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ORIGINAL RESEARCH

Neck Circumference and Risk of Incident Atrial Fibrillation in the Framingham Heart Study

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BACKGROUND: Increased neck circumference, a proxy for upper-body subcutaneous fat, is associated with cardiovascular risk and metabolic risk factors, accounting for body mass index (BMI) and waist circumference. The association between neck circumference and incident atrial fibrillation (AF) is unclear. The aim of current study was to evaluate the association between neck circumference and incident AF.

METHODS AND RESULTS: We selected participants from the Framingham Heart Study aged ≥55 years without diagnosed AF and with available neck circumference, BMI, and waist circumference measurements. We defined high neck circumference as ≥14 inches in women and ≥17 inches in men on the basis of the Contal and O'Quigley changepoint method. We used Fine-Gray models to estimate subdistribution hazards ratios (sHRs) for the association between neck circumference and incident AF accounting for the competing risk of death. We adjusted models for clinical risk factors. We then additionally adjusted separately for BMI, waist circumference, and height/weight. The study sample included 4093 participants (mean age 64±7 years, 55% female). During 11.2±5.7 mean years of follow-up, incident AF occurred in 571 participants. High neck circumference was associated with incident AF (sHR for high versus low: 1.58; 95% CI, 1.32–1.90, *P*<0.0001). The association remained significant after adjustment for BMI (sHR, 1.51; 95% CI, 1.21–1.89; *P*=0.0003), waist circumference (sHR, 1.47; 95% CI, 1.18–1.83; *P*<0.0001), and height/weight (sHR, 1.37; 95% CI, 1.09–1.72; *P*=0.007).

CONCLUSIONS: High neck circumference was associated with incident AF adjusting for traditional adiposity measures such as BMI and waist circumference.

Key Words: atrial fibrillation ■ epidemiology ■ fat depot ■ incidence ■ neck circumference

Atrial fibrillation (AF) is increasing in prevalence and incidence globally and leads to many adverse outcomes, including increased mortality.[1,2] Obesity is a known risk factor for AF,[3] which has been demonstrated consistently in epidemiological studies of body mass index (BMI) and AF. Overweight and obesity are the second-largest contributors to AF incidence after elevated blood pressure and account for ≈18% of AF cases.[4] Furthermore, findings from a Mendelian randomization study provide evidence consistent with a causal relation between BMI and AF.[5]

Obesity is typically measured using standard anthropometric measures such as BMI, waist circumference, or waist-to-hip ratio.[6] Recent work on the cause of AF has highlighted the importance of body fat distribution, which may not be captured using an overall adiposity measurement such as BMI.[7,8] Quantification of individual fat depots may provide further insights into the mechanisms of AF development.

Upper-body subcutaneous fat is a unique fat deposit, and its measurement can be approximated using neck circumference. Neck circumference has

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CLINICAL PERSPECTIVE

What Is New?

- Individuals with high neck circumference had increased risk for incident atrial fibrillation, after adjustment for known clinical risk factors of atrial fibrillation.
- This association remained after additionally adjusting further for body mass index, waist circumference, or height/weight.
- The association between neck circumference and atrial fibrillation risk was strongest among participants with obesity.

What Are the Clinical Implications?

- High neck circumference is associated with risk of incident atrial fibrillation beyond "classic" obesity measures.
- Neck circumference could be useful as a risk factor in individuals with unfavorable cardiovascular risk profile.

Nonstandard Abbreviations and Acronyms

CHARGE-AF	Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation
FHS	Framingham Heart Study
sHR	subdistribution hazard ratios

been shown to be associated with increased cardiovascular risk.[9] There is evidence that free fatty acid release from upper-body subcutaneous fat is higher compared with lower-body subcutaneous fat.[10] Prior work in the FHS (Framingham Heart Study) as well as other studies have reported associations between high neck circumference and diabetes, insulin resistance, and elevated blood pressure, all of which are risk factors for AF.[11–15] Importantly, the association between neck circumference and metabolic risk factors persisted after accounting for traditional adiposity measurements such as BMI and waist circumference.[16,17] Furthermore, there is evidence that individuals with high neck circumference have increased risk of obstructive sleep apnea, which is also associated with AF.[14,18]

Considering the association between cardiometabolic risk factors, sleep apnea, and AF,[19] neck circumference may provide additional insights into the biologic mechanisms predisposing to AF. We hypothesized that larger neck circumference is associated with incident AF. We assessed whether neck circumference is associated with incident AF above and beyond traditional anthropometric measures such as BMI, waist circumference, and weight.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Study Sample

Starting from October 1948, 5209 participants who were residents of Framingham, Massachusetts, were enrolled in the Original Cohort of FHS.[20] Enrollment of the FHS Offspring Cohort began in 1971 with inclusion of 5124 children (and their spouses) of the Original Cohort participants.[21] In 1994, the Framingham Heart Study's Omni 1 Cohort began and included 507 African American, Hispanic, Asian, Indian, Pacific Islander, and Native American participants from Framingham and surrounding towns. The New Offspring Spouse Cohort, with 171 participants in 2003 to 2005, and multiethnic Omni 2 Cohort with 410 participants enrolled in 2003 to 2005.[20–22] The Original Cohort participants underwent biennial clinic examinations, whereas other cohorts were seen every 4 to 8 years. The FHS protocols are reviewed by the Institutional Review Board of Boston University Medical Center, and all participants provided informed consent.

For the present analysis, we included participants who were free of AF at the time of their "index" exam, defined as the first exam attended at age ≥55 years with available neck circumference, BMI, and waist circumference measurements. We used an age cutoff of 55 years in accordance with prior analyses in the FHS, and since AF pathophysiology in individuals younger than 55 years is likely different than that in older individuals.[23,24] Neck circumference has been measured in the following FHS cohorts/exams: Offspring exams 7 (1998–2001) and 9 (2011–2014), Omni 1 exams 2 (1999–2001) and 4 (2011–2014), Third Generation exam 2 (2008–2011), New Offspring Spouse exam 2 (2008–2011), and Omni 2 exam 2 (2009–2011).

A total of 4614 participants attended at least one exam at age ≥55 in which neck circumference was assessed. We excluded participants with missing adiposity measurements (neck circumference, waist circumference, and/or BMI, n=236), prevalent AF at their index exam (n=209), lack of follow-up for AF events (n=43), and missing covariate information (n=33). Details of the study sample selection are shown in Figure 1. Participants were followed from the date of their index exam until development of AF, death, loss to follow-up, or December 31, 2018, whichever occurred first.

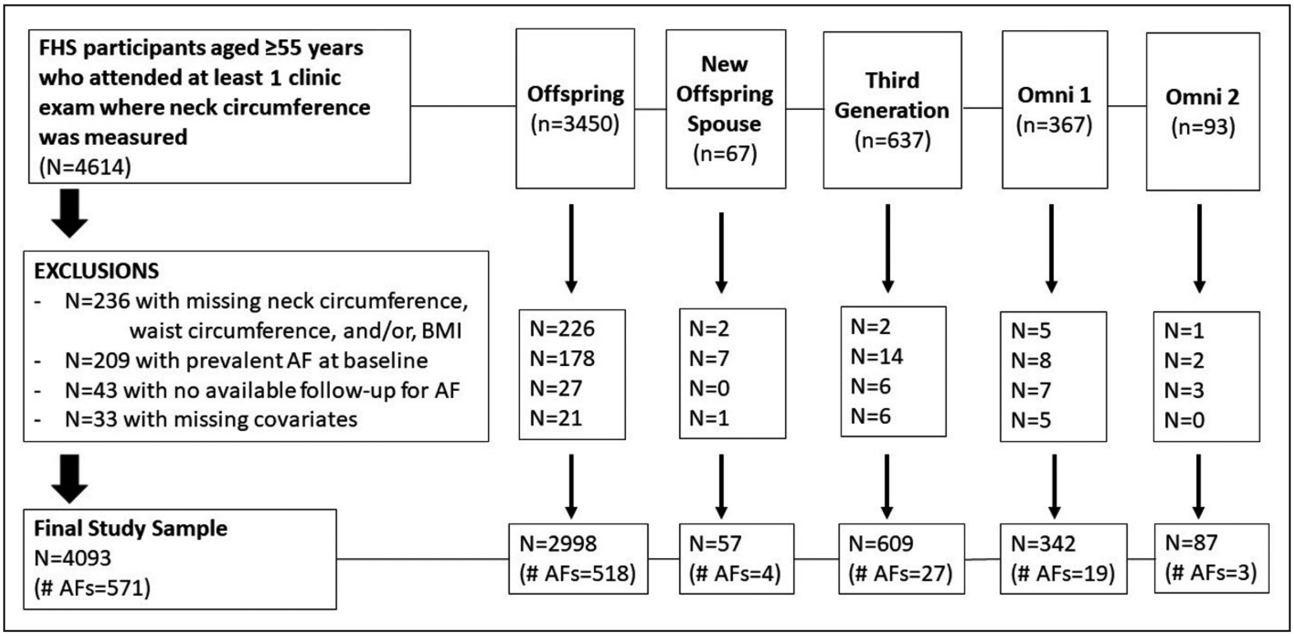

Figure 1. Flow chart of study sample selection.
AF indicates atrial fibrillation; BMI, body mass index; and FHS, Framingham Heart Study.

Exposure Assessment—Adiposity Measurement

For measurement of neck circumference, participants were instructed to stand erect with their head positioned in the Frankfort horizontal plane.[17] The superior border of a tape measure was placed right below the laryngeal prominence, perpendicular to the long axis of the neck. Waist circumference was measured using a tape measure placed at the umbilicus level. Both neck and waist circumference were measured to the nearest quarter inch. Standardized protocols were used to measure height and weight. BMI was calculated as the weight in kilograms, divided by the square of height in meters (kg/m^2).

Cardiovascular Event and Mortality Ascertainment

Ascertainment of AF in FHS has been described previously.[25] All participants underwent an ECG as a routine part of their FHS clinic exam. A diagnosis of AF was given if either AF or atrial flutter was observed on the ECG or if AF was documented in a participant's outside medical records, interim hospitalizations, outside ECGs, or Holter monitor results.

The study participants are continuously monitored for the development of any cardiovascular event and/or death. All events are adjudicated by a panel of 2 to 3 clinicians (the Framingham Endpoint Review Committee) using FHS research center information and outside medical records or hospitalization charts. Heart failure was diagnosed based on the presence of at least 2 major criteria *or* 1 major criterion and 2 minor criteria as previously described.[26] History of myocardial infarction was designated if there were at least 2 of 3 findings: (1) symptoms indicative of ischemia; (2) changes in blood biomarkers of myocardial necrosis; (3) serial changes in the ECGs. Deaths were documented by death certificates.

Covariate Assessment

At each FHS study visit, participants reported their medical history and underwent a physical examination. Systolic and diastolic blood pressure were measured twice by a study physician, and the 2 values were averaged. Diabetes was defined as fasting plasma glucose ≥126 mg/dL (or nonfasting plasma glucose ≥200 mg/dL) or treatment with insulin or a hypoglycemic agent. A participant was considered a current cigarette smoker if they reported ≥1 cigarettes per day over the previous year. A standardized commercial assay was used to measure serum concentrations of high-sensitivity CRP (C-reactive protein).[27] Sleep apnea was self-reported and was considered present if the participant answered "Yes" to the question "Have you ever had the following condition diagnosed by a doctor or health care professional: Sleep Apnea."

Statistical Analysis

Descriptive statistics were calculated using means and standard deviations, medians (25th, 75th percentile), or frequency counts and percentages, as appropriate.

Due to the differing ranges of values between men and women, all adiposity measurements (neck circumference, waist circumference, BMI, height, weight) were standardized within each sex to a mean of 0 and a SD of 1. Both a quadratic term and cubic splines were used to explore the possibility of a nonlinear association between neck circumference and the risk of AF. We constructed restricted cubic spline plots,[28–30] with knots placed at the 25th, 50th, and 75th percentiles for sex-standardized neck circumference using the whole study sample (Figure S1). We also constructed similar cubic spline plots separately for each sex, using the raw values of neck circumference (Figure 2). The plots were adjusted for the mean level of age, sex, systolic and diastolic blood pressure, hypertension treatment, diabetes, current smoking, history of heart failure, and history of myocardial infarction. To test for nonlinearity, a likelihood ratio test was used to compare the model with only the linear term to the model with both the linear and cubic spline (or quadratic) terms. We used Contal and O'Quigley's method to determine the cut point for high neck circumference, separately for each sex, to the nearest half inch.[31,32] This method uses a log rank statistic to categorize individuals into high- and low-risk groups for time-to-event outcomes. The log rank statistic is calculated for different thresholds of the exposure variable and is maximized to determine the optimal cut point.

Fine-Gray subdistribution hazard models, which account for the competing risk of mortality,[33] were used to calculate subdistribution hazard ratios (sHRs) and 95% CIs for the association between neck circumference (high versus low neck circumference) and incident AF. All models were stratified by study cohort (Offspring, New Offspring Spouse, Third Generation, Omni 1, Omni 2). The proportional hazards assumption was assessed by creating an interaction term between each variable and time and testing its statistical significance using a chi-squared test. All variables satisfied the proportional hazards assumption except for age. Thus, all models included an interaction term for age×time. In Tables S1 through S3 we additionally present cause-specific hazards ratios from the conventional Cox model, which are not adjusted for the competing risk of mortality.

Five separate models were constructed. Model 1 was adjusted for age and sex. A multivariable-adjusted model 2 was further adjusted for all variables associated with AF from the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation) risk model excluding height and weight (systolic and diastolic blood pressure, hypertension treatment, current cigarette smoking, diabetes, history of myocardial infarction, and history of heart failure).[34] Model 3 adjusted for all model 2 covariates plus BMI (per SD increment). Model 4 adjusted for all model 2 covariates plus waist circumference (per standard deviation increment). Model 5 adjusted for all model 2 covariates plus height and weight (per SD increment).

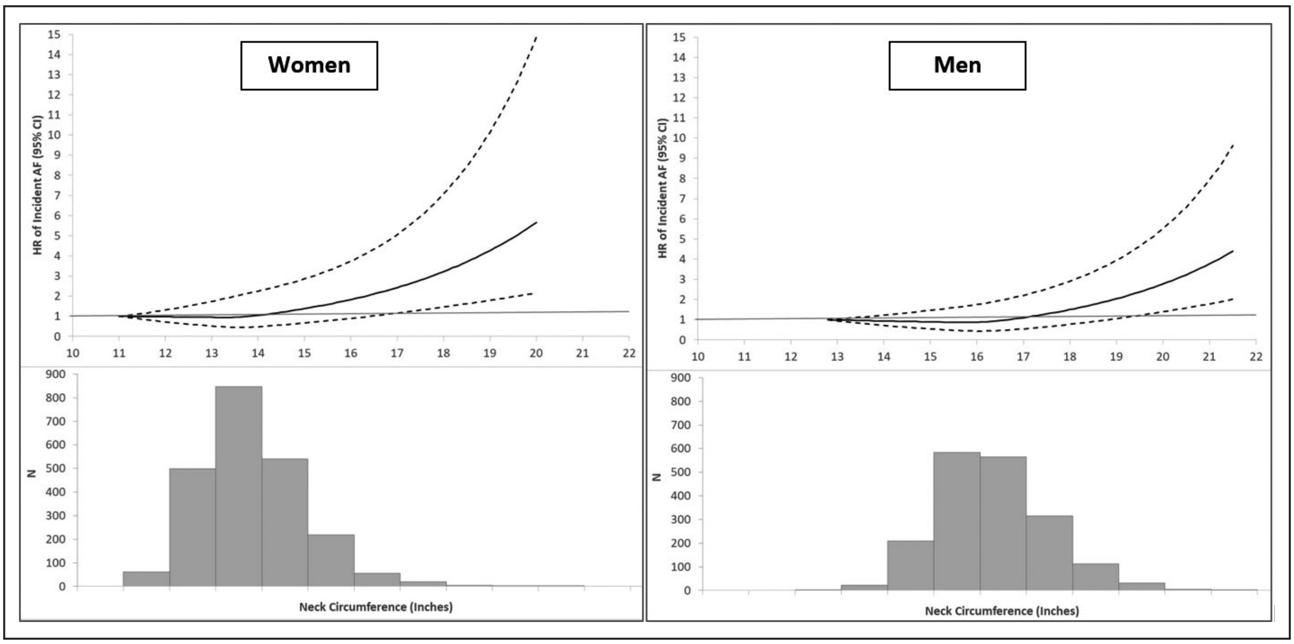

Figure 2. Restricted cubic splines for the association between neck circumference and risk of AF, by sex (top panel). The *x* axis (in the middle) represents neck circumference in women and men in inches for top and bottom panels. The *y* axis reports subdistributional hazard ratios (95% CI) of incident AF (top panel) or N (bottom panel). Curves are adjusted for the mean level of age, sex, systolic and diastolic blood pressure, hypertension treatment, diabetes, current smoking, history of heart failure, and history of myocardial infarction. The *P*-value for the test of overall significance of the curve was <0.0001 for both women and men. Distribution of neck circumference by sex (bottom panel). AF indicates atrial fibrillation; and HR, hazard ratio.

In secondary analyses, model 2 was additionally adjusted for self-reported sleep apnea (n=2069) and for natural log transformed CRP (n=3881), which were available only in a subset of the study sample.

To assess the presence of effect modification by BMI, sex, and age, a cross-product term between each factor and neck circumference was included in the model, and its statistical significance was assessed using a Wald chi-square test. Stratum-specific estimates were calculated for each of the 3 factors. For BMI, we used the categories 18.5 to 24.9, 25.0 to 29.9, and ≥30 kg/m^2, and for age we used the categories ≥65 and <65 years. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A 2-sided P<0.05 was considered statistically significant.

RESULTS

Study Sample Characteristics

The present analysis included 4093 participants (mean age, 63.6±6.6 years; 55% women) from the FHS Offspring (n=2998), New Offspring Spouse (n=57), Third Generation (n=609), Omni 1 (n=342) and Omni 2 (n=87) cohorts (Table 1, Figure 1). Participants were followed for a mean of 11.2±5.7 years (range, 0.04–20.3 years). During follow-up, there were 571 (12.5 per 1000 person-years) incident AF events (low neck circumference, N=344, 10.8 per 1000 person-years; high neck circumference, N=227, 16.2 per 1000 person-years). A total of 686 (15.0 per 1000 person-years) participants died during follow-up (low neck circumference, N=452, 14.2 per 1000 person-years; high neck circumference, N=234, 16.7 per 1000 person-years).

The mean neck circumference was 13.7±1.1 inches in women and 16.1±1.2 inches in men (Figure 2). We did not observe significant evidence of a quadratic association between neck circumference and AF in the multivariable-adjusted cause-specific hazards model (P value for neck circumference–squared term=0.07). However, the multivariable-adjusted cubic spline plot for sex-standardized neck circumference and risk of AF did show evidence of a nonlinear association (P value for nonlinearity=0.01; Figure S1). The cut point for high neck circumference was identified as ≥14 inches in women and ≥17 inches in men, using the Contal and O'Quigley method.[31]

Association Between Neck Circumference and Incident AF

Table 2 shows the subdistribution hazard model results for the association between neck circumference and AF. In multivariable model 2 (adjusted for age, sex, and CHARGE-AF risk factors), participants with high neck circumference had increased risk of AF as compared to those with low neck circumference (sHR=1.58; P<0.0001; Table 2, Figure 3). The sHRs comparing high to low neck circumference were slightly attenuated after additional adjustment for other measures of adiposity but remained statistically significant in all models (BMI [model 3]: sHR, 1.51; P=0.0003; waist circumference [model 4]: sHR, 1.47; P=0.0007; height and weight [model 5]: sHR=1.37; P=0.007). Model results for the cause-specific Cox proportional hazards models, which do not account for the competing risk of mortality, are shown in Table S1. Additionally, the model results using sex-standardized neck circumference are shown in Table S2.

In the secondary analyses, we additionally adjusted model 2 for sleep apnea and natural log transformed CRP, both of which were available only in a subset of our study sample. The association between neck circumference and AF remained statistically significant and did not change meaningfully (for model 2+sleep apnea [n=2069]: sHR, 1.61; 95% CI, 1.12–2.34; P=0.01; and for model 2+CRP [n=3881]: sHR,1.52; 95% CI, 1.26–1.83; P<0.0001).

Finally, the associations between neck circumference and incident AF stratified by BMI, sex, and age are presented in Table 3. There was a statistically significant interaction between neck circumference and BMI (kg/m^2) (P value for interaction=0.04). The association between neck circumference and incident AF was stronger for higher BMI. The sHR for high as compared with low neck circumference was 1.84 (95% CI, 1.29–2.62; P=0.0008) among participants with obesity (BMI ≥30 kg/m^2), 1.48 (95% CI, 1.04–2.12; P=0.03) among overweight participants (BMI, 25.0–29.9 kg/m^2) and 1.21 (95% CI, 0.52–2.82; P=0.66) among normal weight participants (BMI, 18.5–24.9 kg/m^2). There was no evidence of significant effect modification by either age or sex for the association between neck circumference and AF. The corresponding model results using sex-standardized neck circumference are shown in Table S3.

DISCUSSION

Principal Findings

In the current study, we examined the association between neck circumference, a proxy for upper-body subcutaneous fat, and risk of incident AF among ≈4000 participants from the FHS. We observed a nonlinear association between neck circumference and risk of AF. In models using dichotomous neck circumference, we observed that individuals with high neck circumference (≥14 inches for women and ≥17 inches for men) had increased risk of incident AF as compared with those with low neck circumference. The association persisted after further adjustment for traditional adiposity measurements, such as BMI, waist

Table 1. Study Sample Characteristics

	Total (N=4093)	High neck circumference (≥14 inches in women, ≥17 inches in men) No (N=2785)	Yes (N=1308)
Age, y	63.6±6.6	63.7±6.6	63.5±6.4
Female sex	2248 (55)	1406 (50)	842 (64)
Years of follow-up for incident AF	11.2±5.7	11.4±5.7	10.7±5.7
Systolic blood pressure, mm Hg	128±18	126±18	131±17
Diastolic blood pressure, mm Hg	74±10	74±10	75±9
Hypertension treatment	1636 (40)	930 (33)	706 (54)
Current smoker	381 (9)	272 (10)	109 (8)
Diabetes	506 (12)	231 (8)	275 (21)
History of heart failure	25 (0.6)	15 (0.5)	10 (0.8)
History of myocardial infarction	127 (3)	88 (3)	39 (3)
Sleep apnea*	177 (9)	73 (5)	104 (16)
C-reactive protein, μg/mL, median (25th–75th percentile)†	1.9 (0.9–4.5)	1.5 (0.7–3.3)	3.4 (1.6–6.4)
Anthropometric measures‡			
Height, in	66±4	66±4	66±4
Weight, lb	175±40	161±31	204±41
Body mass index, kg/m^2	28.4±5.5	26.1±3.6	33.2±5.7
BMI category			
<18.5 kg/m^2	28 (0.7)	28 (1.0)	0 (0.0)
18.5–24.9 kg/m^2	1127 (28)	1086 (39)	41 (3)
25.0–29.9 kg/m^2	1658 (41)	1307 (47)	351 (27)
≥30 kg/m^2	1280 (31)	364 (13)	916 (70)
Waist circumference, in	39.6±5.6	37.4±4.3	44.3±5.3
Neck circumference, in			
Women, N	2248	1406	842
Mean (SD)	13.7±1.1	13.0±0.6	14.8±0.9
Median (25th, 75th percentile)	13.5 (13.0, 14.25)	13 (12.5, 13.5)	14.5 (14.25, 15.25)
Minimum, maximum	11.0, 20.0	11.0, 13.75	14.0, 20.0
Men, N	1845	1379	466
Mean (SD)	16.1±1.2	15.6±0.8	17.7±0.8
Median (25th, 75th percentile)	16.0 (15.25, 17.0)	15.75 (15.0, 16.25)	17.5 (17.0, 18.0)
Minimum, maximum	12.75, 21.5	12.75, 16.75	17.0, 21.5

Table values represent mean±SD or n (%), unless otherwise indicated. AF indicates atrial fibrillation; and BMI, body mass index.
*A total of 2069 participants (51%) had available data for sleep apnea.
†A total of 3881 participants (95%) had available data for C-reactive protein.
‡Height, waist circumference, and neck circumference are measured to the next lower quarter inch.
§*P* value comparing high vs low neck circumference was calculated using a chi-squared test, 2-sample *t* test, or Kruskal-Wallis test, as appropriate.

circumference, height, and weight. Finally, our results suggested that BMI may be an effect modifier of the association between neck circumference and risk of AF; the strongest association was observed among participants with obesity.

Comparison With Other Studies

There has been limited study of the association between neck circumference and incident AF. A cross-sectional study of the association between AF and sleep apnea found that patients undergoing electrical cardioversion for AF had higher mean neck circumference compared with general cardiology patients without AF.[35] A small case-control study (N=115) demonstrated that high neck circumference (>40 cm) was associated with 5.2 times higher odds of AF, after adjustment for BMI and waist circumference.[36]

Different studies link neck circumference with obesity,[6] cardiovascular risk factors,[17,37,38] obstructive sleep apnea,[39] diabetes,[40] metabolic syndrome,[41] and renal dysfunction,[42] which are known risk factors associated with AF. Other studies have demonstrated that neck circumference may be a useful alternative for waist

Table 2. Subdistribution Hazards Ratios and 95% CI for the Association Between Neck Circumference and Incident Atrial Fibrillation (N=4093)

Model number	Model adjustment	High (≥14 inches in women, ≥17 inches in men) vs low neck circumference	
		sHR (95% CI)	*P* value
1	Age/sex	1.72 (1.44–2.04)	<0.0001
2	Multivariable*	1.58 (1.32–1.90)	<0.0001
3	Multivariable*+BMI	1.51 (1.21–1.89)	0.0003
4	Multivariable*+waist circumference	1.47 (1.18–1.83)	0.0007
5	Multivariable*+height+ weight	1.37 (1.09–1.72)	0.007

All models are stratified by Framingham Heart Study study cohort (Offspring/New Offspring Spouse, Third Generation, Omni 1, Omni 2) and adjusted for the competing risk of mortality. BMI indicates body mass index; and sHR, subdistribution hazards ratios.

*Adjusted for age, age×time, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment, current smoking, diabetes, history of myocardial infarction, and history of heart failure.

circumference measurement because of its reproducibility and little daily variation.[41,43] Prior work in the FHS has shown an association between neck circumference and various cardiovascular disease risk factors, including blood pressure, triglycerides, measures of insulin resistance, and diabetes. The associations persisted after accounting for BMI and visceral adipose tissue.[15,17] In an African American population, neck circumference was associated with cardiometabolic risk factors.[44] Nevertheless, several studies analyzed association between neck circumference and cardiovascular events, but the results have been inconsistent.[17,45] Using FHS data, Preis et al[17] reported that there was no association between neck circumference and incident cardiovascular disease or heart failure, while a recent cross-sectional study reported a positive association between neck circumference and estimated 10-year cardiovascular risk as measured by the Framingham Global Risk Score, after adjustment for other body adiposity measures such as BMI and waist circumference.[45] Interestingly, an association with cardiovascular risk factors and neck circumference was more apparent in women.[13,17,45] Furthermore, the association between neck circumference and other obesity measures was much higher in women than men, though the authors did not test for a statistical interaction. One explanation of the sex differences may be the higher release of free fatty acid from visceral adipose tissue to the liver in women compared with men.[46] In our study, we found that neck circumference was associated with incident AF beyond BMI and waist circumference supporting our hypothesis that subcutaneous fat depositions in the upper body are associated with AF initiation. However, we did not observe any effect modification by sex on the association between neck circumference and AF.

Mechanisms of Association Between Neck Circumference and Cardiovascular Health

The association between obesity and incident AF, AF burden, and AF progression is well described.[47,48] There are several potential mechanisms to explain the association between neck circumference, a surrogate measure for upper-body fat depot, and AF. First, neck circumference may mechanistically contribute to AF initiation. Larger neck circumference is strongly associated with sleep apnea, which is a risk factor for AF.[18] High levels of upper-body fat deposited around the airways may narrow the lumen, making it susceptible to collapse, and can ultimately result in hypopnea or apnea episodes.[19]

Secondly, neck circumference may indirectly contribute to AF initiation through activation of neurohormonal and inflammatory factors. Along with ectopic fat depots in pericardium and liver,[49] subcutaneous neck adipose tissue is one of the *ectopic* fat depots in human body[50] resulting from deposits of triglycerides in nonadipose tissue.[51,52] Ectopic fat causes activation of proinflammatory cytokines,[53] endothelial dysfunction,[54] oxidative stress, and, as a consequence, chronic inflammation and impaired lipid metabolism.[55] A relatively small study of men reported that magnetic resonance–derived upper-body subcutaneous fat was associated with unfavorable lipoprotein (low-density lipoprotein and high-density lipoprotein) and cholesterol levels.[56] On a neurohormonal level, relative to visceral fat, subcutaneous fat in the upper body releases a higher level of free fatty acids to the systemic circulation. The proportion of free fatty acids in subcutaneous fat depots has been shown to be higher in women than in men.[57,58] Elevated free fatty acid levels contribute to insulin resistance and oxidative stress.[17,46] Of note, systemic free fatty acid release depends on metabolic profile and is higher in obese individuals compared with normal-weight women and men,[57] which may explain the stronger association between neck circumference and AF that we observed among individuals with obesity.

Limitations

There are several limitations we would like to highlight, which may alter the interpretation of our results. First, the FHS is an observational study, therefore residual confounding cannot be ruled out, and the study cannot establish causal relations. The data on sleep apnea and CRP were incomplete, and sleep apnea was self-reported; therefore, we were not able to fully assess the association between neck circumference or CRP

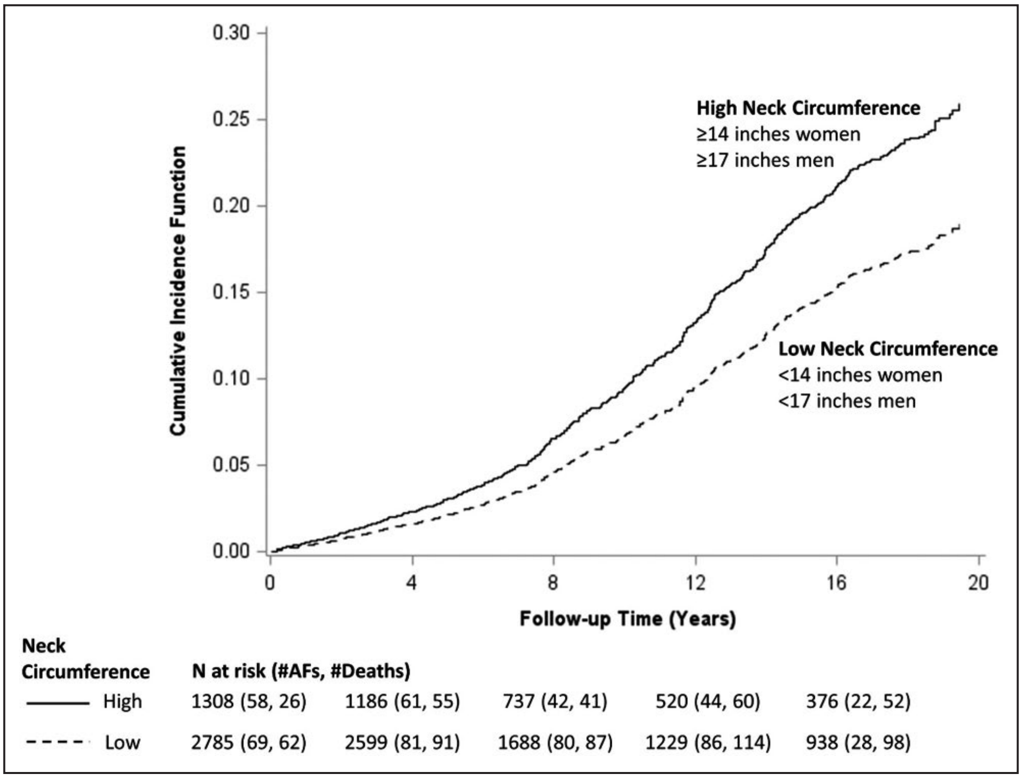

Figure 3. Cumulative incidence function for AF by neck circumference classification (high vs low).

Curves are adjusted for the mean level of age, sex, systolic and diastolic blood pressure, hypertension treatment, diabetes, current smoking, history of heart failure, and history of myocardial infarction and are adjusted for the competing risk of mortality. AF indicates atrial fibrillation.

and sleep apnea. The analyses should be considered hypothesis generating. Second, the current study included individuals largely of European ancestry and living in New England. Although the analysis included participants from other race/ethnic groups, the number of individuals from the FHS Omni 1 and 2 cohorts comprised only a small proportion of the study sample. Therefore, the generalizability to younger ages, other races/ethnicities, and other regions/countries is unknown and should be addressed in other studies. Furthermore, neck circumference is only a proxy for upper-body subcutaneous fat. However, a prior study examining computed tomographic measurement of neck fat demonstrated a high correlation with neck

Table 3. Subdistribution Hazards Ratios for the Association Between Neck Circumference and Incident Atrial Fibrillation, Stratified by BMI Group, Sex, and Age Group

Variable	Level	# AF cases/# participants	High (≥14 inches in women, ≥17 inches in men) vs low neck circumference		*P* value for interaction*
			sHR (95% CI)†	*P* value	
BMI	18.5–24.9 kg/m²	145/1127	1.21 (0.52–2.82)	0.66	0.04
	25.0–29.9 kg/m²	207/1658	1.48 (1.04–2.12)	0.03	
	≥30 kg/m²	215/1280	1.84 (1.29–2.62)	0.0008	
Sex	Men	316/1845	1.78 (1.39–2.26)	<0.0001	0.13
	Women	255/2248	1.35 (1.04–1.75)	0.03	
Age	<65 y	198/2494	1.70 (1.26–2.28)	0.0005	0.26
	≥65 y	373/1599	1.49 (1.19–1.87)	0.0005	

All models are stratified by cohort membership (Offspring, New Offspring Spouse, Gen 3, Omni 1, Omni 2) and are adjusted for the competing risk of mortality. BMI indicates body mass index; and sHR, subdistribution hazards ratios.

*Interaction between neck circumference and continuous body mass index and continuous age.

†Adjusted for age, age×time, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment, current smoking, diabetes, history of myocardial infarction, and history of heart failure.

circumference.[59] Finally, AF is frequently undiagnosed; there may be misclassification of occurrence and timing of onset AF.

Considering the relations between subcutaneous fat depot and several cardiovascular risk factors related to AF,[17] the examination of the use of neck circumference as a simple and easy measurable marker associated with AF risk is warranted. In individuals at high risk of AF (eg, with unfavorable cardiovascular risk profile, unknown cause for thromboembolic event, unawareness of underlying disease, social determinants predictive of AF),[60] future studies should address whether neck circumference is useful for planning and defining AF management with appropriate screening, prevention, and treatment. Since neck circumference is associated with AF in adjusted analyses, its measurement may provide directions for future studies of the role of obesity in AF initiation and progression.

CONCLUSIONS

Individuals with high neck circumference had increased risk of incident AF compared with those with low neck circumference. This association remained statistically significant after adjustment for BMI, waist circumference, height, and weight. The association between neck circumference and AF risk was strongest among participants with obesity.

Therefore, our findings indicate that neck circumference potentially may be used as an easily obtainable measure for assessing risk of incident AF. Further study is warranted to help understand the causal relation between upper-body subcutaneous fat and AF initiation, and also its role in primary and secondary prevention of AF.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Cause-specific hazards ratios (HR) and 95% confidence intervals (95% CI) for the association between neck circumference and incident atrial fibrillation (N=4093).

Model Number	Model Adjustment	High (≥14 inches in women, ≥17 inches in men) versus Low Neck Circumference	
		Cause-specific HR (95% CI)	P-value
1	Age/sex	1.79 (1.51-2.12)	<0.0001
2	Multivariable*	1.62 (1.36-1.94)	<0.0001
3	Multivariable* + BMI	1.57 (1.26-1.96)	<0.0001
4	Multivariable* + Waist circumference	1.49 (1.20-1.86)	0.0003
5	Multivariable* + Height + Weight	1.43 (1.14-1.79)	0.002

All models are stratified by FHS study cohort (Offspring/New Offspring Spouse, Third Generation, Omni-1, Omni-2).

*Adjusted for age, age*time, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment, current smoking, diabetes, history of MI, and history of CHF.

Table S2. Hazards ratios (HR) and 95% confidence intervals (95% CI) for the association between neck circumference (per standard deviation [SD] increment) and incident atrial fibrillation (N=4093).

Model Number	Model Adjustment	HR per SD Increment of Neck Circumference*			
		Subdistribution HR (95% CI)	P-value	Cause-specific HR (95% CI)	P-value
1	Age/sex	1.29 (1.19-1.40)	<0.0001	1.33 (1.23-1.44)	<0.0001
2	Multivariable**	1.22 (1.12-1.33)	<0.0001	1.25 (1.15-1.36)	<0.0001
3	Multivariable** + BMI	1.21 (1.07-1.38)	0.003	1.28 (1.13-1.46)	0.0001
4	Multivariable** + Waist circumference	1.18 (1.04-1.33)	0.01	1.22 (1.08-1.38)	0.002
5	Multivariable** + Height + Weight	1.12 (0.98-1.28)	0.10	1.18 (1.03-1.35)	0.01

All models are stratified by FHS study cohort (Offspring/New Offspring Spouse, Third Generation, Omni-1, Omni-2). Subdistribution hazards ratios account for the competing risk of mortality.

* Neck circumference is standardized within sex and hazard ratios are expressed per 1 SD increment. A 1 SD increment equals 1.1 inches in women and 1.2 inches in men.

**Adjusted for age, age*time, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment, current smoking, diabetes, history of MI, and history of CHF.

Table S3. Subdistribution hazards ratios (sHR) for the association between neck circumference (per standard deviation [SD] increment) and incident atrial fibrillation, stratified by BMI group, sex, and age group.

Variable	Level	# AF cases/ #Participants	HR per SD Increment of Neck Circumference*		P-value for Interaction**
			sHR (95% CI) †	P-value	
BMI	18.5-24.9 kg/m^2	145/1127	1.24 (0.91-1.70)	0.18	0.04
	25.0-29.9 kg/m^2	207/1658	1.15 (0.92-1.44)	0.22	
	≥30 kg/m^2	215/1280	1.27 (1.09-1.47)	0.002	
Sex	Men	316/1845	1.21 (1.08-1.35)	0.001	0.92
	Women	255/2248	1.23 (1.08-1.39)	0.002	
Age	<65 years	198/2494	1.26 (1.09-1.45)	0.001	0.67
	≥65 years	373/1599	1.19 (1.07-1.32)	0.002	

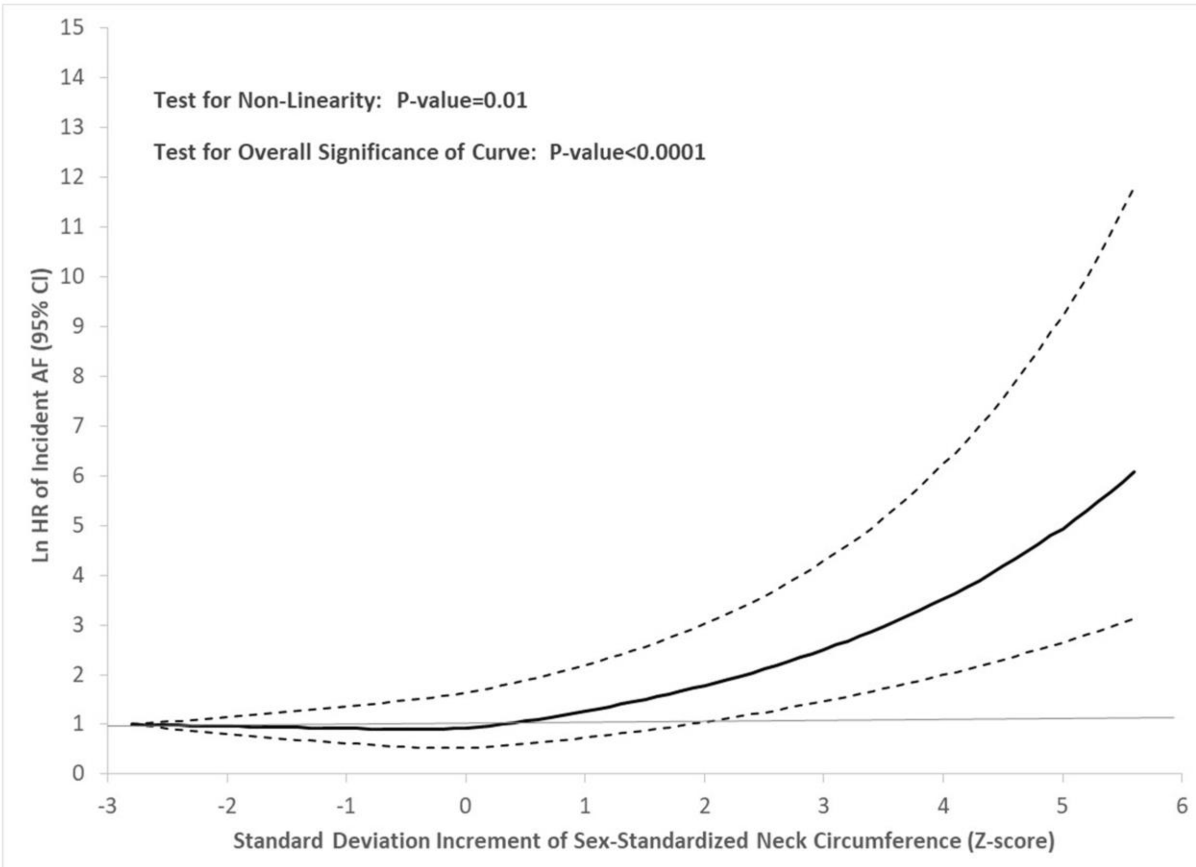
All models are stratified by cohort membership (Offspring/NOS, Gen 3, Omni-1, Omni-2) and are adjusted for the competing risk of mortality.

* Neck circumference is standardized within sex and hazard ratios are expressed per 1 SD increment. A 1 SD increment equals 1.1 inches in women and 1.2 inches in men.

** Interaction between neck circumference and continuous body mass index and continuous age.

†Adjusted for age, age*time, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment, current smoking, diabetes, history of MI, and history of CHF.

Figure S1. Restricted cubic splines for the association between standard deviation (SD) increment of sex-standardized neck circumference and risk of AF.



A 1 SD increment of neck circumference equals 1.1 inches in women and 1.2 inches in men.
Curves are adjusted for the mean level of age, sex, systolic and diastolic BP, hypertension treatment, diabetes, current smoking, history of CHF, and history of MI.