are presented as adjusted hazard ratios with the 95% confidence interval shown as shading. The restricted cubic spline models were adjusted for age, sex, ethnicity, educational attainment, Townsend deprivation index, smoking status, alcohol consumption, diet score, sleep score, systolic blood pressure, body mass index, and clinical comorbidities, including type 2 diabetes, dyslipidemia, ischemic heart disease, stroke, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, end-stage renal disease, and cancer.

can increase the vulnerability of the cardiovascular system to degenerative VHD. However, further research into the underlying mechanisms of frailty categories and VHD is essential for a comprehensive understanding of the increased VHD risk among pre-frail and frail individuals, potentially guiding the development of targeted interventions.

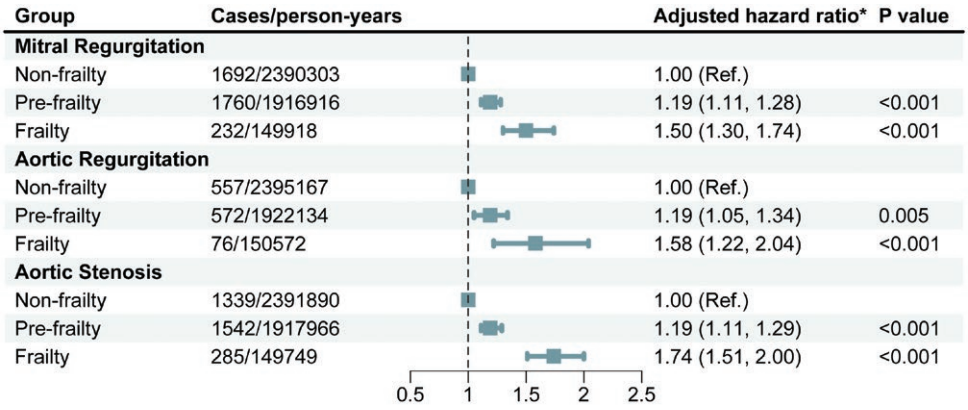

Figure 3. Associations between frailty phenotype and risk of valvular heart disease. Cox proportional hazards models were adjusted for age, sex, ethnicity, educational attainment, Townsend deprivation index, smoking status, alcohol consumption, diet score, sleep score, systolic blood pressure, body mass index, and clinical comorbidities, including type 2 diabetes, dyslipidemia, ischemic heart disease, stroke, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, end-stage renal disease, and cancer.

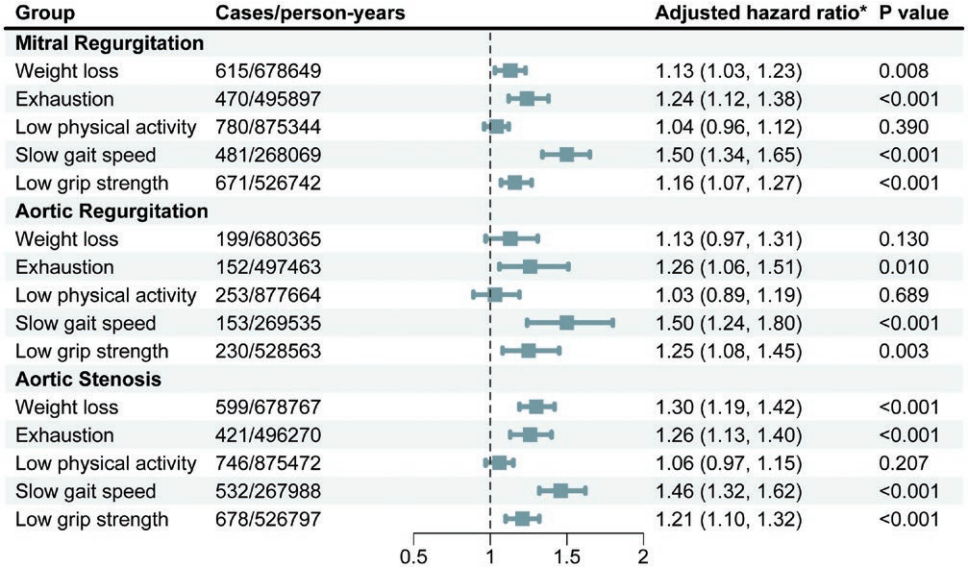

Figure 4. Associations between frailty phenotype components and risk of valvular heart disease. Cox proportional hazards models were adjusted for age, sex, ethnicity, educational attainment, Townsend deprivation index, smoking status, alcohol consumption, diet score, sleep score, systolic blood pressure, body mass index, and clinical comorbidities, including type 2 diabetes, dyslipidemia, ischemic heart disease, stroke, cardiomyopathy, atrial fibrillation, chronic obstructive pulmonary disease, end-stage renal disease, and cancer.

Frailty status is a dynamic process, with individuals transitioning between frailty, pre-frailty, and non-frailty states over time, indicating its modifiability. Our study found that pre-frailty and frailty were prevalent among middle-aged and older individuals, posing an elevated risk of degenerative VHD. Given the ease of assessing frailty in clinical practice and the lack of effective prevention strategies for degenerative VHD, evaluating physical pre-frailty and frailty is of crucial clinical significance. For those with frailty, especially pre-frailty, implementing suitable physical activity plans is essential for their overall health. Recommending tailored and healthy diet regimens based on the patient's condition can help transition from frailty to pre-frailty or even non-frailty states, potentially preventing or delaying the onset of VHD.

Furthermore, incorporating the assessment and close monitoring of the frailty phenotype in older adults into primary prevention strategies for degenerative VHD is essential. Regular multimodal imaging assessments, such as echocardiography and computed tomography, should be conducted in older adults with pre-frailty and frailty to enable early detection of valvular degenerative changes and facilitate timely intervention. For individuals with degenerative VHD, monitoring and addressing physical frailty can decelerate progression and improve prognosis. In summary, significant efforts are required to reduce adverse VHD events associated with frailty, improve health-related quality of life, and lower healthcare costs for both patients and society.

Limitations

First, most frailty features, except for grip strength, relied on self-reported data, which could be susceptible to reporting biases. Second, frailty was assessed only once at baseline in the UK Biobank, but frailty status is dynamic and often worsens over time (41). Therefore, our results may have underestimated the risk associated with frailty. Moreover, despite our comprehensive consideration of numerous potential

confounding factors and the execution of various sensitivity analyses, it is challenging to eliminate residual confounding factors and potential bias. Finally, most participants in the UK Biobank were Caucasian, implying that our findings may not be readily applicable to other demographic groups. Further research is required to investigate these associations in populations of different ethnicities and races.

Conclusion

In this large-scale prospective cohort study, both pre-frailty and frailty were significantly associated with various types of degenerative VHD, emphasizing the importance of frailty assessment in the routine care of middle-aged and older adults. Future guidelines should incorporate these findings into high-risk population assessment and VHD disease management, which could reduce the VHD-related burden and enhance the quality of life among older adults.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

All authors declare no conflict of interest. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

Data from the UK Biobank can be available by submitting an application at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. The code used for the analysis will be accessible to other researchers upon reasonable request. The studies reported in the manuscript were not preregistered.

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Ethics Statement and Patient Consent Statement

This research was conducted using the UK Biobank Resource under application number 91035. The UK Biobank study received approval from the Northwest Multi-center Research Ethics Committee (REC reference 11/NW/0382), and all participants provided written informed consent. Participants were not involved in the design, conduct, reporting, or dissemination plans of the research.

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