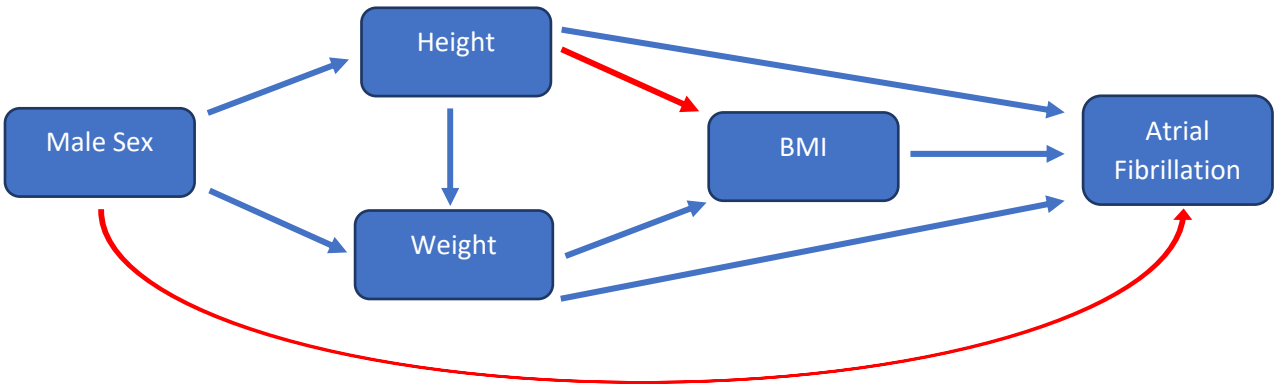
Supplementary Online Content

Siddiqi HK, Vinayagamoorthy M, Gencer B, et al. Sex differences in atrial fibrillation risk: the VITAL Rhythm Study. *JAMA Cardiol*. Published online August 31, 2022. doi:10.1001/jamacardio.2022.2825

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Schematic Showing the Proposed Relationship Between Sex, Anthropometric Measures, and Atrial Fibrillation



<u>eFigure legend:</u> This directed acyclic graph shows the proposed relationship between male sex, anthropometric measures and atrial fibrillation. The red arrows show inverse effects, whereas blue arrows show direct effects. Male sex is associated with a lower direct risk of atrial fibrillation relative to females when accounting for height and weight.

eTable 1. Baseline and AF Characteristics for Individuals Who Developed Incident AF

Characteristic	All participants	Male	Female
N (%)	900	495 (55%)	405 (45%)
Age, years (SD or N)	74.4 (7.2)	73.7 (7.3)	75.2 (6.9)
<65	150 (17%)	105 (21%)	45 (11%)
65- <75	490 (54%)	261 (53%)	229 (57%)
75+	260 (29%)	129 (26%)	131 (32%)
Race/ethnicity			
White	772 (86%)	429 (87%)	343 (85%)
Black	52 (6%)	19 (4%)	33 (8%)
Other/Unknown	76 (8%)	47 (10%)	29 (7%)
Body mass index, kg/m^2	28.7 (6.34)	28.6 (5.2)	28.8 (7.5)
Height, inches	68.2 (4.0)	70.8 (2.75)	64.9 (2.75)
Weight, pounds	189.8 (44.0)	204.0 (38.06)	172.3 (44.62)
Body surface area, m^2	2.02 (0.26)	2.14 (0.21)	1.88 (0.25)
Average Alcohol use			
Never or <1 drink/week	166 (19%)	119 (24%)	177 (44%)
1-6 drinks/week	125 (14%)	166 (34%)	138 (34%)
1 drink/day	304 (34%)	78 (16%)	47 (12%)
2+ drinks/day	296 (33%)	126 (26%)	40 (10%)
Income			
<$50000	282 (34%)	103 (22%)	179 (49%)
$50000 – $120000	369 (45%)	230 (50%)	139 (38%)
>$120000	170 (21%)	126 (28%)	44 (12%)
Smoker			
Never smoker	400 (45%)	211 (44%)	189 (48%)
Former smoker	443 (50%)	254 (53%)	189 (48%)
Current smoker	38 (4.3%)	19 (4%)	19 (5%)
Diabetes	123 (14%)	82 (17%)	41 (10%)
Hypertension	557 (62%)	296 (60%)	261 (65%)
Thyroid conditions	115 (13%)	22 (5%)	93 (24%)
Physical exercise, in tertiles by MET hours			
Lowest tertile	298 (33%)	144 (30%)	154 (38%)
Middle tertile	302 (34%)	153 (31%)	149 (37%)
Highest tertile	292 (33%)	191 (39%)	101 (25%)
Symptoms at AF diagnosis[a]	557 (69%)	273 (63%)	284 (77%)
Type of AF[b]			
Paroxysmal AF	526 (60%)	267 (56%)	259 (65%)
Persistent AF	262 (30%)	153 (32%)	109 (28%)
Chronic/permanent AF	84 (10%)	56 (12%)	28 (7%)
Initial Therapy for AF (first month)			
Rate control with medication	702 (80%)	364 (76%)	338 (84%)
Rhythm control with medication	227 (26%)	128 (27%)	99 (25%)

Maze or AF Ablation	26 (2.9%)	15 (3.1%)	11 (2.7%)
Rate Control with AVJ ablation/PPM	4 (0.5%)	2 (0.4%)	2 (0.5%)
Atrial flutter ablation	21 (2.4%)	14 (2.9%)	7 (1.7%)
Oral anticoagulant prescribed	622 (69%)	334 (68%)	288 (71%)

eTable 1 legend: Characteristics of the 900 individuals in the VITAL Rhythm study who developed incident AF, stratified by sex.
[a]Symptoms at AF diagnosis were determined by patient report on paper surveys and/or by medical record review.
[b]Type of AF was assigned based on cardiologist adjudication of the available medical records for each patient, including medical provider documentation and electrocardiograms
Abbreviations: AVJ = atrioventricular junction, PPM = permanent pacemaker

eTable 2. Sensitivity Analyses for Adjusted Sex-Specific Risk of Incident AF for Females Compared With Males, Restricting to Key Subgroups

Subgroup	Cox-Proportional Hazards Model	Hazard ratio (95% Confidence Interval)	P-value
Height 64-68 inches	Base model[a], BMI	1.19 (0.91, 1.55)	0.21
	Base model[a], height, weight	1.57 (1.16, 2.11)	0.003
Age≥55 years	Base model[a], BMI	0.73 (0.63, 0.85)	<0.0001
	Base model[a], height, weight	1.49 (1.21, 1.83)	0.0002
Overall height quintiles	Base model[a], overall height quintiles, weight	1.61 (1.30, 2.01)	0.0001
Sex-specific standard score models[b]	Base model[a], standardized BMI	0.76 (0.66, 0.89)	0.0003
	Base model[a], standardized height, standardized weight	0.78 (0.67, 0.90)	0.0008

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

[b]The sex-specific standard score model incorporated BMI or height and weight using sex-specific Z-scores for each of these anthropometric measures.