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Sex Differences in Atrial Fibrillation Risk - Insights from the VITAL-Rhythm study.

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3 Key Points:

Question: Are women at lower risk for atrial fibrillation (AF) after accounting for other AF risk factors and do risk factors for AF differ for men versus women?

Findings: Women were at greater risk for developing AF than men when height and weight, rather than BMI, were controlled for in multivariable models. AF risk factors were similar for women versus men.

Meaning: For a given height and weight, women are at higher risk for incident AF compared to men and primary prevention with risk factor modification should be equally effective. These findings emphasize need for AF prevention in women.

Tweet:

In an analysis of VITAL Rhythm including 25,871 subjects without CVD (51% female), women were at higher risk for incident atrial fibrillation compared to men after controlling for height and weight, emphasizing the need for AF prevention across sexes.

Abstract

Importance: Women have a lower incidence of atrial fibrillation (AF) compared to men in several studies, but it is unclear whether this sex difference is independent of sex differences in prevalent cardiovascular disease (CVD), body size, and other risk factors.

Objective: To examine sex differences in AF incidence and whether AF risk factors differ by sex in a contemporary cohort of men and women without prevalent CVD.

Design, Setting and Participants: Prospective cohort analysis within the Vitamin D and Omega-3 Trial (VITAL) Rhythm Study, a randomized trial that examined the effect of vitamin D and omega-3 fatty acid supplementation on incident AF among 25,119 individuals (mean age 67.0±7.1 years; 51% women) without prevalent AF, CVD, or cancer at baseline.

Exposures: Sex, height, weight, body mass index (BMI), body surface area (BSA), and other AF risk factors at study enrollment.

Main outcome and measure: Incident AF confirmed by medical record review.

Results: Over median follow-up of 5.3 years, 900 confirmed incident AF events occurred among 12362 men (495 events, 4.0%) and 12757 women (405 events, 3.2%). After adjustment for age and treatment assignment, women were at lower risk for incident AF than men (HR 0.68, 95% CI 0.59-0.77; p<0.0001). The inverse association between female sex and AF persisted after adjustment for race/ethnicity, smoking, alcohol intake, hypertension, diabetes, thyroid disease, exercise, and BMI (HR 0.73, 95% CI 0.63-0.85; p=<0.0001). However, female sex was positively associated with AF when height (HR 1.39, 95% CI 1.14-1.72; p=0.001), height and weight (HR 1.49, 95% CI 1.21-1.82; p=0.0002) or BSA (HR 1.25, 95% CI 1.06-1.49; p=0.009)

were substituted for BMI in the multivariate model. In stratified models, risk factor associations with incident AF were similar for women and men.

Conclusions and Relevance: After controlling for height and/or body size, women without CVD at baseline were at higher risk for AF than men, suggesting that sex-differences in body size account for much of the protective association between female sex and AF. These data underscore the importance of AF prevention in women.

Introduction:

Atrial fibrillation (AF) is the most prevalent arrhythmia in the world and is associated with an increased risk of stroke, heart failure and overall mortality.[1] As the population ages, the number of patients with AF is expected to burgeon. Similar to other cardiovascular disorders, there are important sex specific differences in the epidemiology and outcomes of AF.[1-5] Women have lower rates of AF than men but are more likely to suffer adverse sequalae of the disease, including stroke, heart failure and death.[4,6-8] Therefore, understanding risk factors that may affect the burden of AF differentially between women and men is of considerable importance.

Body size[9-12], height[13], and adiposity[14-18], which significantly vary by sex, are important contributors to AF risk[11]; and thus may underlie, in part, the observed sex differences in AF risk. (eFigure 1) Data from observational studies that enrolled populations in the 1970s-80s suggest that BMI might have a stronger relation to AF in men[5,12]; whereas, height may have a stronger association with AF in women.[18] A single prospective study suggested that this strong association between height and AF may mediate the sex-differences in AF risk in an elderly population.[11] However, data on sex-differences in AF risk in contemporary populations are lacking.

In the present study, we examine sex-differences in incident AF risk in a contemporary cohort of 25,119 men and women without prior cardiovascular disease (CVD) enrolled in the Vitamin D and Omega-3 Trial (VITAL) Rhythm study, a sub-study of the randomized VITAL.[19-21] We then evaluate the contribution of anthropometric measures and other AF risk factors to sex-differences in incident AF risk as well as examine whether AF risk factors differ for women versus men.

Methods:

Study Design and Participants

VITAL is a large US-based, randomized, primary prevention placebo-controlled trial that utilized a 2x2 design to assess the effect of Vitamin D3 (2000 IU per day) and marine omega-3 fatty acids (840 mg of omega−3 fatty acids, including 460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) on the primary prevention of cardiovascular disease and cancer in 25,871 participants enrolled between November 2011 and March 2014 in the United States.[19,20] The VITAL Rhythm study (a sub-study of VITAL) tested the effects of long-term administration of marine omega-3 fatty acids and vitamin D on incident AF.[21] Men ≥50 years and women ≥55 years of age without a prior history of CVD or cancer were eligible for the study. Patients who reported a prior diagnosis of AF at baseline (n=752) were excluded from VITAL Rhythm and the present analysis. Baseline questionnaires collected data on clinical and lifestyle risk factors including anthropometric measures of height and weight. In a sub-cohort of 1,019 VITAL participants, in-clinic assessments of height and weight were performed at the Clinical and Translational Science Center (CTSC). The trial was approved by the institutional review board of Partners HealthCare–Brigham and Women's Hospital.

Incident AF ascertainment and confirmation:

Incident AF was identified through two methods in the VITAL Rhythm study.[21] First, participants self-reported new AF diagnoses on annual follow-up questionnaires. Second, the VITAL population was linked to claims data from the Centers for Medicare and Medicaid Services (CMS), and ICD codes for AF (ICD-9 diagnosis code 427.31 and ICD-10 diagnosis code I48.91) and atrial flutter (ICD-9 diagnosis code 427.32 and ICD-10 diagnosis code I48.92)

were ascertained. For all subjects with an incident AF diagnosis, either by self-report or CMS linkage, we requested permission to obtain medical records pertaining to the AF diagnosis. An endpoint committee consisting of cardiologists confirmed AF events according to predefined criteria.[21,22] ECG evidence of AF or a physician's report outlining a diagnosis of AF were required for confirmation. Only AF events confirmed by medical record review are included in the analyses. Presentation characteristics at time of AF diagnosis were abstracted from the medical record where available. Pattern of AF at the time of diagnosis was classified in accordance with the latest ACC/AHA/HRS and ESC guidelines.[23,24]

Statistical Analysis

For the entire cohort, baseline characteristics are presented as mean ± standard deviation or median [25^{th} – 75^{th} percentile] for continuous variables and percentages for categorical variables, stratified by sex, and compared using ANOVA and chi-square tests as appropriate. In the CTSC sub-cohort, Spearman correlations (r) were estimated for self-reported and measured height and weight to provide estimates for validity of the self-reported measures. In the entire cohort. multivariable Cox proportional hazards models were used to determine the association between sex and AF after adjustment for various risk factors. The proportionality assumption was tested for the full Cox models using interaction terms with log time and no violation was found. To assess the contributions of AF risk factors and body size measures to the observed relationship between sex and AF, sequential multivariable models were constructed. The first controlled for age, sex and trial treatment assignment. The second (base model) additionally controlled for common AF risk factors including diabetes, thyroid disease, hypertension, average alcohol intake (categorized by frequency on a weekly or daily level), smoking status (as never smoker, former smoker, or current smoker), and weekly leisure-time physical activity [categorized as tertiles of

total weekly metabolic equivalent task (MET) hours]. Third, each anthropometric measure (BMI (kg/m^2), height (inches), weight (pounds), and body surface area (BSA, m^2) calculated as $[(\text{weight (kg)} \times \text{height (cm)})/3600]^{½}$) was separately added to this base model. An additional model including both height and weight was also constructed. To determine whether AF risk factor associations differed between men and women, sex-stratified models were performed, and sex-interaction terms were included in the full multivariable model

Several secondary sensitivity analyses were conducted to determine result reproducibility of the multivariable models examining the association between sex and AF. First, since the age enrollment criteria in VITAL differed for men (age ≥ 50 years) and women (age ≥ 55 years), we conducted a sensitivity analysis restricting the population to those 55 years or older. Second, given the major sex differences in height distribution, sensitivity analysis limited to a height range that included a sizable representation of both sexes (64-68 inches) was performed. Third, to determine the sensitivity of the result to extreme values in height, overall population-derived quintiles were substituted for continuous height in the multivariable models. Fourth, sex-specific spline modeling was used to compare the multivariable hazard of incident AF in females as compared to males across ranges of BMI and height. Finally, in order to adjust for height within each sex separately, sex-specific Z-scores (standard scores) for height were calculated for each participant as the number of standard deviations from the sex-specific mean height, and then these Z-scores were substituted for crude height in the multivariable models.

All analyses were performed using SAS 9.4 for Windows (Cary, North Carolina, USA). A 2-sided $P < 0.05$ was used to define statistical significance.

Results:

Baseline population:

25,119 participants were included in the analysis, with 51% female and 20% black participants (Table 1). The mean age at randomization was 67.0 ± 7.1 years. On average, women were older (per study enrollment protocol), more often black, and had a higher prevalence of hypertension and thyroid disorders than men. Conversely, women were less likely to have ever smoked cigarettes, drank less alcohol, exercised less, and reported a lower income than men. All body size parameters differed significantly between men and women. Compared to men, women had a higher mean BMI (28.4 ± 6.6 kg/m^2 vs. 27.8 ± 4.7 kg/m^2, p<0.001), lower mean height (64.4 ± 2.8 inches vs. 70.2 ± 2.8 inches, p<0.001), lower mean weight (167.5 ± 40.0 pounds vs. 194.8 ± 36.7 pounds, p<0.001), and lower mean BSA (1.85 ± 0.2 m^2 vs. 2.08 ± 0.2 m^2, p<0.001). Self-reported height and weight were both highly correlated to measured values in the CTSC cohort (height r = 0.96; weight r = 0.97). Accuracy was slightly greater among women (height r = 0.95; weight r = 0.97) compared to men (height r = 0.91; weight r = 0.94) with both sexes overestimating height and underestimating weight to a small degree.

Incident AF population:

In total, 900 participants in VITAL Rhythm had confirmed incident AF over a median of 5.3 years of follow-up (eTable 1). At 5 years, the corresponding age-adjusted cumulative incidence of AF was 5.7 events per 1000 person-years for women as compared to 8.0 events per 1000 person-years for men (absolute rate difference 2.3 [95% CI 1.4-3.3] events per 1000 person-years). Mean age of participants who developed AF was 74.4 ± 7.2 years and 405 (45%) were women. Women with incident AF differed in their initial presentation. Women were more likely

to have symptoms at time of AF diagnosis (77% in women vs. 63% in men, p<0.001) and tended to present with paroxysmal rather than persistent or permanent forms of AF (65% vs. 28% vs. 7%, respectively) compared to men (56% vs. 32% vs. 12%, respectively; p=0.008 for sex interaction).

Sex and Incident AF Risk:

Women had a 32% lower risk of incident AF than men (HR 0.68, 95% CI 0.59-0.77, p<0.0001) (Table 2) after adjusting for age and treatment assignment. This sex difference was attenuated but remained significant in the multivariable model that included non-anthropometric AF risk factors (HR 0.75, 95% CI 0.65-0.86, p<0.0001). Although BMI was associated with AF, further adjustment for BMI on top of these risk factors did not materially alter the association between female sex and AF (HR 0.73, 95% CI 0.63-0.85, p<0.0001). When height and weight were substituted for BMI in the multivariable model, female sex became positively associated with AF (HR 1.49, 95% CI 1.21-1.82, p=0.0002). This result was primarily due to adjustment for height (HR 1.39, 95% CI 1.14-1.70, p=0.001) as compared to weight (HR 1.05, 95% CI 0.90-1.23, p=0.56). After adjustment for BSA, women continued to have a greater risk of incident AF compared to men (HR 1.25, 95% CI 1.06-1.49, p=0.009). Sex-stratified cumulative incidence curves adjusting for BMI, height and weight, and BSA are displayed in Figure 1A, 1B, and 1C, respectively.

Sensitivity analyses:

Several sensitivity analyses were performed to explore the association between female sex and AF in height adjusted models. First, results were similar when limited to participants ≥ 55 years of age (eTable 2), the age range at which both sexes were enrolled in the trial. Second, female

sex remained positively associated with AF risk (HR 1.57, 95% CI 1.16-2.11, p=0.003) when the population was restricted to a height range between 64 to 68 inches, where there was significant representation by both genders (3188 men, 7056 women; 41% of the total population). Results were also similar in models that controlled for height in quintiles. In sex-specific spline models (Figure 2A), the higher relative hazard of incident AF in women compared to men persisted over the full range of height, although confidence intervals overlapped. This relationship was reversed when considering BMI rather than height (Figure 2B). When comparing the hazard ratio for incident AF at sex-specific median heights, the hazard ratio appeared lower in women than men (female median height denoted by triangle, men median height denoted by square, Figure 2A). Similarly, when sex-specific height and weight Z-scores were used to adjust for height within each sex separately, the positive association between female sex and AF reverted back to the inverse association found in crude models that did not include height and weight (HR 0.78, 95% CI 0.67-0.90, p=0.0008).

Risk Factors for Incident AF in Women versus Men:

In sex-stratified Cox models, age, height, weight, BMI, and hypertension were all significantly associated with an increased risk of incident AF in women and men (Table 3). Black race was associated with lower AF incidence in both sexes. The magnitude of the associations for BMI and alcohol intake and AF were greater in men compared to women, but the test for interaction was not significant. Other AF risk factor associations were also generally similar across men and women, except for diabetes which was associated with a lower multivariable adjusted risk of incident AF only in women (p, sex interaction = 0.03). When BMI was substituted for height and weight in the multivariable model, the interaction between sex and diabetes was no longer significant (P, sex interaction=0.10).

Discussion:

In this contemporary, prospective observational cohort of over 25,000 individuals without prior CVD or AF with equal representation of women and men and overrepresentation of black participants, women were at lower risk for the development of incident AF than men in age-adjusted and multivariate models including BMI, a measure of adiposity. When crude measures of height and weight or BSA were substituted for BMI, the association reversed direction and female sex was associated with a higher risk for AF. In sex-stratified analyses, all anthropometric risk factors, including BMI, were significantly associated with incident AF in women and men. Other AF risk factors such as age, race, and hypertension were significantly associated with AF in both sexes, and definitive evidence for sex-differences in risk factor associations with AF was not found.

Large epidemiologic studies have shown that women appear to have both a lower incidence and lifetime risk of AF compared to men.[1] For example, in the Framingham Heart Study, the most recent assessments of age-adjusted incidence rates of AF from 1998-2007 were 8.6 events per 1000-person years in women and 13.4 events per 1000 person-years in men[1]. In the present study, which was performed in the subsequent decade (2011-2018) among individuals without CVD at baseline, women were again at lower age-adjusted cumulative incidence of AF (5.7 events per 1000 person-years for women and 8.0 events per 1000 person-years for men). The lower overall incidence of AF in our cohort compared to prior epidemiologic studies is likely due to exclusion of patients with established CVD, which elevates risk of AF[25,26]. The persistence of the sex difference in AF incidence in this population without CVD argues that sex-differences in prevalent CVD do not entirely account for sex-differences in AF incidence observed in prior studies.

While prior studies have demonstrated a higher incidence of AF in men compared to women[1,27,28], the CHARGE-AF risk prediction model derived and replicated in various US and European cohorts did not find that sex improved AF risk prediction after accounting for other AF risk factors including height.[29] In the Cardiovascular Health Study, control for height attenuated the elevated risk of incident AF in men compared to women[30]. In our contemporary cohort without CVD, adjustment for height not only attenuated, but reversed the protective association between female sex and AF. When we accounted for the differences in height within each sex separately using sex-specific standardized Z-scores, the positive association between female sex and AF was no longer seen. These data, in combination with prior studies, suggest that sex-differences in height account for much of the lower AF risk in women. Our results also raise the possibility that at a given height, women without CVD may have a higher risk of developing AF than men. However, it is important to recognize the marked sex-difference in height distributions when interpreting this finding such that a given height may be extreme in one sex but not in the other. There are also sex differences in the relationship of height to BMI, such that these measures are negatively correlated in women as opposed to positively correlated in men[31]. The latter association might account for the greater magnitude of the BMI and AF association in men observed here and reported in the literature[5,12].

There are potential biologic pathways through which women might have a higher risk for developing AF at a given body size compared to men. In one magnetic resonance imaging study involving 60 patients with AF, female sex was associated with higher levels of atrial fibrosis measured as a percentage of the left atrial wall compared to men[32]. Since body size and height are correlated with left atrial size[33,34], these data raise the possibility that for a given height and similarly sized atrium, there may be a higher degree of atrial fibrosis in women compared to

men. As compared to men, women may also be more likely to manifest left atrial dilation and/or dysfunction resulting in AF[35,36]. Also, since height is inversely associated with CVD[37], it is feasible that the elevation in AF risk in women observed after controlling for height may be specific to patient populations without CVD.

Although AF risk factors were generally similar between men and women in our study, the clinical presentation differed. As compared to men, women were more likely to be symptomatic and less likely to present with persistent forms of AF at the time of incident AF diagnosis. In the recently reported EAST-AFNET trial, women were similarly more likely to be symptomatic at the time of initial presentation[38], and several studies have reported more symptoms and reduced quality of life in women with prevalent AF as compared to men.[39-41] In the CABANA trial, a large scale randomized trial of AF ablation versus drug therapy, women were also more likely to be symptomatic and to have paroxysmal forms of AF at the time of enrollment[42]. Paroxysmal forms of AF tend to be more symptomatic, and these sex-differences in the ability to sustain AF could be due to differences in left atrial electrophysiology[43,44]. However, there may be systematic biases which could result in differential detection of AF (symptomatic and/or asymptomatic) between women and men which could account for these findings[43,44]. Large scale population level screening studies will help answer these questions and allow for better strategies for AF detection for men and women.

Strengths and Limitations:

Strengths of this study include the large contemporary racially diverse population of over 25,000 participants comprised of 50% women and 20% black participants. AF ascertainment was performed using two complimentary methods, and incident AF outcomes were rigorously

adjudicated by medical record review. There are also important limitations to consider. First, the data must be interpreted in the context of the study design as a secondary analysis of a randomized controlled trial. Second, the study population was older, with an average age of 67 years at randomization, and 74 years at the time of incident AF diagnosis. Therefore, generalizability of these findings to younger subjects may be limited. Third, subjects with underlying CVD were excluded from the trial; thus, these findings may not be generalizable to patients with established CVD. Fourth, ascertainment of AF was based solely on clinical diagnoses, which would be expected to be dependent, at least to some degree, on health care utilization and/or likelihood of undergoing ECGs or rhythm monitoring during health care evaluations. Thus, the lack of protocolized AF screening in all study patients could manifest as a systematic bias if one sex was more likely to seek healthcare and/or receive an ECG and/or cardiac monitor, either due to symptoms or for other reasons. Fifth, we used self-reported height and weight leading to some misclassification, which based on our validation data would be expected to minimal and unlikely to account for the findings observed.

Conclusion:

In this large contemporary trial of women and men without CVD at baseline, women had a lower risk of developing incident AF; however, after controlling for height, female sex was associated with a higher risk for AF. These data suggest that sex-differences in body size account for much of the previously reported protective association between female sex and AF and underscore the importance of AF prevention in women.

References:

1. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *The Lancet*. 2015/07// 2015;386(9989):154-162. doi:10.1016/S0140-6736(14)61774-8

2. Dagres N, Nieuwlaat R, Vardas PE, et al. Gender-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe. *Journal of the American College of Cardiology*. 2007/02// 2007;49(5):572-577. doi:10.1016/j.jacc.2006.10.047

3. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol*. 2016/06// 2016;13(6):321-332. doi:10.1038/nrcardio.2016.45

4. Madan N, Itchhaporia D, Albert CM, Aggarwal NT, Volgman AS. Atrial Fibrillation and Heart Failure in Women. *Heart Failure Clinics*. 2019/01// 2019;15(1):55-64. doi:10.1016/j.hfc.2018.08.006

5. Peters SAE, Woodward M. Established and novel risk factors for atrial fibrillation in women compared with men. *Heart*. 2019/02// 2019;105(3):226-234. doi:10.1136/heartjnl-2018-313630

6. Ball J, Carrington MJ, Wood KA, Stewart S, the SI. Women Versus Men with Chronic Atrial Fibrillation: Insights from the Standard Versus Atrial Fibrillation spEcific managemenT studY (SAFETY). *PLoS ONE*. 2013/05/29/ 2013;8(5):e65795. doi:10.1371/journal.pone.0065795

7. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study. *Circulation*. 1998/09/08/ 1998;98(10):946-952. doi:10.1161/01.CIR.98.10.946

8. Barillas-Lara MI, Monahan K, Helm RH, et al. Sex-Specific Prevalence, Incidence, and Mortality Associated With Atrial Fibrillation in Heart Failure. *JACC Clin Electrophysiol*. Apr 2021;doi:10.1016/j.jacep.2021.02.021

9. Andersen K, Rasmussen F, Neovius M, Tynelius P, Sundström J. Body size and risk of atrial fibrillation: a cohort study of 1.1 million young men. *J Intern Med*. 04 2018;283(4):346-355. doi:10.1111/joim.12717

10. Feng T, Vegard M, Strand LB, et al. Weight and weight change and risk of atrial fibrillation: the HUNT study. *European Heart Journal*. 2019/09/07/ 2019;40(34):2859-2866. doi:10.1093/eurheartj/ehz390

11. Rosenberg MA, Patton KK, Sotoodehnia N, et al. The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study. *European Heart Journal*. 2012/11// 2012;33(21):2709-2717. doi:10.1093/eurheartj/ehs301

12. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation*. 2017/10// 2017:1. doi:10.1161/CIRCULATIONAHA.117.028981

13. Marott JL, Skielboe AK, Dixen U, Friberg JB, Schnohr P, Jensen GB. Increasing population height and risk of incident atrial fibrillation: the Copenhagen City Heart Study. *Eur Heart J*. 12 2018;39(45):4012-4019. doi:10.1093/eurheartj/ehy367

14. Aune D, Sen A, Schlesinger S, et al. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose–response meta-analysis of prospective studies. *Eur J Epidemiol*. 2017/03// 2017;32(3):181-192. doi:10.1007/s10654-017-0232-4

15. Ball J, Løchen ML, Wilsgaard T, et al. Sex Differences in the Impact of Body Mass Index on the Risk of Future Atrial Fibrillation: Insights From the Longitudinal Population-Based Tromsø Study. *JAHA*. 2018/05// 2018;7(9)doi:10.1161/JAHA.117.008414

16. Chatterjee NA, Giulianini F, Geelhoed B, et al. Genetic Obesity and the Risk of Atrial Fibrillation: Causal Estimates from Mendelian Randomization. *Circulation*. 2017/02/21/ 2017;135(8):741-754. doi:10.1161/CIRCULATIONAHA.116.024921

17. Tedrow UB, Conen D, Ridker PM, et al. The Long- and Short-Term Impact of Elevated Body Mass Index on the Risk of New Atrial Fibrillation. *Journal of the American College of Cardiology*. 2010/05// 2010;55(21):2319-2327. doi:10.1016/j.jacc.2010.02.029

18. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: The Danish Diet, Cancer, and Health Study. *The American Journal of Medicine*. 2005/05// 2005;118(5):489-495. doi:10.1016/j.amjmed.2005.01.031

19. Manson JE, Cook NR, Lee IM, et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*. 2019/01/03/ 2019;380(1):23-32. doi:10.1056/NEJMoa1811403

20. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med*. 2019/01/03/ 2019;380(1):33-44. doi:10.1056/NEJMoa1809944

21. Albert CM, Cook NR, Pester J, et al. Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial. *JAMA*. Mar 16 2021;325(11):1061-1073. doi:10.1001/jama.2021.1489

22. Conen D. Alcohol Consumption and Risk of Incident Atrial Fibrillation in Women. *JAMA*. 2008/12/03/ 2008;300(21):2489. doi:10.1001/jama.2008.755

23. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Journal of the American College of Cardiology*. 2014/12// 2014;64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022

24. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016/10/07/ 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

25. Kwok MK, Schooling CM. Mendelian randomization study on atrial fibrillation and cardiovascular disease subtypes. *Sci Rep*. Sep 21 2021;11(1):18682. doi:10.1038/s41598-021-98058-w

26. Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA: The Journal of the American Medical Association*. 1994/03/16/ 1994;271(11):840-844. doi:10.1001/jama.271.11.840

27. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. Jan 2012;5(1):85-93. doi:10.1161/CIRCOUTCOMES.111.962688

28. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. Apr 2011;123(14):1501-8. doi:10.1161/CIRCULATIONAHA.110.009035

29. Alonso A, Krijthe BP, Aspelund T, et al. Simple Risk Model Predicts Incidence of Atrial Fibrillation in a Racially and Geographically Diverse Population: the CHARGE-AF Consortium. *JAHA*. 2013/03/12/ 2013;2(2)doi:10.1161/JAHA.112.000102

30. Karas MG, Yee LM, Biggs ML, et al. Measures of Body Size and Composition and Risk of Incident Atrial Fibrillation in Older People: The Cardiovascular Health Study. *Am J Epidemiol*. 2016/06/01/ 2016;183(11):998-1007. doi:10.1093/aje/kwv278

31. Sperrin M, Marshall AD, Higgins V, Renehan AG, Buchan IE. Body mass index relates weight to height differently in women and older adults: serial cross-sectional surveys in England (1992-2011). *J Public Health (Oxf)*. Sep 2016;38(3):607-613. doi:10.1093/pubmed/fdv067

32. Cochet H, Mouries A, Nivet H, et al. Age, Atrial Fibrillation, and Structural Heart Disease Are the Main Determinants of Left Atrial Fibrosis Detected by Delayed-Enhanced Magnetic Resonance Imaging in a General Cardiology Population: Atrial Fibrosis on MRI in Patients. *J Cardiovasc Electrophysiol*. 2015/05// 2015;26(5):484-492. doi:10.1111/jce.12651

33. Aurigemma GP, Gottdiener JS, Arnold AM, Chinali M, Hill JC, Kitzman D. Left atrial volume and geometry in healthy aging: the Cardiovascular Health Study. *Circ Cardiovasc Imaging*. Jul 2009;2(4):282-9. doi:10.1161/CIRCIMAGING.108.826602

34. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol*. Mar 19 2003;41(6):1036-43. doi:10.1016/s0735-1097(02)02981-9

35. Proietti M, Raparelli V, Basili S, Olshansky B, Lip GY. Relation of female sex to left atrial diameter and cardiovascular death in atrial fibrillation: The AFFIRM Trial. *Int J Cardiol*. Mar 15 2016;207:258-63. doi:10.1016/j.ijcard.2016.01.169

36. Yoshida K, Obokata M, Kurosawa K, Sorimachi H, Kurabayashi M, Negishi K. Effect of Sex Differences on the Association Between Stroke Risk and Left Atrial Anatomy or Mechanics in Patients With Atrial Fibrillation. *Circ Cardiovasc Imaging*. Oct 2016;9(10)doi:10.1161/CIRCIMAGING.116.004999

37. Khetan AK, Leong DP, Gupta R, et al. Variations in the association of height with mortality, cardiovascular disease and cancer in low-, middle- and high-income countries. *Int J Epidemiol*. Dec 22 2021;doi:10.1093/ije/dyab268

38. Willems S, Borof K, Brandes A, et al. Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial. *European Heart Journal*. 2021;doi:10.1093/eurheartj/ehab593

39. Piccini JP, Simon DN, Steinberg BA, et al. Differences in Clinical and Functional Outcomes of Atrial Fibrillation in Women and Men: Two-Year Results From the ORBIT-AF Registry. *JAMA Cardiol*. 06 2016;1(3):282-91. doi:10.1001/jamacardio.2016.0529

40. Blum S, Muff C, Aeschbacher S, et al. Prospective Assessment of Sex-Related Differences in Symptom Status and Health Perception Among Patients With Atrial Fibrillation. *J Am Heart Assoc*. Jun 2017;6(7)doi:10.1161/JAHA.116.005401

41. Reynolds MR, Lavelle T, Essebag V, Cohen DJ, Zimetbaum P. Influence of age, sex, and atrial fibrillation recurrence on quality of life outcomes in a population of patients with new-onset atrial fibrillation: the Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle (FRACTAL) study. *Am Heart J*. Dec 2006;152(6):1097-103. doi:10.1016/j.ahj.2006.08.011

42. Russo AM, Zeitler EP, Giczewska A, et al. Association Between Sex and Treatment Outcomes of Atrial Fibrillation Ablation Versus Drug Therapy: Results From the CABANA Trial. *Circulation*. Feb 16 2021;143(7):661-672. doi:10.1161/CIRCULATIONAHA.120.051558

43. Linde C, Bongiorni MG, Birgersdotter-Green U, et al. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace*. Oct 1 2018;20(10):1565-1565ao. doi:10.1093/europace/euy067

44. Gillis AM. Atrial Fibrillation and Ventricular Arrhythmias: Sex Differences in Electrophysiology, Epidemiology, Clinical Presentation, and Clinical Outcomes. *Circulation*. Feb 7 2017;135(6):593-608. doi:10.1161/CIRCULATIONAHA.116.025312

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Figure Legends:

Figure 1 Cumulative Incidence of incident AF during VITAL, stratified by sex, adjusting for different body size surrogates Sex-stratified cumulative incidence of atrial fibrillation, adjusted for a) BMI b) height and weight and c) BSA, as well as age, trial treatment assignment, race, thyroid disease, hypertension, diabetes, physical activity, alcohol intake and smoking.

Figure 2 Risk of incident AF in the study population, adjusting for A) height and B) BMI: Spline modeling of the hazard ratios for incident AF, stratified by sex, across the range of a) height and b) BMI in the study population. Histograms below each graph show the distribution of a) height and b) BMI in the study population. Sex specific median values of a) height and b) BMI for women and men are represented by triangles and squares in each graphic, respectively.

Table 1: Baseline characteristics for the complete VITAL study population

Characteristic	All participants	Male	Female	p-value[a]
N (%)	25119	12362 (49%)	12757 (51%)	
Age, years	67.0 (7.1)	66.0 (7.1)	68.1 (6.8)	<0.001
Age categories, years				
<65	9696 (39%)	5732 (46%)	3964 (31%)	<0.001
65- <75	12267 (49%)	5321 (43%)	6946 (54%)	
75+	3156 (13%)	1309 (11%)	1847 (15%)	
Race/ethnicity				
White	17425 (69%)	8995 (73%)	8430 (66%)	<0.001
Black	5052 (20%)	1927 (16%)	3125 (25%)	
Other	2642 (11%)	1440 (12%)	1202 (9%)	
Body mass index, kg/m^2	28.1 (5.7)	27.8 (4.7)	28.4 (6.6)	<0.001
Height, inches	67.2 (4.0)	70.2 (2.8)	64.4 (2.8)	<0.001
Weight, pounds	180.9 (40.8)	194.8 (36.7)	167.5 (40.0)	<0.001
Body surface area, m^2	1.96 (0.3)	2.08 (0.2)	1.85 (0.2)	<0.001
Average Alcohol use				
Never or <1 drink/week	9658 (39%)	3670 (30%)	5988 (48%)	<0.001
1-6 drinks/week	8638 (35%)	4223 (35%)	4415 (35%)	
1 drink/day	2892 (12%)	1723 (14%)	1169 (9%)	
2+ drinks/day	3509 (14%)	2529 (21%)	980 (8%)	
Annual income				
<$50000	8297 (37%)	3120 (28%)	5177 (46%)	<0.001
$50000 – $120000	10224 (45%)	5378 (48%)	4846 (43%)	
>$120000	4079 (18%)	2803 (25%)	1276 (11%)	
Smoker				
Never smoker	12835 (52%)	5970 (49%)	6865 (55%)	<0.001
Former smoker	10111 (41%)	5291 (44%)	4820 (38%)	
Current smoker	1798 (7%)	913 (8%)	885 (7%)	
Diabetes (%)	3442 (14%)	1666 (14%)	1776 (14%)	0.317
Hypertension (%)	12911 (52%)	6066 (49%)	6845 (54%)	<0.001
Thyroid conditions (%)	2923 (12%)	602 (5%)	2321 (19%)	<0.001
Weekly total MET, hours[b]				
Lowest tertile	8295 (33.3%)	3581 (29.3%)	4714 (37.3%)	<0.001
Middle tertile	8298 (33.4%)	4019 (32.8%)	4279 (33.9%)	
Highest tertile	8282 (33.3%)	4637 (37.9%)	3645 (28.8%)	

Randomized to Vitamin D	12553 (50.0%)	6169 (49.9%)	6384 (50.0%)	0.824
Randomized to Omega-3	12542 (49.9%)	6174 (49.9%)	6368 (49.9%)	0.968

Table 1 legend: Continuous variables are listed as mean (standard deviation). Categorical variables are listed as absolute number (percentage of population).
[a]p-value for comparison between male and female groups.
ANOVA and chi-squared tests were used to test for p-values as appropriate.
[b]Weekly MET hours were calculated from participant responses to survey questions about their weekly leisure time physical activity.

Table 2: Sex-specific risk for incident AF for females compared to males

Cox-Proportional Hazards Model	Hazard ratio (95% Confidence Interval)	P-value
Age, trial treatment group	0.68 (0.59, 0.77)	<0.0001
Base model[a]	0.75 (0.65, 0.86)	<0.0001
Base model[‡], body mass index	0.73 (0.63, 0.85)	<0.0001
Base model[‡], weight	1.05 (0.90, 1.23)	0.56
Base model[‡], height	1.39 (1.14, 1.70)	0.001
Base model[‡], height, weight	1.49 (1.21, 1.82)	0.0002
Base model[‡], body surface area	1.25 (1.06, 1.49)	0.009

[a]Base Cox-proportional model adjusted for trial treatment group, age at randomization, race, average alcohol use per day, history of smoking, thyroid disease, diabetes, hypertension, amount of weekly leisure time physical activity.

Table 3: Predictors of incident AF stratified by sex in a multivariate model accounting for height and weight or BMI.

	Men		Women		P for sex interaction
Characteristic	**N (%)**	**HR[a] (95%CI)**	**N (%)**	**HR[a] (95%CI)**	
Mean Age at randomization, years					
<65	5396 (47)	Reference	3726 (31)	Reference	0.97
65- <75	5003 (43)	2.41 (1.90, 3.06)	6542 (55)	2.31 (1.63, 3.28)	
75+	1189 (10)	5.90 (4.46, 7.81)	1690 (14)	5.49 (3.76, 8.03)	
Race/ethnicity					
White	8524 (74)	Reference	8015 (67)	Reference	0.14
Black	1732 (15)	0.25 (0.15, 0.41)	2844 (24)	0.29 (0.20, 0.44)	
Other	1332 (11)	0.76 (0.55, 1.05)	1099 (9)	0.63 (0.42, 0.95)	
Body mass index (per kg/m^2 increase)[b]		1.07 (1.04, 1.09)		1.04 (1.02, 1.05)	0.06
Height (per inch increase)		1.06 (1.02, 1.10)		1.08 (1.04, 1.12)	0.51
Weight (per pound increase)		1.01 (1.01, 1.01)		1.01 (1.00, 1.01)	0.69
Average Alcohol use					
Never or <1 drink/week	3489 (30)	Reference	5647 (47)	Reference	0.58
1-6 drinks/week	4046 (35)	1.19 (0.93, 1.52)	4229 (35)	1.02 (0.81, 1.30)	
1 drink/day	1635 (14)	1.25 (0.92, 1.68)	1140 (10)	1.18 (0.83, 1.66)	
2+ drinks/day	2418 (21)	1.53 (1.17, 1.99)	942 (8)	1.19 (0.82, 1.72)	
Smoker					
Never smoker	5686 (49)	Reference	6521 (55)	Reference	0.29
Former smoker	5046 (44)	1.10 (0.91, 1.33)	4593 (38)	1.28 (1.04, 1.58)	
Current smoker	856 (7)	0.83 (0.51, 1.35)	844 (7)	1.04 (0.62, 1.75)	
Diabetes	1538 (7)	1.13 (0.87, 1.46)	1611 (7)	0.65 (0.46, 0.93)	0.03
Hypertension	5677 (49)	1.33 (1.10, 1.62)	6398 (54)	1.64 (1.31, 2.05)	0.33
Leisure time physical activity (weekly total MET hours)					
Lowest tertile	3360	Reference	4403	Reference	0.14
Middle tertile	3818	1.03 (0.81, 1.31)	4074	1.01 (0.79, 1.28)	

Highest tertile	4410	1.23 (0.97, 1.55)	3481	0.91 (0.69, 1.19)	

[a]Multivariable models simultaneously adjusted for trial treatment group assignment, height, weight, and all listed variables except BMI.
[b]BMI substituted for height and weight, all other variables the same.