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Reciprocal Relations between Physical Disability, Subjective Health, and Atrial Fibrillation: The Framingham Heart Study

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Abstract

Background—Atrial fibrillation (AF)-related symptoms and physical performance are relied upon to guide therapeutic management of patients with AF. We sought to understand whether AF predisposes to or is a result of physical disability and poor subjective health in the community.

Methods—We studied relations between physical disability (Rosow-Breslau Functional Health Scale), subjective health (self-report) and incident AF, and the converse, in the Framingham Heart Study.

Results—In 3609 participants (age 73±8 years, 59% women), a subset of 861 participants (24%) had prevalent physical disability at baseline. During 5.8±1.8 years follow-up, 555 participants (10-year age- and sex-adjusted incidence rate 13%) developed incident AF. Prevalent physical disability was related to incident AF (multivariable-adjusted hazard ratio [HR], 1.25; 95% CI, 1.02–1.54; *P*=0.03). In 3525 participants, prevalent poor subjective health (*n*=333) also was related to incident AF (*n*=552; multivariable-adjusted HR, 1.31; 95% CI, 1.00–1.70; *P*=0.048). Conversely, in 2080 participants (age 69±6 years, 55% women), interim AF (*n*=106) was associated with newly reported physical disability (*n*=573) at a follow-up examination (multivariable-adjusted odds ratio [OR], 1.58; 95% CI, 1.08–2.31; *P*=0.01). In 1954 participants, interim AF (*n*=96) likewise was related to newly reported poor subjective health (*n*=224; multivariable-adjusted OR, 1.83; 95% CI, 1.10–3.02; *P*=0.02).

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Potential Conflicts of Interest

None.

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Conclusions—Physical disability and poor subjective health were related to incident AF in a community-based cohort. Conversely, interim AF was related to newly reported physical disability and poor subjective health. Since AF guidelines incorporate symptoms, it is essential to clarify the temporality and mechanisms linking physical disability, subjective health and AF.

Keywords

Atrial fibrillation; functional status; disability; epidemiology; risk factor

Reducing cardiovascular morbidity and mortality is a principal goal of atrial fibrillation (AF) therapy. Hence, minimizing AF-related symptoms, and improving both physical performance and quality of life have become major considerations in individualizing therapy for patients with AF.¹

The relations between AF and physical disability and poor subjective health are complex and incompletely understood as reviewed elsewhere.² Whether AF predisposes to or is a result of impaired physical performance is uncertain. AF may compromise cardiac output and subsequently lead to physical disability. Physical performance is reduced in a substantial number of people with AF.³ However, impaired physical performance is not specific for AF. Physical disability may be caused by other conditions, such as musculoskeletal disorders, stroke, cancer, diabetes, heart failure, obesity, or advancing age. Thus, physical disability may represent the burden of underlying conditions, many of which have been identified individually as risk factors for AF. Further, physical disability itself may contribute causally to incident AF.

We hypothesized a reciprocal relation between physical disability and incident AF. Specifically, we postulated that physical disability and poor subjective health are associated with increased risk of incident AF. We further hypothesized that incident AF is associated with increased physical disability and poor subjective health during follow-up.

Methods

Setting and Participants

Participants of the Framingham Heart Study Original Cohort⁴ are examined every two years and participants of the Offspring Cohort⁵ are examined every four to eight years. We used Original Cohort examination cycles 19 (1985–88), 22 (1990–94) and 25 (1997–99) and Offspring Cohort examination cycles 5 (1991–95) and 7 (1998–2001), all with Rosow Breslau and Subjective Health questionnaire data availability. We used examination cycles with overlapping calendar times, and comparable follow-up between examination cycles of both Cohorts. *A priori*, we excluded participants under age 60 years (because of anticipated low incidence rates of both AF and disability), and those with prevalent AF, resulting in 3681 participants (6140 examinations). In 468 participants the questionnaires were obtained at off-site visits, of which 188 were conducted at nursing homes. A flowchart with the exclusions and number of examinations and participants for each analysis is provided in Figure 1. Participants were monitored until the first AF event with ten years maximum follow-up duration. The last follow-up date was August 31, 2009.

For the primary analysis, we excluded participants missing physical performance measurements (355 examinations) when examining physical disability as the exposure and incident AF as the outcome. For the analysis using subjective health as the exposure, we started with the sample used for the primary analysis (Figure 1). From that sample we excluded examinations with missing subjective health (85 examinations). To study whether the occurrence of interim AF (exposure) was related to newly reported physical disability

(outcome), we additionally excluded examinations with prior stroke (86 examinations), prevalent physical disability (1623 examinations), and missing follow-up examinations (1158 examinations; Figure 1). For the analysis using newly reported poor subjective health as outcome, we additionally excluded examinations with missing subjective health (5 examinations), prevalent poor subjective health (155 examinations), and missing follow-up examinations (30 examinations). Newly reported physical disability and poor subjective health were measured at the last examination of each 6 to 8-year time-period. The Framingham Heart Study protocol was approved by Boston University Medical Center's Institutional Review Board. All participants provided written informed consent at each examination.

Outcomes and Follow-up

Atrial fibrillation was diagnosed if atrial flutter or fibrillation was present on an electrocardiogram or Holter monitoring, obtained at Framingham Heart Study clinic visits, outside clinician, or hospital visits. At least two Framingham Heart Study cardiologists reviewed electrocardiograms to verify AF.

Clinical covariates—Body mass index was calculated as weight in kilograms divided by height in meters squared. Current smoking was defined as regular use of cigarettes in the preceding year. Moderate to heavy alcohol use was defined as weekly consumption of at least 14 drinks for men or at least seven drinks for women. A clinically significant heart murmur was diagnosed when a systolic murmur exceeded grade II/VI, or any diastolic murmur was auscultated. Diabetes was defined by fasting blood glucose of 126 mg/dL or greater, or use of insulin or oral hypoglycemic agents. Coronary artery bypass graft surgery was validated with medical records. Participants were diagnosed with heart failure based on standard major and minor clinical criteria.⁶ A committee of three Framingham Heart Study physicians adjudicated heart failure and coronary heart disease (new-onset angina, coronary insufficiency, or myocardial infarction) events.

Physical disability was determined during Framingham examinations by self-report utilizing responses to the Rosow-Breslau Functional Health Scale, with high test-retest reliability.^{7,8} The Rosow-Breslau Functional Health Scale consists of three questions regarding ability to walk 0.5 mile, walk up and down one flight of stairs, and do heavy work around the house.^{9,10} Participants responded whether they were able or unable to do each task without help. Physical disability was considered present when one of the three Rosow-Breslau questions was answered unable.

Subjective health was measured during Framingham examinations with the question: "In general, how is your health now?" or "In general, how would you say your health is?" The participant response was reduced to good health (responses of good, very good, and excellent) or poor health (responses of poor or fair).¹⁰

Statistical Analyses

We tested the hypothesis that physical disability as an exposure is related to the outcome of incident AF during 10-years follow-up using cross-sectional pooling across multiple non-overlapping examinations and Cox proportional hazards models.¹¹ Participants were included at baseline, and were followed up to ten years and were eligible to re-enter the analyses after 12 years of follow-up if they did not develop interim AF. Specific covariates are denoted in the table legends. Briefly, we conducted a series of 3 models. **Model 1** was age- and sex-adjusted; **model 2** was multivariable-adjusted for the components of the AF risk score (age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, heart murmur, heart failure) and plausible baseline confounders; and **model 3**

was model 2 with interim events entered as time-dependent covariates including heart failure, coronary heart disease, coronary artery bypass graft surgery, and stroke occurring between baseline and before incident AF, or if no AF occurred, between baseline and end of follow up.

The hypothesis that interim AF as an exposure is related to the outcome of newly reported physical disability was tested using cross-sectional pooling and logistic regression analyses. Participants were included at baseline and were eligible to re-enter the analyses after six to eight years of follow-up without development of physical disability. The three models were the same as above except Model 3 additionally adjusted for interim cancer occurring between baseline and before physical ability measurement.

In secondary analyses we examined the Subjective Health question instead of physical disability, using the same analytical approach as outlined above. We studied age and sex interactions for the primary analyses. As an exploratory analysis, we examined Kaplan Meier curves adjusted for the competing risk of death. A two-tailed $P < 0.05$ was considered statistically significant except we used $P < 0.10$ for the interaction assessment. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The Framingham Heart Study is supported by the National Heart, Lung and Blood Institute (contract NO1-HC-25195).

Results

Physical disability and incident AF

The sample to examine the association between physical disability and incident AF included 3609 participants (5785 examinations) with a mean age 73 ± 8 years and comprised of 59% women. A subset of 861 participants (1623 examinations) had physical disability (Table 1 and Supplementary Table 1).

During a mean of 5.8 ± 1.8 years follow-up, 555 participants (10-year age- and sex-adjusted incidence rate 13%) developed incident AF (194 with physical disability at baseline; Table 2 and Figure 2A). Physical disability was significantly related to incident AF after multivariable-adjustment including cardiovascular conditions (hazard ratio [HR], 1.25; 95% CI 1.02–1.54; $P = 0.03$) (Table 2). After additional adjustment for interim events (delineated in Supplementary Table 2), baseline physical disability was also statistically significantly related to incident AF (HR, 1.27; 95% CI 1.00–1.61; $P = 0.049$). Age ($P = 0.88$) and sex ($P = 0.91$) did not significantly modify the association between physical disability and AF.

Poor subjective health and incident AF

In secondary analyses, we tested the hypothesis that poor subjective health is related to incident AF in 3525 participants (5700 examinations). At baseline, 333 participants (776 examinations) had poor subjective health (Table 1 and Supplementary Table 1).

During follow up, 552 participants (10-year age- and sex-adjusted incidence rate 13%) developed incident AF (111 with poor subjective health at baseline; Table 2 and Figure 2B). Multivariable models revealed that poor subjective health was related to incident AF, even after adjusting for multiple AF risk factors, cardiovascular conditions, and interim events (HR, 1.31; 95% CI 1.00–1.70; $P = 0.048$; Table 2).

Interim AF and newly reported physical disability

The sample used for the analysis relating interim AF to newly reported physical disability consisted of 2080 participants (2918 examinations, all without physical disability at baseline). Of these, 106 participants (175 examinations) were diagnosed with interim AF in the six to eight-year time window before the follow-up physical disability assessment (Supplementary Table 3).

At the end of the six to eight-year time windows, 573 participants reported physical disability, and 64 of them were diagnosed with interim AF prior to physical ability assessment. Interim AF was significantly related to newly reported physical disability with an odds ratio (OR) of 2.07 (95% CI 1.45–2.96; $P<0.0001$), after multivariable-adjustment (Table 3). After additional adjustment for interim events (delineated in Supplementary Table 4), AF remained significantly related to newly reported physical disability (OR, 1.58; 95% CI 1.08–2.31; $P=0.01$). Again, no significant age ($P=0.22$) or sex ($P=0.65$) interactions were found.

Interim AF and newly reported poor subjective health

The sample to test the hypothesis that interim AF is related to newly reported poor subjective health, consisted of 1954 participants (2728 examinations; Supplementary Table 3). A subset of 96 participants (160 examinations) was diagnosed with interim AF in the six to eight-year time-window before subjective health assessment.

At the end of the six to eight-year time windows, 224 participants newly reported poor subjective health. Of these, 29 were diagnosed with AF prior to subjective health assessment. Interim AF diagnosed before subjective health assessment was related to newly reported poor subjective health, even after adjusting for multiple AF risk factors, cardiovascular conditions, and interim events (OR, 1.83; 95% CI 1.10–3.02; $P=0.02$; Table 4 and Supplementary Table 4).

Competing risk of death

To address a potential bias, we examined Kaplan Meier curves accounting for the potential competing risk of death. We found comparable risk estimates; the cumulative incidence of AF by presence or absence of physical disability, and by presence or absence of poor subjective health are depicted in Supplementary Figure 1A and 1B).

Discussion

In a community-based cohort we observed that physical disability and poor subjective health were associated with increased risk of incident AF. Conversely, interim AF was related to increased risk of newly reported physical disability and poor subjective health. Physical disability and AF are common in the elderly and frequently coexist.² Both conditions are associated with an increased risk of death and hospitalization, and may lead to poor quality of life, a reduction in work capacity, and impaired performance of activities of daily living. Consequently, both conditions are accompanied by high socioeconomic costs due to increased healthcare utilization and inability to work.

Based on our observations, over ten percent of individuals reporting a physical disability in the community will develop AF within the next ten years. Because disability has been associated with cardiovascular risk factors such as advancing age,^{12,13} smoking,^{12,13} higher body mass index,¹³ hypertension,^{12,13} diabetes,¹³ less physical activity,¹² and stroke,^{13,14} we adjusted for these covariates in our analysis. We observed that the relation between self-reported physical disability, poor subjective health and incident AF was not markedly

attenuated by established risk factors for AF,¹⁵ and other prevalent cardiovascular conditions. Further adjustments for interim cardiovascular events did not dramatically change the hazard ratio; the relation remained statistically significant for both physical disability and poor subjective health.

Although cardiovascular conditions have been related to physical disability, more often physical disability occurs as a result of non-cardiovascular disorders.⁶ The heterogeneity in the potential causes of physical disability makes it difficult to study the mechanisms underlying physical disability and incident AF. Several studies have linked diminished physical activity to increased risk of AF.¹⁶ In addition, physical disability and AF share common risk factors. A potential biological mechanism underlying a decline in physical performance is inflammation. In older adults, inflammation is related to a decline in physical performance¹⁷; inflammation may increase AF risk.¹⁸ In a Japanese community-dwelling study, N-terminal B-type natriuretic peptide was related to disability.¹⁹ Natriuretic peptides are also associated with an increased risk for AF.¹⁸ In addition, obstructive sleep apnea is a risk factor for both disability and AF.²⁰ Another possibility is that physical disability in older adults is merely a marker of an increased AF risk. Other socioeconomic and lifestyle factors associated with physical disability may increase the risk for AF. Whether physical disability is causally related to AF is uncertain and will warrant further investigation.

We also observed that about one third of the individuals with interim AF reported a disability at a subsequent physical disability assessment. Again, adjustments for other cardiovascular conditions did not eliminate the relation between AF and newly reported physical disability or poor subjective health. Our findings support and extend prior observations on associations between AF and impaired functional performance and capacity.^{2,21} It has been proposed that AF may compromise cardiac output, as a result of impaired diastolic filling, left ventricular systolic dysfunction, and loss of atrioventricular synchrony.^{22,23} Data from small observational studies suggest that functional capacity, an individual's maximum potential to carry out activities of daily living or self-care,²⁴ is reduced by approximately 10–15% in individuals with AF.³ Termination of AF with electrical cardioversion has been reported to be associated with an improvement in functional capacity to a similar degree;²⁵ however the improvement documented in more recent randomized trials was rather modest.^{21,26} Whether therapies aiming to treat or control AF may improve physical disability or subjective health, needs to be demonstrated.

Strengths of our study include a large, well-characterized cohort with systematic ascertainment of AF, cardiovascular disease risk factors, and self-reported physical disability and subjective health. Our study is also subject to several limitations. We assessed physical disability and subjective health using short, easy-to-use and well-validated subjective questionnaires. More objective measures of physical performance, such as exercise tests or walking speed measures were not available in a substantial number of participants. Including objective measures of physical performance and functional status would have strengthened our analyses. Our participants were at least 60 years of age at the baseline examination, non-hospitalized and virtually all of European ancestry; whether our results are generalizable to other races and ethnicities, younger individuals, and hospitalized individuals is uncertain. Although our findings suggest a bidirectional relation between physical disability, subjective health, and incident AF, the design of the Framingham Heart Study, with two-year examination cycles in the Original Cohort and four-year cycles in the Offspring Cohort precludes definitive conclusions regarding the temporality of interim AF and subsequent physical disability or poor subjective health. At some time in the years before physical disability or poor subjective health was assessed, interim AF occurred. Since we were unable to assess physical ability or subjective health directly before and after incident AF occurred, it remains uncertain whether AF itself or other factors may have

contributed to the decrease in physical ability or subjective health. The diagnosis of interim AF, and the associated treatment strategies, may have negatively influenced the patients' perception of physical disability or subjective health. We sought to address the role of interim events by adjusting for them. Residual confounding from multiple potential etiologies for disability, or treatment of AF is also possible, e.g. we did not systematically ascertain and account for data regarding non-cardiovascular conditions potentially influencing physical disability and subjective health, and for the effectiveness of AF management. We acknowledge that an observational study such as Framingham, cannot establish causal relations between AF, physical disability and poor subjective health. Finally, we did not distinguish between paroxysmal, persistent and permanent AF, and asymptomatic AF may have been overlooked; we note that the relations between physical disability, subjective health and AF may vary by AF subtype and AF symptoms.

A cornerstone in the decision-making for the most optimal therapy for AF, according to the most recent guidelines for AF,¹ are symptoms related to AF. Our findings suggest that physical disability and subjective health may not only be the result of AF but may be risk markers for incident AF.

We observed a bidirectional association between physical disability and poor subjective health, and incident AF in the community. Whether therapies aiming to improve physical performance and subjective health will prevent AF, and alternatively, whether treatment of AF may impact physical performance and subjective health, needs to be determined. AF symptom status is incorporated into AF guidelines. Hence, future studies need to delineate the mechanisms linking physical disability, subjective health and AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart with the exclusions and number of examinations and participants in each analysis. Blue boxes = Framingham Heart Study sample and subset; Red boxes = Subsets for analyses with incident AF as dependent variable, and physical disability/ poor subjective health as exposures; Green boxes = Subsets for analyses with newly reported physical disability/ poor subjective health as dependent variables and interim AF as exposure.

Figure 2.

Cumulative incidence of AF by presence or absence of physical disability (**A**), and by presence or absence of poor subjective health (**B**).

Table 1

Characteristics of participants at baseline examinations, according to presence or absence of physical disability or poor subjective health.*

Variable	Baseline Physical Disability		Baseline Poor Subjective Health	
	Absent	Present	Absent	Present
N, participants	2748	861	3192	333
N, examinations	4162	1623	4924	776
Age (years)	71±7	78±8	72±8	76±8
Women	2234 (54%)	1195 (74%)	2878 (58%)	487 (63%)
Current smoking	444 (11%)	168 (10%)	508 (10%)	104 (13%)
Alcohol use	803 (19%)	223 (14%)	930 (19%)	95 (12%)
Body mass index (kg/m ²)	27.2±4.5	27.3±5.4	27.2±4.6	27.3±5.4
Systolic blood pressure (mmHg)	137±20	139±21	137±20	141±22
Hypertension	2537 (61%)	1155 (72%)	3086 (63%)	568 (73%)
Antihypertensive therapy	1723 (42%)	884 (55%)	2155 (44%)	419 (55%)
Diabetes	466 (11%)	242 (15%)	566 (12%)	129 (17%)
PR interval duration (msec)	169±29	171±31	169±29	171±31
Heart murmur	83 (2%)	56 (4%)	109 (2%)	28 (4%)
Heart failure	24 (0.6%)	100 (6%)	73 (1%)	47 (6%)
Coronary heart disease	532 (13%)	411 (25%)	710 (14%)	214 (28%)
Previous coronary artery bypass graft surgery	82 (2%)	50 (3%)	104 (2%)	28 (4%)

* Data presented are related to number of examinations.

Data presented as mean ± standard deviation or n (%).

Table 2

Models relating physical disability or poor subjective health to incident AF

Table 2a: Samples and Rates				
Exposure	Physical Disability		Poor Subjective Health	
	Absent	Present	Absent	Present
N, examinations	4162	1623	4924	776
Outcome Incident AF				
N, participants	555		552	
10-year age- and sex-adjusted incidence rate (95% CI)	13% (11 – 15%)		13% (11 – 15%)	
N, participants with outcome by absence vs. presence of physical disability or poor subjective health	361	194	441	111
10-year age- and sex-adjusted incidence rate (95% CI)	12% (10 – 14%)	15% (12 – 17%)	12% (10 – 14%)	17% (13 – 20%)

Table 2b: Cox proportional hazards models relating physical disability or poor subjective health to incident AF

Model Adjustment	HR (95% CI)	P value	HR (95% CI)	P value
Model 1=age and sex	1.44 (1.18–1.75)	0.0003	1.57 (1.26–1.94)	<0.0001
Model 2=Multivariable	1.25 (1.02–1.54)	0.03	1.42 (1.13–1.79)	0.002
Model 3=Model 2 + Time varying covariates*	1.27 (1.00–1.61)	0.049	1.31 (1.00–1.70)	0.048

Model 2 = Multivariable AF risk score covariates [age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, heart murmur, heart failure] + smoking, alcohol, diabetes, coronary heart disease, coronary artery bypass grafting surgery, and stroke *(baseline stroke is excluded for the poor subjective health analysis)

Model 3 = Model 2 + time-varying: heart failure, coronary heart disease, coronary artery bypass grafting surgery, and stroke

Abbreviations: CI = confidence interval; HR = hazards ratio

Table 3

Models relating interim AF to newly reported physical disability or poor subjective health.

Table 3a: Samples by interim AF status				
Exposure	Interim AF			
	Absent	Present	Absent	Present
N, Participants	1974	106	1858	96
N, examinations	2743	175	2568	160
Outcome	Newly reported physical disability		Newly reported poor subjective health	
N, participants with outcome	573		224	
N, participants with outcome by absence vs. presence of interim AF	509	64	195	29

Table 3b: Pooled logistic regression models relating interim AF to newly reported physical disability or poor subjective health.				
Model Adjustment	OR (95% CI)	P value	OR (95% CI)	P value
Model 1=age and sex	2.42 (1.72–3.39)	<0.0001	2.40 (1.55–3.72)	<0.0001
Model 2=Multivariable	2.07 (1.45–2.96)	<0.0001	2.24 (1.40–3.57)	0.0008
Model 3=Model 2 + Interim cardiovascular events*	1.58 (1.08–2.31)	0.01	1.83 (1.10–3.02)	0.02

Model 2 = Multivariable, AF risk score covariates + smoking, alcohol, diabetes, coronary heart disease, coronary artery bypass grafting surgery, cancer and stroke *(baseline stroke is excluded for the poor subjective health analysis)

Model 3 = Model 2 + interim: heart failure, coronary heart disease, coronary artery bypass grafting surgery, and stroke

Abbreviations: CI = confidence interval; OR = odds ratio