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Frailty Predicts Incident Atrial Fibrillation in Women but Not in Men: The Kuopio Ischaemic Heart Disease Risk Factor Study

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Keywords
Frailty · Arrhythmia · Atrial fibrillation · Population study

Abstract

Introduction: Frailty and atrial fibrillation (AF) are common aging problems and increasing globally. The association(s) between frailty and AF has been inconclusive. The purpose of this prospective population-based cohort was to investigate the associations between frailty and incident AF in older men and women. ***Methods:*** In total 839 participants, women (n = 458) and men (n = 381), aged 61–74 years from the Kuopio Ischaemic Heart Disease Risk Factor Study were included (March 1, 1998, to December 31, 2001). At the baseline, frailty prevalence was 49.3% (n = 414), and non-frailty 50.7% (n = 425) of the total population. Frailty was ascertained with the presence of 3–5 and prefrailty 1–2 of the following criteria: weight loss (highest 20% over 7 years), self-reported tiredness, weakness (measured by handgrip strength), slow walking speed (walking pace), and low physical activity (lowest 20%). AF events were obtained by record linkages from the national computerized hospitalization registry in Finland up to December 31, 2019. Multivariate Cox proportional hazard regression estimated the hazard ratio (HR) of incident events, adjusted for potential confounders. ***Results:*** During the mean follow-up of 14.2 years, 288 AF cases (169 women; 119 men) occurred. After adjustment for possible confounders, the HRs (95% confidence intervals [CIs]) for AF was 1.46 (1.48–1.85) in the frail population, compared to the non-frail group. The association was observed only among older frail women (multivariable-adjusted HR 1.78, 95% CI [1.28–2.48]) (p for interaction = 0.04). No statistically significant associations were observed between frailty and future AF incident among men (multivariable-adjusted HRs 1.12, 95% CI (0.77–1.63)). ***Conclusions:*** In this population-based epidemiological cohort, the risk of developing AF was increased in women affected by frailty at baseline but not in men.

Introduction

Frailty is an emerging global health burden, with major implications for clinical practice and older adults [1, 2]. Atrial fibrillation (AF) is the most common sustained arrhythmia seen in the clinical practice worldwide, with an estimated 6–12 million people worldwide suffering this condition in the USA by 2050 and 17.9 million people in Europe by 2060 [3]. Unsurprisingly, frailty prevalence and incidence of AF increase with age [4] and are

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associated with an increased risk of mortality and morbidity from stroke, heart failure and dementia, and high healthcare costs [5–7].

There are also sex-specific differences in the epidemiology and clinical presentation of many cardiovascular disorders, including AF [8]. Evidence from large observational studies reported that AF incidence in men is higher than in women [9, 10]. The Framingham Heart Study reported that AF incidence in women is 1.6 cases per 1,000 person-years compared with 3.8 cases per 1,000 person-years in men [11]. Therefore, it would be important to investigate the risk factors of AF in an aging population on a sex-based approach.

Aging frailty is captured by the decline in biological functions, deterioration of physiological performance, reduction in the ability to respond to external stressors, and an associated increase in vulnerability [12, 13]. Indeed, frailty and AF can be understood both as consequences of biological aging and conditions that worsen biological aging. Cardiologists use frailty as an established care pathway to determine procedural risks and treatment strategies for the patient [5]. Common risk factors such as chronic inflammation have been identified for frailty and cardiovascular diseases (CVD), hospitalization [14], multimorbidity [15], and mortality [16]. A recent systematic review and meta-analysis showed a link between frailty and multimorbidity, with the latter contributing to incident AF, stroke, and other cardiovascular conditions [17–19]. Large observational studies have also indicated that frailty is highly prevalent among patients with diabetes mellitus [20], CVD [14, 21], AF [17], and heart failure [22]. One Swiss study showed that frailty predicted unplanned hospitalization, stroke, bleeding, and death in AF [23]. However, studies investigating frailty as predictor of incident AF are scarce. For example, Framingham Heart Study did not find significant association between frailty and AF, but the sex-frailty interaction was not reported [24]. In this population-based study, we investigated frailty as a predictor of AF incident in older adults in total population and by sex, utilizing data from the Kuopio Ischaemic Heart Diseases Risk Factor Study (KIHD).

Material and Methods

The KIHD is a population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in men from eastern Finland [25]. A total of 2,682 men (82.9% of those eligible) who were 42, 48, 54, or 60 years old and living in the city of Kuopio or its surrounding areas were recruited for the baseline examinations in 1984–1989. These participants underwent re-examinations at 4 years, 11 years, and 20 years after baseline. During the 11-year follow-up examination, women were invited to join the study. The current analysis is based on 11 years of follow-up and initially comprised 2,358 participants (1,007 men and 1,351 women). Of those, 2,072 participants were found to be potentially eligible, 193 did not agree to participate, 66 did not respond to the invitation, and 39 declined to provide informed consent, which left 1,774 aged 53–74 years participants who had baseline assessments carried out between March 1998 and February 2001 [26].

The KIHD protocol was approved by the Research Ethics Committee of Kuopio University and Kuopio University Hospital on December 1, 1983 (at that time the date served as the decision reference number) and again on October 27, 1997 (the decision reference number 143/97). All the subjects signed written informed consent. Study participants were not involved in the design, conduct, reporting, or dissemination plans of the current study. Subjects with a history of AF at baseline (n = 54) were excluded from the analyses. We also excluded participants with missing data on frailty (n = 881), leaving 839 participants, women (n = 458) and men (n = 381).

The Assessment of AF

All AF incident AF events that occurred from 11-year follow-up through December 31, 2019, were included. Data on events were obtained by record linkages from the national computerized hospitalization registry, which covers every hospitalization and visit in outpatient specialized healthcare in Finland (Permission THL/93/5.05.00/2013). Subjects were hospitalized because of AF or had AF when they were hospitalized for other reasons. Data on vital status were obtained from Statistics Finland (Permission TK/782/07.03.00/2021). Cardiovascular causes of AF were coded according to International Classification of Diseases codes (8th revision code 427.4, 9th revision code 427.3, and 10th revision code I48), and the accuracy was verified by a physician.

Frailty Ascertainment

We have defined frailty at 11 years of follow-up using criteria developed originally by Fried and colleagues [13]. To define frailty, we used variables in five domains according to the frailty phenotype definition (handgrip strength, walking speed, physical activity, weight loss, and exhaustion) [13]. All the assessment was performed by trained nurses for KIHD study.

Handgrip strength was measured by a hand dynamometer (Martin-Balloon-Vigorimeter; Gebrüder Martin, Tuttlingen, Germany). Measurements were taken with the subjects standing in an upright position and their arms parallel to their bodies. Two measurements were taken for the dominant hand and the mean of both values was used for analysis. A one-minute resting gap was given between both handgrip measurements [27]. Study subjects belonging to the lowest quintile, separately for men and women, were considered frail and scored one for the analyses. We also applied frailty phenotype cut-offs of <27 kg/m^2 for men and <16 kg/m^2 for women but these resulted in lower n compared to the corresponding lowest quintiles. Walking speed was captured by assessing the walking speed as the mean of two attempts to walk a constant distance. Low walking speed was defined as belonging to the lowest 20%. Those belonging to low walking speed received 1 score and otherwise 0.

For the physical activity, the method of assessment and the intra-person variability of various physical activities in the KIHD were described in detail by Lakka and Salonen [28]. Briefly, data on

the total leisure-time physical activity were available for the 12-month activity history with a questionnaire modified from the Minnesota leisure-time activity questionnaire (Taylor Questionnaire). All KIHD subjects were asked to fill in the frequency, duration, and intensity of each activity performed during the previous 12 months. For this study, low physical activity was defined as belonging to the lowest 20%, and those belonging to low physical activity levels received 1 score and otherwise 0.

The weight change criteria according to the frailty phenotype refer to a loss of ≥5% of body weight over 12 months. In these data, we used a surrogate indicating a longer term weight change for 7 years before frailty ascertainment, which may have effect on the proportion of frailty. Those belonging to the highest 20%, i.e., the highest weight changed over the past 7 years corresponded to ca. ≥16% change in weight. Subjects in the highest 20% of weight loss received 1 score and otherwise 0.

Self-reported exhaustion was defined by Fried and colleagues [13] using two questions from the Center for Epidemiologic Studies Depression Scale (CESD) ("I felt that anything I did was a big effort" and "I felt that I could not keep on doing things"). In the KIHD data, the assessment of tiredness (exhaustion) was conducted by merging two measurements for feeling tired over the past 12 months and feeling for lack of energy over the past 12 months before frailty ascertainment at 11 years of follow-up. If the response to both questions was yes, daily, the subject received 1 score and otherwise 0. According to the frailty phenotype [13], the final frailty score was computed by adding the results from these five categories. Frailty was present for the score of 3 or more and robust for score of 0.

Other Measurements

Comprehensive descriptions of the sociodemographic and lifestyle characteristics, prevalent medical conditions, and use of medications have been reported previously [26]. Education and annual income were assessed using self-administered questionnaires. Dietary intakes were assessed using 4-day food recording at the time of blood sampling [29]. Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters. Obesity was defined the BMI higher than 25 kg/m^2.

Statistical Analysis

The univariate associations of frailty scores with demographic, lifestyle, and clinical characteristics at baseline were assessed by linear regression for continuous variables and χ^2 test for categorical variables. To ensure that those excluded from the study did not differ significantly for their baseline characteristics, we performed an independent sample *t* test, and results did not show any significant difference for included versus excluded subjects. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) of incident events. The validity of the proportional hazard assumption was evaluated using Schoenfeld residuals, and the assumptions were met. Furthermore, the analyses were controlled for possible confounders, which were selected based on established risk factors for AF, or on associations with exposures or outcomes in the present analysis. Given the objective of our study, all analyses were conducted for men and women separately.

Two different models were used to control for confounding factors. Model 1 was adjusted for age (years), gender, and examination year. The multivariate model 2 included model 1 smoking (pack/years), years of education, intake of alcohol (grams/week), obesity, systolic and diastolic blood pressure (mm Hg), and use of anti-hypercholesterolemia or antihypertensive medications at baseline or during follow-up (yes or no). Additional adjustment for LDL-cholesterol, HDL-cholesterol, serum triglyceride concentration, BMI, heart diseases such as ischemic heart disease, valvular disease, and heart failure, and diabetes, renal dysfunction, and sleep apnea syndrome did not materially alter the associations. Statistical significance of the interactions on a multiplicative scale was assessed by stratified analysis according to gender and likelihood ratio tests with a cross-product term. All *p* values were two-sided ($\alpha = 0.05$). Data were analyzed using the SPSS software version 27 for Windows (IBM Corp.; Armonk, NY, USA).

Results

Baseline Characteristics

Among the 839 (458 women and 381 men) participants aged 68.6 ± 2.9 years, frailty prevalence was 49.3% ($n = 414$), and non-frail 50.7% ($n = 425$). Table 1 shows the baseline characteristics of the entire population, women, and men. Women were older, more educated, had higher BMI, and were more often users of antihypertensive and anti-hypercholesterolemia medications, had lower physical activity, lower alcohol intake, and less likely to be smokers compared with men.

Baseline characteristics of the participants according to their frailty status are presented in Table 2. Compared with non-frail women, frail women were older, less educated, less physically active, had higher BMI, higher systolic blood pressure, consumed less alcohol, were more likely to be antihypertensive medication users, and had lower handgrip strength (Table 2). The associations were generally similar among frail men (Table 2).

Frailty Score and AF

During a mean follow-up of 14.2 years, 288 AF cases (169 cases in women, 119 cases men) occurred. After adjustment for age, sex, and examination year, frailty was associated with higher HRs of AF (HR 1.52, 95% confidence interval (CI), 0.1.21–1.94; $p = 0.003$) (model 1, Table 3). Further adjustment for potential confounders did not materially change the association (HR 1.46, 95% CI, 0.1.48–1.85; $p = 0.002$) (model 2, Table 3).

We found statistically significant interactions between the women and men for frailty score (p for interaction = 0.04). We observed statistically significant associations between the frailty and risk of AF only in frail women (multivariate-adjusted HRs 1.78 [95% CI, 1.28–2.48, p = 2.58, 95% CI, 1.38–4.68, $p = 0.001$]). No significant associations were observed between frailty score and risk of AF among men (multivariate-adjusted HRs 1.12, 95% CI [0.77–1.63], $p = 0.54$).

Table 1. Baseline characteristics of the study population

Characteristic	All (n = 839)	Women (n = 458)	Men (n = 381)	Without AF (n = 551)	With AF (n = 288)
Age, years	68.6 (2.9)	68.8 (2.9)*	68.3 (2.9)	68.3 (2.9)	69.0 (2.9)*
Education, years	8.7 (3.4)	9.0 (3.4)*	8.4 (3.4)	8.8 (3.5)	8.6 (3.3)
BMI, kg/m^2	28.0 (4.4)	28.7 (4.9)*	27.2 (3.5)	27.8 (4.3)	28.5 (4.4)*
Physical activity, kcal/day	178 (179)	173 (173)	183 (187)*	179 (178)	176 (183)
Obesity (%)	75.1	76.9*	72.9	73.7	77.8*
Current smoker (%)	35.1	22.9	61.7*	37	31.3
Alcohol intake, g/week	34 (72)	23 (25)	49 (97)*	36 (70)	29 (76)
Diabetes (%)	15.1	14.4	15.7	15.8	13.5
Anti-hypercholesterolemia medication (%)	6.4	7.6*	5.1	7.1	5.2
Antihypertensive medication (%)	51.2	54.6*	47.0	44.5	63.9*
Sex hormone medication (%)	13.3	24.2	0.3	14.9*	10.4
Systolic blood pressure, mm Hg	139 (18)	140 (18)	137 (18)	138 (18)	141 (18)
Diastolic blood pressure, mm Hg	80 (9)	79 (9)	81 (9)	80 (9)	80 (9)
Handgrip strength, kPA	76.0 (21.0)	75.4 (24.1)	76.6 (16.4)*	76.6 (22.6)	74.7 (17.4)
Non-frail (%)	50.7	46.5	55.6	52.3	45.1
Frail (%)	49.3	53.5	44.4	47.7	54.9

Independent sample t test was used to calculate means, SD, and frequency. *p value ≤0.05 for the comparison between genders.

Table 2. Baseline characteristics according to frailty status

	All participants (n = 839)		Women (n = 458)		Men (n = 381)	
	frailty status		frailty status		frailty status	
	non-frail	frail	non-frail	frail	non-frail	frail
No. of subjects (%)	425 (50.7)	414 (49.3)	213 (46.5)	245 (53.5)	212 (55.6)	169 (44.4)
Age, years	68.2 (2.9)	68.9 (2.6)*	68.4 (2.8)	69.1 (2.8)*	68.1 (2.9)	68.4 (2.4)*
Education, years	9.0 (3.6)	8.4 (2.9)*	9.3 (3.5)	8.7 (3.3)*	8.7 (3.6)	8.1 (3.2)*
Body mass index, kg/m^2	27.2 (3.8)	28.8 (4.4)*	27.4 (4.1)	29.8 (5.1)*	27.1 (3.5)	27.3 (3.5)*
Physical activity, kcal/day	213 (201)	144 (147)*	207 (194)	144 (148)*	215 (208)	142 (142)*
Current smoker (%)	35.6	36.3	10.0	14.8	61.8	68.3*
Alcohol consumption, g/week	36.6 (66.8)	31.4 (77.4)	13.6 (23.9)	11.9 (26.9)*	59.4 (85.5)	59.6 (99.7)*
Diabetes (%)	13.4	16.7*	12.2	16.3	14.6	17.2
Anti-hypercholesterolemia medication (%)	7.1	5.8	8.9	6.5	5.2	4.7
Antihypertensive medication (%)	45.9	56.5*	47.4	60.8*	44.3	50.3*
Systolic blood pressure, mm Hg	139 (18)	138 (19)	140 (18)	141 (18)*	138 (18)	136 (16)
Diastolic blood pressure, mm Hg	80 (9)	79 (9)*	80 (9)	80 (8)	81 (9)	80 (8)
Handgrip strength, kPA	82.2 (22.4)	69.1 (17.8)*	82.1 (23.9)	69.6 (18.6)*	82.1 (21.6)	69.8 (16.9)*

Results being presented are mean (SD) for continuous variables and n (%) for categorical data. *$p \leq 0.05$.

Discussion

In this study, our main finding showed that the risk of developing AF during a mean follow-up of 14.2 years in those affected by frailty at baseline only in women. Data on the association between AF and frailty have been conflicting, and previous studies conducted analysis to report frailty as a prevalent condition in patients with AF [18, 30]. Frailty also predicts mortality and length of hospitalization in AF patients [18]. Although frailty has

Table 3. HRs and 95% CIs for the association between frailty and incident AF

		Frailty Score	
		non-frail	frail
Total population			
AF events/participants	228/839	131/425	157/414
Model 1	–	1 (reference group)	1.52 (1.21–1.94)*
Model 2	–	1 (reference group)	1.46 (1.48–1.85)*
Women			
AF events/participants	169/458	61/213	108/245
Model 1	–	1 (reference group)	1.94 (1.22–2.67)*
Model 2	–	1 (reference group)	1.78 (1.28–2.48)*
Men			
AF events/participants	119/381	70/212	49/169
Model 1	–	1 (reference group)	1.13 (0.79–1.64)
Model 2	–	1 (reference group)	1.12 (0.77–1.63)

Model 1: adjusted for age and examination year. Model 2: adjusted for model 1 plus smoking, years of education, intake of alcohol, obesity, systolic and diastolic blood pressure, and use of anti-hypercholesterolemia or antihypertensive medications at baseline or during follow-up. *p* value ≤0.01. *Values are hazard ratios (95% confidence interval).

been identified as an important predictor of cardiovascular outcomes [21], prospective data on the association of frailty with incident AF are scarce.

While the finding of association between frailty and AF was perhaps expected, the findings for this association being only in women were less predictable. Although many risk factors for AF have been identified in their relative effect between sexes, in contrast other important cardiovascular risk factors such as hypertension (odds ratio [OR], 1.5 in men; 1.4 in women), diabetes mellitus (OR, 1.4 in men; 1.6 in women), obesity (OR, 1.8 in men; 1.4 in women), and myocardial ischemia (OR, 1.4 in men; 1.2 in women) appear more consistent between the sexes [8, 11, 31]. The adjustment for these risk factors in our study did not materially change our findings. This study also showed a significant sex-frailty interaction, and BMI was the only significant risk factor, which was higher in women compared to men.

Our findings were in alignment with gender-specific mechanisms involved in cardiovascular and frailty development. The finding from a nationwide analysis of sex differences in patients with AF showed that women have more symptoms, more functional impairment, and worse quality of life despite less persistent from AF [32, 33]. In addition, previous studies have shown that women experience greater levels of frailty than men [34, 35]. However, the lack of a significant association in men in this study could be due to other factors such hormones and genetic exposures which can be sex-dependent and could be affecting the link between frailty in women but not men in this study.

In the Framingham Heart Study Offspring Cohort, prospective findings indicated no statistically significant association between frailty (defined by Fried phenotype and Rockwood score) and incident AF [24], while the authors of that study have used pleiotropy of aging as an explanation for this finding and suggested that AF may represent the physiologic change of aging independent of those associated with risk of frailty, and compared this with the development of cataracts, which occur as part of the normal aging process in most people [24], but also acknowledged that there are multiple common pathways for frailty and AF. They did not report whether the association was different between men and women. In contrast, Polidoro et al. [36] found that AF was strongly associated with frailty status independent of age, sex, and common diseases of elderly people. A systematic review by Guo et al. [17] concluded that frailty affects both the management and prognosis of AF in the geriatric population. Hence, the move toward a more holistic and integrated approaches to AF characterization [37] and management, based on the Atrial Fibrillation Better Care pathway [38]. Adherence to the latter has been shown to be associated with a significantly better prognosis in terms of mortality, stroke, bleeding, and hospitalizations [39–41].

Chronic inflammation is a major pathogenic factor of frailty caused by oxidative stress, hormonal, and metabolic alterations [21, 34, 42], which are systematic manifestations of atherosclerosis and cardiovascular risk

factors [43–45]. Sex differences for inflammation and frailty have also been reported [46, 47]. Higher levels of inflammatory markers have been reported in patients with AF [48, 49]. Inflammation and oxidative stress are pivotal mechanisms in the setting of hypertension, which may also promote AF [48, 49]. In addition, inflammation is an important pathophysiological mechanism of AF in patients with obesity. Obesity is associated with a higher risk of AF and frailty, and in the current study, women had higher BMI compared with men, which could potentially explain the significant association between frailty and AF.

We acknowledge that our study has limitations. Due to low number of participants in the frail category and to increase the statistical power in Cox regression analysis, frail and prefrail were grouped together. This was an observational cohort study, and although we have accounted for many confounders, residual confounding or establishing causal relations with AF and frailty cannot be excluded. Prior studies have used different measures of frailty such as Rockwood [50] or Fried [13] definitions, which can partly explain the discrepancies. AF events were low over the follow-up, we may have failed to detect true associations of smaller magnitude between AF and frailty. Given the trajectory of frailty, more participants would expect to become frail over the follow-up time, yet in our study the existing association could capture the association of frailty at baseline with AF and having frailty data for follow-up could increase the magnitude of this association but not the clinical significance.

Conclusion

In conclusion, in this population-based epidemiological cohort, frailty was associated with incident AF in women but not in men. Further investigations into frailty and AF with longer follow-up are warranted to substantiate these results.

Statement of Ethics

The KIHD protocol was approved by the Research Ethics Committee of Kuopio University and Kuopio University Hospital on December 1, 1983 (at that time the date served as the decision reference number) and again on October 27, 1997 (the decision reference number 143/97). All the subjects signed written informed consent.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

B.T. and T.-P.T. acquired the data and designed and conducted the research; B.T. and M.I. had equal contribution in conceptualization, methodology, and writing the first draft. B.T. and A.V. worked on data curation and B.T. conducted the main data analysis. All other authors, T.-P.T., A.V., A.L., J.K., and G.Y.H.L. critically revised the manuscript for important intellectual content, writing review, and editing.

Data Availability Statement

The KIHD data are not publicly available. The use of the KIHD data is authorized by the University of Eastern Finland (UEF). All authorizations are personal and fixed-duration. If a researcher would like to join the KIHD study group, he/she must first contact the principal investigator of KIHD at the UEF Institute of Public Health and Clinical Nutrition. Further inquiries can be directed to the corresponding author.

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