

Longitudinal Anthropometric Measures and Risk of New-Onset Atrial Fibrillation Among Community-Dwelling Men and Women



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Abstract

Objective: To assess the sex-specific evolution of various anthropometric measures and the association of their longitudinal trajectories with new-onset atrial fibrillation (AF).

Methods: Among 5266 men and 7218 women free of AF at baseline from the prospective population-based Rotterdam Study, each anthropometric measure was measured 1 to 5 times from 1989 to 2014. Anthropometric measures were standardized to obtain hazard ratios per 1 SD increase to enable comparison. Joint models were used to assess the longitudinal association between anthropometric measures and incident AF. Use of the joint models is a preferred method for simultaneous analyses of repeated measurements and survival data for conferring less biased estimates.

Results: Mean (SD) age was 63.9 (8.9) years for men and 64.9 (9.8) years for women. Median follow-up time was 10.5 years. Longitudinal evolution of weight, height, waist circumference, hip circumference, and body mass index was associated with an increased risk of new-onset AF in both men and women. In joint models, larger height in men (hazard ratio [95% credible interval] per 1 SD, 1.27 [1.17 to 1.38]) and weight in women (1.24 [1.16 to 1.34]) showed the largest associations with AF. In joint models, waist to hip ratio was significantly associated with incident AF only in women (1.10 [1.03 to 1.18]).

Conclusion: Considering the entire longitudinal trajectories in joint models, anthropometric measures were positively associated with an increased risk for new-onset AF among men and women in the general population. Increase in measure of central obesity showed a stronger association with increased risk of AF onset among women compared with men.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia with significant health burden and socioeconomic impact.¹ Worldwide prevalence of AF was estimated around 46.3 million individuals in 2016.² Notably, recent evidence suggests differences in epidemiology and risk factors of AF between men and women.^{3,4} Thus, a better understanding of modifiable AF risk factors among men and women is imperative to improve personalized prevention of AF.

Obesity is a well-established risk factor for incident AF.^{5,6} The risk for development

of AF is estimated to increase by 49% in obese compared with nonobese individuals.^{7,8} Various anthropometric measures have been shown to be significantly associated with a higher risk of AF.⁹⁻¹² The available evidence, however, has primarily focused on a single baseline assessment of anthropometric measures in association with the risk of AF. Anthropometric measures tend to change over time. Therefore, solely focusing on baseline assessment of anthropometric measures fails to account for changes in anthropometric measurements over time that may affect the risk.



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Moreover, comprehensive assessment of the association between various anthropometric measures and incident AF among men and women is sparse.

Compared with the traditional time-varying covariate Cox model, joint modeling can infer more accurate estimates in the association between an observed longitudinal measure of a marker and the hazard of an event by simultaneously modeling the profile of the marker and the time to event data.¹³⁻¹⁵ Taking advantage of the joint modeling approach, we aimed to investigate the evolution of several anthropometric measures over time and furthermore to assess their associations with new-onset AF among men and women from the large population-based Rotterdam Study.

METHODS

Study Population

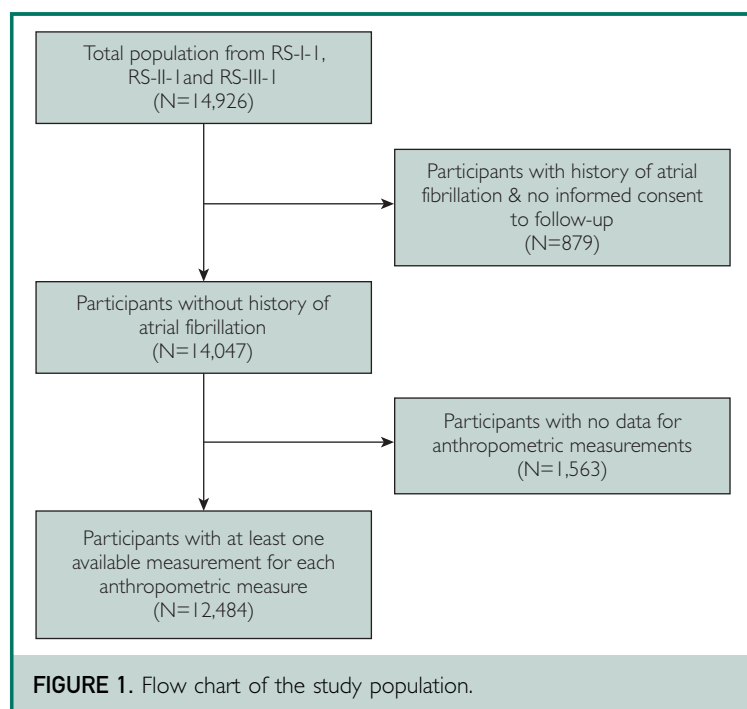
The study was conducted within the framework of the Rotterdam Study.¹⁶ During 1990 to 1993, 7983 participants of Ommoord district in the city of Rotterdam in The Netherlands aged 55 years and older were recruited in the first cohort (RS-I). In

2000, the cohort was extended with 3011 participants who had become 55 years of age and older or had migrated into the research area (RS-II). In 2006, the cohort was again extended with 3932 participants who were 45 years of age and older (RS-III). The overall response rate at baseline was 72%. Participants attended follow-up examinations every 3 to 4 years. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands Trial Register (www.trialregister.nl) and into the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. Detailed description of the Rotterdam Study may be found in the [Supplementary Methods](#) (available online at <http://www.mayoclinicproceedings.org>).

For this study, we included participants from the first examination of the original cohort and the extended cohorts (total participants, 14,926). The first measurement of anthropometrics for each participant was used as the baseline. Participants with prevalent AF at baseline ($n=574$), no informed consent for follow-up data collection ($n=305$), or no available data for anthropometric measures ($n=1563$) were excluded. After exclusions, 12,484 participants were included in the analysis (Figure 1).

Assessment of Anthropometric Measures

Height and weight were measured with the participants standing without shoes and heavy outer garments. Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference (WC) was measured at the level midway between the lower rib margin and the iliac crest. Hip circumference (HC) was measured as the distance around the largest part of the hips. Waist to hip ratio (WHR) was calculated by dividing WC by HC. For every participant, at least 1 anthropometric



measure was assessed between 1 and 5 times during the follow-up period. Therefore, the number of participants included for analysis for different anthropometric measures could slightly vary. Height and weight were measured at 5 visits in RS-I (RS-I-1 to RS-I-5), 3 visits in RS-II (RS-II-1 to RS-II-3), and 2 visits in RS-III (RS-III-1 and RS-III-2). The WC and HC were measured at 4 visits in RS-I (RS-I-1, RS-I-3, RS-I-4, and RS-I-5), 3 visits in RS-II (RS-II-1 to RS-II-3), and 2 visits in RS-III (RS-III-1 and RS-III-2).

Assessment of AF

Methods on event adjudication for prevalent and incident AF have been described in detail previously.¹⁷ In short, to assess AF at baseline and follow-up examinations, a 10-second 12-lead electrocardiogram (ECG) was used with an ACTA Gnosis IV ECG recorder (Esaote Biomedica). The ECG records were stored digitally and analyzed with the modular ECG analysis system. Subsequently, 2 research physicians validated the diagnosis of AF. Additional follow-up data were obtained from medical files of participating general practitioners, hospitals, outpatient clinics, national registration of all hospital discharge diagnoses, and follow-up examinations at the research center. The date of incident AF was defined as the date of the first occurrence of symptoms suggestive of AF with subsequent electrocardiographic verification obtained from the medical records. Participants were observed from the date of enrollment in the Rotterdam Study until the date of onset of AF, date of death, loss to follow-up, or January 1, 2014, whichever occurred first.

Assessment of Cardiovascular Risk Factors

Methods for assessment of cardiovascular risk factors are detailed in the online [Supplementary Methods](#).

Statistical Analyses

Characteristics of the participants are presented as mean with standard deviation or proportions as appropriate. Differences between men and women were examined by Student *t*-tests for continuous variables and

χ^2 tests for categorical variables. Each anthropometric measure was standardized to obtain hazard ratios (HRs) per 1 SD increase to enable comparison.

Traditional Cox proportional hazards regression analysis with delayed entry and age as a time scale¹⁸ was performed to investigate the relationship between anthropometric measures at baseline and incident AF. The HR with 95% CI was calculated to quantify the association. We first used each anthropometric measure as a continuous variable to assess the HR for incident AF. For continuous exposure variables, an examination of the shape of relation with incident AF was performed using natural cubic splines. No deviation from linearity was found. Then, each anthropometric measure was categorized in deciles with the first decile as a reference to plot the graphical relationship, and *P* values for trend were derived. The proportional hazard assumptions were tested by Schoenfeld residual tests and were found to be satisfied.

Next, linear mixed effects models were fitted for the changes in anthropometric measures over time and to account for the correlation of repeated measurements. Time was represented by age in years, and only age and sex were treated as fixed effects in all models ([Supplemental Tables 1 to 6](#), available online at <http://www.mayoclinicproceedings.org>). Each model included random intercept and slope and an unstructured covariance matrix. Natural cubic splines of age with 2 or 3 knots were used to check the nonlinear changes of each anthropometric measure over time. Likelihood ratio tests were used to choose the best model. Then, we used final linear mixed effect models to plot the evolution of each anthropometric measure with age among men and women.

Furthermore, to investigate the association between the longitudinal anthropometric measurements and the risk of incident AF, we used joint models for longitudinal and time to event data. The joint models were fitted in R using package JMBayes, which fitted joint models under a Bayesian approach using Markov chain Monte Carlo algorithms,¹⁹ and HRs with 95% credible intervals (CrIs)

TABLE 1. Baseline Characteristics of the Study Population^{a,b}

	Men	Women	P value ^c
No. of participants	5266	7218	—
Age, years	63.87 (8.86)	64.94 (9.80)	<.001
Weight, kg	82.36 (12.82)	71.56 (12.74)	<.001
Height, cm	175.86 (7.03)	162.30 (6.68)	<.001
BMI, kg/m ²	26.59 (3.52)	27.16 (4.50)	<.001
Waist circumference, cm	96.63 (10.45)	88.71 (11.77)	<.001
Hip circumference, cm	101.60 (7.55)	103.42 (9.52)	<.001
WHR	0.95 (0.07)	0.86 (0.08)	<.001
Total cholesterol, mmol/L	5.89 (1.18)	6.36 (1.24)	<.001
HDL cholesterol, mmol/L	1.23 (0.33)	1.49 (0.40)	<.001
Systolic blood pressure, mm Hg	139.08 (20.69)	137.61 (22.06)	<.001
Diastolic blood pressure, mm Hg	78.64 (11.88)	76.55 (11.70)	<.001
Smoking, %			<.001
Never smoked	14.2	45.3	—
Former smoker	56.6	34.2	—
Current smoker	29.1	20.6	—
Use of medication, %			
Blood pressure—lowering medication	27.5	29.5	.02
Lipid-lowering medication	6.4	5.3	.02
Cardiac medication	11.6	9.0	<.001
History of diseases, %			
Coronary heart disease	10.6	2.9	<.001
Heart failure	1.4	1.5	.75
Diabetes mellitus	11.0	8.4	<.001

^aBMI, body mass index; HDL, high-density lipoprotein; WHR, waist to hip ratio.

^bValues are mean (standard deviation) or median (interquartile range) for continuous variables and percentage for categorical variables.

^cP values derived from the Student *t*-test or χ^2 test for the difference between men and women.

were calculated. We checked for an interaction between sex and each anthropometric measure by running the models in the total population and adding an interaction term for “sex” in the joint models.

All analyses were performed in men and women separately. Survival models were adjusted for baseline age and the Rotterdam Study cohort (model 1) and additionally for baseline cardiovascular risk factors, including total and high-density lipoprotein cholesterol, systolic blood pressure, history of diabetes mellitus, history of coronary heart disease, history of heart failure, smoking status, use of lipid-lowering medication, blood pressure—lowering medication, and cardiac medication (model 2). In an alternative analysis, models were adjusted for all risk factors as time-varying covariates

instead of baseline values. Correlation analyses were used to determine possible multicollinearity between the covariates. Missing values in covariates were imputed under the assumption of missing at random using multiple imputation.²⁰ For multiple imputation, all available data were used to generate 5 imputed data sets for traditional Cox proportional hazards regression analysis. For the joint model analysis, 1 randomly chosen data set was used as the JMbayes R package could not handle the pooled results.²¹

In sensitivity analysis, we stratified participants by BMI categories (<25 kg/m², ≥25 kg/m² to <30 kg/m², and ≥30 kg/m²). We also stratified participants by baseline age (at the age of 65 years). In addition, we performed the analysis only among participants for whom complete data were available.

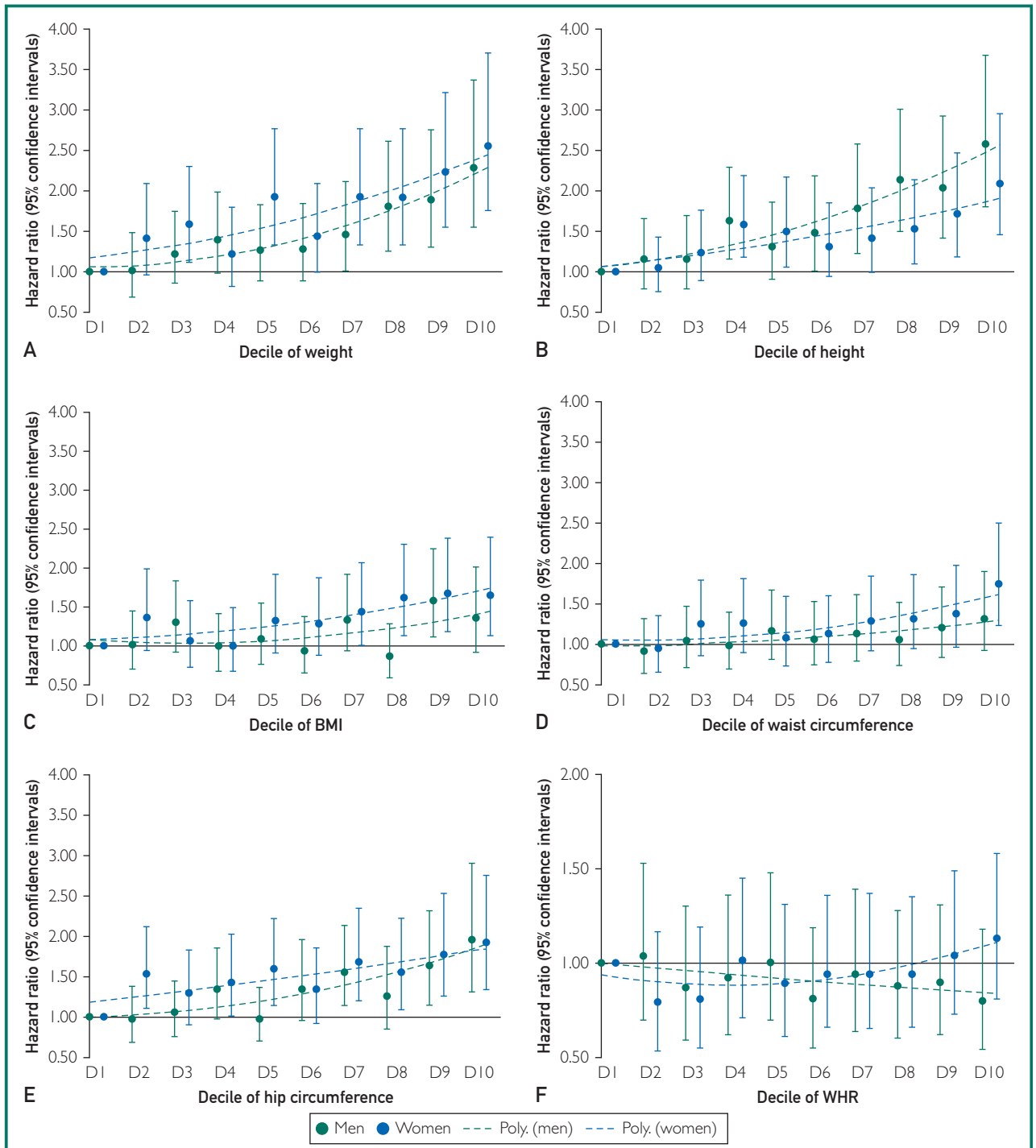


FIGURE 2. Multivariate adjusted hazard ratios with 95% CIs for incident atrial fibrillation by deciles of each anthropometric measure among men and women. Dashed lines fitted by quadratic polynomial. Corresponding decile values of anthropometric measures for men and women can be found in [Supplemental Table 12](http://www.mayoclinicproceedings.org) (available online at <http://www.mayoclinicproceedings.org>). Model adjusted for age, cohort, high-density lipoprotein and total cholesterol levels, smoking, systolic blood pressure, use of blood pressure-lowering medication, use of lipid-lowering medication and cardiac medication, history of diabetes mellitus, history of heart failure, and history of coronary heart disease.

Statistical significance was considered at a 2-tailed *P* value of less than .05. The analyses were done using R software (R 4.0.0; R Foundation for Statistical Computing).

RESULTS

Baseline characteristics for men and women are shown in [Table 1](#). Of 12,484 participants for the study, 5266 (42.2%) were men. During a median follow-up of 10.5 years (interquartile range, 6.4 to 15.4 years), 630 (12.0%) men and 692 (9.6%) women experienced new-onset AF (incidence density, 11.2 per 1000 person-years among men and 8.1 per 1000 person-years among women).

Baseline Measures of Anthropometric Parameters and Associations With New-Onset AF

[Supplemental Table 7](#) (available online at <http://www.mayoclinicproceedings.org>) shows HR with 95% CI for incident AF per 1 SD increase in baseline measures of anthropometric parameters among men and women based on traditional Cox models. In general, joint model analyses yielded slightly larger HRs for all anthropometric measures compared with a traditional Cox regression model, with the exception of height. [Figure 2](#) presents the multivariable adjusted HRs (95% CIs) per decile of each anthropometric measure. As shown, positive associations with risk of new-onset AF were seen for weight, height, BMI, WC, and HC in men and women (*P* for trend, <.001). The WHR showed a significant positive association with incident AF in women (*P* for trend, .02) but not in men (*P* for trend, .20). No nonlinearity was observed in any of the associations.

Evolution of Anthropometric Parameters Over Time and Associations With New-Onset AF

[Figure 3](#) shows the evolution of anthropometric parameters among men and women. For weight, both men and women underwent a slight increase before the age of 62 years in men and 67 years in women, followed by rapid decrease in the rest of their lifetime. For height, a significant decrease

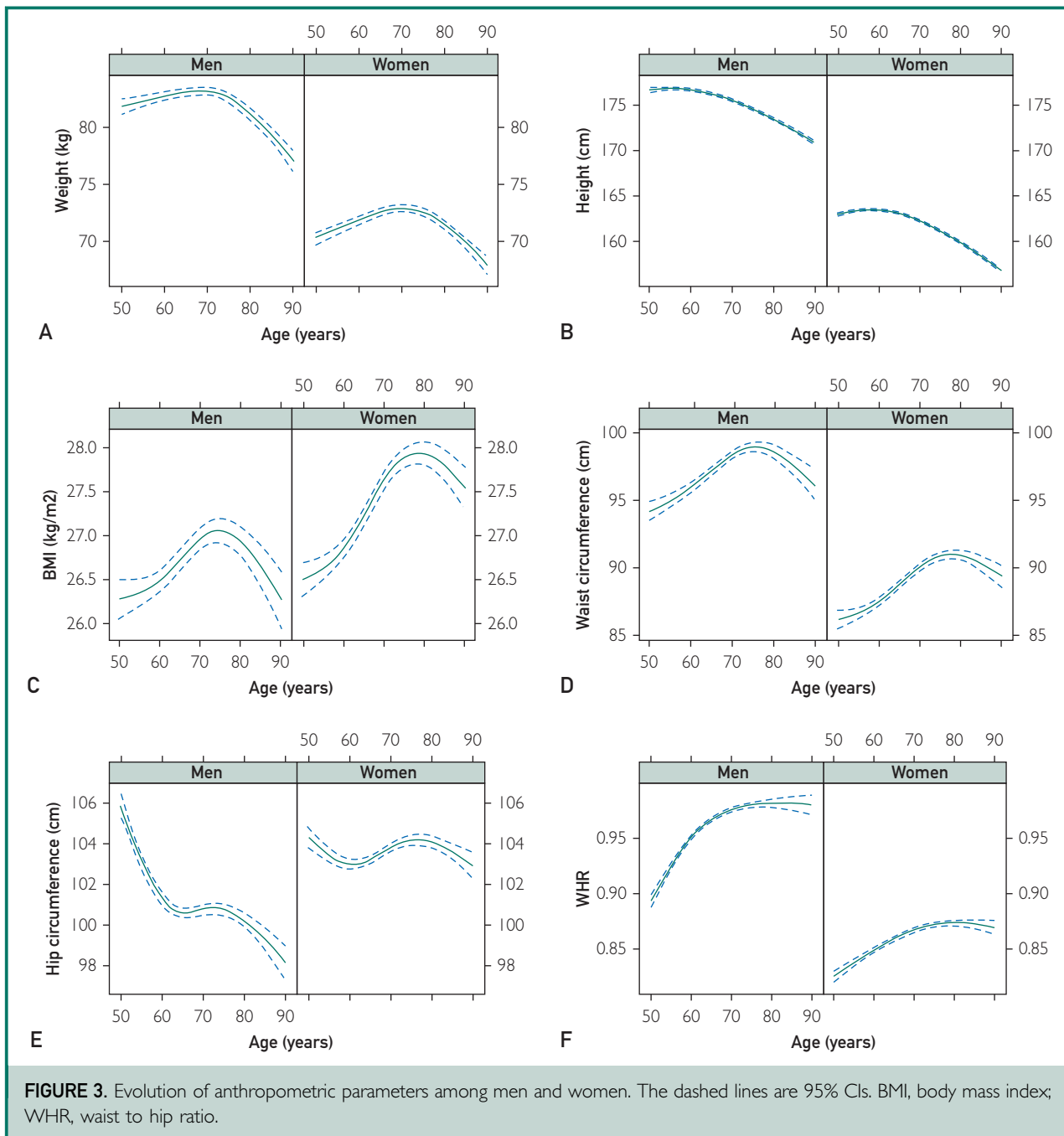
was observed among men and women after 62 years. Significantly rapid increases in BMI were observed until 62 years of age, after which BMI tended to remain stable among men and women. No significant interaction between sex and age was found in evolution of WC. Both men and women showed a similar pattern in evolution of WC as an increase before 67 years of age and a stable pattern thereafter. For HC, men showed a significant decrease until 62 years of age, whereas women showed a gradual decrease over the entire included age range with a slight fluctuation. The WHR underwent a significant rapid increase among men before the age of 70 years and a gradual increase among women before the age of 72 years, followed by a stable trend.

[Table 2](#) shows HRs with 95% CIs for incident AF per 1 SD increase in anthropometric measures among men and women based on the joint models. The largest multivariate adjusted HR (95% CrI) was 1.30 (1.20 to 1.41) for height in men, followed by 1.29 (1.19 to 1.40) for weight, 1.23 (1.13 to 1.32) for HC, 1.13 (1.04 to 1.22) for WC, and 1.12 (1.03 to 1.21) for BMI. In women, the largest HR (95% CrI) was 1.24 (1.16-1.34) for weight and then 1.21 (1.12 to 1.30) for WC, 1.18 (1.10 to 1.27) for BMI, 1.17 (1.09 to 1.25) for HC, and 1.12 (1.04 to 1.21) for height. Larger WHR was significantly associated with increased risk of AF in women (1.10 [1.03 to 1.18]) but not in men (0.98 [0.90 to 1.06]). The *P* values were significant for interaction between sex and height (*P*=.006) and sex and WHR (*P*=.049).

[Supplemental Table 8](#) (available online at <http://www.mayoclinicproceedings.org>) shows results of joint models adjusted for all potential confounders as time-varying covariates, which were not different from our main analyses for both men and women.

Sensitivity Analyses

Sensitivity analyses in joint models that included only participants for whom complete data were available yielded similar results ([Supplemental Table 9](#), available online at <http://www.mayoclinicproceedings.org>).



In addition, after stratification by BMI categories, the association between longitudinal BMI measures and incident AF was significant only among overweight individuals ($BMI \geq 25 \text{ kg/m}^2$ to $<30 \text{ kg/m}^2$; HR [95% CrI] per 1 SD larger BMI, 1.43 [1.20 to 1.72] in men and 1.68 [1.36 to 2.09] in women; Supplemental Table 10, available

online at <http://www.mayoclinicproceedings.org>). We also performed joint models among men and women in subgroups stratified by baseline age older or younger than 65 years (Supplemental Table 11, available online at <http://www.mayoclinicproceedings.org>). Similar results were observed in women in 2 age subgroups. However, increased weight,

TABLE 2. Association of Longitudinal Anthropometric Measures With Incident Atrial Fibrillation Among Men and Women^{a,b}

	Men		Women	
	Model 1	Model 2	Model 1	Model 2
Weight	1.33 (1.22-1.43)	1.29 (1.19-1.40)	1.32 (1.23-1.41)	1.24 (1.16-1.34)
Height ^c	1.27 (1.17-1.38)	1.30 (1.20-1.41)	1.12 (1.04-1.21)	1.12 (1.04-1.21)
BMI	1.18 (1.09-1.27)	1.12 (1.03-1.21)	1.27 (1.19-1.36)	1.18 (1.10-1.27)
WC	1.19 (1.09-1.28)	1.13 (1.04-1.22)	1.26 (1.17-1.36)	1.21 (1.12-1.30)
HC	1.25 (1.15-1.34)	1.23 (1.13-1.32)	1.25 (1.17-1.34)	1.17 (1.09-1.25)
WHR ^c	1.06 (0.98-1.14)	0.98 (0.90-1.06)	1.14 (1.06-1.22)	1.10 (1.03-1.18)

^aBMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist to hip ratio.

^bValues are shown as hazard ratios (95% credible intervals) per 1 SD increase in the corresponding anthropometric measure.

^c $P < .05$ for sex interaction.

Model 1 adjusted for age and Rotterdam Study cohort.

Model 2 additionally adjusted for high-density lipoprotein and total cholesterol levels, smoking, systolic blood pressure, use of blood pressure-lowering medication, use of lipid-lowering medication and cardiac medication, history of diabetes mellitus, history of heart failure, and history of coronary heart disease.

BMI, WC, HC, and WHR in men showed larger associations with incident AF in the younger group (<65 years) than in the older group (≥ 65 years; $P < .05$ for all interactions).

DISCUSSION

In this large prospective population-based cohort study, longitudinal trajectories of anthropometric measures were significantly associated with new-onset AF among both men and women. In joint models that allow both individual-level and cohort-level trajectories, height in men and weight in women showed the strongest associations with new-onset AF. Increase in measure of central obesity showed a stronger association with incident AF among women compared with men.

Our study extends previous evidence by assessing the longitudinal evolution of anthropometric measures among men and women and correlating the longitudinal trajectories with AF development during a long follow-up. Although several previous studies have investigated the associations between baseline measures of anthropometric parameters and AF, it is reasonable to imagine that changes of anthropometric parameters during follow-up may alter the impact of anthropometric parameters on AF development. Indeed, Feng et al¹² reported that obesity earlier in life and BMI changes

exerted cumulative effects on AF development in the HUNT study. Thus, studies using only baseline measures discard the information on variations of anthropometric parameters during follow-up, in particular during longer follow-up terms. To our knowledge, our study is the first to assess the longitudinal anthropometric measures and risks of incident AF. Taking into account the entire longitudinal trajectories of anthropometric measures in joint models, higher values of anthropometric measures over time were significantly associated with new-onset AF. After adjustment for cardiovascular risk factors, the associations did not change. These findings are in line with previous studies^{22,23} and further support the hypothesis that traditional cardiovascular risk factors might not play a substantial role in the association between anthropometric measures and AF in both men and women. In fact, obesity is an established independent risk factor for cardiovascular conditions underlying AF.^{5,6} Increased BMI is strongly related to ventricular remodeling, impaired left ventricular relaxation, and elevated left ventricular diastolic filling pressure.²⁴ Obesity has been shown to be associated with hypoxia of the expanding adipose tissue, resulting in adipose fibrosis and the production of adipocytokines that further contributes to generation of epicardial fat

and myocardium damage.^{25,26} It seems likely that the combination of these mechanisms represents the association between anthropometric measures and AF.

Notably, our results underline the significant sex differences in associations between height and AF. In this study, women had a lower mean height than men, and results of longitudinal models suggested that women had a more rapid shrinkage of height with aging compared with men. Thus, both may partly explain the lower risk of height for AF among women. Moreover, this study found that height serves as the predominant risk factor for new-onset AF in men. Several mechanisms have been proposed to explain the relationship between height and AF. Left atrial volume is significantly associated with height even after adjustment for age and sex.^{9,27} As large left atrial size is highly associated with AF,²⁵ tall stature may contribute to AF development, at least partly, induced by large left atrial size. Besides, taller height has been suggested to be associated with reduced PR interval and QRS duration among healthy individuals.²⁸ These findings suggest an underlying pathway from height-induced electrophysiologic dysfunction of the heart to AF occurrence. Our results found a strong positive association between height and incident AF among both men and women. Although height is an unmodifiable risk factor, our study could underscore the potential value for AF prevention in an older population by screening AF among taller individuals.

We also found a robust sex difference in the association between WHR and AF. The WHR is a specific measurement for body fat distribution that can be used to denote central fat accumulation.²⁹ To our knowledge, 3 previous studies have assessed sex differences in the relationship between anthropometric measures at baseline and incident AF.^{10,22,23} Contrary to our results, significant associations between WHR and AF were previously found in men but not in women.^{10,22} Of note, population differences between this study and previous reports should be taken into consideration. First, our participants were older than the

population in the aforementioned studies, and predisposing comorbidities with aging may have a large impact on AF development. Men had higher AF risks because of unhealthy lifestyles and a higher prevalence of baseline cardiovascular disease than women.³ This could have diluted the association between WHR and AF in men. Second, women in this study had larger values of baseline WHR than in the previous studies. This implies more abdominal fat and thus a larger risk for AF among women in our population.²⁹ Moreover, WHR and central fat have previously been associated with poorer cardiac mechanisms, including worse global longitudinal and diastolic strain rate of the heart as well as ventricular concentric remodeling, and this may increase AF susceptibility.^{30,31} Commonly, men are more likely than women to have a central fat distribution. However, postmenopausal women tend to accumulate more abdominal fat because of the lack of estrogens.³² With aging, there is a clear shift from primarily subcutaneous adipose tissue to central fat accumulation in both men and women.³³ Taken together, these data suggest that at older ages, women are more susceptible than men to the hazardous impact of central fat in AF development.

Strengths of our study include its prospective design, long follow-up time with meticulous adjudication of AF events, and availability of a broad range of confounders and possible intermediate risk factors of AF. Particularly, our study is the first study that has examined sex differences in the longitudinal anthropometric measures and their associations with risk of new-onset AF. Compared with a single measurement, use of joint modeling and repeated anthropometric measurements over time allows assessment of varying effects of exposure and therefore provides more information for unbiased assessment of AF risks.¹⁵ However, we acknowledge several limitations within this study. First, most of our participants were White and older adults, limiting the generalizability of our findings to other ethnicities and younger populations. Second, given the observational study design, and

although we adjusted for many potential confounders for AF, we cannot rule out the possibility of residual or unmeasured confounding. Third, because AF may be paroxysmal and asymptomatic, we might have underestimated the true number of AF cases in our study population. However, it is estimated that more than 75% of AF cases among the European population are permanent or persistent AF, and most paroxysmal AF cases end as the permanent form.³⁴ In addition, the prevalence of AF in the Rotterdam Study is approximately 4%, which is in line with the global estimate of AF prevalence.³⁵ Moreover, the possible underestimation of AF prevalence could not affect the direction of our results as the resulting misclassification most likely happened independent of the exposures stats.

CONCLUSION

We found robust associations between evolution of anthropometric measures and risk of new-onset AF. Our results from a joint modeling approach highlight height as a predominant risk factor for new-onset AF in men and weight as the predominant risk factor in women. Moreover, increased central obesity showed a stronger association with incident AF among women compared with men. These findings also underscore the importance of sex-specific approaches for screening and monitoring of anthropometric measures for AF prevention.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AF, atrial fibrillation; BMI, body mass index; Crel, credible interval; HC, hip circumference; HR, hazard ratio; WC, waist circumference; WHR, waist to hip ratio

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