

Supplemental Materials

Outcomes of Interest

Our primary outcome of interest was physician adjudicated incident HF hospitalization event. Specifically, potential HF hospitalizations were first identified from hospital discharge records or death certificates that indicated HF with *International Classification of Diseases (ICD), 9/10th Revision* codes 428x followed by comprehensive abstraction of hospitalization data. Incident HF events were subsequently adjudicated based on the signs and symptoms of congestion, LVEF assessment (if available), and chest x-ray findings at the time of hospitalization as reported previously.^{1, 2} Among HF subtypes, HFpEF was defined by incident HF hospitalization event with LVEF $\geq 50\%$.³ HFrEF was identified by LVEF $< 50\%$ at the time of HF hospitalization. For hospitalization events without assessment of LVEF, the most recent LVEF within 6 months of the index hospitalization was used to identify HF subtypes. Our secondary outcome of interest was all-cause mortality and ascertained through either annual cohort follow-up, death registries, or hospital surveillance. The date and cause of death were confirmed using the National Death Index.⁴ All events were adjudicated by the event adjudication committee.

Clinical covariates

History of heart failure (HF) was defined as previous adjudicated HF, HF hospitalization with *ICD* code 428x (prior to 2005), Gothenburg stage 3 symptomatic HF⁵, or self-reported HF medications. CVD was defined as a history of myocardial infarction, angina pectoris, coronary revascularization, or stroke. Diabetes mellitus was defined as random glucose ≥ 200 mg/dL, fasting glucose ≥ 126 mg/dL, or diabetic medication use. Hypertension was defined as systolic

blood pressure (BP) \geq 140 mmHg, diastolic BP \geq 90 mmHg, or antihypertensive medication use. Income was classified as less than \$5,000, \$5,000 to \$7,999, \$8,000 to \$11,999, \$12,000 to \$15,999, \$16,000 to \$24,999, \$25,000 to \$34,999, \$35,000 to \$49,999, \$50,000 to \$74,999, \$75,000 to \$99,999, and more than \$100,000. We used the midpoint between ranges with the highest bracket interpreted as \$125,000 as previously described.⁶

Cardiac biomarkers

High-sensitivity cardiac troponin-T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were measured as previously described using standard assays.⁷ Briefly, hs-cTn concentration was measured using a high-sensitivity sandwich immunoassay with stored plasma samples.⁸ Samples were analyzed at the Baylor College of Medicine (Houston, Texas) and the University of Minnesota (Minneapolis) with an automated analyzer (Cobas e411; Roche Diagnostics).⁹ The lower measurable limit of hs-cTnT was 3 ng/L with a coefficient of variation $<10\%$ below 14 ng/L. The same collection protocol and automated analyzer were used to measure NT-proBNP concentrations with a lower measurable limit of 5 ng/L. For participants with concentrations below the detectable limit, we assigned a value of half the lower measurable limit (i.e., 1.5 ng/L for hs-cTnT and 2.5 pg/mL for NT-proBNP).

Frailty and Functional Status Assessment

The frailty phenotype was defined using the Cardiovascular Health Study components as previously described by Fried *et al.*^{10, 11} Briefly, frailty phenotype was identified by the presence of the following components: 1) weight loss of ≥ 10 pounds or $\geq 5\%$ of body weight in the prior year; 2) body mass index (BMI) and sex-adjusted grip strength in lowest quintile; 3) self-reported exhaustion on CES-D questionnaire¹²; 4) height and sex-adjusted gait speed in lowest

quintile; and 5) kilocalories per week in the lowest quintile. Grip strength, a measure of upper-extremity performance, was assessed using a dynamometer in the participant's preferred hand. Gait speed was assessed by timing participants walking 4 meters at their usual speed. Individuals with three or more components were categorized as *frail*, one or two defined as *prefrail*, and none defined as *robust*. As this study excluded participants classified as *frail*, only participants categorized as *prefrail* or *robust* were included.

The Short Physical Performance Battery (SPPB) score, a standardized objective screening tool for primary lower-extremity functional impairment, was also calculated for each individual.¹³ SPPB comprises of three components: standing balance, timed repeated chair rise, and gait speed. Each component is scaled and scored from 0 to 4 based on specific cut points (**Supplemental Table 1**). The components are then summed for a total score ranging from 0 to 12.

References

- [1] Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol.* 2008;**101**: 1016-1022.
- [2] Rosamond WD, Chang PP, Baggett C, *et al.* Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail.* 2012;**5**: 152-159.
- [3] Butler J, Anker SD, Packer M. Redefining Heart Failure With a Reduced Ejection Fraction. *JAMA.* 2019.
- [4] White AD, Folsom AR, Chambless LE, *et al.* Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol.* 1996;**49**: 223-233.
- [5] Eriksson H, Caidahl K, Larsson B, *et al.* Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. *Eur Heart J.* 1987;**8**: 1007-1014.
- [6] Wang SY, Tan ASL, Claggett B, *et al.* Longitudinal Associations Between Income Changes and Incident Cardiovascular Disease: The Atherosclerosis Risk in Communities Study. *JAMA Cardiol.* 2019;**4**: 1203-1212.

- [7] Nambi V, Liu X, Chambless LE, *et al.* Troponin T and N-terminal pro-B-type natriuretic peptide: a biomarker approach to predict heart failure risk--the atherosclerosis risk in communities study. *Clin Chem.* 2013;**59**: 1802-1810.
- [8] Myhre PL, Claggett B, Ballantyne CM, *et al.* Association Between Circulating Troponin Concentrations, Left Ventricular Systolic and Diastolic Functions, and Incident Heart Failure in Older Adults. *JAMA Cardiol.* 2019;**4**: 997-1006.
- [9] McEvoy JW, Chen Y, Ndumele CE, *et al.* Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA Cardiol.* 2016;**1**: 519-528.
- [10] Kucharska-Newton AM, Palta P, Burgard S, *et al.* Operationalizing Frailty in the Atherosclerosis Risk in Communities Study Cohort. *J Gerontol A Biol Sci Med Sci.* 2017;**72**: 382-388.
- [11] Fried LP, Tangen CM, Walston J, *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;**56**: M146-156.
- [12] Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *Journal of Clinical Psychology.* 1986;**42**: 28-33.
- [13] Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *The New England journal of medicine.* 1995;**332**: 556-561.

Supplemental Table 1. Components of the frailty phenotype defined by Fried's criteria.

Frailty Component	Definition
Weight loss	Weight loss of ≥ 10 pounds or $\geq 5\%$ of body weight in the prior year
Grip strength	Body mass index and sex-adjusted grip strength in lowest quintile
Exhaustion	Self-reported exhaustion on CES-D questionnaire
Gait speed	Height and sex-adjusted gait speed in lowest quintile
Energy expenditure	Kilocalories per week in the lowest quintile

Supplemental Table 2. Components and scoring of the Short Physical Performance Battery (SPPB).

SPPB Component	Definition	Scoring
Balance test	Patient is asked to stand in a semi-tandem position for 10 seconds; if the patient is able, he/she then stands in full tandem position for 10 seconds; if not able, he/she stands in side-by-side position for 10 seconds	0 = Side by side 0-9s or unable to perform 1 = Side by side 10s 2 = Full tandem 0-2 s 3 = Full tandem 3-9s 4 = Full tandem 10s
Chair rise test	Patient is seated and asked to stand up 5 times as quickly as possible with arms folded across his/her chest	0 = Unable to perform 1 = ≥ 16.7 s 2 = 12.7-16.6s 3 = 11.2-13.6s 4 = < 11.2 s
5-meter gait speed test	Patient walks at a comfortable pace for 5 meters; repeated 3 times and averaged	0 = Unable to perform 1 = ≥ 11.6 s 2 = 8.3-11.5s 3 = 6.5-8.2s 4 = < 6.5 s

Supplemental Table 3. Frailty measures and association with cardiac stress markers and abnormal remodeling patterns.

	hs-TnT (ng/L)*		NT-proBNP (pg/mL)*	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Prefrailty (ref: robust)	0.08 (0.05, 0.10)	<0.001	0.03 (0.02, 0.05)	<0.001
SPPB score (per 1-unit decrease)	0.04 (0.04, 0.05)	<0.001	0.01 (0.01, 0.02)	<0.001
Grip strength (per 1SD decrease)	0.05 (0.03, 0.07)	<0.001	0.03 (0.02, 0.03)	<0.001
4M Walk time (per 1SD increase)	0.07 (0.05, 0.08)	<0.001	0.02 (0.01, 0.03)	<0.001
<p><i>*log-transformed</i></p> <p><i>Models were adjusted for age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, statin medication, eGFR, HDL-c, and HbA1c levels.</i></p> <p><i>Abbreviations:</i></p> <p><i>CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery</i></p>				

Supplemental Table 4. Multivariable adjusted associations of Fried scores and risk of incident heart failure.

	HF events (%)	Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Score = 0 (n=2,645)	72 (2.7%)	Ref.	-	Ref.	-
Score = 1 (n=1,850)	113 (6.1%)	1.81 (1.34, 2.44)	<0.001	1.72 (1.27, 2.33)	<0.001
Score = 2 (n=715)	47 (6.6%)	1.57 (1.07, 2.29)	0.02	1.49 (1.02, 2.18)	0.04

Baseline covariates = age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, cardiovascular disease, statin medication, eGFR, HDL-c, and HbA1c levels.

Model 1 = baseline covariates + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Model 2 = baseline covariates + hs-cTn + NT-proBNP + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Abbreviations:
CI, confidence interval; HF, heart failure; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery

Supplemental Table 5. Sensitivity analysis: Multivariable adjusted associations of frailty measures and risk of incident heart failure in following subgroups: (top) the subset excluding prior CVD; (bottom) in landmarked analysis excluding participants with HF event within 12 months of baseline.

Covariate	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<i>Excluding participants with prior history of CVD (N = 4557)</i>				
Prefrailty (ref: robust)	1.98 (1.39-2.81)	<0.001	1.88 (1.32-2.68)	<0.001
SPPB (per 1-unit decrease)	1.15 (1.07-1.23)	<0.001	1.10 (1.02-1.18)	0.01
Grip strength (per 1SD decrease)	1.30 (1.02-1.65)	0.03	1.25 (0.98-1.59)	0.07
4M Walk time (per 1SD increase)	1.12 (0.99-1.26)	0.06	1.11 (0.98-1.23)	0.11
<i>Excluding participants with HF event within 12 months of baseline (N = 5107)</i>				
Prefrailty (ref: robust)	2.04 (1.48, 2.80)	<0.001	1.87 (1.36, 2.58)	<0.001
SPPB (per 1-unit decrease)	1.11 (1.05, 1.18)	<0.001	1.09 (1.03, 1.16)	0.002
Grip strength (per 1SD decrease)	1.41 (1.15, 1.73)	0.001	1.33 (1.08, 1.64)	0.006
4M Walk time (per 1SD increase)	1.16 (1.05, 1.28)	0.004	1.14 (1.02, 1.26)	0.02
<p><i>Baseline covariates = age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, cardiovascular disease, statin medication, eGFR, HDL-c, and HbA1c levels.</i></p> <p><i>Model 1 = baseline covariates + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)</i></p> <p><i>Model 2 = baseline covariates + hs-cTn + NT-proBNP + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)</i></p> <p><i>Abbreviations:</i> <i>CI, confidence interval; HF, heart failure; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery</i></p>				

Supplemental Table 6. Sensitivity analysis: Multivariable adjusted associations of frailty measures and risk of incident heart failure stratified by heart failure with reduced (HF_rEF) and preserved (HF_pEF) ejection fraction excluding participants with a prior history of cardiovascular disease.

Covariate	HF _r EF				HF _p EF			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P-value	HR (95% CI)	P-value
Prefrailty (ref: robust)	1.55 (0.92, 2.64)	0.10	1.52 (0.89, 2.58)	0.12	1.98 (1.19, 3.32)	0.009	1.91 (1.14, 3.20)	0.01
SPPB (per 1-unit decrease)	1.13 (1.02, 1.24)	0.02	1.12 (1.01, 1.23)	0.03	1.14 (1.04, 1.25)	0.004	1.14 (1.04, 1.25)	0.006
Grip strength (per 1SD decrease)	1.19 (0.84, 1.70)	0.33	1.14 (0.79, 1.64)	0.48	1.35 (0.95, 1.93)	0.10	1.30 (0.91, 1.88)	0.15
4M Walk time (per 1SD increase)	1.01 (0.80, 1.28)	0.91	0.99 (0.78, 1.26)	0.95	1.20 (1.03-1.40)	0.02	1.17 (1.01-1.35)	0.04

Baseline covariates = age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, statin medication, eGFR, HDL-c, and HbA1c levels.

Model 1 = baseline covariates + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Model 2 = baseline covariates + hs-cTn + NT-proBNP + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Abbreviations:

CI, confidence interval; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery

Supplemental Table 7. Sensitivity analysis: Fine-Gray model associations of frailty measures and risk of incident heart failure stratified by heart failure with reduced (HF_rEF) and preserved (HF_pEF) ejection fraction. All-cause mortality and the other heart failure subtype were treated as competing risk events.

Covariate	HF _r EF				HF _p EF			
	Model 1		Model 2		Model 1		Model 2	
	HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P-value	HR (95% CI)	P-value
Prefrailty (ref: robust)	1.41 (0.91, 2.20)	0.13	1.42 (0.91, 2.23)	0.13	1.86 (1.17, 2.97)	0.009	1.83 (1.14, 2.92)	0.01
SPPB (per 1-unit decrease)	1.08 (1.01, 1.16)	0.02	1.07 (1.00, 1.15)	0.04	1.12 (1.01, 1.23)	0.03	1.11 (1.01, 1.22)	0.04
Grip strength (per 1SD decrease)	1.36 (1.05, 1.78)	0.02	1.30 (0.98, 1.72)	0.07	1.35 (1.01, 1.80)	0.04	1.31 (0.97, 1.75)	0.08
4M Walk time (per 1SD increase)	1.01 (0.88, 1.18)	0.85	0.99 (0.85, 1.15)	0.88	1.19 (1.07, 1.31)	0.001	1.16 (1.05, 1.29)	0.004

Baseline covariates = age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, statin medication, eGFR, HDL-c, and HbA1c levels.

Model 1 = baseline covariates + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Model 2 = baseline covariates + hs-cTn + NT-proBNP + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)

Abbreviations:

CI, confidence interval; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery

Supplemental Table 8. Event rates and Cox proportional hazard model associations of individuals with high (NT-proBNP \geq 125 pg/mL) vs. low (NT-proBNP $<$ 125 pg/mL) natriuretic peptide levels and risk of heart failure.

	Events (event rate)			Overall		HF _r EF		HF _p EF	
	Overall	HF _r EF	HF _p EF	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
NT-proBNP $<$ 125 pg/mL	26 (1.1%)	7 (0.3%)	13 (0.5%)	Ref.	-	Ref.	-	Ref.	-
NT-proBNP \geq 125 pg/mL	206 (7.5%)	95 (3.5%)	84 (3.1%)	5.69 (3.73, 8.70)	$<$ 0.001	9.60 (4.36, 21.11)	$<$ 0.001	4.70 (2.55, 8.66)	$<$ 0.001
<p><i>Model adjusted for age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, statin medication, eGFR, HDL-c, HbA1c levels, and hs-cTn.</i></p> <p><i>Abbreviations:</i> <i>CI, confidence interval; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide</i></p>									

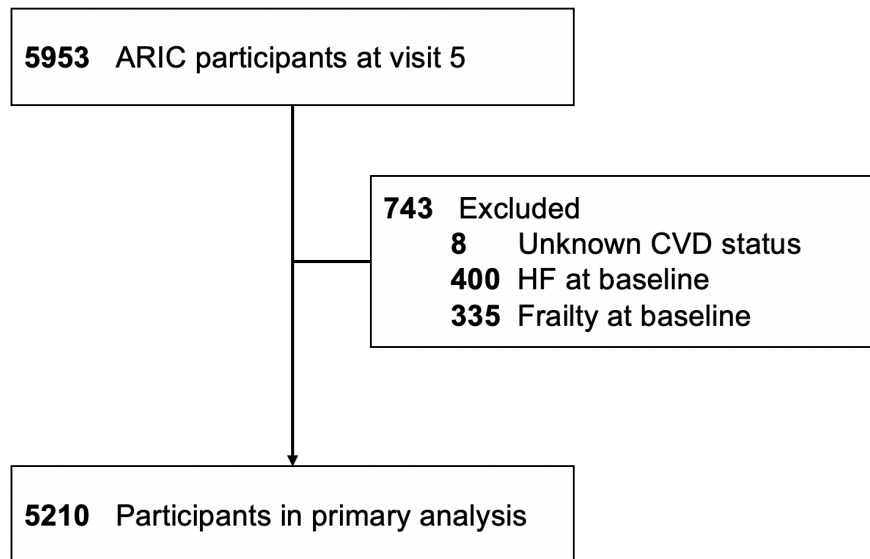
Supplemental Table 9. Sensitivity analysis: Multivariable adjusted associations of frailty measures and risk of incident heart failure in participants with NT-proBNP < 125 pg/mL (top) and ≥ 125 pg/mL (bottom).

Covariate	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<i>Participants with NT-proBNP < 125 pg/mL (N = 2475)</i>				
Prefrailty (ref: robust)	3.16 (1.25, 8.01)	0.02	3.07 (1.21, 7.82)	0.02
SPPB (per 1-unit decrease)	1.13 (0.94, 1.34)	0.18	1.10 (0.93, 1.31)	0.26
Grip strength (per 1SD decrease)	1.73 (0.98, 3.05)	0.06	1.81 (1.04, 3.22)	0.04
4M Walk time (per 1SD increase)	1.38 (1.05, 1.81)	0.02	1.35 (1.02, 1.78)	0.04
<i>Participants with NT-proBNP ≥ 125 pg/mL (N = 2475)</i>				
Prefrailty (ref: robust)	1.42 (1.05, 1.92)	0.02	1.35 (1.00, 1.83)	0.05
SPPB (per 1-unit decrease)	1.10 (1.04, 1.16)	0.001	1.09 (1.03, 1.15)	0.003
Grip strength (per 1SD decrease)	1.15 (0.95, 1.39)	0.15	1.10 (0.91, 1.33)	0.31
4M Walk time (per 1SD increase)	1.08 (0.97, 1.22)	0.17	1.06 (0.94, 1.19)	0.33
<p><i>Baseline covariates = age, sex, race, education level, income, systolic blood pressure, body mass index, hypertension, smoking status, diabetes status, cardiovascular disease, statin medication, eGFR, HDL-c, and HbA1c levels.</i></p> <p><i>Model 1 = baseline covariates + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)</i></p> <p><i>Model 2 = baseline covariates + hs-cTn + NT-proBNP + exposure variable of interest (grip strength, 4M walk time, prefrailty, or SPPB score each in a separate model)</i></p> <p><i>Abbreviations:</i> <i>CI, confidence interval; HF, heart failure; HR, hazard ratio; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; SD, standard deviation; SPPB, Short Physical Performance Battery</i></p>				

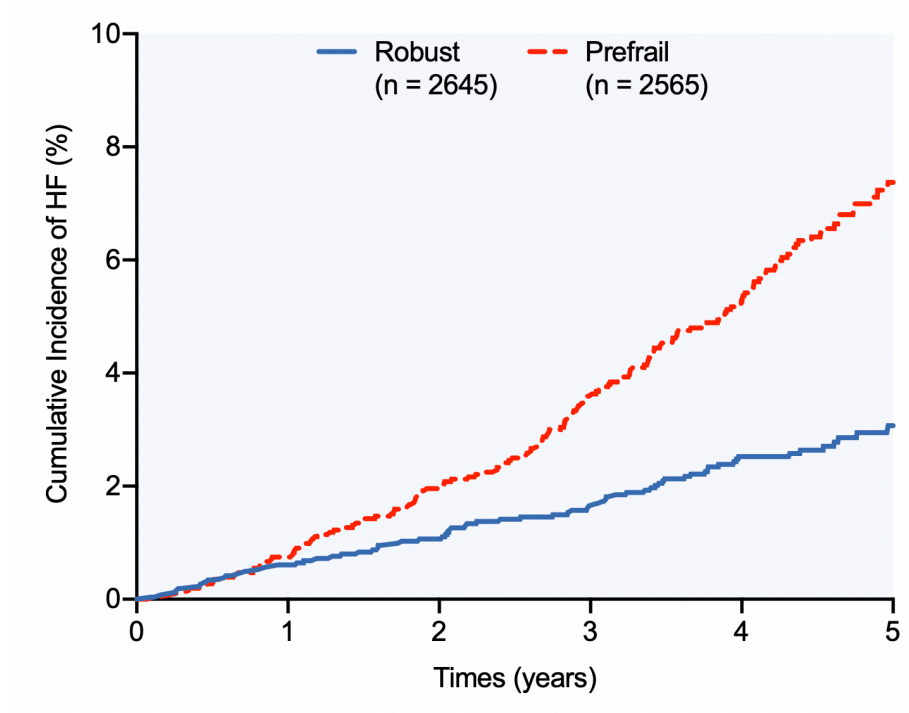
Supplemental Table 10. Harrel’s *C*-index for predicting risk of incident heart failure (HF) with the ARIC HF risk score and addition of different frailty measures. The De Long’s test compares the *C*-index between the ARIC risk score and the ARIC risk score + frailty measure.

Model	C-index	Continuous Net Reclassification Index	De Long’s Test <i>P</i>-value
ARIC risk score	0.76	<i>Ref.</i>	<i>Ref.</i>
ARIC risk score + Prefrailty	0.79	0.44 (0.32, 0.54)	0.004
ARIC risk score + SPPB score	0.78	0.31 (0.18, 0.43)	0.06
ARIC risk score + Grip strength	0.77	0.13 (-0.05, 0.23)	0.16
ARIC risk score + 4M Walk time	0.77	0.18 (-0.04, 0.39)	0.09
<i>Abbreviations:</i> <i>SPPB, Short Physical Performance Battery</i>			

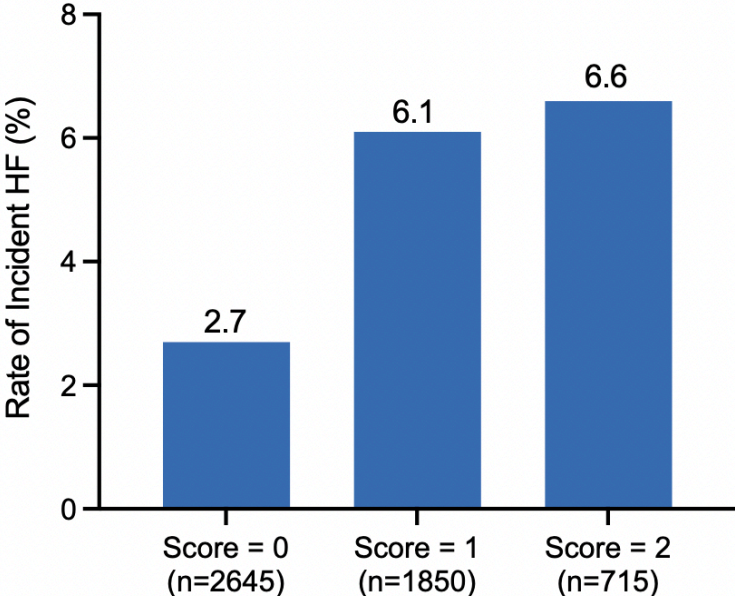
Supplemental Figure 1. CONSORT diagram of analysis participants.



Supplemental Figure 2. Cumulative incidence plots of overall heart failure stratified by frailty criteria.



Supplemental Figure 3. Rates of overall heart failure stratified by Fried criteria.



Supplemental Figure 4. Rate of incident heart failure with reduced ejection fraction (HF_rEF) and heart failure with preserved ejection fraction (HF_pEF) stratified frailty status with **A)** NT-proBNP levels < 125 pg/mL and **B)** NT-proBNP ≥ 125 pg/mL.

