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The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study

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Aims Atrial fibrillation (AF) is the most common sustained arrhythmia. Increased body size has been associated with AF, but the relationship is not well understood. In this study, we examined the effect of increased height on the risk of AF and explore potential mediators and implications for clinical practice.

Methods and results We examined data from 5860 individuals taking part in the Cardiovascular Health Study, a cohort study of older US adults followed for a median of 13.6 (women) and 10.3 years (men). Multivariate linear models and age-stratified Cox proportional hazards and risk models were used, with focus on the effect of height on both prevalent and incident AF. Among 684 (22.6%) and 568 (27.1%) incident cases in women and men, respectively, greater height was significantly associated with AF risk [hazard ratio $(HR)_{women}$ per 10 cm 1.32, confidence interval (CI) 1.16–1.50, $P < 0.0001$; HR_{men} per 10 cm 1.26, CI 1.11–1.44, $P < 0.0001$]. The association was such that the incremental risk from sex was completely attenuated by the inclusion of height (for men, HR 1.48, CI 1.32–1.65, without height, and HR 0.94, CI 0.85–1.20, with height included). Inclusion of height in the Framingham model for incident AF improved discrimination. In sequential models, however, we found minimal attenuation of the risk estimates for AF with adjustment for left ventricular (LV) mass and left atrial (LA) dimension. The associations of LA and LV size measurements with AF risk were weakened when indexed to height.

Conclusion Independent from sex, increased height is significantly associated with the risk of AF.

Keywords Atrial fibrillation • Cardiovascular risk factors • Echocardiography • Risk prediction

Introduction

The prevalence of atrial fibrillation (AF) in the population is increasing.[1] It is estimated that 2.3 million adults in the USA currently have AF, and that this will increase to 5.6 million by the year 2050.[2] Among the numerous risk factors that have been described for AF,[3] one of the more complex and poorly understood is that of body size.

A number of studies have noted the association between AF and body size in a range of populations, including in Japanese patients,[4] patients with LV dysfunction,[5] Scandinavian men,[6] European patients,[7] Chinese patients,[8] and older adults.[9] The challenge in these studies is that in most cases, little distinction is made between increased body size reflected in increased body weight, and often obesity, and increased body frame. Nowhere was the complexity of this distinction more evident than in the recent study by Conen *et al.*, [10] which found that in women over 45 years of age followed for 14.5 years, increased birth weight was significantly associated with the development of incident AF. Interestingly, the effect was attenuated when adult height was included in

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the model. Other studies have found that height, either in addition to or independent of weight, increases the risk of AF.[4,6,7,9] However, despite these findings, few risk scores include height as a risk factor for AF,[11] and the epidemiological relationship between height and other AF risk factors has not been well described. Further, recent findings from genome-wide association studies that genes near loci associated with increased AF risk, PITX2[12] and ZFHX3,[13] are also associated with growth pathways[10,12,13] imply that height may be a result of a pleotropic process that increases the risk of AF.

In this study, we evaluate the hypothesis that increased height is associated with an increased risk of AF in a well-characterized, community-based cohort of older adults followed for over a decade.

Methods

Population

The design and objectives of the Cardiovascular Health Study have been previously described.[14] In brief, the Cardiovascular Health Study (CHS) is a longitudinal study of men and women aged 65 years or older, randomly selected from Medicare lists in Pittsburgh, PA; Forsyth County, NC; Sacramento, CA; and Hagerstown, MD. The original cohort of 5201 participants was enrolled in 1989–90; a second cohort of 687 African-Americans was recruited in 1992–93. Except where specified otherwise, both cohorts were used in this analysis, providing a total of 5888 participants. The institutional review board at each centre approved the study, and each participant gave informed consent.

The baseline examination included a standardized questionnaire assessing a variety of risk factors, including smoking, alcohol intake, history of stroke, coronary heart disease, and heart failure, self-reported health status, and medication use on enrolment. Methods of determining prevalent cardiovascular disease were previously validated by Psaty *et al.*[15] The physical examination included measurements of standing height, weight, and seated blood pressure (measured with a random-zero sphygmomanometer),[15] as well as a resting 12-lead electrocardiogram (ECG). Fasting laboratory measurements included total cholesterol, high-density lipoprotein cholesterol, glucose, C-reactive protein, serum creatinine,[16] and N-terminal-pro-brain natriuretic peptide (NT-proBNP),[17] although NT-proBNP was only available in 3464 individuals in the analytic data set (see below).

Of the initial 5888 individuals in the study population, we excluded 11 who were missing height and 17 participants missing education data, leaving a total of 5860 patients for the analysis of prevalent AF (*Table 1*). For incident AF, we excluded individuals with prevalent AF ($n = 157$), as well as individuals who were taking digoxin ($n = 387$) or had a history of stroke ($n = 199$) due to concerns of undetected prevalent AF in these individuals, leaving 5117 participants.

For substudies that included echocardiography variables, we could only include the original cohort of 5201 participants as the subsequent African-American cohort did not undergo echocardiography measurements during initial examination. For these studies, we excluded 281 people who were missing major echocardiographic measurements. In addition to 130 participants who had prevalent AF and 180 with a history of stroke, we excluded 130 participants due to the presence of mitral stenos is or greater than moderate aortic insufficiency or mitral regurgitation to avoid confounding of diastolic measurements, leaving a final study population of 4480 subjects for these substudies.

For sensitivity analyses, NT-proBNP was available in 3464 individuals in the analytic data set, and left atrial (LA) volume measurements were obtained from a second echocardiogram from 1994 to 1995 in which LA volume was measured in a subset of 686 CHS participants.[18]

Echocardiography

The design of the echocardiography protocol used in CHS has been described in detail elsewhere.[19] Echocardiographic parameters included M-mode-based parasternal long-axis LA dimension, left ventricular (LV) dimensions, fractional shortening, and calculated LV mass, as well as Doppler mitral valve inflow, consisting of early and late peak velocities. Left atrial volume measurements were available in a subset of 657 participants.

Determination of incident atrial fibrillation

Participants were contacted every 6 months for follow-up, alternating between a telephone interview and a clinic visit for the first 10 years and by telephone interview only after that. An annual resting ECG was obtained yearly through the ninth year of follow-up, and discharge diagnoses for all hospitalizations were collected. We identified cases of AF in two ways. Annual study ECGs were interpreted by the EPICARE ECG reading centre, where the diagnoses of AF or a trial flutter were verified.[9] Hospital discharge diagnoses that included codes for AF and flutter were also included, although AF or flutter diagnoses that were made during the same hospitalization as coronary artery bypass surgery or heart valve surgery were not counted. Prior evaluation in CHS determined the positive predictive value of hospital discharge diagnosis to be 98.6% for diagnosis of AF[9] and a Holter substudy identified that only 1 in 819 subjects (0.1%) had persistent or intermittent AF not identified by the above measures.[20]

Analysis

In studies of prevalent AF, we examined the mean height between participants with and without prevalent AF according to sex using Student's *t*-test. For the adjusted analysis, we used generalized linear models of height stratified by sex, with adjustment for age, body mass index (BMI), clinic site, highest grade achieved, and race.

For analysis of incident AF, we used the Cox proportional hazards regression modelling with stratification by sex, age-specific hazard functions, and adjustment for BMI, clinic site, highest grade achieved, and race as our base model for all analyses, since we considered these to be the only variables that were conceivably established prior to the attainment of adult height (i.e. 'upstream' of height). Time-varying covariates were assessed to check for violation of the proportional hazards assumption and quadratic terms and logarithmic transformations for non-linear effects of height. Analysis was performed using height, per standard deviation, and per unit of measurement (10 cm), as well as using pre-defined cut-points in 5 cm categories. Similarly, we present the Kaplan–Meier curves stratified by sex and age dichotomized at 75.

To examine possible mediators of height-associated incident AF risk, and to assess the independent association of height with AF after adjustment for well-recognized risk factors, we sequentially added potential anatomical and physiological mediators (listed in *Table 5*) into the base model, as well as inclusion of all variables together. We also repeated all of our base analyses with additional adjustment for systolic blood pressure and the use of antihypertensive agents, given the high burden of AF attributable to hypertension.[21] For completeness, we also examined the effect of adjusting for other downstream covariates, including diabetes, kidney function, and the presence of valve disease.

The current guidelines from the Chamber Quantification Writing Group of the American Society of Echocardiography's Guidelines

Table 1 Baseline characteristics by height (prevalent analysis group)

Group	Characteristic	Group 1	Group 2	Group 3	Group 4	Group 5
Women ($n = 3378$)	Height (cm)	≤150	150–155	155–160	160–165	>165
	Number	255	667	1116	820	520
	Mean height in cm (SD)	147 (3)	153 (1)	158 (1)	163 (1)	169 (3)
	Mean age in years (SD)	75.6 (6.2)	73.8 (5.7)	72.6 (5.5)	71.5 (4.9)	71.0 (4.5)
	Black race (%)	34 (13)	110 (17)	189 (17)	144 (18)	102 (20)
	Income (% below median)†	160 (63)	352 (53)	549 (49)	358 (44)	216 (42)
	Education (% HS grad or better)†	162 (64)	437 (66)	770 (69)	627 (76)	393 (76)
	Diabetes (%)	34 (13)	88 (13)	175 (16)	104 (13)	84 (16)
	CHD (%)	41 (16)	133 (20)	160 (14)	123 (15)	65 (13)
	Current smoking (%)	23 (9)	79 (12)	136 (12)	117 (14)	67 (13)
	Treated HTN (%)*	189 (74)	489 (73)	745 (67)	501 (61)	328 (63)
	CVA (%)	11 (4)	24 (4)	31 (3)	21 (3)	17 (3)
	Mean BMI (SD)	27.4 (5.7)	27.1 (5.3)	27.1 (5.3)	26.5 (5.2)	26.9 (5.3)
	Mean SBP in mmHg (SD)	140 (22)	140 (22)	138 (22)	134 (22)	135 (23)
	Mean creatinine in mg/dL (SD)	0.94 (0.35)	0.92 (0.25)	0.94 (0.28)	0.94 (0.26)	0.94 (0.21)
	Mean LA diameter in cm (SD)	3.83 (0.75)	3.76 (0.65)	3.77 (0.64)	3.76 (0.63)	3.83 (0.67)
	Mean NT-proBNP in pg/dL (SD)	430 (1420)	271 (728)	260 (484)	199 (370)	256 (569)
Men ($n = 2482$)	Height (cm)	≤165	165–170	170–175	175–180	>180
	Number	280	547	734	578	343
	Mean height in cm (SD)	162 (3)	168 (1)	173 (1)	177 (1)	184 (3)
	Mean age in years (SD)	75.7 (6.4)	74.1 (6.0)	73.1 (5.4)	72.5 (5.4)	71.7 (5.1)
	Black race (%)	37 (13)	67 (12)	111 (15)	82 (14)	48 (14)
	Income (% below median)†	111 (40)	192 (35)	244 (33)	160 (28)	77 (22)
	Education (% HS grad or better)†	173 (62)	378 (69)	518 (71)	399 (69)	274 (80)
	Diabetes (%)	50 (18)	98 (18)	131 (18)	124 (21)	72 (21)
	CHD (%)	78 (28)	152 (28)	166 (23)	144 (25)	74 (22)
	Current smoking (%)	25 (9)	69 (13)	73 (10)	68 (12)	37 (11)
	Treated HTN (%)*	195 (70)	382 (70)	474 (65)	359 (62)	202 (59)
	CVA (%)	22 (8)	35 (6)	43 (6)	23 (4)	16 (5)
	Mean BMI (SD)	26.6 (4.0)	26.8 (4.1)	26.4 (3.6)	26.3 (3.6)	26.3 (4.0)
	Mean SBP in mmHg (SD)	140 (23)	137 (21)	137 (21)	134 (22)	132 (19)
	Mean creatinine in mg/dL (SD)	1.23 (0.33)	1.24 (0.33)	1.25 (0.32)	1.23 (0.29)	1.19 (0.25)
	Mean LA diameter in cm (SD)	3.96 (0.69)	4.07 (0.71)	4.03 (0.66)	4.04 (0.66)	4.10 (0.70)
	Mean NT-proBNP in pg/dL (SD)	334 (596)	392 (871)	348 (1144)	291 (752)	246 (452)

All tests of heterogeneity had 4 degrees of freedom.
*$P < 0.005$ (χ^2 test).
†$P < 0.0001$ (χ^2 test).

and Standards Committee recommend indexing anthropomorphic measures to body size.[22] Recent analyses have demonstrated that in heart failure hospitalizations, cardiovascular mortality, or all-cause mortality, this indexing did not affect predictiveness of these measures.[23] To examine the effect on prediction of incident AF of indexing echocardiographic measures to body surface area (BSA), we analysed the associations of LA dimension, LV mass, and LV diastolic dimension on prediction of AF in adjusted and unadjusted models, and with and without adjustment for height, BSA, and weight.

For correlation studies of variables with height, we performed partial Spearman's correlation with adjustment for age and sex. Correlation studies performed on LA volume measures used the same methods as above in a subset of patients in whom these measures were available.

To examine whether height improved standard prediction models of incident AF, we applied the regression model developed from the Framingham Health Study cohort,[11] and compared Harrell's *c*-statistics before and after inclusion of height. We used self-reported diagnosis of any valve disease by a physician in place of 'any heart murmur' used in the Framingham score[11] because information about physical examination findings by a physician was unavailable for the entire CHS cohort. Confidence intervals (CIs) for this metric were created using bootstrap resampling, with 1000 iterations.

We used SAS, version 9.2, for all analyses except for bootstrapping of the *c*-statistic, performed in Stata IC10. As previously described, we used singly imputed data for the baseline examination, which was performed in CHS with S-PLUS software (MathSoft, Inc., Seattle, WA, USA).[24,25] In the full data set, data were missing on <5% of variables for >85% of the original variables considered for imputation. As described by Arnold *et al.*,[25] the covariate set employed and the model form of each imputed variable were determined individually to maximize the accuracy of imputation. As a consequence, results from single imputation across several outcomes in CHS (including time-to-event) have been found not to differ meaningfully from those using multiple imputation.

Results

Baseline characteristics of the total study population, stratified by sex and separated into pre-defined cut-points of height, are shown in *Table 1*.

Among 5860 participants, there were 157 cases of prevalent AF, as shown in *Table 2*. The mean height was higher in prevalent cases than in participants free of AF in both sexes, although the difference was statistically significant only in men. After multivariable adjustment, the mean height was significantly greater among individuals with prevalent AF among both sexes. When inserted in logistic regression models, adjusted for age, BMI, clinic site, race, and education, the OR for prevalent AF was 1.68/cm (CI 1.19–2.37, $P = 0.003$) for men and 1.61/cm (CI 1.08–2.39, $P = 0.02$) for women.

Among 5117 individuals followed for development of incident AF, 1252 (24.5%) developed incident AF; of these, 684 were women (22.6%) and 568 were men (27.1%). The median follow-up was 13.6 years (IQR 8.2–17.2 years) for women and 10.3 years

Table 2 Mean height among men and women according to prevalent AF at baseline

Sex	Group	Unadjusted			Adjusted[a]		
		Mean height (cm)	Standard error	*P*-value	Mean height (cm)	Standard error	*P*-value
Women	AF ($n = 71$)	159.3	0.8	0.58	160.5	0.7	0.02
	No AF ($n = 3300$)	158.9	0.1		158.8	0.1	
Men	AF ($n = 86$)	174.7	0.8	0.02	175.1	0.7	0.003
	No AF (2393)	173.0	0.1		173.0	0.1	

[a]Adjusted for age, BMI, clinic site, race, and education.

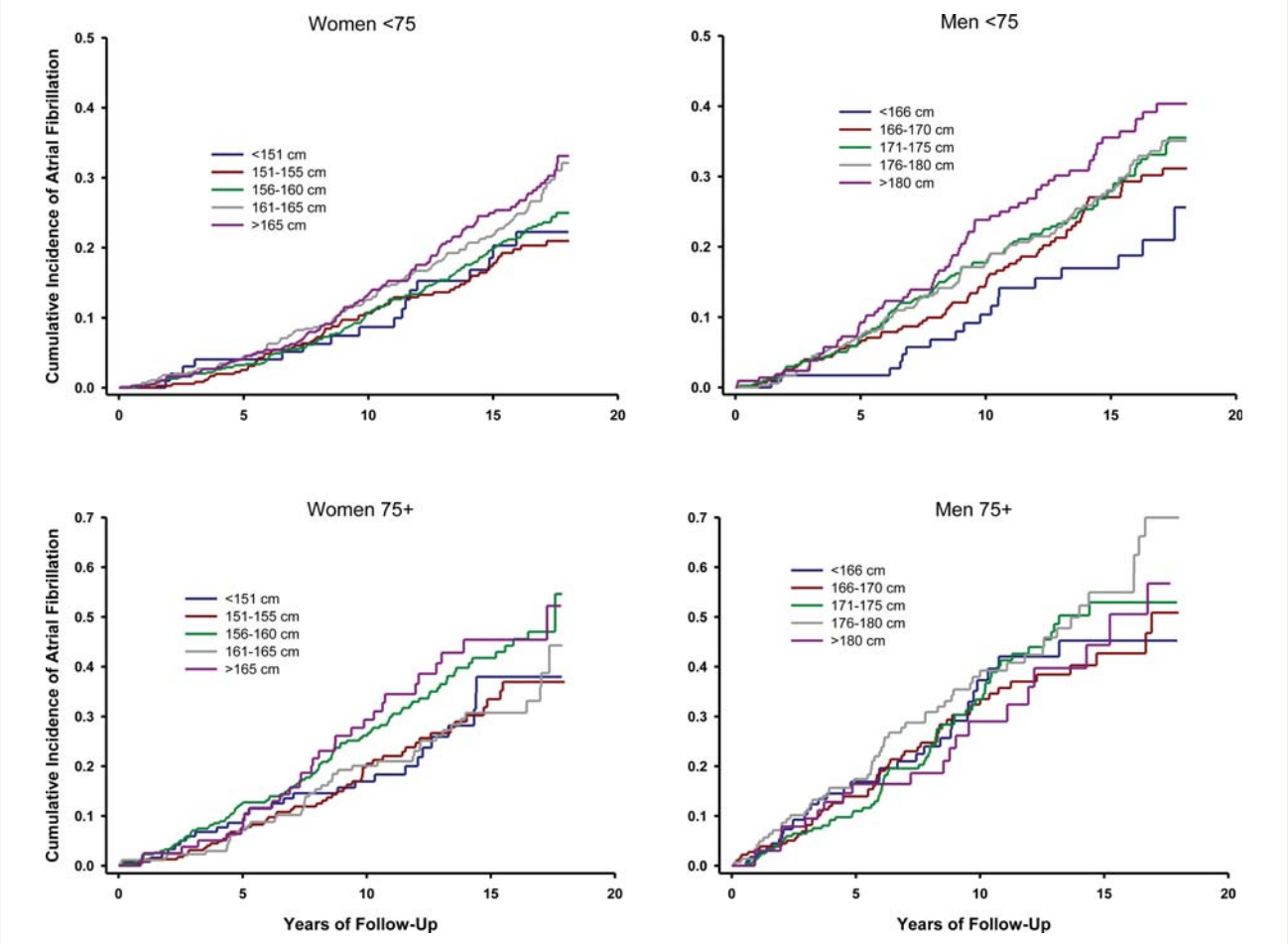

Figure 1 Kaplan–Meier event curves stratified by sex and age under/over 75 years for each of the pre-determined height cut-points. For all graphs, the abscissa is the years in follow-up and the ordinate is the event fraction (incident AF). $P < 0.05$ for all curves except men over 75 years old (log-rank test).

(IQR 5.6–15.5 years) for men. As shown in *Figure 1*, increased height was associated with increased risk of incident AF in three of four age-sex groups in unadjusted analyses, although the effect did not reach statistical significance in men over 75.

After adjustment for BMI, clinic site, race, and highest level of education attained, and stratified by age and sex, height was significantly associated with the development of incident AF (*Table 3*). There was no evidence of non-linear effects with height and AF in either sex. Moreover, sex was no longer significantly associated with incident AF when height was added to an adjusted model with sex as a covariate: hazard ratio (HR) for male sex 1.48, CI 1.32–1.65 ($P < 0.0001$) without height included, and HR for male sex 0.94, CI 0.85–1.20 ($P = 0.94$) with height included.

Given the large contribution of blood pressure to AF, we repeated all of our analyses with additional adjustment for systolic blood pressure and antihypertensive agent use (see Supplementary material online, *Tables*); in general, because height tends to be associated with lower blood pressure (*Table 5*), these adjusted analyses showed slightly stronger risks of AF associated with taller height.

Height was not included in the original Framingham AF risk score,[11] although this score has been evaluated in the CHS cohort without height.[26] To examine the effect of height on the Framingham model, with the covariates as identified in this study,[11] we calculated *C*-statistics of the Framingham model with and without inclusion of height as an additional variable. The total *C*-statistic for the Framingham model in this cohort was

Table 3 Relationship of height with incident AF in men and women

Sex	Group	Height (cm)	AF cases	HR[a]	CI	Significance
Women ($n = 3022$)	1 ($n = 255$)	≤150	44	0.74	0.53–1.04	0.079
	2 ($n = 667$)	150–155	113	0.76	0.60–0.96	0.019
	3 ($n = 1116$)	155–160	228	1	—	—
	4 ($n = 820$)	160–165	174	1.11	0.91–1.35	0.326
	5 ($n = 520$)	>165	125	1.31	1.05–1.64	0.017
		Per SD		1.19	1.10–1.29	<0.001
		Per 10 cm		1.32	1.16–1.50	<0.001
Men ($n = 2095$)	1 ($n = 280$)	≤165	50	0.73	0.52–1.00	0.053
	2 ($n = 547$)	165–170	119	0.86	0.67–1.10	0.220
	3 ($n = 734$)	170–175	166	1	—	—
	4 ($n = 578$)	175–180	144	1.10	0.87–1.37	0.433
	5 ($n = 343$)	>180	89	1.18	0.91–1.54	0.215
		Per SD		1.16	1.07–1.27	<0.001
		Per 10 cm		1.26	1.11–1.44	<0.001

All analyses stratified by age; adjusted for BMI, clinic site, race, and education (highest level attained).
[a]HR for groups based on cut-points are derived from risk relative to the median height group (Group 3). HR for the bottom two analyses are based on incremental risk relative to the shortest participants for each sex. $n = 5117$.

Table 4 Associations of selected echocardiographic parameters with incident AF, before and after adjustment for height or body surface area

Parameter	Variable	HR (CI)	χ^2	*P*-value
LA diameter (LAD)				
	LAD (per SD)	1.31 (1.23–1.40)	72.85	<0.001
	LAD/height (per SD)	1.26 (1.18–1.34)	52.10	<0.001
	LAD/BSA (per SD)	1.18 (1.11–1.26)	24.93	<0.001
LV mass (LVM)				
	LVM (per SD)	1.28 (1.21–1.36)	68.18	<0.001
	LVM/height (per SD)	1.25 (1.18–1.33)	57.92	<0.001
	LVM/BSA (per SD)	1.21 (1.14–1.28)	41.93	<0.001
LV diastolic dimension (LVDD)				
	LVDD (per SD)	1.18 (1.11–1.25)	25.42	<0.001
	LVDD/height (per SD)	1.11 (1.04–1.18)	11.00	<0.001
	LVDD/BSA (per SD)	1.00 (0.94–1.07)	0.01	0.92

All analyses adjusted for clinic site, race, and education; stratified by age and sex. LA diameter measured in cm, LV mass measured in g, and LV diastolic dimension measured in cm. All HR are reported per unit of measurement. $n = 4528$.

Table 5 Associations of height with incident AF before and after adjustment for potentially mediating factors

	HR per SD height	CI	*P*-value
Women			
Base model	1.21	1.12–1.33	<0.001
+LA diameter[a]	1.19	1.10–1.30	<0.001
+LV mass[a]	1.18	1.08–1.29	<0.001
+LV diastolic dimension[a]	1.21	1.11–1.33	<0.001
+SBP or history of treated hypertension	1.24	1.13–1.35	<0.001
+Peak E velocity (m/s)[a]	1.22	1.12–1.33	<0.001
+Peak A velocity (m/s)[a]	1.22	1.12–1.33	<0.001
Combined above (excluding NT-proBNP)	1.20	1.10–1.31	<0.001
Base model (NT-proBNP available)	1.23	1.12–1.36	<0.001
+ NT-proBNP	1.23	1.12–1.36	<0.001
Combined (including NT-proBNP)	1.20	1.09–1.33	<0.001
Men			
Base model	1.17	1.07–1.28	<0.001
+LA diameter[a]	1.16	1.06–1.27	0.002
+LV mass[a]	1.14	1.04–1.25	0.005
+LV diastolic dimension[a]	1.15	1.05–1.26	0.003
+SBP or history of treated hypertension	1.20	1.10–1.32	<0.001
+Peak E velocity (m/s)[a]	1.18	1.07–1.29	<0.001
+Peak A velocity (m/s)[a]	1.17	1.07–1.28	<0.001
Combined above (excluding NT-proBNP)	1.16	1.06–1.27	0.002
Base model (NT-proBNP available)	1.24	1.11–1.38	<0.001
+NT-proBNP	1.27	1.14–1.41	<0.001
Combined (including NT-proBNP)	1.26	1.13–1.42	<0.001

All models adjusted for BMI, clinic site, race, and education; stratified by age.
LA, diameter measured in cm; LV, mass measured in g; LV, diastolic dimension measured in cm; SBP, measured in mmHg, and NT-proBNP measured in pg/dL. All HR are reported per unit of measurement. *n* for total population = 4480. *n* for NT-proBNP studies = 3464.
[a]Quantiles of Peak E velocity, Peak A velocity, LA diameter, LV mass, LV diastolic dimension, PR interval used due to non-linearity; BNP and BNP-squared included due to non-linear effects.

0.649, and it increased by 0.010 (CI 0.004–0.017) to 0.659 with the inclusion of height ($P < 0.0001$). When included in the Framingham model, a 10 cm increment in height was associated with an HR of 1.36 (CI 1.24–1.50).

To examine the impact of indexing echocardiographic measures to body size, we analysed the associations of LA dimension, LV mass, and LV diastolic dimension with the risk of AF with and without adjustment for height, BSA, and weight. As shown in *Table 4*, inclusion of indexed measures decreased the HR for all measures in both adjusted and unadjusted models, with indexing to BSA causing the greatest decrement. For LV diastolic dimension, indexing to BSA caused this measure to no longer be associated with AF incidence.

To explore potential mechanisms of height and increased incidence of AF, we examined the base model (including height after adjustment for BMI, clinic site, race, and education and stratification by age) with inclusion—individually and combined—of various potential mediators of increased AF risk. *Table 5* displays results for inclusion of various anatomical and physiological parameters that might be mediators of height-induced increase in AF incidence. Each of these parameters was a significant risk factor for AF incidence. Among the potential mediators, none attenuated the effect of height on increased incident AF. The measure with the strongest association in both men and women was LV mass, which was the most strongly correlated with height in men (*Table 6*). LA dimension, commonly thought to be the primary mediator of height-induced AF, was not significantly correlated with height, and inclusion did not significantly change the HR for the association of height with incident AF. (Note that the differences in the HR for the base models in *Tables 3* and *5* are due to fewer participants included in the analysis of *Table 5* due to lack of echocardiography data—see the Methods section for details.). Adjustment for kidney function, diabetes or fasting glucose, and the presence of valve disease had no effect attenuation on the risk of AF with increased height (data not shown).

To ensure that the lack of association of height with atrial size was not related to its unidimensional measurement, we examined the association of height with LA volume in a subset of participants in whom LA volume measurements were made later during follow-up. In these participants, LA volume still correlated only weakly with height ($r = 0.10$, $P = 0.01$) after adjustment for age, sex, and race.

Table 6 Partial Spearman's correlations of height with selected cardiovascular parameters

Sex	Parameter	Spearman correlation coefficient, *r* (*P*-value)
Women	LA dimension (cm)	0.05 (0.02)
	LV mass (g)	0.21 (<0.001)
	LV diastolic dimension (cm)	0.21 (<0.001)
	Peak mitral E velocity (m/s)	−0.01 (0.53)
	Peak mitral A velocity (m/s)	−0.06 (0.007)
	Fractional shortening (%)	−0.04 (0.05)
	Quantitative EF (%)	0.00 (0.88)
	NT-proBNP (dg/mL)	0.01 (0.80)
	Average systolic blood pressure (mmHg)	−0.07 (0.001)
Men	LA dimension (cm)	0.06 (0.02)
	LV mass (g)	0.13 (<0.001)
	LV diastolic dimension (cm)	0.10 (<0.001)
	Peak mitral E velocity	−0.07 (0.02)
	Peak mitral A velocity	−0.10 (<0.001)
	Fractional shortening (%)	−0.06 (0.02)
	Quantitative EF (%)	−0.03 (0.23)
	NT-proBNP (dg/mL)	0.00 (0.87)
	Average systolic blood pressure (mmHg)	−0.11 (<0.001)

Spearman coefficient (*P*-value); partial age, BMI, clinic site.
n for total population = 4480. *n* for NT-proBNP studies = 3464.

Discussion

In this large cohort of older adults, increased height was associated with incident and prevalent AF after adjustment for confounders of both height and AF, as well as after adjustment for other risk factors of AF. We also demonstrated that height significantly increased the discrimination of standard models of risk prediction, and that indexing anthropomorphic echocardiography measures to body size using either height or the BSA, as is common in clinical practice, lowered their relationship with the risk of AF, and in some cases caused formerly significant predictors to no longer significantly predict AF incidence. Adjustment for multiple physiological and anatomical risk factors, nearly all of which were themselves significantly associated with incident AF, had only limited effect on the association of height with AF; indeed, we were unable to detect any particular measure that appeared to be the mediator of height on increased AF risk.

While height has been found to be associated with AF in other large cohort studies,[11,27,28] it has rarely been the focus of investigation. In the Framingham cohort, height was of borderline significance in predicting incident AF, and was thus excluded from the risk score model developed.[11] This population, unlike ours, included young participants as well (range 45–95), and thus had a lower cumulative incidence of AF of 10%.[11] A similar study in the ARIC cohort, which was composed of individuals under 65 years of age but included African-Americans, had a lower cumulative incidence of AF (3.5%), but found that height was significantly associated with AF.[28] These findings suggest that not only is height a parameter that should be considered in any risk factor assessment for AF, but that its impact does not appear to be specific for elderly individuals alone.

An intriguing finding, although one that itself would require further exploration given the multiple confounders of circulating hormone levels and differing body composition, was that when height was included in the model, sex was no longer a significant predictor of incident AF. As other models, such as that used in the Framingham study,[11] have included sex, this finding suggests that further research is necessary to truly understand the role of sex in the development of AF.

Increased atrial size as a risk factor for the development of AF has long been recognized,[29] and numerous studies have found a positive correlation between increased atrial size and AF.[30–32] However, the process of measuring and reporting atrial size with adjustment for body size has been less straightforward.[33] The use of indexed measures in echocardiography and other physiological modalities is a common practice, and is recommended by advisory committees such as the American Society of Echocardiography.[22] The concept behind this recommendation is that anatomic measures can increase either from pathophysiological processes or from larger body size, and that by adjusting, observed abnormalities will only reflect underlying pathophysiology. When carefully studied, and appropriately applied,[34–36] indexing has been shown to improve the predictiveness of the anthropometric variable (especially when the indexed metric, i.e. height or weight, is inversely correlated with the outcome, as is the case for coronary artery disease and height[37]). However, when body size itself is a risk factor for disease, as observed in this study, these adjustments can be counter-productive. Larger cardiac structure size, be it proportional to natural growth or due to a pathophysiological process, can still results in cardiac diseases. In AF, increased LA size alone theoretically affects the ability of multiple wavelets to reenter and propagate the arrhythmia.[38]

We were unable to substantiate increased LA dimension or LA volume as an anthropomorphic or physiological mediator of increased AF risk due to height. Left atrial dimension, as well as LA volume that was measured in a subgroup, was only mildly correlated with height, and inclusion in the model did little to attenuate the risk attributable to height. Left ventricular mass, which has been consistently associated with the risk of AF,[39–42] was the parameter most strongly correlated with height, yet it attenuated only a small amount of the risk attributable to height. As a result, we are left to speculate that height may have a separate effect on increasing the risk of AF. Among other potential mechanisms for height-mediated increased AF risk, possibilities may lie in the results from recent genome-wide association studies. Among the significant AF-associated genes, PITX2[12] and ZFHX3[13] are also associated with growth pathways.[12,13] Like these genes themselves, height obviously cannot be modified with intervention, but our findings suggest that it can provide potential clues to other mechanisms of disease. Further evaluation of the interrelationships of height, growth-related genes, and risk of AF in both animal models and human studies may shed light on some such candidate pathways.

One potential limitation to this study is the survival bias inherent in any study of an elderly population. Prior AF studies in younger cohorts have identified height as a risk factor,[28] indicating that the

risk is likely applicable across populations of varying age. In addition, the consonance of our results from both prevalent and incident AF argues against differential survival as an explanation for our findings.

Another important potential limitation is that because the HRs, and impact on the Framingham risk score, were modest, it is difficult to attribute significance to the observation that increased height is associated with AF. Although we were unable to detect any specific mechanism via which increased height was associated with AF, one potential explanation is that height is simply identifying residual confounding or uncontrolled bias of cohort studies. We chose to include in our base model only variables that could realistically be considered confounders of both AF and height, with further 'mechanistic' analysis including insertion of potential downstream mediators of height, such as LA size, and other possible mediators, such as valve disease. None of these analyses found any meaningful attenuation of the height-mediated risk of AF with inclusion of any variable, but further exploration of the mechanisms via which increased height mediates risk of AF is necessary before one can dismiss this potential limitation.

In summary, our results suggest that height is consistently associated with risk of AF, that its inclusion in models of AF risk statistically significantly improves the discrimination of existing prediction models, and that standard echocardiographic measures alone do not appear to mediate its full effect on risk. As a result of these findings, unlike other studies of cardiac disease, we found that indexing anthropometric measures to height actually weakens the associations of cardiac structure size with the risk of AF. Further evaluation of the genetic basis underlying height may provide novel clues to the aetiology of this common arrhythmia.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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