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ORIGINAL RESEARCH

Physical Frailty, Genetic Predisposition, and Incident Heart Failure

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ABSTRACT

BACKGROUND There is growing interest in the intersection of frailty and heart failure (HF); however, large-sample longitudinal studies in the general population are lacking.

OBJECTIVES The goal of this study was to examine the longitudinal relationship between frailty and incident HF, and whether age and genetic predisposition could modify this association.

METHODS This prospective cohort study included 340,541 participants (45.7% male; mean age 55.9 ± 8.1 years) free of HF at baseline in the UK Biobank. Frailty was assessed by using the Fried frailty phenotype and included weight loss, exhaustion, low physical activity, slow gait speed, and low grip strength. The weighted polygenetic risk score was calculated. Cox models were used to estimate these associations and the interaction between the 2 factors.

RESULTS During a median 14.1 years of follow-up, 7,590 patients with HF were documented. Compared with nonfrail participants, both prefrail and frail participants had a positive association with the risk of incident HF (prefrail HR: 1.40 [95% CI: 1.17-1.67]; frail HR: 2.07 [95% CI: 1.67-2.57]). Exhaustion (HR: 1.21; 95% CI: 1.03-1.43), slow gait speed (HR: 1.62; 95% CI: 1.39-1.90), and low grip strength (HR: 1.31; 95% CI: 1.14-1.51) were associated with a greater risk of incident HF. Furthermore, genetic susceptibility did not significantly modify the associations ($P_{interaction} = 0.094$), and the association was significantly strengthened in younger participants ($P_{interaction} = 0.008$).

CONCLUSIONS Frailty status was associated with a higher risk of incident HF independent of genetic risk. A younger population may be more susceptible to HF when exposed to frailty. Whether the modification of frailty status represents another avenue for preventing HF warrants further investigation. (JACC: Asia 2024;4:547–556) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Frailty is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors.[1] Today, the prevalence and severity of frailty are increasing, placing a heavy burden on health and aged care systems.[2] The implications of frailty are substantial not only for public health but also for individuals, who are at a greater risk of premature death, various negative health outcomes, and poor quality of life.[3] With aging and increasing patient complexity, frailty has been recognized as a pivotal element in the evaluation of patients with cardiovascular disease.[4]

With a tendency to occur in younger people,[5] heart failure (HF) is a complex clinical syndrome resulting

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

FI = frailty index

HF = heart failure

ICD-10 = International Classification of Diseases-10th Revision

PRS = polygenic genetic score

TDI = Townsend Deprivation Index

UKB = UK biobank

from structural or functional impairment of ventricular filling or ejection of blood.[6] It remains a leading cause of morbidity and mortality globally[7] with growing preventive significance. HF and frailty often coexist.[8] Frailty mainly affects the loss of resilience of muscle, endocrine, cardiovascular, and other systems,[9,10] while abnormal myocardium and neurohumoral regulatory mechanisms may cause HF.[11] Previous studies have shown that prefrail or frail individuals have a significant association with high cardiovascular disease morbidity and mortality,[12,13] and adherence to ideal cardiovascular health is associated with decreased cardiovascular disease risk in frail patients.[12] Cross-sectional studies have also indicated a significant correlation between frailty and HF risk.[14] In addition, frail patients with HF have a greater risk of hospitalization and all-cause mortality than nonfrail patients;[15,16] however, there is a paucity of longitudinal data. Only 2 longitudinal studies have revealed the association between baseline frailty and incident HF, and these studies have limitations such as small sample sizes and short follow-up times.[17,18] In addition, both studies included participants older than 70 years exclusively, which may have little significance for the prevention and management of HF in younger people.[19] Longitudinal studies with large sample sizes in middle-aged and older populations are needed to provide updated and more comprehensive evidence.

The onset of HF may be related to a variety of genetic and environmental factors, but to our knowledge, no study has evaluated the relationship between genetic and physical frailty and the risk of incident HF. In this work, we calculated the polygenic genetic score (PRS) to fill the knowledge gaps mentioned earlier. With respect to this prospective cohort of 340,541 participants from the UK Biobank (UKB), we aimed to measure the associations between frailty status and incident HF and between frailty status and its components. The modification effect of age and genetic predisposition defined by the PRS on these associations was further examined.

MATERIALS AND METHODS

STUDY DESIGN AND SAMPLE. The UKB is a large-scale biomedical database and research resource that contains information on >500,000 participants across England, Scotland, and Wales. A wide variety of health-related information was collected from participants via touch-screen questionnaires, physical measurements, and biological samples. The baseline data were collected between 2006 and 2010, and the censoring date was March 30, 2023. Before participating in the survey, all participants signed an informed consent form. The specific study designs have been described previously.[20] The UKB has received ethical approval from the NHS England, the North West National Research Ethics Service, the National Health and Social Care Information Governance Board for England and Wales, and the Scottish Community Health Index Advisory Group.

A total of 502,417 participants 37 to 73 years of age were included in the UKB cohort. We excluded 2,742 participants who were diagnosed with HF before baseline, 116,532 participants who had missing data on frailty phenotypes, and 42,602 participants who had missing data on any covariates. The main analysis included 340,541 participants. Furthermore, to increase the accuracy of the studies involving genes, also excluded were participants who had no genetic data (n = 27,074) or who had any kinship with other individuals (n = 94,531). Thus, 218,936 participants were included in the genomic analysis. A flowchart is presented in Supplemental Figure 1.

EXPOSURE: PHYSICAL FRAILTY AND PRS. Based on the recommendations of previous cohort studies on various frailty scores,[18] we chose the Fried approach,[21] in which frailty was assessed from 5 aspects, namely, low physical activity, low grip strength, slow walking speed, exhaustion, and weight loss. A detailed definition of frailty is provided in Supplemental Table 1. Participants with ≥3 phenotypes of standards were defined as frail, those with 1 or 2 phenotypes of standards were defined as prefrail, and those who did not meet the criteria were classified as nonfrail.

The PRS was calculated based on the genome-wide association studies conducted with 12 single nucleotide variants found to be related to HF.[22] Detailed information on these 12 single nucleotide variants is shown in Supplemental Table 2. The weighted calculation method was used to obtain the HF-PRS score, as suggested in a previous study.[23] In this way, a higher HF-PRS indicates a greater genetic predisposition to HF. For further analysis, participants were divided into 3 groups based on the HF-PRS score: low (the lowest PRS quartile, n = 54,090; scoring 1.95-9.78), intermediate (the middle 2 PRS quartiles, n = 109,062; scoring 9.79-12.69), and high (the highest PRS quartile, n = 55,784; scoring 12.70-19.70) for further genetic-related analysis. The PRS results were approximately consistent with a normal distribution (Supplemental Figure 2). The risk relationship between the PRS was calculated as a

continuous variable or categorical variable and the incidence of HF.

OUTCOME: INCIDENT HF. The outcome of incident HF was obtained by the UKB using the International Classification of Diseases-10th Revision (ICD-10) mapped to diagnosis code I50 and whether this code occurred in other source(s) with the same or a later event date. The detailed ICD-10 codes for the outcomes and other relevant adjusted covariates are presented in Supplemental Table 3. The cumulative incidence of HF in different age subgroups and follow-up population survival curves are shown in Supplemental Figure 3.

COVARIATES. A self-completed questionnaire was used to collect information on relative covariates, including age, sex, ethnicity (White/others), smoking status (never, previous, and current), and alcohol intake frequency (≥3 times per week and ≤2 times per week). Other confounders were the Townsend Deprivation Index (TDI), which reflects socioeconomic status (continuous); BMI (weight in kilograms divided by square of height in meters); systolic blood pressure; and related diseases, including diabetes (yes/no), cancer (yes/no), and use of antihypertensive medicine (yes/no). The DASH (Dietary Approaches to Stop Hypertension) diet with 8 components (high intake of fruits, vegetables, nuts and legumes, whole grains, low-fat dairy, and low intake of sodium, red and processed meats, and sweetened beverages) and the Mediterranean Eating Pattern for Americans[24] were used as standards to calculate a diet score. The total score was divided into 3 categories: 0 to 50 (as reference group), 50 to 80, and 80 to 100.

STATISTICAL ANALYSES. Baseline characteristics were calculated as the means for continuous variables or as percentages for categorical variables according to group.

The multivariable Cox proportional hazards regression model was used to estimate the HRs and 95% CIs for the associations between physical frailty or PRS and the risk of incident HF; participants with nonfrailty (according to the Fried approach) or low PRS were treated as the reference group. Participants were further divided into 4 categories based on age (37-45, 46-55, 56-65, and 66-73 years, as used similarly in previous articles)[25] to calculate the risk of frailty for incident HF. We also conducted a joint analysis of the association between frailty and genetic risk of HF with 3 × 3 groups, treating participants with nonfrailty and a low PRS as the reference group. Model 1 was adjusted for age, sex, ethnicity (White/others), and the TDI (continuous); Model 2 was further adjusted for diet (3 categories), smoking status (never, previous, and current), alcohol intake frequency (≥3 times per week and ≤2 times per week), BMI (continuous), and systolic blood pressure; and Model 3 was further adjusted for diabetes (yes/no), cancer (yes/no), and antihypertensive medicine (yes/no). All reported HRs were based on models without the interaction. We also used restricted cubic spline models to examine the potential association of the Fried frailty score and incident HF.

Stratified analyses were performed according to sex, BMI (<25 or ≥25 kg/m^2), race (White or non-White), and TDI (at or above the median for high deprivation or below the median as low deprivation). Several sensitivity analyses were also performed. First, we explored the relationship between frailty and HF after multiple imputation of missing covariate data, and missing data for participants had at least 4 components of the Fried approach to frailty according to age subgroups. Second, to avoid reverse causation, participants who developed HF in the first 2 years were excluded. Third, to verify the reliability of the different methods of assessing physical frailty, we assessed the Rockwood frailty index (FI) of the participants that was used in a previous article[26] (as detailed in Supplemental Tables 4 and 5) and examined the association between FI and incident HF. Furthermore, the associations between frailty and different causes of death were compared by using a competing risk analysis.

All statistical analyses were performed by using IBM SPSS Statistics version 26 (IBM SPSS Statistics, IBM Corporation) and R version 4.2.2 (R Foundation for Statistical Computing). All tests of significance were two sided, and a P value <0.05 (2-sided) was used to indicate statistical significance.

RESULTS

A total of 340,541 participants (45.7% male; mean age 55.9 ± 8.1 years [56.1 ± 8.2 years for men; 55.7 ± 8.0 years for women]) were included in the study; 173,188 (50.9%) were nonfrail, 154,412 (45.3%) were prefrail, and 12,941 (3.8%) were frail (**Table 1**). Compared with participants who were nonfrail, those who were prefrail or frail were more likely to be women, non-White, or former smokers and have a lower socioeconomic status, less frequent alcohol intake, and a higher BMI. In addition, a higher incidence of diabetes, cancer, and the use of antihypertensive drugs was observed in participants who were prefrail and frail. The baseline table was further classified according to whether the genetic data were complete,

TABLE 1 Baseline Characteristics of Participants in This Study by Frailty Category

	Frailty Phenotype			
	Nonfrail (n = 173,188, 50.9%)	Prefrail (n = 154,412, 45.3%)	Frail (n = 12,941, 3.8%)	*P* Value
Age, y	55.6 ± 8.1	56.1 ± 8.1	57.0 ± 7.7	<0.001
Male	83,552 (48.2)	67,690 (43.8)	4,504 (34.8)	<0.001
Diet				
Unhealthy	35,492 (20.5)	32,650 (21.1)	2,795 (21.6)	<0.001
Healthy	76,124 (44.0)	69,368 (44.9)	6,153 (47.5)	
Ideal	61,572 (35.6)	52,394 (33.9)	3,993 (30.9)	
Systolic blood pressure, mm Hg	137.5 ± 18.6	136.9 ± 18.4	136.5 ± 18.1	<0.001
Ethnicity, White	167,152 (96.5)	145,909 (94.5)	11,713 (90.5)	<0.001
Body mass index, kg/m^2	26.3 ± 4.0	27.8 ± 4.8	30.7 ± 6.5	<0.001
Body mass index group				
<25 kg/m^2	70,803 (40.9)	45,791 (29.7)	2,366 (18.3)	<0.001
≥25 kg/m^2	102,385 (59.1)	108,621 (70.3)	10,575 (81.7)	
Smoking status				
Never	98,841 (57.1)	85,676 (55.5)	6,545 (50.6)	<0.001
Previous	59,133 (34.1)	52,901 (34.3)	4,371 (33.8)	
Current	15,214 (8.8)	15,835 (10.3)	2,025 (15.6)	
Alcohol status				
≥3 times a week	133,364 (77.0)	106,224 (68.8)	6,441 (49.8)	<0.001
<2 times a week	39,824 (23.0)	48,188 (31.2)	6,500 (50.2)	
Townsend Deprivation Index score	-1.70 ± 2.9	-1.38 ± 3.0	-0.34 ± 3.4	<0.001
Baseline diabetes	4,066 (2.3)	8,274 (5.4)	1,854 (14.3)	<0.001
Baseline cancer	14,574 (8.4)	14,184 (9.2)	1,642 (12.7)	<0.001
Use of antihypertensive drugs	23,883 (13.8)	30,377 (19.7)	4,232 (32.7)	<0.001

Values are mean ± SD or n (%).

and the main characteristics were comparable between subsamples with and without genetic samples (Supplemental Table 6).

During a median follow-up of 14.1 years (4,780,504 person-years), 7,590 incident HF events were recorded (**Table 2**). After multivariable adjustments, participants with prefrailty and frailty had a significantly greater risk of incident HF than nonfrail participants. According to Model 3, after adjusting for demographic variables, lifestyle, and cardiometabolic factors, prefrail and frail participants had 40% and 107% greater risks of incident HF, respectively, than nonfrail participants (HR: 1.40 [95% CI: 1.17-1.67] and HR: 2.07 [95% CI: 1.67-2.57], respectively). The absolute rate differences per 1,000 person-years were 1.58 (95% CI: 1.51-1.66) for prefrailty and 3.75 (95% CI: 3.46-4.06) for frailty.

Table 3 shows the associations of the 5 components of frailty with the risk of incident HF. According to the multivariable adjusted Model 3, exhaustion (HR: 1.21; 95% CI: 1.03-1.43), slow gait speed (HR: 1.62; 95% CI: 1.39-1.90), and low grip strength (HR: 1.31; 95% CI: 1.14-1.51) were significantly associated with incident HF. Weight loss and low physical activity both showed positive associations with incident HF, although the results were not significant. Furthermore, a positive association between the cumulative number of frailty components and the risk of incident HF was found (*P* for nonlinearity = 0.321) (Supplemental Figure 4, Supplemental Table 7). With the increase in frailty components, the risk of incident HF gradually increases.

When age was divided into 4 categories, prefrailty and frailty were found to significantly increase the risk of incident HF in all age groups (**Figure 1**). Interestingly, the risk was greater in the younger group than in the older group for frailty and incident HF (HR: 2.46 [95% CI: 1.42-4.26] vs HR: 2.65 [95% CI: 2.13-3.30] vs HR: 2.03 [95% CI: 1.80-2.29] vs HR: 1.85 [95% CI: 1.59-2.15], from young to old, respectively). The results of the nonlinear analysis were similar (Supplemental Figure 4).

The PRSs of the participants were normally distributed (Supplemental Figure 2), and there was no significant relationship between the PRS and frailty (HR: 1.00; 95% CI: 0.99-1.02; $P = 0.713$). The group with high genetic risk had a 29% (95% CI: 19%-40%) greater risk of incident HF (Supplemental Table 8).

TABLE 2 Association Between Physical Frailty and Incident Heart Failure

	Nonfrail	Prefrail	Frail
Cases/person-years	2,839 of 2,441,275	3,974 of 2,161,104	777 of 178,125
Incident cases per 100,000 person-years	116.3	183.9	436.2
Model 1 HR (95% CI)	1.00 (Reference)	1.55 (1.48-1.62)	3.41 (3.15-3.69)
Model 2 HR (95% CI)	1.00 (Reference)	1.35 (1.29-1.42)	2.28 (2.10-2.49)
Model 3 HR (95% CI)	1.00 (Reference)	1.40 (1.17-1.67)	2.07 (1.67-2.57)
Absolute rate difference per 100,000 person-years (95% CI)	0 (Reference)	1.58 (1.51-1.66)	3.75 (3.46-4.06)

Model 1 was adjusted for age, sex, the Townsend Deprivation Index, and race. Model 2 was adjusted for Model 1 plus lifestyle factors, including smoking status, alcohol intake frequency, diet score, body mass index, and systolic blood pressure. Model 3 was adjusted for Model 2 plus related diseases, including baseline diabetes incidence, cancer incidence, and use of antihypertensive medicine.

Among the different genetic risk groups, frailty was significantly associated with a higher risk of HF. With nonfrailty as a reference, frailty status was associated with an increased risk of incident HF by 57% (95% CI: 22%-101%), 73% (95% CI: 48%-103%), and 31% (95% CI: 3%-67%) in the low, intermediate, and high PRS groups, respectively, although the influence of this interaction was not significant ($P_{\text{interaction}} = 0.094$) (**Table 4**). Frailty was significantly associated with the incidence of HF after correction of PRS (Supplemental Table 9).

We further explored the joint association between the frailty phenotype and the PRS on incident HF (**Figure 2**). As expected, weighted PRSs were positively associated with incident HF risk, and participants with a high PRS had a broadly greater risk than those with a low PRS (HR: 1.33 [95% CI: 1.21-1.45] for nonfrail; HR: 1.19 [95% CI: 1.01-1.38] for prefrail; and HR: 1.72 [95% CI: 1.36-2.18] for frail). In addition, frail participants with an intermediate PRS had the highest risk of incident HF compared with nonfrail participants with a low PRS (HR: 2.06; 95% CI: 1.75-2.42).

We further conducted stratified analyses according to sex, age, BMI, and race to evaluate whether there was a different association between the frailty phenotype and incident HF (Supplemental Table 10). The association between frailty and incident HF risk was strengthened in women (HR: 2.20 [95% CI: 1.94-2.50] vs HR: 1.97 [95% CI: 1.75-2.22]), participants with a BMI <25 kg/m^2 (HR: 2.32 [95% CI: 1.86-2.88] vs HR: 1.96 [95% CI: 1.79-2.16]), and those with a TDI below the median (HR: 2.10 [95% CI: 1.82-2.42] vs HR: 2.04 [95% CI: 1.83-2.28]).

According to the sensitivity analyses, the results were not significantly altered after imputation of the missing covariates (Supplemental Table 11), multiple imputation with participants having at least 4 components of the Fried approach of frailty (Supplemental Table 12), or exclusion of participants developing HF within 2 years (Supplemental Table 13). The HR between frailty and incident HF calculated using the FI was even greater than that calculated using the Fried frailty phenotype (Model 3, HR: 1.42 [95% CI: 1.34-1.50] and HR: 2.33 [95% CI: 2.16-2.52], respectively) (Supplemental Table 14). According to our competing risk analysis, no significant competing risk was detected for the effect of death on the association between frailty and the occurrence of HF (Supplemental Table 15). After we adjusted for additional diseases, the results remained similar (Supplemental Table 16).

DISCUSSION

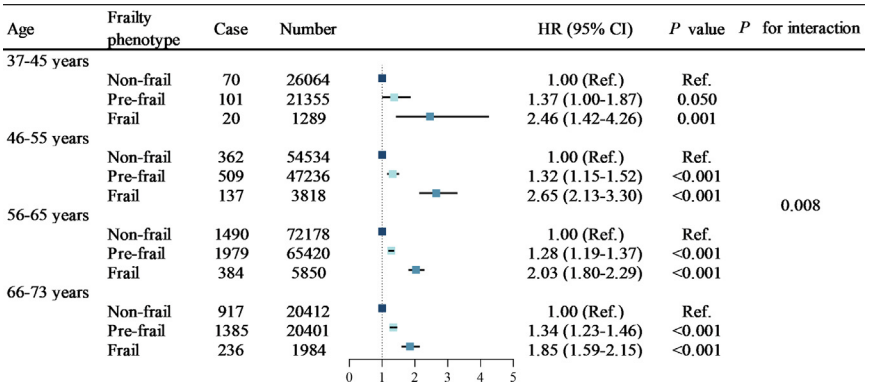
With respect to this large-scale cohort with a 14.1-year follow-up time, we found that frailty and its

TABLE 3 Association Between Physical Frailty Components and Incident Heart Failure

	Model Without Any Adjustment	*P* Value	Model 1	*P* Value	Model 2	*P* Value	Model 3	*P* Value
Weight loss	1.23 (1.16-1.31)	<0.001	1.05 (0.91-1.22)	0.508	1.08 (0.94-1.26)	0.283	1.13 (0.97-1.30)	0.115
Exhaustion	1.41 (1.32-1.50)	<0.001	1.56 (1.33-1.84)	<0.001	1.36 (1.16-1.60)	<0.001	1.21 (1.03-1.43)	0.022
Low physical activity	1.21 (1.13-1.29)	<0.001	1.43 (1.24-1.64)	<0.001	1.19 (1.04-1.37)	0.014	1.06 (0.92-1.23)	0.426
Slow gait speed	3.69 (3.50-3.91)	<0.001	2.46 (2.14-2.84)	<0.001	1.77 (1.52-2.06)	<0.001	1.62 (1.39-1.90)	<0.001
Low grip strength	2.13 (2.03-2.24)	<0.001	1.58 (1.38-1.81)	<0.001	1.41 (1.23-1.62)	<0.001	1.31 (1.14-1.51)	<0.001

Model 1 was adjusted for age, sex, the Townsend Deprivation Index, and race. Model 2 was adjusted for Model 1 plus lifestyle factors, including diet score, smoking status, alcohol intake frequency, body mass index, systolic blood pressure, and related diseases (baseline diabetes, cancer, and the use of antihypertensive medicine). Model 3 was adjusted for Model 2 plus 5 frailty components (mutual adjustment).

FIGURE 1 Association Between Frailty and Incident HF According to Age Subgroups



A multivariable Cox proportional hazards regression model was used to estimate the HRs and 95% CIs for the associations between physical frailty and the risk of incident heart failure (HF) according to age subgroups, and corresponding forest maps were drawn. The multivariable model was adjusted for demographic variables (including age, sex, and ethnicity), the Townsend Deprivation Index, lifestyle factors (smoking status, alcohol intake frequency, and healthy diet score), body mass index, systolic blood pressure, baseline cancer incidence, diabetes incidence, and use of antihypertensive medicine at baseline.

components, except for weight loss, were independently associated with an increased risk of incident HF. Frailty was significantly associated with incident HF in all 4 age groups, with the risk being greater in the younger groups. The positive association between frailty and incident HF held true regardless of genetic risk (**Central Illustration**). In addition, the association was strengthened for women, non-White individuals, and individuals with a BMI <25 kg/m^2.

To our knowledge, this is the first large sample-size longitudinal study covering a wide range of age groups from 37 to 73 years, to explore the association between frailty and incident HF, and to further explore the genetic interaction involved in this association. Most of the previous studies were cross-sectional, and only limited longitudinal studies have indicated the association between baseline frailty and incident HF in very old individuals.[14] The Health ABC (Health Aging and Body Composition Study) cohort of 2,825 participants 70 to 79 years of age reported that individuals with moderate and severe frailty classified by using the Gill index were at increased risk for HF.[17] In addition, BRHS (British Regional Heart Study), which included 1,722 men aged 72 to 91 years, reported that frailty, as assessed by using the Fried phenotype and the Gill index, was not significantly associated with HF risk.[18] The conclusions remain inconsistent, which may be due to differences in frailty assessment criteria and study designs, such as limited samples or special populations.

To clarify the association between frailty and the occurrence of HF in different age groups, we further divided the participants into 4 categories and found that the risk of incident HF in the younger groups was even greater than that in the older group. Taken together, these findings suggest that not only elderly people but also middle-aged people should pay more attention to frailty because once frailty occurs, it is more likely to lead to the outcome of HF among middle-aged people. In view of decreasing trends in age associated with frailty and HF,[2,5] our findings sound a warning for middle-aged and older people to work together to increase awareness and prevention of physical frailty, which may improve the global health governance system.

Further analysis of frailty components revealed that the 5 frailty components may increase the risk of incident HF to varying degrees; in particular, slow

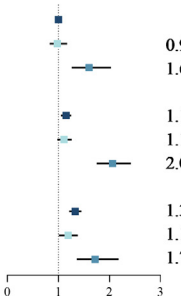
TABLE 4 Risk of Incident Heart Failure According to Frailty Status Within the Polygenic Risk Category

	PRS (HR [95% CI])			
	Low	Intermediate	High	$P_{interaction}$ Value
Nonfrail	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.094
Prefrail	0.97 (0.82-1.15)	0.96 (0.86-1.08)	0.89 (0.77-1.04)	
Frail	1.57 (1.22-2.01)	1.73 (1.48-2.03)	1.31 (1.03-1.67)	

The multivariable model was adjusted for demographic variables, including age, sex, ethnicity, the Townsend Deprivation Index, lifestyle factors (smoking status, alcohol intake frequency, and healthy diet score), body mass index, systolic blood pressure, baseline cancer incidence, diabetes incidence, and use of antihypertensive medicine at baseline.

FIGURE 2 **Risk of Incident Heart Failure According to Genetic Risk**

Genetic risk	Frailty phenotype	Case	Number	HR(95% CI)	*P* value	*P* for interaction
Low						
	Non-frail	785	43639	1.00 (Ref.)	Ref.	
	Pre-frail	159	8886	0.98 (0.83-1.17)	0.838	
	Frail	75	1565	1.60 (1.26-2.03)	<0.001	
Intermediate						
	Non-frail	1831	88056	1.15 (1.05-1.25)	0.001	0.094
	Pre-frail	366	17980	1.11 (0.98-1.26)	0.104	
	Frail	185	3026	2.06 (1.75-2.42)	<0.001	
High						
	Non-frail	1073	44947	1.33 (1.21-1.45)	<0.001	
	Pre-frail	206	9307	1.19 (1.01-1.38)	0.035	
	Frail	78	1530	1.72 (1.36-2.18)	<0.001	



The multivariable Cox proportional hazards regression model was used to estimate the HRs and 95% CIs for the associations between physical frailty and the risk of incident heart failure according to genetic risk, and corresponding forest maps were drawn. The multivariable model was adjusted for demographic variables (including age, sex, and ethnicity), the Townsend Deprivation Index, lifestyle factors (smoking status, alcohol intake frequency, and healthy diet score), body mass index, systolic blood pressure, baseline cancer incidence, diabetes incidence, and use of antihypertensive medicine at baseline.

walking speed, exhaustion, and low handgrip strength were independently and significantly associated with incident HF. It has been suggested that frailty leads to a catabolic environment in which muscle breakdown exceeds muscle production, leading to a gradual decline in muscle mass and strength;[4] moreover, we speculate that such structural changes in muscle may occur in the myocardium. Whereas a previous observational study suggested that muscle atrophy resulting in decreased exercise capacity, and muscle strength is one of the comorbidities of HF,[27] our study clarified that muscle loss represented by decreased grip strength may be significant before HF onset. The conclusion that a slow walking speed increases the risk of HF is similar to that from a previous cohort study comparing different frailty scores.[18] We hypothesized that the loss of muscle mass is replaced by fat, which may be the reason for the lack of a significant correlation between weight loss and HF. Thus, the evidence from our separate analyses of frailty components, particularly with respect to the maintenance of walking speed and handgrip strength, provides new insights into the prevention of HF.

According to the results of the joint and stratified analyses of genetic susceptibility and frailty on incident HF, we observed that the frailty-related high HF risk was strengthened by the genetic risk, but the test result for an interaction between physical frailty and genetic susceptibility was not significant. The variance explained <10% of the variance in HF risk, which may partially explain the negative interaction.[22] Interestingly, frail participants with intermediate HF-PRS had the highest risk of HF, which may be due to differences in the distribution of PRSs according to the frailty classification. Available evidence suggests that frailty may contribute to HF by affecting the function and structure of cardiomyocytes through chronic inflammatory mechanisms.[4] Moreover, genetic loci for HF identified in genome-wide association studies were associated with left ventricular structure and function. In addition, the loci linked to declining left ventricular systolic function or atrial fibrillation were associated with cardiac development, protein homeostasis, and cellular senescence.[22] Hence, we speculate that frailty and genetic factors potentially have different biological mechanisms in the development of HF and can interact to attenuate new-onset HF risk. However, further research is warranted to prove these speculations.

According to our subgroup comparisons, sex and physical frailty had significant effects on the incidence of HF; this may be due to women's tendency to experience greater levels of comorbidity and disability than men.[28] These risk factors have also been mentioned in previous studies.[29] Together with the current results, existing evidence from other studies highlights the importance of frailty-related fitness assessments for building an accurate screening and predictive metric models for HF within different populations.[30,31]

Our findings have important implications for the prevention of HF by averting or reversing frailty, which is promising because frailty treatments are

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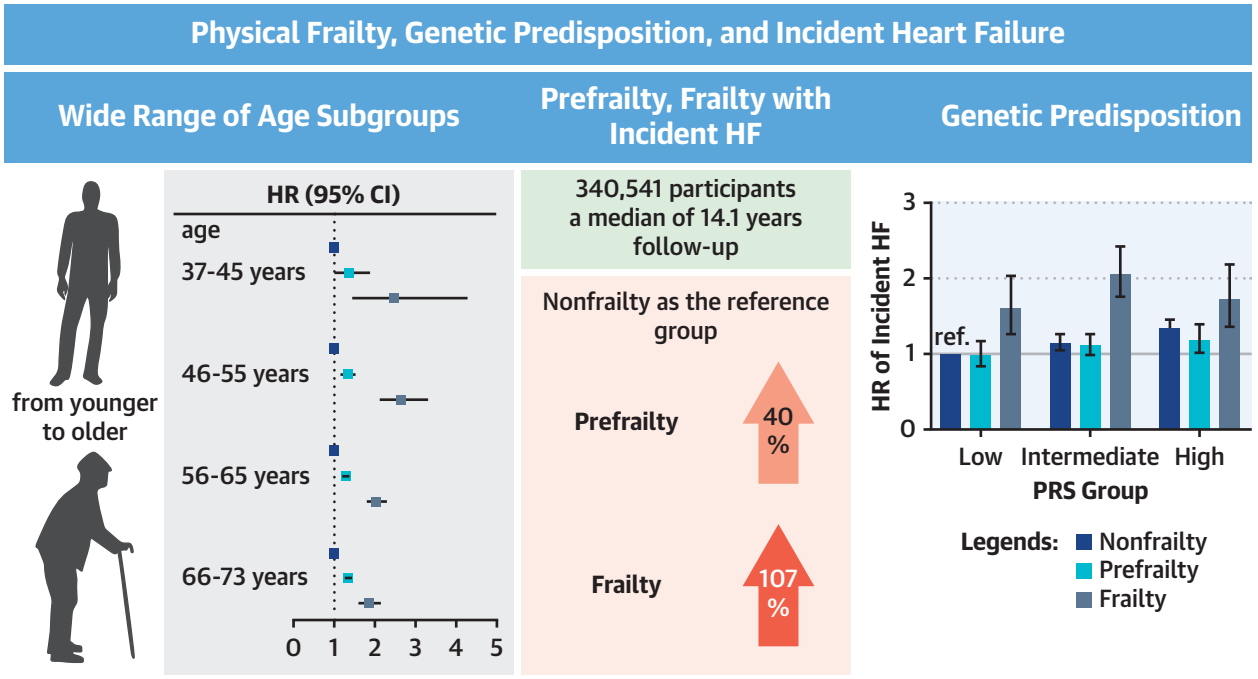
CENTRAL ILLUSTRATION **Association of Frailty and Incident Heart Failure in General Populations**



Shi Q, et al. JACC: Asia. 2024;4(7):547–556.

The red arrow indicates that prefrailty and frailty increased the risk of heart failure (HF) by 40% and 107%, respectively, compared with the nonfrailty group. Forest plots represent HR and 95% CI for each age subgroup, and bar plots and error bars represent HR and 95% CI for each gene phenotype. PRS = polygenic genetic score.

effective and economical, and a combination of strength exercises and protein supplementation is the most effective and easiest way to implement interventions to delay or reverse frailty.[32] Our results also support the need to evaluate frailty to ascertain the risk of future HF, providing insight into clinical measures, such as taking the state of frailty into account when determining whether a patient's risk level is high enough to require intervention along with lifestyle-based prevention.

STUDY STRENGTHS AND LIMITATIONS. Given the limited number of longitudinal studies on the association between physical frailty and incident HF, we provided firsthand prospective evidence in this regard. The large sample size and relatively long follow-up duration increased the credibility of our results. We also collected a number of covariates, including demographic information, lifestyle variables, metabolic factors, and medications, which allowed for rigorous adjustment. This study also has several limitations. First, the UKB had a low response rate (5.47%) and was subject to selection bias, although recent evidence from a meta-analysis suggested that the risk factor associations in the UKB seem to be generalizable despite the very low response rate.[33] Second, we excluded many participants because data on frailty or genetic assessments were missing, covariates could introduce potential bias, and biased estimates may not be possible. Third, except for grip strength, frailty components and some covariates were self-reported, and reporting bias might exist. However, a study of self-reported frailty components revealed that the characteristics of frailty are similar regardless of whether self-reported or test-based measures are used.[34] Fourth, the occurrence of HF was defined only by the ICD-10 code, and recurrent HF was not considered due to the limitations of the UKB. Fifth, as an observational study, the association between frailty phenotype and incident HF cannot be interpreted as causal. Sixth, although we carefully adjusted for various confounders, bias from unmeasured confounding may still exist. Therefore, caution is warranted when generalizing summary statistics to the general population.

CONCLUSIONS

The current study indicated that frailty and 3 of its components were significantly associated with an increased risk of incident HF, whereas there was no significant interaction between PRS and frailty. The significance of frailty in the pathogenesis of HF should be considered for individuals of each genotype and in the middle-aged population, not only for elderly individuals. Further study is warranted to determine if modifying frailty status might represent another avenue to improve the primary prevention of HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Frailty and its components (exhaustion, slow gait speed, and low grip strength) are significantly associated with an increased risk of HF, regardless of genotype, especially in middle-aged individuals.

COMPETENCY IN PATIENT CARE: Frailty should be considered when assessing patients' risk of HF.

TRANSLATIONAL OUTLOOK: Future studies should seek to establish whether reversing the state of frailty can reduce the risk of HF.

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KEY WORDS cardiovascular disease, frailty, genetic risk, heart failure, middle-aged

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

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