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Association Between Frailty and Atrial Fibrillation in Older Adults: The Framingham Heart Study Offspring Cohort

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ORIGINAL RESEARCH

Association Between Frailty and Atrial Fibrillation in Older Adults: The Framingham Heart Study Offspring Cohort

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BACKGROUND: Frailty is associated bidirectionally with cardiovascular disease. However, the relations between frailty and atrial fibrillation (AF) have not been fully elucidated.

METHODS AND RESULTS: Using the FHS (Framingham Heart Study) Offspring cohort, we sought to examine both the association between frailty (2005–2008) and incident AF through 2016 and the association between prevalent AF and frailty status (2011–2014). Frailty was defined using the Fried phenotype. Models adjusted for age, sex, and smoking. Cox proportional hazards models, adjusted for competing risk of death, assessed the association between prevalent frailty and incident AF. Logistic regression models assessed the association between prevalent AF and new-onset frailty. For the incident AF analysis, we included 2053 participants (56% women; mean age, 69.7±6.9 years). By Fried criteria, 1018 (50%) were robust, 903 (44%) were prefrail, and 132 (6%) were frail. In total, 306 incident cases of AF occurred during an average 9.2 (SD, 3.1) follow-up years. After adjustment, there was no statistically significant association between prevalent frailty status and incident AF (prefrail versus robust: hazard ratio [HR], 1.22 [95% CI, 0.95–1.55]; frail versus robust: HR, 0.92 [95% CI, 0.57–1.47]). At follow-up, there were 111 new cases of frailty. After adjustment, there was no statistically significant association between prevalent AF and new-onset frailty (odds ratio, 0.48 [95% CI, 0.17–1.36]).

CONCLUSIONS: Although a bidirectional association between frailty and cardiovascular disease has been suggested, we did not find evidence of an association between frailty and AF. Our findings may be limited by sample size and should be further explored in other populations.

Key Words: association study ■ atrial fibrillation ■ frailty

As the population successfully ages, the incidence of atrial fibrillation (AF) will continue to increase.[1] Frailty, a common geriatric syndrome that is associated with increased risk of morbidity and mortality,[2] is associated with both subclinical and overt cardiovascular disease (CVD).[3,4] To date, the only proven approach for frailty prevention involves physical activity,[2] which is also a component of AF prevention.[5,6] However, the relations between frailty and AF have are not fully understood and may present an important opportunity for prevention of both AF and frailty.

Many factors have been associated with an increased risk of frailty, including age, low physical activity, smoking, metabolic syndrome, and CVD, all of which are also risk factors for AF.[5,7-10] A survey sent to 41 centers that participate in the European Heart Rhythm Association Electrophysiology Research Network reported that the prevalence of AF in frail patients was 72%, more common than heart failure

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CLINICAL PERSPECTIVE

What Is New?

- The relationship between cardiovascular disease and frailty is thought to be bidirectional.
- Atrial fibrillation (AF) and frailty are associated in cross-sectional studies, but whether AF and frailty share a bidirectional relationship is unclear.
- In this study of 2053 participants in the FHS (Framingham Heart Study), we did not find a statistically meaningful relationship between AF and frailty.

What Are the Clinical Implications?

- It is possible that the development of AF may have differing mechanisms than atherosclerotic cardiovascular disease, which is closely associated with development of frailty.
- Further work is needed to understand the relationship between AF and frailty.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
CHS	Cardiovascular Health Study
FHS	Framingham Heart Study

(69%), diabetes mellitus (36%), or coronary artery disease (31%).[11] In a cohort of 132 older adults (mean age, 73 years) who were hospitalized with AF in Poland, frailty was diagnosed in 60%.[12]

We hypothesized that AF and frailty are reciprocally related. We sought to examine whether (1) frailty is associated with increased risk of incident AF and (2) AF is associated with increased risk of new-onset frailty.

METHODS

The FHS (Framingham Heart Study) data used in this publication are available at dbGaP, BioLINCC, and the FHS data service center (https://framinghamheartstudy.org/fhs-for-researchers/data-available-overview/).

Study Sample

The present study was based on the FHS Offspring cohort.[13,14] FHS procedures have been described previously.[14-16] Briefly, the FHS Original cohort began in 1948 with the enrollment of 5209 study participants residing in the community of Framingham, MA. In 1971, the children of the Original cohort participants and their spouses were enrolled into the FHS Offspring cohort. Offspring participants were invited to an in-person study examination every 4 to 8 years.[13,14] The Offspring examinations included detailed information obtained by trained study personnel on medical history, laboratory measures, and assessments of cognitive and physical function. All study participants provided informed consent to participate in this study. All protocols were approved by the Institutional Review Board at Boston University Medical Center (Boston, MA).

Our study sample was derived from the 3021 participants who attended Offspring cohort examination cycle 8 (2005–2008), the index examination. Participants were excluded if they were aged <60 years at the time of their study visit (n=693), had missing or incomplete Fried frailty scores (defined as missing ≥2 components of the Fried score; n=63), or were missing covariate information for smoking status (n=3).

The present analysis is based on 2 different analytic samples. For the first analysis of the association between the Fried frailty status and incident AF, we excluded participants who had prevalent AF at the time of their index examination (n=205) or had no AF follow-up information (n=4), resulting in a final sample size of 2053. For the second analysis of the association between prevalent AF at the index examination and new-onset frailty at the follow-up examination, we excluded participants who did not attend examination 9 (n=572), had a missing or incomplete Fried frailty score at examination 9 (n=72), or had prevalent frailty at the index examination (n=52). In a secondary analysis, we reconstructed the samples using the Rockwood frailty definition, as previously defined in a prior Framingham study.[17] Details of the study sample selection are shown in Figure 1.

Frailty

In FHS, frailty was defined according to 2 leading definitions: the phenotypic characterization developed by Fried and colleagues in the CHS (Cardiovascular Health Study)[8] and the deficit accumulation model demonstrated by Rockwood and associates in the Yale Precipitating Events Project and elsewhere.[17-19] Our primary analysis was done using a modified Fried method, and a secondary analysis was done applying the Rockwood frailty definition. Briefly, the Fried method is based on a physical phenotype of frailty that includes 5 measures of function.[8] Individuals are frail if they have at least 3 of the following: unintentional weight loss of ≥10 pounds in the past year, self-reported exhaustion, weakness (as measured by grip strength), slow walking speed, and decreased physical activity. Those with 1 to 2 deficits are prefrail, whereas those with 0 deficits are nonfrail. Participants

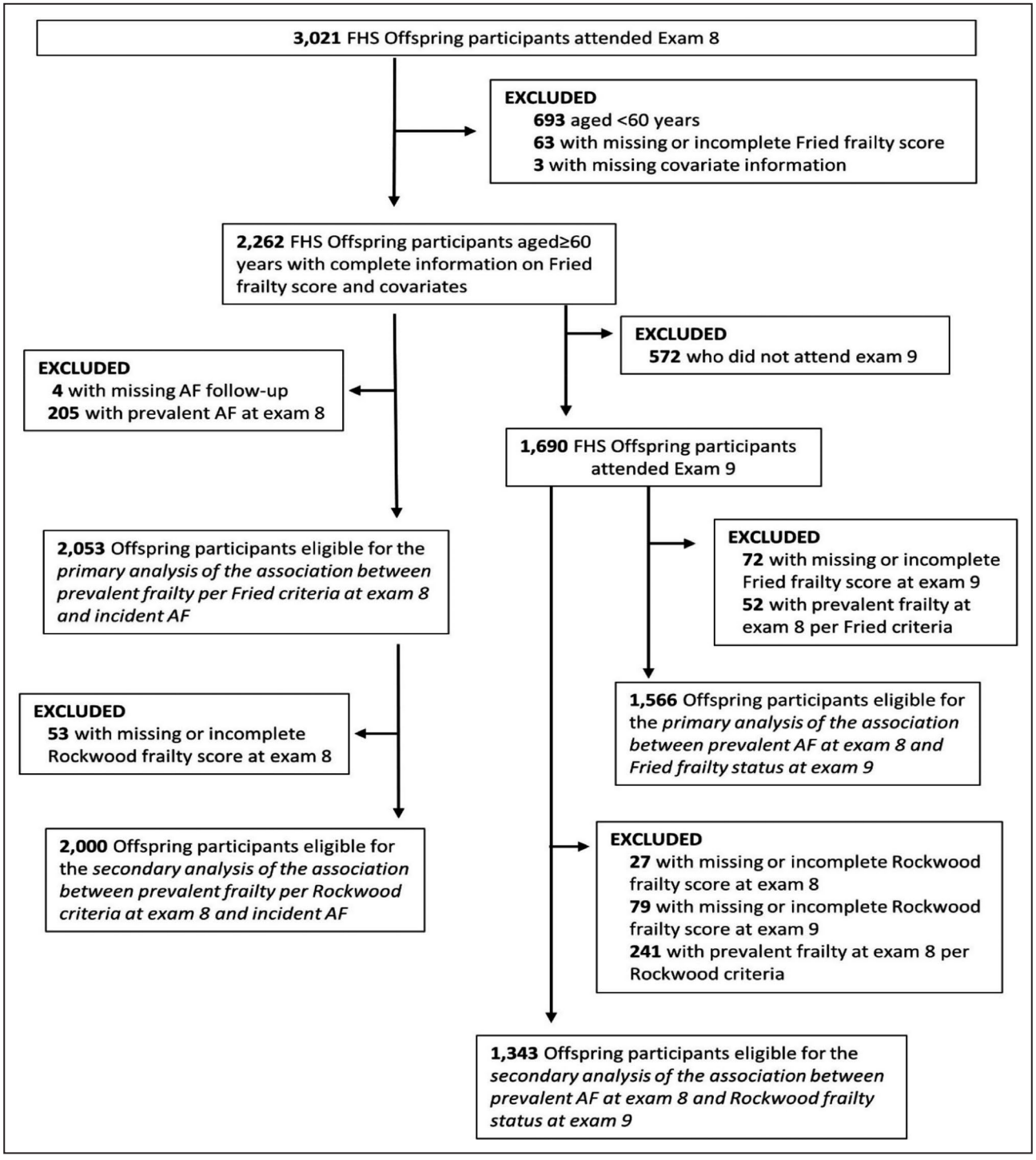

Figure 1. Study sample selection.
AF indicates atrial fibrillation; Exam, examination; and FHS, Framingham Heart Study.

who were unable to complete the walk test and/or grip strength test because of a noted physical limitation were classified as having a deficiency.

In a secondary analysis, we defined frailty according to the cumulative deficit method developed by Rockwood, using 37 variables related to cognition, physical function, mood, and morbidity, as we have previously defined in the FHS.[17] Frailty indexes were calculated for each participant by dividing the number of accumulated deficits by the total number of possible deficits.[20] A score of 0 to 0.1 was considered robust, a score of >0.1 to 0.21 was considered as prefrail, and a score of >0.21 was considered as frail.[21]

AF and Coronary Heart Disease Assessment

All cardiovascular events were adjudicated by a panel of 3 FHS physicians based on a review of medical records, ECGs, and physician/hospital reports, as previously described.[22] Ongoing surveillance for CVD events is achieved through mailed medical history questionnaires and/or telephone interviews in between the official study visits. AF was considered present if either AF or atrial flutter was diagnosed on ECG or Holter monitoring at an FHS research visit, during examination by an outside clinician, or on inpatient admission to hospital.[23] Coronary heart disease was defined as the occurrence of myocardial infarction, angina, coronary insufficiency, or coronary heart disease–associated death. Diagnosis of congestive heart failure was performed using standardized criteria.[24]

Covariates

All covariates were measured at the index examination to characterize participant phenotypes relevant to downstream risks. Height and weight were assessed using a standardized protocol. If a participant was missing height, we carried forward his/her height measurements from prior FHS examinations, if available. Smoking was classified as present if the participant reported smoking cigarettes in the year before the index examination. Systolic and diastolic blood pressure values were taken as the average of 2 physician readings using a sphygmomanometer. Antihypertensive and diabetes mellitus medications were assessed as part of a systematic drug inventory. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or use of oral hypoglycemic medications or insulin, as indicated on medication inventory. A clinically significant murmur was defined as having a systolic murmur of grade ≥3 of 6 or any diastolic murmur, as assessed by the research center physician. PR interval and left ventricular hypertrophy were obtained from ECG obtained in the research center.

Statistical Analysis

Descriptive statistics were calculated using means and SDs for continuous variables and frequency counts and percentages for categorical variables. For the analysis of prevalent frailty at the index examination and incident AF, participants were followed up from the date of their index examination until AF occurrence, death, loss to follow-up, or December 31, 2016, whichever occurred first. Cox proportional hazards models were used to estimate hazard ratios (HRs) and compute associated 95% CIs, quantifying the association between frailty group (prefrail versus robust or frail versus robust) and incident AF. The proportional hazards assumption was verified by including a term for the interaction between the log of the survival time and each predictor in the model. An initial model (model 1) was adjusted for age and sex, and a second model (model 2) was further adjusted for current smoking. We additionally constructed a third model that was further adjusted for height, weight, systolic and diastolic blood pressure, antihypertensive treatment, diabetes mellitus, PR interval, left ventricular hypertrophy, murmur, prevalent coronary heart disease, and prevalent heart failure. For all models, the Fine-Gray model was used to account for the competing risk of mortality.[25]

Unlike cardiovascular events, which are continuously monitored in between study visits, frailty status is only assessed during a participant's study visit so it is not possible to obtain the survival time for frailty onset. Thus, logistic regression models were used for the analysis of prevalent AF at the index examination, and new-onset frailty (frail versus prefrail/robust) was assessed at the follow-up examination (FHS examination cycle 9 [2011–2014]). Multivariable models were adjusted for the same covariates used in the incident AF analysis, described above. Frailty group was defined using the Fried frailty criteria in our primary analysis, and the Rockwood Index was used in our secondary analysis. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

For our analysis of the association between the Fried frailty score and incident AF, our study sample included 2053 participants (56% women; mean age, 69.7±6.9 years). A total of 306 incident cases of AF occurred during an average of 9.2±3.1 years of follow-up. Details of the study sample selection are shown in Figure 1.

Table 1 shows a summary of the study sample characteristics by Fried frailty category. Overall, frail participants were older, were heavier, had slower walking speeds, and were more likely to be current smokers, have diabetes mellitus, use hypertensive treatment, and have prevalent coronary heart disease and heart failure, compared with participants who were robust or prefrail. Table 2 shows a summary of the study sample characteristics stratified by the presence of AF at the time of the index examination. Participants with AF were older, were more likely to be men, and were more likely to have a higher burden of CVD risk factors as opposed to participants without AF. Summary statistics for the secondary analysis using the Rockwood frailty index are presented in Tables S1 and S2.

Table 1. Study Sample Characteristics of the FHS Offspring Cohort Participants Included in the Analysis of Fried Frailty Group at Examination 8 and Incident AF (N=2053)

Characteristic	All Participants (n=2053)	Fried Frailty Group		
		Robust (n=1018)	Prefrail (n=903)	Frail (n=132)
Age, mean (SD), y	69.7 (6.9)	67.9 (6.1)	70.8 (7.0)	75.7 (7.3)
Women, n (%)	1153 (56.2)	535 (52.6)	540 (59.8)	78 (59.1)
Current smoker, n (%)	155 (7.6)	65 (6.4)	73 (8.1)	17 (12.9)
Diabetes mellitus, n (%)	299 (14.9)	117 (11.6)	150 (17.1)	32 (27.1)
Height, mean (SD), in	65.3 (3.8)	65.9 (3.8)	64.9 (3.7)	64.1 (3.7)
Weight, mean (SD), lb	171 (38)	169 (37)	174 (38)	172 (46)
Systolic blood pressure, mean (SD), mm Hg	131 (17)	130 (17)	131 (17)	132 (19)
Diastolic blood pressure, mean (SD), mm Hg	73 (10)	74 (10)	72 (10)	68 (10)
Antihypertensive treatment, n (%)	1104 (53.9)	498 (49.0)	519 (57.6)	87 (65.9)
PR interval, mean (SD), ms	17.0 (2.9)	16.9 (2.7)	17.0 (3.0)	17.5 (3.2)
Heart murmur, n (%)	63 (3.2)	25 (2.6)	32 (3.7)	6 (5.2)
Left ventricular hypertrophy, n (%)	15 (0.75)	5 (0.50)	9 (1.0)	1 (0.82)
Prevalent heart failure, n (%)	25 (1.2)	6 (0.59)	14 (1.6)	4 (3.8)
Prevalent coronary heart disease, n (%)	212 (10.3)	80 (7.9)	108 (12.0)	24 (18.2)
Fried frailty score, mean (SD)	0.78 (0.97)	0 (0.0)	1.28 (0.45)	3.32 (0.51)
Rockwood Frailty Index score, mean (SD)	0.14 (0.11)	0.093 (0.065)	0.17 (0.098)	0.35 (0.13)
Usual walking speed, mean (SD), m/s	1.17 (0.27)	1.29 (0.21)	1.09 (0.25)	0.78 (0.20)

Participants with prevalent AF at examination 8 (n=205) were excluded. Characteristics were measured at examination 8. AF indicates atrial fibrillation; and FHS, Framingham Heart Study.

Among the 2328 participants aged ≥60 years at the index examination, ≈3% (n=63) were missing the Fried frailty score (defined as missing ≥2 of 5 possible components) and ≈5% (n=112) were missing the Rockwood frailty index (defined as missing ≥5 of 37 possible components). Compared with participants with complete Fried frailty scores, those with missing scores were older (80.0 versus 70.1 years; $P<0.0001$), had lower diastolic blood pressure (69 versus 72 mm Hg; $P=0.01$), were more likely to be women (70% versus 55%; $P=0.02$), and had a higher prevalence of hypertension treatment (71% versus 55%; $P=0.01$), coronary heart disease (25% versus 13%; $P=0.004$), congestive heart failure (11% versus 3%; $P=0.004$), and AF (18% versus 9%; $P=0.02$) at the index examination (Table S3). Participants with missing Fried frailty scores were more likely to develop incident AF (27% versus 15%) or to die (62% versus 19%) during the follow-up period ($P<0.0001$). Mean systolic blood pressure and percentage of current smokers were similar between those with and without missing Fried frailty status (Table S3).

Association Between Frailty Status at Index Examination and Incident AF

Using the Fried criteria, 1018 (50%) participants were robust, 903 (44%) were prefrail, and 132 (6%) were frail at the index examination. After adjustment for age, sex, and smoking, and accounting for the competing risk of mortality, we found no statistically significant association between index frailty status and incident AF (pre-frail versus robust: HR, 1.22 [95% CI, 0.95–1.55] [$P=0.11$]; frail versus robust: HR, 0.92 [95% CI, 0.57–1.47] [$P=0.72$]), with similar results after full model adjustment (Table 3). In secondary analysis using the Rockwood frailty definition, there was a suggestion of a positive association between frailty status and incident AF (prefrail versus robust: HR, 1.32 [95% CI, 1.01–1.72] [$P=0.04$]; frail versus robust: HR, 1.32 [95% CI, 0.96–1.83] [$P=0.09$]). However, the results were attenuated in the fully adjusted model and were comparable to the results using the Fried criteria (Table 3). Model results unadjusted for the competing risk of mortality are presented in Table S4.

Association Between Prevalent AF and New-Onset Frailty

In the analysis of new-onset frailty at the follow-up examination, 86 (5.5%) participants had AF at the index examination. There was a total of 111 new-onset cases of frailty at the follow-up examination (mean time between index and follow-up examination, 5.8±0.6 years). After adjustment for age, sex, and smoking, there was no statistically significant association between prevalent AF and incident frailty (odds ratio [OR], 0.48 [95% CI, 0.17–1.36] [$P=0.17$]). When using the Rockwood frailty definition, the OR was 1.47 (95% CI, 0.79–2.73; $P=0.22$). Results

Table 2. Study Sample Characteristics of the FHS Offspring Cohort Participants Included in the Analysis of Prevalent AF at Examination 8 and New-Onset Frailty, as Defined Using Fried Criteria, at Examination 9 (N=1566)

Characteristic	All Participants (n=1566)	Prevalent AF	
		No (n=1480)	Yes (n=86)
Age, mean (SD), y	68.3 (6.2)	68.2 (6.1)	71.0 (6.4)
Women, n (%)	861 (55.0)	831 (56.2)	30 (34.9)
Current smoker, n (%)	105 (6.7)	101 (6.8)	4 (4.7)
Diabetes mellitus, n (%)	204 (13.2)	187 (12.8)	17 (20.2)
Height, mean (SD), in	65.6 (3.8)	65.5 (3.8)	67.0 (4.0)
Weight, mean (SD), lb	173 (38)	172 (37)	190 (41)
Systolic blood pressure, mean (SD), mm Hg	130 (17)	130 (17)	127 (18)
Diastolic blood pressure, mean (SD), mm Hg	73 (10)	73 (10)	72 (9)
Antihypertensive treatment, n (%)	806 (51.5)	750 (50.7)	56 (65.1)
PR interval, mean (SD), ms	16.9 (2.8)	16.8 (2.7)	18.2 (3.3)
Heart murmur, n (%)	47 (3.1)	44 (3.1)	3 (3.6)
Left ventricular hypertrophy, n (%)	9 (0.59)	8 (0.55)	1 (1.27)
Prevalent heart failure, n (%)	20 (1.3)	10 (0.68)	10 (11.6)
Prevalent coronary heart disease, n (%)	157 (10.0)	129 (8.7)	28 (32.6)
Fried frailty score, mean (SD)	0.55 (0.69)	0.54 (0.68)	0.70 (0.75)
Rockwood Frailty Index score, mean (SD)	0.12 (0.085)	0.12 (0.084)	0.16 (0.091)
Usual walking speed, mean (SD), m/s	1.22 (0.25)	1.22 (0.25)	1.13 (0.26)

Participants with prevalent frailty using Fried criteria at examination 8 (n=52) were excluded. Characteristics were measured at examination 8. AF indicates atrial fibrillation; and FHS, Framingham Heart Study.

were similar in the fully adjusted multivariable model (Table 4).

DISCUSSION

In this prospective cohort study, we did not find evidence of a statistically significant association between frailty and incident AF or AF and new-onset frailty, defined according to the 2 leading frailty definitions, once the intervening influences of age, sex, and current smoking status were considered (Figure 2). Data on the association between AF and frailty have been conflicting to date and largely have focused on prevalent conditions.

CVD and frailty are thought to share a bidirectional relationship[3]; however, our findings do not support this relationship for AF and frailty. The development of AF may have differing mechanisms than atherosclerotic CVD, which is closely associated with development of frailty. Normal physiologic aging of the

Table 3. Subdistribution HRs and 95% CIs for the Association Between Frailty Status at Examination 8 and Incident AF

Model Adjustment	Group	Frailty Definition					
		Fried (N=2053)			Rockwood (N=2000)		
		No. of AF Events/No. of Participants	HR (95% CI)	*P* Value	No. of AF Events/No. of Participants	HR (95% CI)	*P* Value
Age/sex	Robust	128/1018	Referent	…	100/860	Referent	…
	Prefrail	155/903	1.22 (0.96–1.55)	0.11	124/746	1.31 (1.01–1.72)	0.05
	Frail	23/132	0.93 (0.58–1.48)	0.75	74/394	1.32 (0.96–1.82)	0.09
Age/sex/smoking	Robust	128/1018	Referent	…	100/860	Referent	…
	Prefrail	155/903	1.22 (0.95–1.55)	0.11	124/746	1.32 (1.01–1.72)	0.04
	Frail	23/132	0.92 (0.57–1.47)	0.72	74/394	1.32 (0.96–1.83)	0.09
Multivariable*	Robust	123/958	Referent	…	96/819	Referent	…
	Prefrail	139/822	1.09 (0.84–1.42)	0.50	117/690	1.16 (0.86–1.56)	0.33
	Frail	15/106	0.64 (0.37–1.12)	0.12	61/338	0.94 (0.64–1.39)	0.77

All models are adjusted for the competing risk of mortality. Participants with prevalent AF at examination 8 are excluded (N=205). For the analysis using the Fried criteria, there were 306 AF events and 398 deaths over the course of the follow-up period. For the analysis using the Rockwood criteria, there were 298 AF events and 375 deaths over the course of the follow-up period. AF indicates atrial fibrillation; and HR, hazard ratio.
*Models are adjusted for age, sex, current smoking, height, weight, systolic and diastolic blood pressure, antihypertensive treatment, diabetes mellitus, PR interval, left ventricular hypertrophy, heart murmur, prevalent coronary heart disease, and prevalent heart failure.

Table 4. ORs and 95% CIs for the Association Between Prevalent AF at Examination 8 and New-Onset Frailty at Examination 9

Model Adjustment	Frailty Criteria					
	Fried (N=1566)			Rockwood (N=1343)		
	No. of Frail/Total No. of Participants	OR (95% CI)	*P* Value	No. of Frail/Total No. of Participants	OR (95% CI)	*P* Value
Age/sex	111/1566	0.48 (0.17–1.36)	0.17	238/1343	1.47 (0.79–2.72)	0.22
Age/sex/smoking	111/1566	0.48 (0.17–1.36)	0.17	238/1343	1.47 (0.79–2.73)	0.22
Multivariable*	101/1447	0.50 (0.12–2.18)	0.36	218/1253	2.01 (0.90–4.51)	0.09

The outcome is frail vs prefrail/robust (referent). Participants with prevalent frailty at examination 8 are excluded (n=52 for Fried criteria, and n=241 for Rockwood criteria). AF indicates atrial fibrillation; and OR, odds ratio.

*Models are adjusted for age, sex, current smoking, height, weight, systolic and diastolic blood pressure, antihypertensive treatment, diabetes mellitus, PR interval, left ventricular hypertrophy, heart murmur, prevalent coronary heart disease, and prevalent heart failure.

cardiovascular system includes adverse cardiac structural and electrophysiological remodeling with age, which predisposes to arrhythmias, most commonly AF.[26] Aging-related changes in the electrical conduction system of the heart may not directly impact other organ systems. This contrasts with other physiologic changes throughout the cardiovascular system, which are related to the development of frailty. For example, the natural increase of collagen cross-linking and reduction in elastin fibers with age lead to increased risk of arterial stiffness and higher afterload and systolic pressure.[27] Similarly, endothelial response to endogenous nitrous oxide declines over the lifespan, which increases the risk of coronary artery disease and peripheral vascular disease.[28] Neither of these physiologic changes is limited to the heart and may be implicated in the bidirectional relationship between CVD and frailty. On the other hand, AF may represent

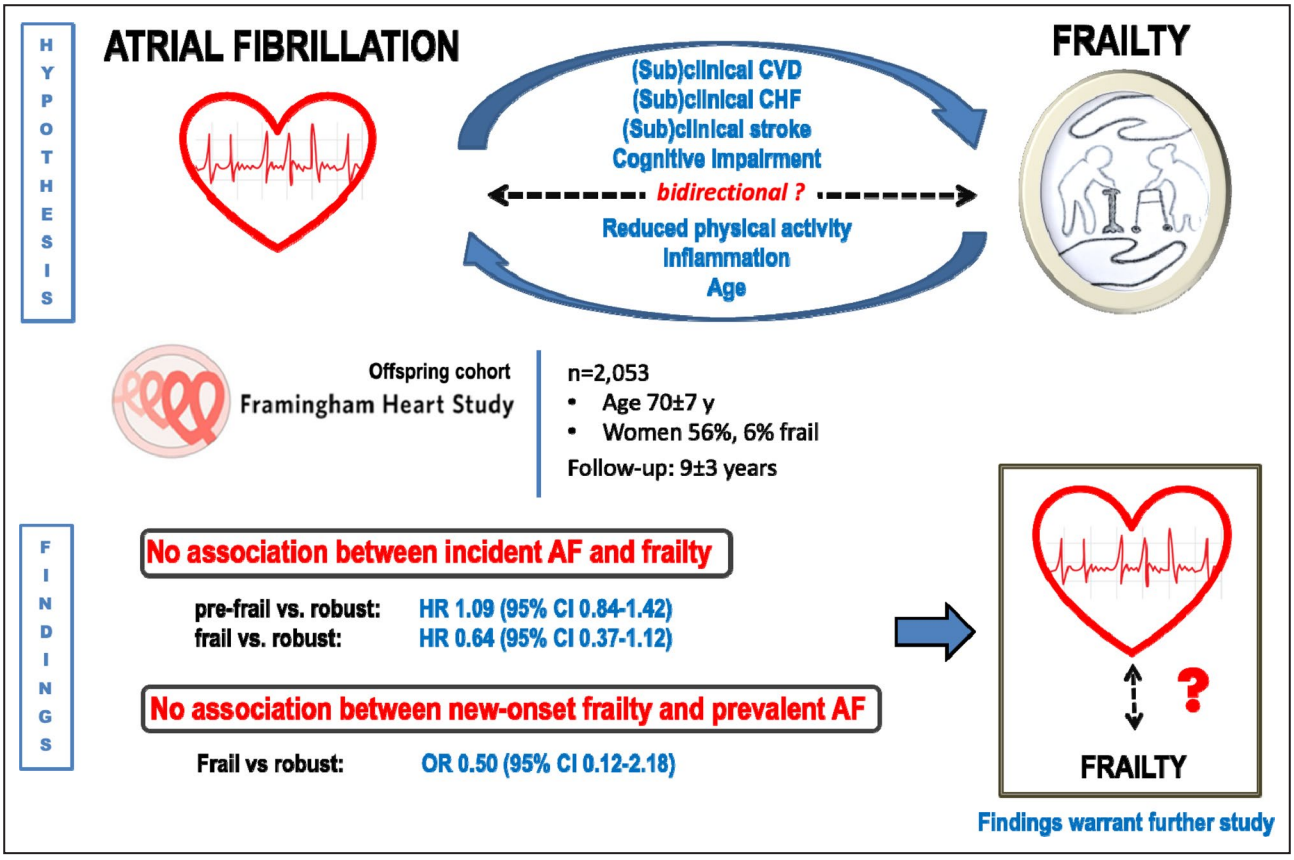

Figure 2. Study summary.
AF indicates atrial fibrillation; CHF, congestive heart failure; CVD, cardiovascular disease; HR, hazard ratio; and OR, odds ratio.

a physiologic change of aging that on its own is not associated with an increased risk of frailty, similar to the development of cataracts, which occur as part of the normal aging process in most people.[19]

Data from the ARIC (Atherosclerosis Risk in Communities) Study reported a higher prevalence of AF among those who were frail (17% versus 7%),[29] as did data from the CHS (4.3% versus 1.5%).[4] The CHS further examined the cross-sectional association between frailty and prevalent AF and found no statistically significant increase in the odds of AF in those who were frail versus nonfrail (OR, 1.90; 95% CI, 0.82–4.39; *P*=0.33), similar to our study.[4] A systematic review conducted in 2017 identified 10 observational cohort studies that explored the relationship between AF and frailty, defined in multiple ways.[30] Results were inconclusive, with an overall suggestion that among those with frailty, AF was common (48%–75%), whereas for those with AF, frailty may be common (4%–75%). Although one included study was longitudinal in design for anticoagulation outcomes,[31] none examined the relationship between frailty and incident AF or AF and incident frailty.

To our knowledge, most studies have instead examined the relationship between poor outcomes and lower use of anticoagulation in those who are frail with AF.[32,33] These are important clinical questions to improve the management of older, frail patients; however, they do not address the underlying questions about whether AF and frailty are related.[34] Further work is needed to understand the interplay between these 2 conditions.

Our study has important limitations. We examined an observational, cohort study; and although we have accounted for many confounders, we cannot exclude residual confounding or establish causal relations. Only those who could complete the frailty assessment for the Fried definition could be included. Participants with missing frailty scores had more adverse risk factor profiles and a higher occurrence of both AF and death, which may have biased the results. The number of events was low, and we may have failed to detect true associations of smaller magnitude between AF and frailty. Results may be not be applicable to other ages and races/ethnicities not represented in the FHS.

This study also has several strengths. FHS has detailed and routinely ascertained covariates, including adjudicated events, such as AF. Using longitudinal data, we were able to examine the bidirectional relationship between the development of AF and frailty. We were able to define frailty according to the 2 leading definitions.

In conclusion, although a bidirectional association between frailty and CVD has been suggested in other studies, we did not find evidence of a relationship between frailty and AF. Our findings may be limited by sample size and should be confirmed in other populations. In addition, further exploration of potential bias attributable to missing frailty status is warranted.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S4

REFERENCES

1. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. DOI: 10.1016/S0140-6736(14)61774-8.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. DOI: 10.1016/S0140-6736(12)62167-9.
3. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014;63:747–762. DOI: 10.1016/j.jacc.2013.09.070.

4. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R, Walston JD, Fried LP. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci*. 2001;56:M158–M166. DOI: 10.1093/gerona/56.3.M158.
5. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222–2231.
6. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol*. 2015;66:985–996.
7. Rienstra M, Lyass A, Murabito JM, Magnani JW, Lubitz SA, Massaro JM, Ellinor PT, Benjamin EJ. Reciprocal relations between physical disability, subjective health, and atrial fibrillation: the Framingham Heart Study. *Am Heart J*. 2013;166:171–178. DOI: 10.1016/j.ahj.2013.02.025.
8. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. DOI: 10.1093/gerona/56.3.M146.
9. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The i.A.N.A Task Force on frailty assessment of older people in clinical practice. *J Nutr Health Aging*. 2008;12:29–37. DOI: 10.1007/BF02982161.
10. Perez-Tasigchana RF, Leon-Munoz LM, Lopez-Garcia E, Gutierrez-Fisac JL, Laclaustra M, Rodriguez-Artalejo F, Guallar-Castillon P. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age Ageing*. 2017;46:807–812. DOI: 10.1093/ageing/afx023.
11. Fumagalli S, Potpara TS, Bjerregaard Larsen T, Haugaa KH, Dobreanu D, Proclemer A, Dagres N. Frailty syndrome: an emerging clinical problem in the everyday management of clinical arrhythmias: the results of the European Heart Rhythm Association survey. *Europace*. 2017;19:1896–1902. DOI: 10.1093/europace/eux288.
12. Mlynarska A, Mlynarski R, Golba KS. Older age and a higher EHRA score allow higher levels of frailty syndrome to be predicted in patients with atrial fibrillation. *Aging Male*. 2017;20:23–27. DOI: 10.1080/13685538.2016.1241761.
13. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham offspring study: design and preliminary data. *Prev Med*. 1975;4:518–525. DOI: 10.1016/0091-7435(75)90037-7.
14. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: the Framingham offspring study. *Am J Epidemiol*. 1979;110:281–290. DOI: 10.1093/oxfordjournals.aje.a112813.
15. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20:1077–1085.
16. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951;41:279–281. DOI: 10.2105/AJPH.41.3.279.
17. Orkaby AR, Lunetta KL, Sun FJ, Driver JA, Benjamin EJ, Hamburg NM, Mitchell GF, Vasan RS, Murabito JM. Cross-sectional association of frailty and arterial stiffness in community-dwelling older adults: the Framingham Heart Study. *J Gerontol A Biol Sci Med Sci*. 2019;74:373–379. DOI: 10.1093/gerona/gly134.
18. Liu CK, Lyass A, Larson MG, Massaro JM, Wang N, D'Agostino RB Sr, Benjamin EJ, Murabito JM. Biomarkers of oxidative stress are associated with frailty: the Framingham Offspring Study. *Age (Dordr)*. 2016;38:1. DOI: 10.1007/s11357-015-9864-z.
19. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24. DOI: 10.1186/1471-2318-8-24.
20. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, Rockwood K. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc*. 2005;53:2184–2189. DOI: 10.1111/j.1532-5415.2005.00506.x.
21. Pajewski NM, Williamson JD, Applegate WB, Berlowitz DR, Bolin LP, Chertow GM, Krousel-Wood MA, Lopez-Barrera N, Powell JR, Roumie CL, et al. Characterizing frailty status in the systolic blood pressure intervention trial. *J Gerontol A Biol Sci Med Sci*. 2016;71:649–655. DOI: 10.1093/gerona/glv228.
22. Abbott RD, McGee DL. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease, Section 37: The Probability of Developing Certain Cardiovascular Diseases in Eight Years at Specified Values of Some Characteristics. Bethesda, MD: National Heart, Lung, and Blood Institute; 1987.
23. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745. DOI: 10.1016/S0140-6736(09)60443-8.
24. Mahmood SS, Wang TJ. The epidemiology of congestive heart failure: the Framingham Heart Study perspective. *Glob Heart*. 2013;8:77–82.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509. DOI: DOI: 10.1080/01621459.1999.10474144.
26. Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S. *Hazzard's Geriatric Medicine and Gerontology*. 6th ed. New York, NY: McGraw-Hill Medical; 2009.
27. Dai X, Hummel SL, Salazar JB, Taffet GE, Zieman S, Schwartz JB. Cardiovascular physiology in the older adults. *J Geriatr Cardiol*. 2015;12:196–201.
28. Herrera MD, Mingorance C, Rodriguez-Rodriguez R, Alvarez de Sotomayor M. Endothelial dysfunction and aging: an update. *Ageing Res Rev*. 2010;9:142–152. DOI: 10.1016/j.arr.2009.07.002.
29. Nadruz W Jr, Kitzman D, Windham BG, Kucharska-Newton A, Butler K, Palta P, Griswold ME, Wagenknecht LE, Heiss G, Solomon SD, et al. Cardiovascular dysfunction and frailty among older adults in the community: the ARIC study. *J Gerontol A Biol Sci Med Sci*. 2017;72:958–964.
30. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R, Onder G, Acampora N. Frailty and atrial fibrillation: a systematic review. *Eur J Intern Med*. 2018;56:33–38. DOI: 10.1016/j.ejim.2018.04.018.
31. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age Ageing*. 2009;38:156–162. DOI: 10.1093/ageing/afn293.
32. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. *Age Ageing*. 2019;48:196–203. DOI: 10.1093/ageing/afy180.
33. Oqab Z, Pournazari P, Sheldon RS. What is the impact of frailty on prescription of anticoagulation in elderly patients with atrial fibrillation? A systematic review and meta-analysis. *J Atr Fibrillation*. 2018;10:1870. DOI: 10.4022/jafib.1870.
34. McManus DD, Kiefe C, Lessard D, Waring ME, Parish D, Awad HH, Marino F, Helm R, Sogade F, Goldberg R, et al. Geriatric conditions and prescription of vitamin K antagonists vs. direct oral anticoagulants among older patients with atrial fibrillation: SAGE-AF. *Front Cardiovasc Med*. 2019;6:155. DOI: 10.3389/fcvm.2019.00155.

Supplemental Material

Table S1. Study Sample Characteristics of the Framingham Heart Study Offspring Cohort Participants Included in the Analysis of Rockwood Frailty Group at Exam 8 and Incident Atrial Fibrillation (N=2,000).

	All Participants (n=2,000)	Rockwood Frailty Group		
		Robust (n=860)	Pre-frail (n=746)	Frail (n=394)
Age, years	69.6 (6.8)	67.7 (6.0)	70.0 (6.8)	72.8 (7.3)
Female	1,125 (56.3)	455 (52.9)	429 (57.5)	241 (61.2)
Current smoker	149 (7.5)	55 (6.4)	54 (7.2)	40 (10.2)
Diabetes	292 (14.9)	37 (4.3)	145 (19.8)	110 (29.5)
Height, inches	65.4 (3.8)	65.9 (3.9)	65.2 (3.7)	64.6 (3.5)
Weight, pounds	171 (38)	165 (33)	174 (40)	180 (43)
Systolic BP, mm Hg	131 (17)	129 (17)	132 (16)	131 (18)
Diastolic BP, mm Hg	73 (10)	74 (9)	73 (10)	69 (11)
Antihypertensive treatment	1,078 (54.0)	351 (40.9)	446 (59.8)	281 (71.7)
PR interval, msec	17.0 (2.9)	16.7 (2.7)	17.0 (2.9)	17.4 (3.1)
Heart Murmur/VHD	63 (3.3)	19 (2.3)	22 (3.1)	22 (6.2)
Left ventricular hypertrophy	14 (0.72)	8 (0.94)	3 (0.42)	3 (0.80)
Prevalent heart failure	25 (1.3)	0 (0.0)	10 (1.3)	15 (3.8)
Prevalent coronary heart disease	207 (10.4)	39 (4.5)	88 (11.8)	80 (20.3)
Fried Frailty score	0.76 (0.95)	0.31 (0.53)	0.77 (0.79)	1.73 (1.18)
Rockwood Frailty Index score	0.14 (0.11)	0.056 (0.028)	0.15 (0.031)	0.32 (0.089)
Usual walking speed, m/s	1.17 (0.26)	1.27 (0.23)	1.17 (0.24)	0.96 (0.25)

All values represent either mean (SD) or n (%). Participants with prevalent AF at exam 8 (n=205) are excluded. Characteristics are measured at exam 8.

msec; milliseconds

m/s; meters/second

Table S2. Study Sample Characteristics of the Framingham Heart Study Offspring Cohort Participants Included in the Analysis of Prevalent Atrial Fibrillation at Exam 8 and New-Onset Frailty, as defined using Rockwood criteria, at Exam 9 (N=1,343).

	All Participants (n=1,343)	Prevalent AF	
		No (n=1,279)	Yes (n=64)
Age, years	68.1 (6.2)	68.0 (6.1)	70.3 (6.4)
Female	702 (53.0)	687 (54.4)	15 (24.2)
Current smoker	80 (6.0)	78 (6.2)	2 (3.2)
Diabetes	139 (10.6)	131 (10.4)	8 (13.1)
Height, inches	65.7 (3.9)	65.6 (3.8)	67.5 (3.9)
Weight, pounds	171 (37)	170 (36)	193 (39)
Systolic blood pressure, mm Hg	129 (17)	129 (17)	127 (17)
Diastolic blood pressure, mm Hg	74 (9)	74 (9)	73 (9)
Antihypertensive treatment	631 (47.7)	595 (47.2)	36 (58.1)
PR interval, msec	16.8 (2.8)	16.8 (2.7)	18.8 (3.2)
Heart murmur	34 (2.6)	33 (2.6)	1 (1.7)
Left ventricular hypertrophy	9 (0.68)	8 (0.65)	1 (1.7)
Prevalent heart failure	10 (0.76)	5 (0.40)	5 (8.1)
Prevalent coronary heart disease	114 (8.6)	95 (7.5)	19 (30.7)
Fried Frailty score	0.48 (0.67)	0.48 (0.68)	0.45 (0.62)
Rockwood Frailty Index score	0.095 (0.053)	0.094 (0.053)	0.11 (0.048)
Usual walking speed, m/s	1.24 (0.24)	1.24 (0.24)	1.18 (0.24)

All values represent either mean (SD) or n (%). Participants with prevalent frailty using Rockwood criteria at exam 8 (n=241) were excluded. Characteristics were measured at exam 8.

msec; milliseconds

m/s; meters/second

Table S3. Summary statistics comparing those with missing or incomplete frailty scores to those with complete frailty scores among FHS Offspring cohort participants aged ≥60 years who attended examination cycle 8 (n=2,328).

Variable	Missing Fried Frailty Score* at Exam 8			Missing Rockwood Frailty Score* at Exam 8		
	No (N=2,265)	Yes (N=63)	P-value**	No (N=2,216)	Yes (N=112)	P-value**
Age, years	70.1 (7.0)	80.0 (7.9)	<0.0001	70.0 (7.0)	77.3 (8.4)	<0.0001
Systolic blood pressure, mm Hg	131 (17)	134 (23)	0.34	131 (17)	134 (20)	0.09
Diastolic blood pressure, mm Hg	72 (10)	69 (10)	0.01	72 (10)	70 (10)	0.02
Female sex	1237 (54.6)	44 (69.8)	0.02	1216 (54.9)	65 (58.0)	0.51
Current smoker	163 (7.2)	4 (6.4)	0.99	158 (7.1)	9 (8.0)	0.72
Hypertension treatment	1254 (55.4)	45 (71.4)	0.01	1231 (55.6)	68 (60.7)	0.29
History of CHD	293 (12.9)	16 (25.4)	0.004	291 (13.1)	18 (16.1)	0.37
History of CHF	71 (3.1)	7 (11.1)	0.004	68 (3.1)	10 (8.9)	0.004
History of AF	206 (9.1)	11 (17.5)	0.02	200 (9.0)	17 (15.2)	0.03
Follow-up status***						
Censored	1350 (65.7)	6 (11.5)	<0.0001	1330 (66.1)	26 (27.7)	<0.0001
Incident AF case	307 (14.9)	14 (26.9)		302 (15.0)	19 (20.2)	
Died	398 (19.3)	32 (61.5)		381 (18.9)	49 (52.1)	

Table values are mean (SD) or n (%) unless otherwise indicated.

*Missingness was defined as ≥2 components for the Fried frailty score or ≥5 components for the Rockwood frailty score.

**P-value calculated using either a t-test, Chi-square test, or Fisher's Exact test, as appropriate.

***Excluding participants with prevalent AF at exam 8 (n=217) or missing AF follow-up information. (n=4).

Table S4. Hazard ratios (HR) and 95% confidence intervals (CI) for the association between frailty status at exam 8 and incident AF*, unadjusted for the competing risk of mortality*.

Model Adjustment	Group	Frailty Criteria					
		Fried (N=2,053)			Rockwood (N=2,000)		
		# AF events/ # participants	HR (95% CI)	P-value	# AF events/ # participants	HR (95% CI)	P-value
Age/sex	Robust	128/1,018	Ref	---	100/860	Ref	---
	Pre-frail	155/903	1.25 (0.98-1.59)	0.07	124/746	1.33 (1.02-1.74)	0.04
	Frail	23/132	1.26 (0.79-2.00)	0.33	74/394	1.64 (1.19-2.25)	0.002
Age/sex/smoking	Robust	128/1,018	Ref	---	100/860	Ref	---
	Pre-frail	155/903	1.24 (0.98-1.58)	0.08	124/746	1.33 (1.01-1.73)	0.04
	Frail	23/132	1.24 (0.78-1.97)	0.38	74/394	1.63 (1.19-2.24)	0.003
Multivariable *	Robust	123/958	Ref	---	96/819	Ref	---
	Pre-frail	139/822	1.10 (0.85-1.42)	0.49	117/690	1.18 (0.88-1.58)	0.27
	Frail	15/106	0.81 (0.46-1.43)	0.54	61/338	1.16 (0.79-1.70)	0.44

*Models are adjusted for age, sex, current smoking, height, weight, systolic and diastolic blood pressure, antihypertensive treatment, current smoking, diabetes, PR interval, left ventricular hypertrophy, heart murmur, prevalent coronary heart disease, and prevalent heart failure.

Participants with prevalent AF at exam 8 are excluded (N=205).