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Characteristics of Atrial Fibrillation Patients with a Family History of Atrial Fibrillation

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Abstract

Background

Family history has been shown to be associated with increased risk of atrial fibrillation (AF). However, the specific AF characteristics that travel with a family history have not yet been elucidated. The purpose of this study was to determine whether a family history of AF is associated with specific patient characteristics in a worldwide, remote cohort.

Methods

From the Health eHeart Study, an internet-based prospective cohort, we performed a cross-sectional analysis of AF participants who reported their family history and completed questionnaires regarding their medical conditions and AF symptoms. We assessed demographics, cardiovascular comorbidities, and AF symptom characteristics in AF participants with and without a family history of AF.

Results

In multivariable analysis of 5,884 participants with AF (mean age 59.9 ± 14.5, 59% male, 92% white), female sex (odds ratio [OR]=1.35, 95% CI, 1.17-1.54, p<0.0001) and birth in the U.S. (OR=2.54, 95% CI, 2.12-3.05, p<0.0001) were independently associated with having a family history of AF. Having a family history of AF was also more commonly associated with symptoms of shortness of breath (OR=1.40, 95% CI, 1.07-1.82, p=0.014), chest pain, pressure, or discomfort (OR=1.95, 95% CI, 1.22-3.13, p=0.0052), and feeling generally "off" about oneself (OR=1.84, 95% CI, 1.27-2.67, p=0.0013).

Conclusions

Patients with a family history of AF are more likely to be female, be US-born, and experience symptoms of AF, suggesting underlying mechanistic differences between those with and without family history of AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting millions of Americans and rapidly increasing in both incidence and prevalence [1-4]. AF doubles mortality and is a common cause of stroke [1,2]. Though the mechanisms underlying AF remain largely unknown, established risk factors, such as age, male sex, white race, hypertension, and other comorbidities, have been identified [5,6]. A family history of AF has similarly emerged as a well-established risk factor for the disease [5-9]. Several common genetic variants have been associated with an increased susceptibility to AF [8,10,11], but the mechanisms underlying those associations remain unclear. One previous registry-based study in the US suggested that patients with a family history of AF develop the disease at a younger age, have less comorbidities, and are more symptomatic [12], but no additional studies have examined these relationships. We therefore sought to compare the characteristics of AF patients with and without a family history of the disease in a worldwide, remote cohort.

Key Words

Atrial fibrillation, Family history, Genetics, Heritability, Phenotype.

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Methods

Study design

We utilized data collected between March 8, 2013 and October 25, 2017 from the Health eHeart Study (www.health-eheartstudy.org), an online-based prospective, longitudinal cohort study. English-speaking adults each with an active email were recruited through academic institutions, lay press, social media and promotional events. Upon enrollment, all participants provided informed consent electronically and were asked to complete a series of online questionnaires regarding demographics, personal and family medical history, habits, symptoms, and quality of life [Supplementary Table 1]. The Health eHeart Study was approved by the UCSF Institutional Review Board.

Assessment of atrial fibrillation and family history

AF was determined by responses to the question, "Have you ever been told by a doctor or nurse that you have, or have been treated for, atrial fibrillation (in the past or currently)?" with response options "Yes", "No" and "Don't know." We included only participants who responded "yes" and treated those who responded as "Don't know" as missing. This approach was previously validated using medical record data among 42 patients [13]. To identify those with any family history of AF, we included participants who reported any family member

Table 1: Baseline characteristics of atrial fibrillation participants with and without any family history of the disease.

	No Family History of AF (n = 4600)	Family History of AF (n = 1284)	p-value
Basic demographics			
Age, mean ± SD, years	56.9 ± 15.4	60.4 ± 11.2	<0.0001
Sex			<0.0001
Male	2009 (61%)	647 (52%)	
Female	1269 (39%)	607 (48%)	
Country of birth			<0.0001
USA	2336 (71%)	1085 (87%)	
Other	939 (29%)	169 (13%)	
Race/Ethnicity, n (%)			0.17
Black	50 (1%)	20 (2%)	
White	2998 (92%)	1144 (91%)	
Asian	89 (3%)	29 (2%)	
Native Hawaiian	4 (0.1%)	0 (0%)	
American Indian	8 (0.2%)	9 (0.7%)	
Other	51 (2%)	15 (1%)	
Don't know	**3 (0.09%)**	**1 (0.08%)**	
Hispanic (ethnicity)	170 (5%)	50 (4%)	0.09
Medical history			
Hypertension	2357 (51%)	676 (53%)	0.38
Diabetes	589 (13%)	155 (12%)	0.48
Coronary artery disease	1029 (22%)	245 (19%)	0.011
Heart attack	583 (13%)	151 (12%)	0.38
Congestive heart failure	734 (16%)	187 (15%)	0.22
Stroke or TIA	533 (12%)	120 (9%)	0.023
Congenital heart disease	433 (9%)	102 (8%)	0.10
Obstructive sleep apnea	1238 (27%)	346 (27%)	0.85
COPD	354 (8%)	104 (8%)	0.70
Asthma	544 (12%)	155 (12%)	0.91
Cardiac arrest	316 (7%)	81 (6%)	0.43
Implantable device	3802 (84%)	1088 (85%)	0.33
Smoking history			
History of smoking regularly	910 (53%)	707 (56%)	0.05
Current smoker	63 (4%)	46 (4%)	0.99
Alcohol Use			
Did you drink alcoholic beverages in the past year?	1334 (77%)	971 (77%)	0.93
Did you drink alcohol more than once or twice in the past?	248 (63%)	186 (66%)	0.54
Drinks of wine/week	4.2 ± 28.1	3.4 ± 5.9	0.38
Drinks of beer/week	1.9 ± 9.5	1.3 ± 3.4	0.061
Drinks of hard liquor/week	1.4 ± 4.2	1.4 ± 4.4	0.098
Drinks in the past 24 hours	0.9 ± 2.6	0.9 ± 1.7	0.071
Approximately how many years ago did you stop drinking?	56.3 ± 289.4	46.2 ± 243.5	0.70
What is the usual number of drinks you consumed per week before you stopped?	13.3 ± 35.9	10.2 ± 19.6	0.29
Atrial fibrillation history			
Symptoms when first diagnosed?	3092 (76%)	1005 (80%)	0.006
Paroxysmal AF	1953 (48%)	627 (50%)	0.29
Hx of cardioversion	1286 (32%)	394 (31%)	0.80
Hx of AF ablation	976 (24%)	330 (26%)	0.12
Atrial fibrillation symptoms (check all that apply)			
Never have symptoms	540 (12%)	138 (11%)	0.33
Palpitations	2675 (58%)	807 (63%)	0.0025
SOB	364 (8%)	152 (12%)	<0.0001
Difficulty exercising	94 (2%)	25 (2%)	0.83
Chest pain/pressure/ discomfort	78 (2%)	36 (3%)	0.01
Dizziness	85 (2%)	16 (1%)	0.14
Feeling generally tired	69 (2%)	21 (2%)	0.73
Feeling generally "off" your normal self	117 (3%)	57 (4%)	0.0004
Other	45 (1%)	12 (1%)	0.89
Don't know	540 (12%)	139 (11%)	0.14

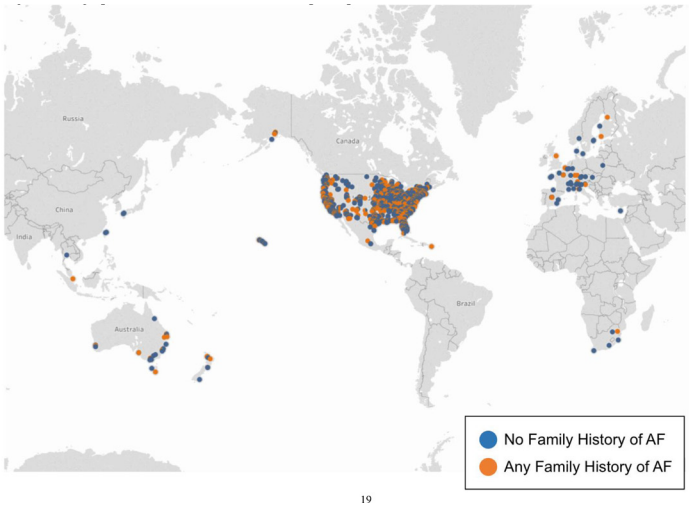

Figure 1: Geographical distribution of Health eHeart participants with atrial fibrillation.

Each dot represents at least one participant in a given zipcode. Blue dots indicate those with a family history of atrial fibrillation, while orange dots indicate those without a family history of atrial fibrillation.

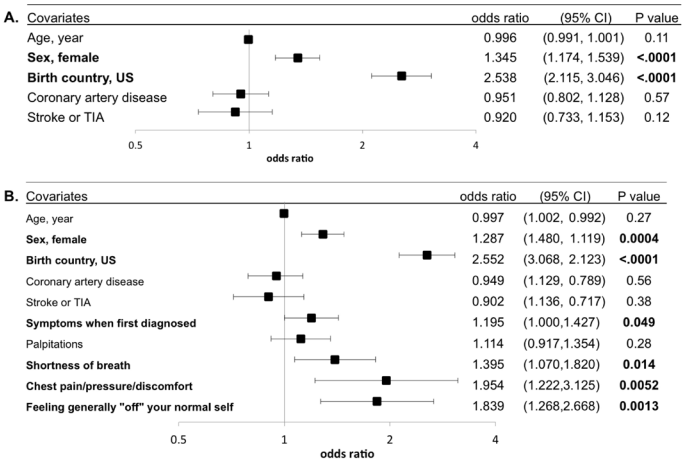

Figure 2: Multivariable adjusted relationships between participant characteristics and any family history of AF.

(A) Adjusted for relevant demographics, medical history and habits. (B) Additionally adjusted for relevant AF- and symptom-related history. Models were adjusted for all covariates listed. Statistically significant relationships are in bold. Y error bars denote 95% confidence intervals.

Table 2: Baseline characteristics of atrial fibrillation participants with and without a first-degree family history of the disease.

	No First-Degree Family History of AF (n = 5136)	First-Degree Family History of AF (n = 748)	p-value
Basic demographics			
Age, mean ± SD, years	57.0 ± 15.5	58.7 ± 12.8	0.0003
Sex			0.004
Male	2266 (60%)	390 (54%)	
Female	1540 (40%)	336 (46%)	
Country of birth			<0.0001
USA	2801 (74%)	620 (85%)	
Other	1002 (26%)	106 (15%)	
Race/Ethnicity, n (%)			0.076
Black	64 (2%)	6 (0.83%)	
White	3458 (91%)	684 (94.34%)	
Asian	103 (3%)	15 (2.07%)	
Native Hawaiian	4 (0.1%)	0 (0.00%)	
American Indian	17 (0.5%)	0 (0.00%)	
Other Don't know	61 (2%) 3 (0.08%)	5 (0.69%) 1 (0.1%)	
Hispanic (ethnicity)	198 (5%)	22 (3%)	0.012
Medical history			
Hypertension	2657 (52%)	376 (50%)	0.45
Diabetes	667 (13%)	77 (10%)	0.038
Coronary artery disease	1148 (22%)	126 (17%)	0.0006
Heart attack	662 (13%)	72 (10%)	0.011
Congestive heart failure	818 (16%)	103 (14%)	0.13
Stroke or TIA	583 (11%)	70 (9%)	0.10
Congenital heart disease	488 (10%)	47 (6%)	0.0041
Obstructive sleep apnea	1376 (27%)	208 (28%)	0.68
COPD	398 (8%)	60 (8%)	0.85
Asthma	617 (12%)	82 (11%)	0.36
Cardiac arrest	357 (7%)	40 (5%)	0.090
Implantable device	832 (16%)	105 (14%)	0.10
Smoking history			
History of smoking regularly	1047 (46%)	324 (44%)	0.35
Current smoker	86 (4%)	23 (3%)	0.41
Alcohol Use			
Did you drink alcoholic beverages in the past year?	1732 (77%)	573 (79%)	0.29
Did you drink alcohol more than once or twice in the past?	336 (65%)	98 (64%)	0.82
Drinks of wine/week	4.0 ± 24.9	3.6 ± 5.3	0.76
Drinks of beer/week	1.7 ± 8.1	1.5 ± 5.6	0.76
Drinks of hard liquor/week	1.4 ± 4.0	1.4 ± 5.0	0.77
Drinks in the past 24 hours	0.8 ± 2.4	1.0 ± 1.5	0.25
Approximately how many years ago did you stop drinking?	57.7 ± 291.4	32.5 ± 181.1	0.42
What is the usual number of drinks you consumed per week before you stopped?	12.4 ± 32.5	10.4 ± 19.2	0.55
Atrial fibrillation history			
Symptoms when first diagnosed?	3517 (75%)	580 (78%)	0.20
Paroxysmal AF	2215 (48%)	365 (49%)	0.53
Hx of cardioversion	1448 (31%)	232 (31%)	0.96
Hx of AF ablation	1098 (24%)	208 (28%)	0.012
Atrial fibrillation symptoms (check all that apply)			
Never have symptoms	610 (12%)	68 (0.09%)	0.026
Palpitations	3008 (59%)	474 (63%)	0.012
SOB	432 (8%)	84 (11%)	0.011
Difficulty exercising	103 (2%)	16 (2%)	0.81
Chest pain/pressure/ discomfort	89 (2%)	25 (3%)	0.0029
Dizziness	93 (2%)	8 (1%)	0.15
Feeling generally tired	79 (2%)	11 (1%)	0.89
Feeling generally "off" your normal self	133 (3%)	41 (5%)	<0.0001
Other	45 (1%)	12 (2%)	0.58
Don't know	610 (12%)	68 (9%)	0.026

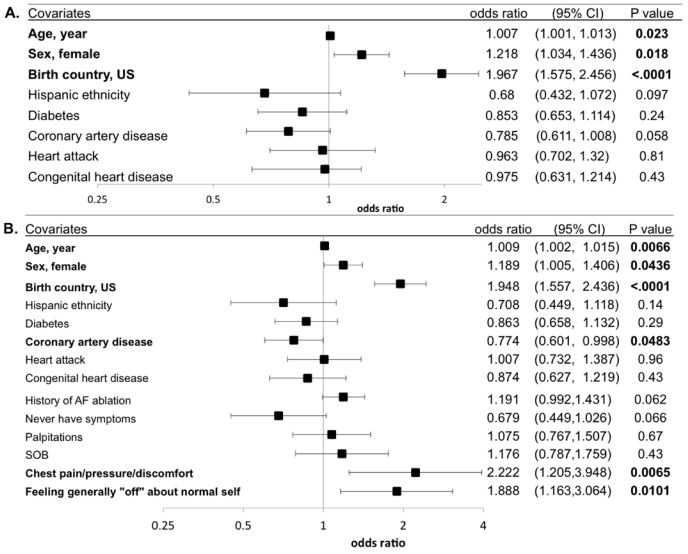

Figure 3: Multivariable adjusted relationships between participant characteristics and a first-degree family history of AF.

(A) Adjusted for relevant demographics, medical history and habits. (B) Additionally adjusted for relevant AF- and symptom-related history. Models were adjusted for all covariates listed. Statistically significant relationships are in bold. Y error bars denote 95% confidence intervals.

(either immediate or extended) with AF. If participants were unsure, the answer was considered negative. Participants were considered to have a first-degree family history of AF if they self-reported at least one biological sister, brother, father, or mother with AF.

Covariate ascertainment

Self-identified race was categorized as white, black, Asian, Native Hawaiian/Pacific Islander, American Indian, or other. Hispanic ethnicity was also assessed. Smoking status was ascertained as never, past, or current smoker, with regular use defined as at least 1 cigarette per day or a total of 100 cigarettes in one's lifetime. Alcohol use was assessed through self-report of consumption over the past year and number of drinks a week. Medical history was determined by participant report that they had specifically received a diagnosis of one of the following from a healthcare professional [Supplementary Table 1]: hypertension, diabetes, coronary artery disease, heart attack, congestive heart failure, cerebrovascular accident (stroke or transient ischemia attack), congenital heart disease, and obstructive sleep apnea. Participants with AF were also asked specific questions regarding their AF history and associated symptoms.

Statistical analysis

Normally distributed continuous variables are presented as means ± SD and were compared using unpaired t-tests. Non-normally distributed continuous variables are presented as medians and interquartile ranges and were compared using Wilcoxon rank-sum tests. Categorical variables were compared using x^2 tests. Multivariable analysis was performed with logistic regression analysis, including only co-variates that exhibited p values < 0.05 in unadjusted analyses. We first performed an analysis to assess relationships between demographics, medical comorbidities, habits and a family history of AF; we then analyzed relationships between a family history and characteristics of the participant's AF itself (such as AF type and associated symptoms) after adjusting for relevant demographics, medical conditions and habits. All analyses were performed using SAS Version 9.4. Two-tailed p values < 0.05 were considered statistically significant.

Results

Any family history of atrial fibrillation

At the time of study analysis, 76,973 of 137,648 Health eHeart participants (49.4%) had completed the survey for medical conditions. Of those, 5,884 (7.6%) reported a diagnosis of AF. Of those with AF, 1,284 (21.8%) had a family history of AF [Figure 1] and [Supplementary Figure 1]. [Table 1] shows the baseline characteristics among those with and without a family history of AF. Those with a family history of AF tended to be older, female, more often from the US, and less often with a history of coronary artery disease or a history of a cerebrovascular accident [Table 1]. In addition, those with a family history were more likely to experience symptomatic AF when they were first diagnosed and continued to manifest more symptoms of AF than AF patients without a family history.

In a multivariable adjusted analysis including relevant demographics, past medical history and habits, those with a family history of AF had a statistically significant 35% greater odds of being female and also had more than 2-fold greater odds of being born in the US [Figure 2]. After including AF-related history and symptoms that met criteria for inclusion in the multivariate model, being female and being born in the US remained significantly associated with a family history of AF [Figure 2]. In addition, AF patients with a family history of AF were more likely to report AF-related shortness of breath, chest pain, pressure, or discomfort, or feeling "off" about one's normal self after adjusting for baseline characteristics [Figure 2].

First-degree family history of atrial fibrillation

Of those with AF, 768 (13.7%) had at least one first degree family member with AF. Baseline characteristics of those with and without first-degree family history are reported in [Table 2]. Those with a first-degree family history of AF were more likely to be older, female, and from the US, but less likely to be of Hispanic ethnicity and have diabetes, coronary artery disease, and congenital heart disease [Table 2]. Though there was no significant differences in having paroxysmal AF or history of cardioversion, those with a first-degree family history of AF were more likely to have had an AF ablation. As with those with any family history of AF, those with a first degree family history were more likely to experience a variety of symptoms during their AF episodes [Table 2].

In a multivariable adjusted analysis including demographics, medical history and habits, older age, female sex, and being born in the US were each significantly associated with having a first-degree family history of AF [Figure 3]. When AF characteristics (including AF type, AF-related history, and AF-related symptoms) were also added to the multivariable model, having a first-degree family history of AF was significantly associated with reporting symptoms of chest pain, pressure, or discomfort and feeling generally "off" about oneself during AF episodes [Figure 3].

Discussion

Among a large, remote cohort of AF patients, a family history of AF was more commonly observed in women and those born in the US. Those with a family history of AF exhibited more symptomatic AF. Our study validates the results of a previous registry-based study that females and those with more symptoms during AF are more likely to report a family history of the disease [12], extending those findings to a worldwide cohort.

The reasons for the consistent relationship between female sex and a family history of AF are unclear. This would appear to run contrary to the consistent observation that women are at a lower risk for AF than men [7,16,17]. Of note, the mechanisms underlying that difference have not been fully elucidated, may be multifactorial, and may be related to differences in body (and left atrial) size and or hormonal influences [18-20]. It is important to acknowledge that women may simply be more likely to report a family history of AF (even in the absence of an actual greater prevalence of a family history) because they are more attune to their family members' health history [21]. This itself may yet be clinically relevant information when considering the reliability of the family history from men versus women. Assuming there is truly a relationship between female sex and a family history of AF, these findings may point to some sex-related mechanisms that affect the penetrance of AF-related genes. In light of the overall greater prevalence of AF among men, such a finding would also suggest that the sex-specific differences influencing AF risk would be potent enough to otherwise suppress the emergence of AF in the general population of women.

In our international cohort, we were able to demonstrate that US-born participants were more likely to report an AF family history. Again, it is difficult to know whether this has more to do with the awareness of health problems and AF among American families versus a "true" phenomenon. It is possible that there are some genetic differences that render certain populations more prone to AF among those more likely to migrate to the US. There may also be some gene-environment interactions that are disproportionally influenced by some particular exposure in the US.

It is well known that AF patients can experience a variety of sensations during their episodes, ranging from completely asymptomatic to suffering debilitating symptoms [22]. While some of

Supplementary Material

Table 1: Online questionnaires from the Health eHeart Study

Basic demographics	
1. What is your biological sex?	□ Male □ Female
2. Where were you born (country)?	□ U.S.A. □ Mexico □ China □ India □ Philippines □ Other country
3. What is your racial background? Check all that apply.	□ Black or African American □ White □ Asian (including South Asian and Asian Indian) □ Native Hawaiian or Pacific Islander □ American Indian or Alaska Native □ Some other race □ Don't know
4. Are you of Hispanic, Latino or Spanish origin or ancestry?	□ No □ Yes, Mexican, Mexican American or Chicano □ Yes, Puerto Rican □ Yes, Cuban □ Yes, Other or Mixed Hispanic, Latino or Spanish origin □ Don't know
Medical history	
Have you ever been told by a doctor or nurse that you have, or have been treated for, any of the following conditions (in the past or currently?)	
1. Hypertension	□ Yes □ No □ Don't know
2. Diabetes? Do not include pre-diabetes.	□ Yes □ No □ Don't know
3. Coronary artery disease (blockages in your heart vessels) or angina (chest pain)?	□ Yes □ No □ Don't know
4. A heart attack?	□ Yes □ No □ Don't know
5. Congestive Heart Failure (CHF, Heart Failure)?	□ Yes □ No □ Don't know
6. Stroke or TIA (Transient Ischemic Attack or Mini-Stroke)?	□ Yes □ No □ Don't know
7. Do you or have you ever had a congenital heart disease (a heart birth defect)?	□ Yes □ No □ Don't know
8. Sleep apnea (obstructive sleep apnea, OSA)?	□ Yes □ No □ Don't know
9.COPD (emphysema, chronic bronchitis, obstructive pulmonary disease)?	□ Yes □ No □ Don't know
10. Asthma, to the point that you use inhalers daily or have been to the hospital for your asthma	□ Yes □ No □ Don't know
11. A cardiac arrest?	□ Yes □ No □ Don't know
12. Do you have an implanted device for your heart? If you have one, you were given a card which has this information on it.	□ No □ Pacemaker (not an ICD) □ ICD (Implantable Cardioverter-Defibrillator) □ Implanted Loop Recorder or rhythm monitor (e.g., Reveal, Confirm) □ Other
Smoking history	
1. Have you ever smoked cigarettes regularly (at least 1 cigarette per day and a total of 100 cigarettes in your lifetime)?	□ Yes □ No
2. Do you smoke now?	□ Daily □ Some days □ No
Alcohol history	
1. Did you drink any alcoholic beverages in the past year?	□ No □ Yes □ Don't know □ I refuse to answer
2. Did you drink alcohol more than once or twice in the past?	□ No □ Yes □ Don't know □ I refuse to answer
3. How many drinks of wine do you usually have per week? A drink is a 5-ounce glass. Round down.	_____ drinks per week
4. How many drinks of beer do you usually have per week? One beer is a 12-ounce glass, can, or bottle. Round down.	_____ drinks per week
5. How many drinks per week do you usually have of hard liquor? Count each shot, which is 1 ½ ounces, as one drink. Round down	_____ drinks per week
6. During the past 24 hours, how many drinks have you had?	_____ drinks per week
7. Approximately how many years ago did you stop drinking? Round do the nearest year except round ½ down; e.g., record 1 ½ as 1).	_____ years
8. What was the usual number of drinks you consumed per week before you stopped? Write in 00 if less than one drink per week.	_____ drinks per week
Atrial fibrillation history	
1. Did you have any symptoms (such as palpitations, dizziness, shortness of breath, chest discomfort, difficulty exercising, or generalized 'feeling bad') when you were first diagnosed (or prior to)?	□ Yes □ No □ Don't know
2. Are you in atrial fibrillation all the time?	□ Yes □ No. It comes and goes on its own □ No. It has stopped because of a shock to your heart or because of a medication □ Don't know
3. Have you ever had a shock to your check or cardioversion?	□ Yes □ No □ Don't know
4. Have you ever had an ablation for your atrial fibrillation?	□ Yes □ No
5. What symptoms do you have when you have atrial fibrillation? It's OK if you only experience these symptoms sometimes. Check all that apply.	□ I never have symptoms □ Palpitations or irregular or "funny" heartbeats □ Shortness of breath of difficulty breathing □ Difficulty exercising or exerting □ Chest pain, pressure, or discomfort □ Dizziness □ Feeling generally tired □ Feeling generally "off" your normal self □ Other □ Don't know

Supplementary Material

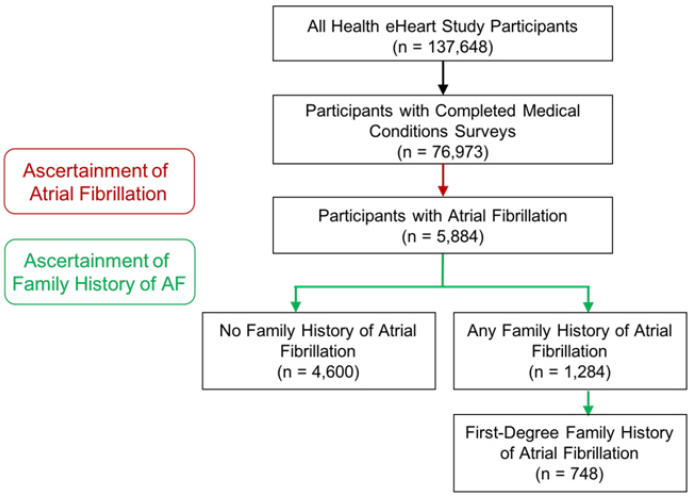

Figure 1 **Health eHeart Study enrollment of atrial fibrillation participants with and without a family history of atrial fibrillation.**

this variability is likely related to ventricular rates and differences in AV nodal conduction properties, the reasons some individuals are more or less symptomatic remain largely unknown. In addition to hemodynamic effects, there are likely neurologic and psychological components related to sensitivity to changes in heart rate and rhythm and reactions to stress [23]. The relationship between having a family history of AF and having more symptomatic AF was very consistent in our cohort, both before and after adjustment for potential confounders and mediators. Those with a family history more commonly described shortness of breath, chest pain, pressure, or discomfort, and feeling "off" during their AF episodes. A possible explanation is that those who tend to be more symptomatic will seek out more family members with AF. Interestingly, it is also possible that having symptomatic AF itself is an inherited characteristic, which would certainly lend itself to becoming more apparent among family members. Inherited AF tends to be more dominant in otherwise healthier and younger individuals with the disease [9,12,24], who are more likely to have robust AV nodal conduction and thus more likely experience symptoms from rapid ventricular rates. While we demonstrated that older age was associated with having a first-degree family history, we were not able to determine the age of diagnosis with our database. Previous studies have reported that earlier diagnosis of AF in patients and their first-degree relatives is associated with higher risk of AF [5-7]. Finally, previous studies have suggested that women tend to experience more AF-related symptoms and worse quality-of-life than men [25-27]. As the relationship between female sex and a family history of AF as well as between symptoms and a family history of AF remained statistically significant after each was adjusted for the other, those previous studies may reveal a heritable AF subtype relevant to both relationships.

Our study has several potential limitations. As eluded to above, these data were based on self-report. However, as also mentioned, even if this explains the results observed, there may be clinically relevant lessons that can be gleaned from the data. We previously validated the accuracy of an AF diagnosis in the Health eHeart Study and found it to be very accurate among a small number of patients with available medical records.[15] In addition, for any misclassification of AF to be important, there would need to be a differential effect by predictor (such as family history of AF) for results to be affected. Although the mean age of our study cohort was 60 and more than 10% were of some race/ethnicity other than non-Hispanic white, Health eHeart Study participants are not completely representative of the general population (particularly as they require some ability to interact on the internet). However, this should limit generalizability of our findings rather than internal validity. We acknowledge that "any family history" is both broad and potentially vague, but our analyses restricted to just a first degree family history did not yield meaningfully different results. Finally, it is possible that we were not aware of or did not include other covariates that may have been important.

Conclusion

Among individuals with AF, a family history of the disease is more common in women, those born in the US, and those with symptomatic AF. These differences may help in understanding mechanisms underlying AF when a family history of the disease is present and may suggest that symptomatic AF reflects a particular biological subtype.

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