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ORIGINAL ARTICLE

Risk Factors for the Development of New-Onset Persistent Atrial Fibrillation: Subanalysis of the VITAL Study

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BACKGROUND: Sustained forms of atrial fibrillation (AF) are associated with lower treatment success rates and poorer prognosis compared with paroxysmal AF. Yet, little is known about risk factors that predispose to persistent AF on initial presentation. Our objective was to define risk factors associated with new-onset persistent AF.

METHODS: We prospectively examined the differential associations between lifestyle, clinical, and socioeconomic risk factors and AF pattern (persistent versus paroxysmal) at the time of diagnosis among 25 119 participants without a history of cardiovascular disease, AF, or cancer in the VITAL rhythm study (Vitamin D and Omega-3).

RESULTS: During a median follow-up of 5.3 years, 900 participants developed AF and 346 (38.4%) were classified as persistent at the time of diagnosis. In multivariable competing risk models, increasing age, male sex, White race, height, weight, body mass index ≥30 kg/m^2, hypertension, current or past smoking, alcohol intake ≥2 drinks/day, postcollege education, and randomized treatment with vitamin D were significantly associated with incident persistent AF. Compared with paroxysmal AF, increasing age, male sex, weight, body mass index ≥30 kg/m^2, and postcollege education were more strongly associated with persistent AF in multivariable models regardless of whether interim cardiovascular disease and heart failure events were censored.

CONCLUSIONS: In a prospective cohort without baseline AF or cardiovascular disease, over one-third of AF at the time of diagnosis is persistent. Older age, male sex, postcollege education, and obesity were preferentially associated with persistent AF and represent a high-risk AF subset for population-based intervention.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arrhythmias ■ atrial fibrillation ■ cardiovascular diseases ■ lifestyle ■ risk factors

Atrial fibrillation (AF), the most common arrhythmic disorder,[1] is associated with significant morbidity, increased mortality, and considerable health care costs.[2,3] The pattern of AF, which varies from short episodes of self-terminating AF to long-lasting persistent AF, has a significant impact on subsequent prognosis. Persistent forms of AF have been associated with a higher risk of stroke or thromboembolism,[4] worse cardiovascular morbidity, and subsequently increased mortality compared with paroxysmal forms.[5–7] Furthermore, patients with persistent forms of AF are less amenable to antiarrhythmic drugs, ablation, and restoration of sinus rhythm.[8,9] Recent efforts have been focused on early treatment to restore sinus rhythm to prevent the progression of paroxysmal to persistent AF.[10] However, many patients present with persistent AF at the time of AF diagnosis before the treatment can be initiated. The importance of risk factor modification in patients with

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WHAT IS KNOWN?

- Atrial fibrillation (AF) is a highly prevalent arrhythmia; current data suggest those with persistent forms of AF have worse outcomes and prognosis.
- A significant proportion of patients present with persistent AF as their first manifestation of AF; thus, strategies aimed at preventing the early development of persistent AF are needed.

WHAT THE STUDY ADDS

- This study identified several risk factors that are associated with new-onset persistent AF, of which increasing age, male sex, increasing weight, higher body mass index, and postcollege education were more strongly associated with persistent AF at initial diagnosis compared with paroxysmal AF.
- Individuals with these risk factors represent a high-risk AF subset, who can be selected for early population-based intervention to prevent persistent AF.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BMI	body mass index
CVD	cardiovascular disease
HR	hazard ratio
ICD	International Classification of Diseases
LA	left atrial
LVEF	left ventricular ejection fraction
VITAL	vitamin D and Omega-3

AF for the reduction in symptoms and burden has been shown[11,12]; thus, understanding the risk factors predisposing to an initial presentation of persistent AF is key.

Clinical and lifestyle risk factors associated with the development of AF are well established[13–18]; however, studies examining which of these risk factors are associated with new-onset persistent AF are sparse. Prior studies have examined cardiovascular risk factors for the development of paroxysmal and persistent AF up to 2 years after the initial diagnosis,[19,20] during which time treatment strategies could have impacted AF pattern. An improved understanding of risk factors that predispose to persistent forms of AF on initial presentation may help to identify a subgroup of patients in whom implementation of preventive strategies could potentially reduce AF-related adverse outcomes.

To address this gap, we utilized the VITAL rhythm trial (Vitamin D and Omega-3), a large contemporary cohort without cardiovascular disease (CVD), prior AF, or cancer, to examine the association between baseline lifestyle, clinical, and socioeconomic risk factors and incident persistent AF. We then examined whether there were differential associations between risk factors and AF pattern (paroxysmal versus persistent) as assessed at the time of initial presentation.

METHODS

Study Design and Study Population

The VITAL trial and the VITAL rhythm study have been previously described.[21,22] The data that support the findings of this study are available from the corresponding author upon reasonable request. Briefly, the VITAL trial was a double-blind, placebo-controlled randomized trial involving 25 871 men ≥50 years of age and women ≥55 years of age with no history of CVD or cancer that utilized a 2×2 factorial design to evaluate daily supplementation with 2000 IU of vitamin D3 and 840 mg of marine omega-3 fatty acids in the primary prevention of CVD and cancer. The VITAL rhythm study was an ancillary trial embedded within the VITAL trial, which examined the impact of vitamin D and omega-3 fatty acids on incident AF risk in 25 119 participants after excluding for prevalent AF (n=752) baseline.[22] The study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, MA.

Risk Factor Assessments

At baseline, all participants completed a questionnaire that collected comprehensive information on demographics, medical history, lifestyle, dietary habits, and clinical risk factors. Predefined covariates included age (years), sex, race (White, Black, or other), weight, height, body mass index (BMI) kg/m^2, history of hypertension, diabetes, smoking (never smoked, former smoker, or current smoker), alcohol frequency (weekly or daily levels), physical activity (tertiles of total weekly metabolic equivalent task hours), annual income (<$50 000, $5000–$120 000, or >$120 000), and education level (categorized as no high school, high school or general educational development, college, or post-college). Additional variables were collected in the patients with AF at the time of incident diagnosis, including rate control, rhythm control, anticoagulation, left ventricular ejection fraction (LVEF), left atrial (LA) enlargement, left ventricular hypertrophy, mitral valve disease, other valvular disease, cardiac device, implantable cardiac device (pacemaker or implantable cardiac defibrillator), acute condition at AF diagnosis, and cardiac or other surgery.

Incident AF Ascertainment and AF Pattern Assignment

Incident AF episodes were identified by self-report on annual follow-up questionnaires and linkage to claims data from the Centers for Medicare and Medicaid Services using validated *International Classification of Diseases* (*ICD*) codes for AF (*ICD*, *Ninth Revision*: 427.31; *ICD*, *Tenth Revision*: I148.0, I48.1, I48.2, and I48.91) and atrial flutter (*ICD*, *Ninth Revision*: 427.32; *ICD*, *Tenth Revision*: I48.3, I48.4, and I48.92). For all new AF diagnoses identified by either method, permission to obtain medical records pertaining to the initial AF diagnosis was requested, and incident AF events and AF pattern at the time of diagnosis were confirmed by an end-point committee comprised of cardiologists blinded to treatment group according to predefined criteria.[22,23] Confirmation of incident AF required ECG evidence and physician

report outlining AF diagnosis. The date of onset was defined as the earliest documented evidence of AF within the medical record. Incident AF pattern was determined through a review of all available medical records inclusive of the documented medical history in the physicians' notes, ECGs, rhythm strips, and ECG monitoring. The pattern of AF at the time of diagnosis was classified in accordance with the latest American College of Cardiology/AHA/HRS and European Society of Cardiology guidelines as paroxysmal AF defined as self-terminating within 7 days and persistent AF as an episode lasting >7 days.[24] Medical record review was also used to obtain information about AF treatment within the first month of diagnosis, echocardiogram results, and comorbid conditions at the time of AF diagnosis.

Statistical Analysis

Baseline characteristics were stratified by AF type and compared using a *t* test or Wilcoxon rank-sum test for continuous variables (depending on normality) and χ^2 test or Fisher exact test for categorical variables. To evaluate differential relationships for AF risk factors according to AF type, we used age- and multivariable-adjusted proportional hazards regression models stratified by paroxysmal and persistent AF according to the competing risk method of Lunn and McNeil.[20,25] This method allows for the assessment of risk factor associations with the 2 AF types simultaneously in a single proportional hazards model and assumes different associations for each risk factor with paroxysmal and persistent AF. To test whether risk estimates for each individual risk factor differ according to the 2 AF patterns, we compared this model to a series of reduced models in which 1 risk factor at a time was forced to have a single effect estimate across both outcomes, while the effects of all other risk factors were allowed to be different. We used likelihood ratio tests to compare the full competing risk model with the individual reduced models. Model 1 controlled for age and randomized treatment. Model 2 additionally controlled for AF risk factors, including sex, race, BMI (kg/m^2), height (cm), and weight (kg), hypertension, diabetes, smoking status, alcohol intake, physical activity (metabolic equivalent task) hours, annual income, and education level. To evaluate the degree to which the association between risk factors and AF types may be mediated by the development of interim cardiovascular events, model 3 censored participants who developed incident CVD (myocardial infarction, cerebral vascular accident, and heart failure) before their AF diagnosis.

Secondary analyses using case-only logistic regression models limited to the population who developed AF were performed with persistent AF as the outcome to determine the sensitivity of the risk factor differences to further control for echocardiographic measures and acute conditions and surgery at the time of AF. All analyses were performed using SAS 9.4 for Windows (Cary, NC). A 2-sided $P<0.05$ was used to define statistical significance.

RESULTS

Baseline Characteristics According to AF Type at Initial Diagnosis

During a median follow-up of 5.3 years, 900 cases of incident AF were confirmed. Of these cases, 526 (58.4%) were paroxysmal, 346 (38.4%) were persistent at the time of initial AF diagnosis, and in 28 (3%), the pattern of AF could not be determined. Compared with those who presented with paroxysmal AF, participants who presented with persistent AF were more likely to be men and taller, weigh more, and have a higher BMI and a history of hypertension (Table 1). Participants with persistent AF were less likely to have been diagnosed following cardiac surgery and were more likely to have a lower LVEF, greater LA enlargement, and valvular disease (all $P<0.001$) on the initial echocardiogram (Table 2).

With respect to the initial treatment strategy, participants presenting with persistent AF were more likely to undergo cardioversion and be treated with oral anticoagulation within the first month of diagnosis but were equally likely to be treated with rate control or antiarrhythmic drugs. Catheter ablation and surgical maze procedures were uncommon in the first month in both groups but tended to be more prevalent in the participants with persistent AF (6.1% versus 3.2%; $P=0.045$).

Risk Factors Associated With Risk of Incident Persistent AF

After multivariable adjustment (Table 3; multivariable model 2), age (hazard ratio [HR], 1.11 [95% CI, 1.09–1.13]), weight (HR, 1.35 [95% CI, 1.26–1.44]), height (HR, 1.29 [95% CI, 1.09–1.52]), BMI (HR, 1.09 [95% CI, 1.07–1.11]), hypertension (HR, 1.65 [95% CI, 1.29–2.11]), current or past smoking (HR, 1.35 [95% CI, 1.08–1.70]), ≥2 alcoholic beverages per day (HR, 1.52 [95% CI, 1.09–2.11]), and postcollege education (HR, 1.66 [95% CI, 1.06–2.60]) were all significantly associated with the development of incident persistent AF in the study population. Randomized treatment with vitamin D was also significantly associated with developing incident persistent AF (HR, 1.27 [95% CI, 1.02–1.58]) after multivariable adjustment. Female sex (HR, 0.57 [95% CI, 0.45–0.73]), and Black race (HR, 0.23 [95% CI, 0.13–0.40]) were inversely associated with the development of persistent AF in multivariable models (Table 3; multivariable model 2).

Differential Relationships of Risk Factors for Persistent Versus Paroxysmal AF

In multivariable-adjusted competing risk models comparing risk factor associations for persistent versus paroxysmal AF, older age, male sex, increasing weight and BMI, and postcollege education level were more strongly associated with persistent AF compared with paroxysmal AF (Table 3; model 2; *P* values for nonequal association).

Each increasing year of age was associated with an 11% risk of persistent AF at initial diagnosis compared with 8% for paroxysmal AF ($P=0.01$). Among men, HR for incident persistent AF was 1.75 (95% CI, 1.37–2.22) compared with 1.11 (95% CI, 0.92–1.35) for paroxysmal

Table 1. Baseline Characteristics

	Persistent AF (n=346)	Paroxysmal AF (n=526)	*P* value
Age, y; median (IQR)	71.1 (66.3–77.6)	70.1 (66.4–75.5)	0.124
Sex, n (%)			0.005
Female	137 (39.6)	259 (49.2)	
Male	209 (60.4)	267 (50.8)	
Race, n (%)			0.536
White	294 (85.0)	458 (87.1)	
Black	19 (5.5)	29 (5.5)	
Other/unknown/missing	33 (9.5)	39 (7.4)	
Height, in., median (IQR)	69.0 (65.0–71.0)	68.0 (65.0–71.0)	0.013
Weight, lbs., median (IQR)	194.0 (163.5–230.0)	180.0 (156.0–208.0)	<0.001
Body mass index, median (IQR)	28.0 (25.0–32.8)	27.1 (24.2–30.7)	0.002
Body mass index categories, kg/m^2			0.007
<25	85 (25.3)	162 (31.6)	
25–29.9	120 (35.7)	203 (39.6)	
≥30	131 (39.0)	148 (28.8)	
Hypertension, n (%)	231 (67.2)	306 (58.4)	0.009
Systolic blood pressure, n (%)*			0.197
<120	70 (20.2)	132 (25.1)	
120–129	103 (29.8)	167 (31.7)	
130–139	84 (24.3)	108 (20.5)	
≥140	41 (11.8)	45 (8.6)	
Diastolic blood pressure, n (%)*			0.091
<80	197 (56.9)	326 (62.0)	
80–89	93 (26.9)	106 (20.2)	
≥90	6 (1.7)	16 (3.0)	
Diabetes, n (%)	54 (15.7)	64 (12.2)	0.148
CHA_2DS_2-VASc, n (%)			0.374
0	18 (5.2)	27 (5.1)	
1	47 (13.6)	90 (17.1)	
≥2	281 (81.2)	409 (77.8)	
Smoking, n (%)			0.065
Never	141 (41.8)	247 (47.8)	
Former	185 (54.9)	244 (47.2)	
Current	11 (3.3)	26 (5.0)	
Alcohol, n (%)			0.153
≥2 drinks per d	73 (21.3)	89 (17.1)	
1 drink per d	40 (11.7)	80 (15.4)	
1–6 drinks per wk	110 (32.2)	186 (35.7)	
<1 drink per wk	119 (34.8)	166 (31.9)	
Weekly MET minutes, n (%)			0.024
Lowest tertile	130 (38.1)	154 (29.4)	
Middle tertile	104 (30.5)	192 (36.7)	
Highest tertile	107 (31.4)	177 (33.8)	
Vigorous MET minutes per wk, n (%)			0.389
0–75 min	183 (53.7)	265 (50.7)	
≥75 min	158 (46.3)	258 (49.3)	
EPA-DHA and vitamin D, n (%)	101 (29.2)	131 (24.9)	0.505
EPA-DHA only	87 (25.1)	136 (25.9)	
Vitamin D only	81 (23.4)	140 (26.6)	
Placebo only	77 (22.3)	119 (22.6)	
Education status, n (%)			0.426
No high school, high school	29 (8.4)	53 (10.1)	
College	140 (40.5)	226 (43.0)	
Post-college	177 (51.2)	247 (47.0)	
Annual income, n (%)			0.176
<$50 000	114 (35.3)	158 (33.5)	
$50 000–$120 000	152 (47.1)	205 (43.4)	
>$120 000	57 (17.6)	109 (23.1)	
Implantable cardiac device			
Pacemaker, n (%)	24 (6.9)	46 (8.7)	0.336
ICD, n (%)	5 (1.4)	4 (0.8)	0.331
Acute condition at AF diagnosis, n (%)	110 (31.8)	146 (27.8)	0.321
AF postcardiac surgery, n (%)	9 (2.6)	55 (10.5)	<0.001

AF indicates atrial fibrillation; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MET, metabolic equivalent task; and SBP, systolic blood pressure.
*Data are missing for SPB and DBP, 14% and 15%, respectively.

AF (*P*=0.004). For each 1-kg/m^2 BMI, the respective increase in the HR was 9% (95% CI, 7%–11%) for persistent AF compared with 3% (95% CI, 1%–5%) for paroxysmal AF (*P*<0.001). For those with a BMI >30 kg/m^2, the HR for developing persistent AF was 2.47 (95% CI, 1.81–3.37) compared with 1.47 (95% CI, 1.15–1.89) for paroxysmal AF; *P*=0.01. For each additional 10 kg of weight, the hazard of developing persistent AF increased by 35% (95% CI, 26%–44%) compared with 14% (95% CI, 7%–21%) for paroxysmal AF (*P*≤0.001). Compared with those with high school education, participants with a postcollege education had a 1.66-fold (95% CI, 1.06–2.60-fold) higher hazard for the development of persistent AF compared with a 0.93-fold (95% CI, 0.67-fold to 1.30-fold) risk of paroxysmal AF (*P*=0.04). Participants with postcollege education were more likely to be of White race, male sex, and taller and consume higher amounts of alcohol intake, whereas all other AF risk factors (obesity, diabetes, hypertension, and smoking) were less prevalent (data not shown). Other risk factor associations, including randomization to vitamin D, did not significantly differ across AF subtypes.

After censoring for interim CVD, the differential associations for age, male sex, weight, BMI, and postcollege education persisted, whereas a marginal differential association for current or past smoking trended toward

Table 2. Results of Initial Echocardiogram and AF Treatment*

AF only variables	Persistent AF (n=346)	Paroxysmal AF (n=526)	*P* value
Rate control, n (%)			
Medication	277 (80.1)	412 (78.3)	0.539
AVJ ablation/PM	4 (1.2)	0 (0)	0.025
Rhythm control, n (%)			
Medication	94 (27.2)	127 (24.1)	0.315
Ablation/maze	21 (6.1)	17 (3.2)	0.045
Cardioversion	99 (28.6)	67 (12.7)	<0.001
Anticoagulation, n (%)	296 (85.5)	319 (60.6)	<0.001
LV ejection fraction, n (%)	58 (51–62)	60 (55–65)	<0.001
LA enlargement, n (%)	223 (64.5)	215 (40.9)	<0.001
LVH, n (%)	119 (34.4)	159 (30.2)	0.212
Mitral valve disease, n (%)	85 (24.6)	51 (9.7)	<0.001
Other valvular disease, n (%)	54 (15.6)	49 (9.3)	0.002

AF indicates atrial fibrillation; AVJ, atrioventricular junction; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; and PM, pacemaker.

*Within 30 d of diagnosis.

significance (HR, 1.40 [95% CI, 1.10–1.77] for persistent AF versus HR, 1.04 [95% CI, 0.86–1.26] for paroxysmal AF; *P*=0.058).

AF Case Only Logistic Regression Analysis

To further explore the differential association between echocardiographic measures and acute conditions present at the time of AF diagnosis, we constructed logistic regression models limited to the AF cases with persistent AF as the outcome. In age-adjusted analysis, LA enlargement, mitral valvular disease, and other valvular diseases were all associated with greater odds of presenting with persistent as opposed to paroxysmal AF, whereas higher LVEF was associated with lower odds of presenting with persistent AF (Table SI; Table 4). In addition, participants who developed incident AF in the setting of cardiac or other surgery had lower odds of presenting with persistent AF compared with paroxysmal AF. After further controlling these 5 variables (LA size, LVEF, mitral valve disease, other valvular diseases, and cardiac and other surgeries), male sex and BMI remained significantly associated with incident persistent AF compared with paroxysmal AF in multivariable-adjusted analysis (Table 4). A trend toward an association with persistent AF remained for postcollege education (*P*=0.071) and obesity (*P*=0.078); however, age was no longer associated with persistent AF after controlling the additional echocardiographic parameters.

DISCUSSION

In this prospective study of over 25 000 healthy participants without CVD, prior AF, or cancer who were followed for over 5 years, we found more than a third of participants with new-onset AF present with a persistent AF at the time of diagnosis. Increasing age, hypertension, higher BMI, increasing weight, smoking, higher alcohol intake, postcollege education, and randomization to vitamin D were significantly associated with an increased risk of new-onset persistent AF after multivariable adjustment for cardiovascular risk factors. We also found that increasing age, male sex, increasing weight, higher BMI, and postcollege education were differentially associated with persistent AF at initial diagnosis compared with paroxysmal AF. After further controlling echocardiographic parameters among AF cases only, age was no longer differentially associated with persistent AF, but the associations for male sex and BMI with persistent AF remained.

Patients who present with an initial diagnosis of persistent AF have been reported to have higher rates of mortality than those who present with paroxysmal AF[7] and poorer outcomes after ablation compared with those who progress to persistent AF from paroxysmal AF.[26,27] Thus, to have an impact on these adverse outcomes, preventive efforts need to begin before AF becomes clinically manifest. If the relationships with incident persistent AF observed in our study are causal, controlling blood pressure, maintaining a healthy weight, avoidance of smoking, and reducing alcohol intake would be expected to reduce the burden of persistent AF within the population. Although randomization to vitamin D was also associated with a significantly elevated hazard for incident persistent AF, this finding should be interpreted with caution because the prespecified age- and treatment-adjusted analyses were not significant.[22] However, these latter results were also more consistent with harm than benefit of this common supplement on persistent AF risk. The relationship between education and persistent AF is also novel and may be due, in part, to greater health literacy and health care utilization resulting in a higher likelihood of receiving an ECG, which may be more likely to pick up persistent forms of AF. Higher levels of education were also associated with greater alcohol intake, which represents an important modifiable risk factor for persistent AF in this subset of the population.

Our results, in combination with prior work examining risk factors for the development of persistent AF within 2 years of AF diagnosis,[19,20] suggest that efforts to decrease adiposity and maintain a healthy weight would be predicted to have the greatest impact on the overall population burden of persistent AF. Among 35 000 women without CVD in the Women's Health Study,[20] BMI and weight, along with age and hemoglobin A1c, were found to be more strongly associated with the development of persistent AF compared with paroxysmal AF at 2 years. Similarly, BMI, along with age, hyperthyroidism, higher heart rate, and heart failure, was found to be associated with the development of persistent AF compared with paroxysmal AF within 2 years of diagnosis in 486

Table 3. Baseline Cardiovascular and Lifestyle Risk Factors for New-Onset Persistent AF: Age- and Multivariable-Adjusted Hazard Ratios (95% CI) for the Development of Persistent vs Nonpersistent AF

	Persistent AF	*P* value*	Paroxysmal AF	*P* value*	*P* value†
Age, y					
Age-adjusted model 1	1.10 (1.08–1.11)	<0.001	1.08 (1.07–1.09)	<0.001	0.083
Multivariable-adjusted model 2	1.11 (1.09–1.13)	<0.001	1.08 (1.07–1.09)	<0.001	0.011
Multivariable-adjusted model 3	1.11 (1.09–1.13)	<0.001	1.08 (1.06–1.09)	<0.001	0.007
Female					
Age-adjusted model 1	0.53 (0.43–0.66)	<0.001	0.81 (0.68–0.97)	0.018	0.003
Multivariable-adjusted model 2	0.57 (0.45–0.73)	<0.001	0.90 (0.74–1.09)	0.270	0.004
Multivariable-adjusted model 3	0.56 (0.43–0.72)	<0.001	0.95 (0.77–1.16)	0.599	0.002
Race					
Age-adjusted model 1					
White	Reference		Reference		
Black	0.32 (0.20–0.52)	<0.001	0.30 (0.20–0.43)	<0.001	0.788
Other	0.73 (0.51–1.04)	0.081	0.55 (0.40–0.77)	<0.001	0.277
Multivariable-adjusted model 2					
White	Reference		Reference		
Black	0.23 (0.13–0.40)	<0.001	0.32 (0.22–0.48)	<0.001	0.333
Other	0.71 (0.48–1.04)	0.081	0.54 (0.38–0.77)	<0.001	0.308
Multivariable-adjusted model 3					
White	Reference		Reference		
Black	0.24 (0.13–0.44)	<0.001	0.33 (0.22–0.51)	<0.001	0.387
Other	0.67 (0.44–1.02)	0.060	0.55 (0.37–0.80)	0.002	0.475
Weight, per 10 kg					
Age-adjusted model 1	1.37 (1.31–1.44)	<0.001	1.14 (1.09–1.19)	<0.001	0.000
Multivariable-adjusted model 2a	1.35 (1.26–1.44)	<0.001	1.14 (1.07–1.21)	<0.001	<0.001
Multivariable-adjusted model 3	1.34 (1.25–1.44)	<0.001	1.14 (1.07–1.22)	<0.001	0.002
Height, per 10 cm					
Age-adjusted model 1	1.57 (1.41–1.74)	<0.001	1.31 (1.20–1.43)	<0.001	0.009
Multivariable-adjusted model 2a	1.29 (1.09–1.52)	0.003	1.34 (1.17–1.53)	<0.001	0.726
Multivariable-adjusted model 3	1.35 (1.14–1.61)	<0.001	1.38 (1.20–1.59)	<0.001	0.869
BMI (per kg/m^2 increase)					
Age-adjusted model 1	1.07 (1.05–1.08)	<0.001	1.02 (1.00–1.03)	0.027	0.000
Multivariable-adjusted model 2a	1.09 (1.07–1.11)	<0.001	1.03 (1.01–1.05)	<0.001	<0.001
Multivariable-adjusted model 3	1.08 (1.06–1.11)	<0.001	1.03 (1.01–1.05)	0.001	0.001
BMI categories					
Age-adjusted model 1					
<25 kg/m^2	Reference		Reference		
25–29.9 kg/m^2	1.26 (0.95–1.66)	0.108	1.08 (0.88–1.33)	0.471	0.388
>30 kg/m^2	2.30 (1.74–3.03)	<0.001	1.26 (1.00–1.58)	0.046	0.001
Multivariable-adjusted model 2					
<25 kg/m^2	Reference		Reference		
25–29.9 kg/m^2	1.14 (0.85–1.53)	0.375	1.07 (0.86–1.33)	0.531	0.732
>30 kg/m^2	2.47 (1.81–3.37)	<0.001	1.47 (1.15–1.89)	0.002	0.010
Multivariable-adjusted model 3					
<25 kg/m^2	Reference		Reference		
25–29.9 kg/m^2	1.08 (0.80–1.47)	0.607	1.01 (0.80–1.28)	0.916	0.729
>30 kg/m^2	2.46 (1.78–3.38)	<0.001	1.45 (1.11–1.89)	0.006	0.013

(*Continued*)

Table 3. Continued

	Persistent AF	*P* value*	Paroxysmal AF	*P* value*	*P* value†
Hypertension					
Age-adjusted model 1	1.73 (1.38–2.17)	<0.001	1.21 (1.02–1.44)	0.032	0.014
Multivariable-adjusted model 2	1.65 (1.29–2.11)	<0.001	1.29 (1.07–1.55)	0.008	0.111
Multivariable-adjusted model 3	1.60 (1.24–2.06)	<0.001	1.37 (1.12–1.67)	0.002	0.336
Diabetes					
Age-adjusted model 1	1.18 (0.88–1.57)	0.275	0.88 (0.68–1.15)	0.359	0.156
Multivariable-adjusted model 2	0.91 (0.66–1.25)	0.568	0.93 (0.70–1.23)	0.604	0.936
Multivariable-adjusted model 3	0.85 (0.60–1.20)	0.356	0.83 (0.61–1.15)	0.270	0.939
Smoking (current or past)					
Age-adjusted model 1	1.49 (1.20–1.85)	<0.001	1.16 (0.98–1.38)	0.090	0.073
Multivariable-adjusted model 2	1.35 (1.08–1.70)	0.009	1.10 (0.92–1.32)	0.289	0.162
Multivariable-adjusted model 3	1.40 (1.10–1.77)	0.006	1.04 (0.86–1.26)	0.681	0.058
Alcohol intake					
Age-adjusted model 1					
<1 drink per wk	Reference		Reference		
1–6 drinks per wk	1.05 (0.81–1.37)	0.691	1.27 (1.03–1.57)	0.025	0.272
1 drink per d	1.07 (0.75–1.53)	0.701	1.55 (1.18–2.02)	0.001	0.105
≥2 drinks per d	1.82 (1.36–2.43)	<0.001	1.55 (1.20–2.01)	<0.001	0.429
Multivariable-adjusted model 2					
<1 drink per wk	Reference		Reference		
1–6 drinks per wk	1.04 (0.78–1.37)	0.804	1.16 (0.93–1.45)	0.193	0.538
1 drink per d	0.98 (0.67–1.44)	0.920	1.29 (0.97–1.72)	0.084	0.263
≥2 drinks per d	1.52 (1.09–2.11)	0.013	1.29 (0.97–1.71)	0.078	0.461
Multivariable-adjusted model 3					
<1 drink per wk	Reference		Reference		
1–6 drinks per wk	1.02 (0.76–1.37)	0.880	1.37 (1.08–1.75)	0.011	0.131
1 drink per d	0.98 (0.66–1.47)	0.932	1.58 (1.16–2.15)	0.004	0.064
≥2 drinks per d	1.46 (1.03–2.06)	0.032	1.55 (1.14–2.10)	0.005	0.805
Physical activity					
Age-adjusted model 1					
Low tertile	Reference		Reference		
Middle tertile	0.80 (0.62–1.03)	0.087	1.24 (1.00–1.53)	0.050	0.010
Highest tertile	0.89 (0.69–1.15)	0.373	1.22 (0.98–1.51)	0.076	0.033
Multivariable-adjusted model 2					
Low tertile	Reference		Reference		
Middle tertile	0.87 (0.66–1.15)	0.326	1.18 (0.94–1.47)	0.157	0.097
Highest tertile	1.02 (0.77–1.36)	0.889	1.19 (0.94–1.50)	0.157	0.424
Multivariable-adjusted model 3					
Low tertile	Reference		Reference		
Middle tertile	0.92 (0.69–1.22)	0.555	1.18 (0.93–1.50)	0.178	0.186
Highest tertile	1.01 (0.75–1.36)	0.951	1.14 (0.89–1.48)	0.299	0.530
Treatment assignment					
EPA-DHA treatment					
Age-adjusted model 1	1.11 (0.90–1.38)	0.317	1.07 (0.90–1.27)	0.458	0.757
Multivariable-adjusted model 2	1.09 (0.88–1.36)	0.423	1.08 (0.91–1.29)	0.385	0.935
Multivariable-adjusted model 3	1.02 (0.81–1.28)	0.881	1.16 (0.96–1.40)	0.125	0.389
Vitamin D treatment					
Age-adjusted model 1	1.19 (0.97–1.48)	0.100	1.03 (0.87–1.23)	0.708	0.297

(*Continued*)

Table 3. Continued

	Persistent AF	*P* value*	Paroxysmal AF	*P* value*	*P* value†
Multivariable-adjusted model 2	1.27 (1.02–1.58)	0.035	1.03 (0.86–1.22)	0.778	0.141
Multivariable-adjusted model 3	1.28 (1.02–1.61)	0.037	1.04 (0.86–1.26)	0.682	0.174
Annual income					
Age-adjusted model 1					
Income <$50,0000	Reference		Reference		
Income $50,0000-$120 000	1.20 (0.94–1.53)	0.144	1.14 (0.92–1.40)	0.227	0.743
Income >$120 000	1.33 (0.96–1.83)	0.085	1.74 (1.36–2.23)	<0.001	0.191
Multivariable-adjusted model 2					
Income <$50,0000	Reference		Reference		
Income $50,0000-$120 000	0.95 (0.72–1.25)	0.722	0.99 (0.79–1.25)	0.942	0.821
Income >$120 000	1.02 (0.71–1.47)	0.901	1.41 (1.06–1.87)	0.019	0.176
Multivariable-adjusted model 3					
Income <$50,0000	Reference		Reference		
Income $50,0000-$120 000	0.93 (0.70–1.24)	0.625	0.97 (0.76–1.25)	0.840	0.811
Income >$120 000	1.08 (0.75–1.58)	0.673	1.45 (1.07–1.96)	0.018	0.242
Education level					
Age-adjusted model 1					
High school	Reference		Reference		
College	1.56 (1.04–2.32)	0.030	1.35 (1.00–1.83)	0.047	0.582
Post-college	1.73 (1.17–2.56)	0.006	1.31 (0.97–1.76)	0.077	0.262
Multivariable-adjusted model 2					
High school	Reference		Reference		
College	1.54 (1.00–2.39)	0.052	1.08 (0.78–1.49)	0.638	0.192
Post-college	1.66 (1.06–2.60)	0.026	0.93 (0.67–1.30)	0.680	0.039
Multivariable-adjusted model 3					
High school	Reference		Reference		
College	1.57 (0.99–2.51)	0.057	1.18 (0.83–1.67)	0.371	0.325
Post-college	1.68 (1.04–2.70)	0.033	0.96 (0.66–1.38)	0.810	0.063

Model 1: age and randomized treatment adjusted analysis. Model 2: additionally adjusted for sex, race, BMI (continuous or categorical BMI), hypertension, diabetes, smoking, alcohol, physical activity, annual income, and education level. Model 2a: height and weight substituted for BMI. Model 3 will censor participants when they develop cardiovascular disease (817 participants censored). AF indicates atrial fibrillation; and BMI, body mass index.

**P* value likelihood ratio test for difference between AF type and no AF.

†*P* value likelihood ratio test for difference between paroxysmal AF and persistent AF.

individuals with AF in the BEAT-AF study (Basal Atrial Fibrillation Study).[19] In addition to the strong observed associations with incident persistent AF, weight gain and elevated BMI have also been associated with increased rates of progression of paroxysmal to persistent AF.[28] Conversely, weight loss has also been associated with reversal of persistent AF to paroxysmal AF,[12] suggesting that the impact of obesity on AF persistence is to some degree reversible arguing for early intervention with weight loss and risk factor modification in patients who present with persistent AF.

There are several potential mechanisms that might predispose obese individuals to more sustained forms of AF. Obesity is known to be associated with LA enlargement; however, the association between elevated weight and BMI persisted even after controlling for LA size, suggesting that other mechanisms contribute to this predisposition. In preclinical models[29] and in patients undergoing ablation,[30] obesity is associated with fibrotic atrial remodeling, slowed atrial conduction velocity, low voltage, and greater fractionation of electrograms, all of which would be predicted to predispose to the persistence of AF. These changes seem to be more pronounced in regions near epicardial fat depots,[30] suggesting a possible local paracrine effect. Weight loss can also reduce pericardial fat volume, which has been associated with more persistent forms of AF.[31]

With regard to patient populations at higher risk for persistent AF, in addition to the elderly, we found that men were more likely to present with persistent AF than women after controlling height or BMI and other AF risk factors. These results are consistent with those

Table 4. Logistic Regression Analysis Within the AF Cases: Risk Factor Associations With Persistent vs Paroxysmal AF

	OR (95% CI)	*P* value
Age, y		
Model 1	1.02 (1.00–1.04)	0.0435
Model 2	1.03 (1.01–1.06)	0.0042
Model 3	1.01 (0.99–1.04)	0.3223
Sex		
Model 1	0.65 (0.49–0.86)	0.0023
Model 2	0.64 (0.46–0.90)	0.0087
Model 3	0.53 (0.36–0.78)	0.0012
BMI		
Model 1	1.05 (1.03–1.08)	<0.0001
Model 2	1.05 (1.02–1.08)	0.0006
Model 3	1.05 (1.01–1.08)	0.0058
Obese		
Model 1	1.87 (1.30–2.69)	0.0008
Model 2	1.62 (1.06–2.48)	0.0266
Model 3	1.55 (0.95–2.51)	0.0777
Hypertension		
Model 1	1.45 (1.09–1.93)	0.0110
Model 2	1.29 (0.93–1.79)	0.1291
Model 3	1.34 (0.93–1.93)	0.1208
Current smoker		
Model 1	0.76 (0.36–1.59)	0.4620
Model 2	0.73 (0.32–1.67)	0.4581
Model 3	0.75 (0.28–1.97)	0.5544
Postcollege education		
Model 1	1.36 (0.83–2.24)	0.2221
Model 2	2.07 (1.15–3.74)	0.0151
Model 3	1.82 (0.95–3.50)	0.0709
LA enlargement		
Model 1	2.65 (1.91–3.68)	<0.0001
Model 2	2.43 (1.70–3.45)	<0.0001
Model 3	2.04 (1.40–2.97)	0.0002
LVEF per 5%		
Model 1	0.85 (0.79–0.91)	<0.0001
Model 2	0.87 (0.81–0.94)	0.0004
Model 3	0.92 (0.85–1.00)	0.0383
Mitral valve disease		
Model 1	2.80 (1.89–4.14)	<0.0001
Model 2	3.05 (2.00–4.64)	<0.0001
Model 3	2.51 (1.59–3.96)	<0.0001
Other valve disease		
Model 1	1.56 (1.02–2.39)	0.0394
Model 2	1.71 (1.09–2.71)	0.0209
Model 3	1.66 (0.99–2.78)	0.0541
Cardiac/other surgeries		
Model 1	0.53 (0.33–0.84)	0.0069
Model 2	0.45 (0.27–0.74)	0.0016
Model 3	0.42 (0.23–0.75)	0.0038

Model 1: adjusted for age and randomized treatment. Model 2: additionally adjusted for sex, race, BMI, hypertension, diabetes, smoking, alcohol, physical activity, annual income, and education level. Model 3: additionally adjusted for LA size, LVEF, mitral valve disease, other valvular disease, and cardiac and other surgeries. AF indicates atrial fibrillation; BMI, body mass index; LA, left atrial; LVEF, left ventricular ejection fraction; and OE, odds ratio.

recently reported in the EAST-AFNET trial (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial-AF Network) where patients were enrolled within 1 year of AF diagnosis.[32] Men were also more likely to have persistent AF at the time of enrollment in the CABANA trial (Catheter Ablation vs Antiarrhythmic Drug Therapy for a Trial Fibrillation Trial) where the median time because of onset of AF was 1.1 years.[33] Studies examining more prevalent forms of AF have had mixed results,[34,35] possibly due to lower use of cardioversion and catheter ablation in women over time.[34–36] Cardiac structural differences between the sexes may account for some of the greater propensity for men to present with persistent AF than women. Women generally have smaller LA,[37] which would lower the risk for persistent AF; however, in our data, men with AF remained more likely to present with persistent AF after controlling LA size, as well as other measures of structural heart disease, including LVEF. Sex differences in electric atrial remodeling that might predispose to a sex difference in persistent AF have been reported, but differences were limited to the comparison between men and premenopausal women,[38] which would not be applicable in this older population. Conversely, other studies have found higher degrees of atrial fibrosis among women compared with men with AF.[39] Potentially, this sex difference may not be due to differences in underlying biology, but rather sex differences in health care utilization may impact diagnosis of persistent versus paroxysmal forms of AF.

Strengths and Limitations

This study presents several strengths, including the large sample size with equal representation of men and women and overrepresentation of Black participants, as well as the unique prospective randomized trial design that identified and confirmed the first presentation of AF. Incident AF events were ascertained using 2 complimentary methods, and incident AF outcomes and AF patterns at presentation were rigorously adjudicated by medical record review. Despite the strengths of the study, there are also several limitations to consider. First, as in other large-scale clinical trials,[32,40] ascertainment of AF events and AF pattern relied on a clinical diagnosis of AF, and long-term monitoring was not performed in this large pragmatic trial. Although we also obtained and reviewed all medical records surrounding the AF diagnosis, there is likely some degree of underdetection of AF and misclassification of the initial AF pattern. Episodes of asymptomatic paroxysmal AF and shorter episodes of persistent AF are more likely to go undetected without monitoring, which may have resulted in an overestimation of the proportion of persistent AF in our new-onset AF cases. However, recent clinical trial data have called into question the clinical significance of these brief episodes of AF detected by monitoring,[41,42] and prior studies reporting on adverse associations between

persistent AF and cardiovascular outcomes have used similar clinical estimations of AF pattern.[40,43–46]

The need for clinical detection may also result in some bias if different subgroups, such as those with higher education or men, are more likely to undergo an evaluation (ie, office ECG) that might result in a greater likelihood of detecting persistent forms of AF. The use of self-reporting and claims data, despite its limitations, offers an opportunity to gather insights in real-world settings that might be missed in more controlled experimental designs. Second, this study enrolled healthy individuals without a history of CVD, and results may not be generalizable to younger patients or patients with CVD. Third, AF risk factor assessments were based on self-report, which may lead to nondifferential misclassification and could have biased results toward the null. However, we observed high correlations between self-reported and directly measured variables, such as weight and BMI, in a subset of VITAL participants enrolled in the Clinical Translational Science Center.[47] Fifth, participants with morbid obesity were underrepresented in the study population; thus, the proportion presenting with paroxysmal AF may, to some degree, be an overestimate of the general population. Sixth, standardized echocardiograms were not systematically collected in this cohort, and, therefore, we were unable to perform a formal mediation analysis. Finally, due to the observational nature of the study, we cannot exclude the possibility that residual or unmeasured confounding may have accounted for part of the associations observed. Importantly, we lacked information on sleep apnea, a risk factor previously shown to be associated with AF.

Conclusions

In this large prospective study of men and women without a prior diagnosis of AF or CVD or cancer who were followed for over 5 years, more than one-third of those who were diagnosed with incident AF over the course of the study presented with persistent AF at the time of their initial diagnosis. Older age, male sex, increasing weight, BMI, and postcollege education were preferentially associated with persistent AF at diagnosis. Participants with these risk factors represent a high-risk AF subset, who can be selected for early population-based intervention.

ARTICLE INFORMATION

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Supplemental Material

Table SI

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