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Body mass index and body fat distribution and new-onset atrial fibrillation: Substudy of the European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) study

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Atrial arrhythmia

Abstract *Background and aim:* Obesity is a recognized risk factor for new-onset atrial fibrillation (AF). The association between body fat distribution, which is measured by body mass index (BMI) and waist–hip ratio (WHR), its changes, and new-onset AF is conflicting.
Methods and results: Participants of the European Prospective Investigation into Cancer and Nutrition in Norfolk cohort study were included, with exclusion criteria of prevalent AF, rheumatic heart disease, and cancer. AF was confirmed by the *International Classification of Diseases-10* hospital discharge code I48. Adjusted sex-specific Cox proportional hazards models were used to quantify the AF risk per 1 standard deviation increase and for quintiles of adiposity indices. A total of 10,885 men and 12,857 women were followed up for a median of 19 years, yielding 451,098 person-years. New-onset AF was diagnosed in 1408 (12.9%) men and 1102 (8.6%) women. Multivariable analyses showed that BMI predicted new-onset AF in all, while WHR predicted only in men. New-onset AF risk gradually increased across the range of adiposity indices: for men in the highest BMI quintile, HR: 1.59 (CI 1.32–1.91, p *for trend*<0.001), whereas for women in the highest BMI quintile, HR: 1.52 (CI 1.23–1.88, p *for trend*<0.001). Further, for men in the highest WHR quintile, HR: 1.31 (CI 1.09–1.57, p *for trend*: 0.01), whereas for women in the highest WHR quintile, HR: 1.12 (CI 0.90–1.41, p *for trend:* 0.17). The change in BMI and WHR was similar in participants with or without new-onset AF.
Conclusions: An increased body mass, as measured by BMI, is associated with an increased risk of developing new-onset AF. More abdominal fat distribution, as measured by WHR, is associated with an increased risk of developing new-onset AF in men but not in women.

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Introduction

Obesity has been associated with an increased risk of new-onset atrial fibrillation (AF) [1–5]. As obesity enhances the risk of CVD, it indirectly contributes to the risk of AF [1,6]. However, obesity may also have a direct casual effect on atrial remodeling, fibrosis, and inflammation, thereby creating an essential arrhythmogenic substrate for AF. In sheep, progressive obesity was associated with changes in atrial size, expression of profibrotic mediators, and, importantly, new-onset AF [7,8]. On the other hand, weight reduction combined with intensive risk factor management reduced cardiac remodeling assessed by transthoracic echography and AF symptom burden [9,10].

Obesity is usually quantified by calculation of the body mass index (BMI), as it provides an indexed weight measure. A more specific measurement for body fat distribution is the waist–hip ratio (WHR), which is the ratio between waist and hip circumferences. WHR can be used to discriminate abdominal fat distribution from peripheral, subcutaneous fat distribution. It is well established that an abdominal fat distribution is more strongly associated with CVD [11]. However, data concerning WHR and the risk of new-onset AF are conflicting [12]. Further, data of change in BMI or WHR with time in relation to AF are scarce.

We hypothesized that not only obesity, defined by BMI, but also a more abdominal fat distribution, described by WHR, increases the risk of developing new-onset AF. This risk may be different for men and women. Furthermore, we hypothesized that changes in BMI and WHR, as assessed during follow-up, will alter the risk of developing new-onset AF. We tested these hypotheses among participants of the European Prospective Investigation into Cancer and Nutrition (EPIC) in Norfolk prospective population study.

Methods

The European Prospective Investigation Into Cancer and Nutrition in Norfolk (EPIC-Norfolk) is a prospective population study of men and women aged 45–79 years. The detailed description of the study design and data collection was published previously [13]. In brief, the study was conducted in Norfolk, United Kingdom, and recruited patients from general practice registers between 1993 and 1997. The study was approved by the Norfolk Health District Ethical Committee, and participants signed an informed consent. Participants underwent a health check at the time of inclusion and were invited back for a follow-up health check three years after inclusion.

Case ascertainment

For the current analysis, all participants with a history of AF were excluded. Case ascertainment of prevalent AF was based on a (reported) prescription of vitamin K antagonists or digitalis, as previously described [14]. Incident AF was defined as the *International Classification of Diseases* (ICD)-10 hospital discharge code I48, including both AF and atrial flutter. Participants with prevalent cancer or rheumatic heart disease were excluded. Vital status was obtained for the whole cohort, and the participants were flagged for death certifications at the Office of National Statistics.

Anthropometric measurements

Trained research nurses obtained anthropometric measurements at the first and the second health check. Participants were measured in light clothing without shoes using a standard protocol [15]. Height was measured to the nearest millimeter using a free-standing stadiometer. Weight was measured to the nearest 0.2 kg using digital scales (Salter, United Kingdom). Body mass index (BMI) was calculated as weight divided by the squared height (kg/m^2). A BMI of <19 kg/m^2 indicates underweight, 19–24.9 kg/m^2 healthy weight, 25–29.9 kg/m^2 overweight, and ≥ 30 kg/m^2 obesity [16]. Body circumferences were measured with a D-loop nonstretch fiberglass tape to the nearest millimeter at the end of expiration. Waist circumference was defined as the minimum circumference at the natural waistline between the lower rib margin and the iliac crest. Hip circumference was defined as the maximum circumference between iliac crest and the crotch. Waist–hip ratio (WHR) was calculated as hip circumference/waist circumference. Abdominal obesity was defined in accordance with the World Health Organization definition as a WHR of 0.90 for men and 0.85 for women [17].

Statistical analysis

Baseline characteristics of study participants with and without new-onset AF were compared. The unpaired sample t-test was used to compare normally distributed continuous variables, expressed as mean ± standard deviation (SD). The Mann–Whitney U test was used for non-normally distributed continuous variables, expressed as median with interquartile range [IQR]. Categorical variables were expressed as frequencies with percentages and compared by the Pearson χ [2] test.

Event rates of new-onset AF per person-year were calculated. The included cohort was divided into quintiles of BMI and WHR using the bottom fifth as the reference group. The AF event rates were calculated per 1000 person-years using corresponding follow-up durations. Tukey honest significant difference test was used to compare event rates per quintile of the adiposity index. Kaplan–Meier estimates were used to compute cumulative incidence of AF, and a log-rank test was used for between-group comparisons.

Sex-specific Cox proportional hazards models were used to quantify the risk of new-onset AF. Observations were censored at the date of the first episode of AF, death, or March 31, 2015. The multivariable models were adjusted for the following clinically significant parameters: age, social class, previous myocardial infarction, prevalent diabetes mellitus, thyroid disease, systolic blood pressure,

and total cholesterol. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for quintiles of adiposity indices. The p-value for trend was calculated. The models were assessed for interaction based on sex.

Changes in body composition were calculated by the delta of the anthropometric measurements obtained at the first and the second health check. A measurement was categorized as stable, if the change between the first and the second health check was less than 1 SD. In case of an increase in 1 SD or more, a participant was categorized as increased and vice versa for 1 SD decrease.

Next, the delta change in body composition was categorized in quartiles per anthropometric measurement: weight per 2.5 kg increase or decrease, and therefore, the fourth category represented patients with a delta change of 7.5 kg or over; waist per 5 cm increase or decrease; BMI per 1 unit increase or decrease; and WHR per 0.05 increase or decrease. The risk of new-onset AF was assessed using multivariable models, adjusted as described above with addition of covariates concerning incidence of ischemic heart disease and systolic and diastolic heart failure during follow-up. Observations were censored at the date of the first episode of AF, death, or March 31, 2015, independent of change in anthropometric measurements.

Data analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, New York, USA), and R version 3.3.2. A two-sided p-value of <0.05 was considered to be significant. The current analysis was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18].

Results

From the EPIC Norfolk cohort, consisting of 25,639 participants, we excluded 1897 participants because of prevalent AF, cancer, or rheumatic heart disease, hence resulting in inclusion of 23,742 participants (10,885 men and 12,857 women). During a median follow-up of 19 years (451,098 person-years), 2510 participants developed new-onset AF, comprising 1408 (12.9%) men and 1102 (8.6%) women.

Participants with versus without new-onset AF were more often male (56.1% vs. 44.6%, $p < 0.001$) and older (64.9 ± 7.8 vs. 58.2 ± 9.2 years, $p < 0.001$). They also had a higher BMI (27.3 ± 4.1 vs. 26.2 ± 3.9 kg/m^2, $p < 0.001$) and WHR (0.89 ± 0.09 vs. 0.85 ± 0.09, $p < 0.001$). Other cardiovascular factors were also more prevalent in participants with new-onset AF (Supplementary Table 1).

New-onset AF

A sex-specific difference in body fat distribution was found in the new-onset AF group. BMI was 27.1 ± 3.4 kg/m^2 in men and 27.4 ± 4.7 kg/m^2 in women, $p < 0.001$. WHR was

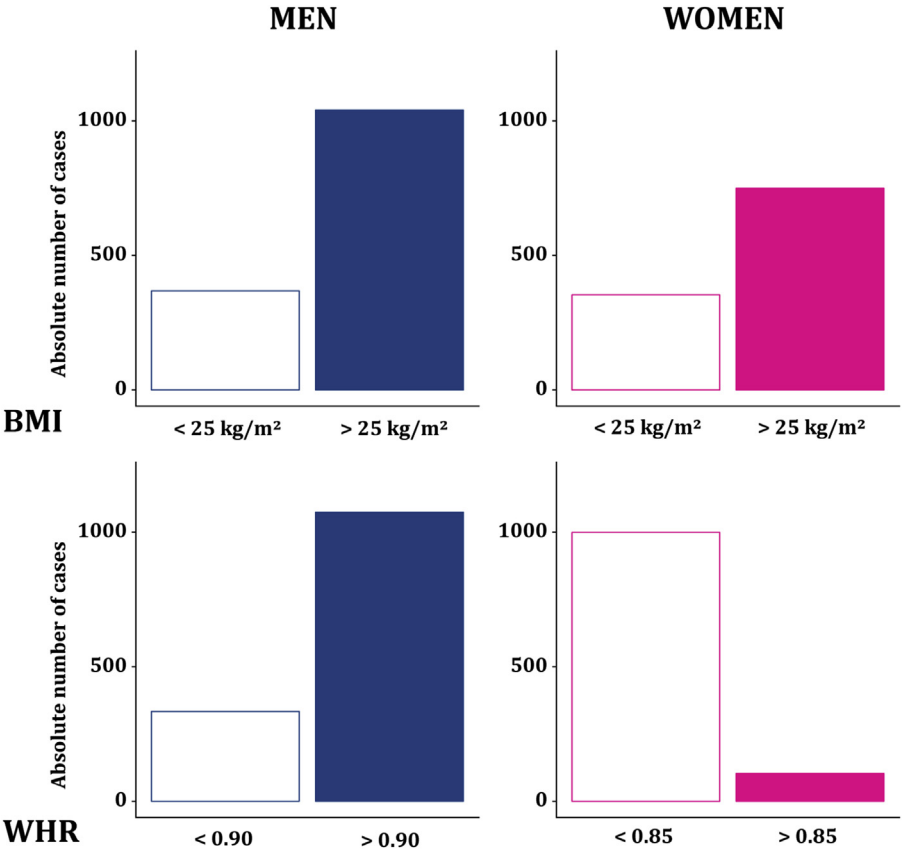

Figure 1 Absolute number of men and women with new-onset atrial fibrillation by the sex-specific WHO cut-off values for overweight. Cut-off values: BMI >25 kg/m^2 and WHR >0.90 (men) or 0.85 (women) indicating obesity.

0.94 ± 0.06 in men and 0.81 ± 0.06 in women, $p < 0.001$. This was driven by an absolute higher waist circumference in men than in women (98.1 ± 10.0 cm vs. 85.9 ± 11.4 cm, $p < 0.001$) (Supplementary Table 2). This resulted in a difference in the distribution of absolute number of cases with new-onset AF between men and women after stratification according to the cutoff values defined by the World Health Organization for obesity (Fig. 1). The majority of men and women with new-onset AF had a high BMI, whereas for WHR, this was only the case in men.

When the cohort was subdivided depending on the cutoff values of BMI and WHR, indicating overweight, the cumulated AF event rate was significantly higher in men and women with a BMI or WHR above the cutoff values (Supplemental Fig. 1). The incidence of new-onset AF increased across the range of body composition indices in men and women (Fig. 2). Strikingly, the majority of the men had a WHR above the cutoff value for obesity, while only the highest quintile of the women had a WHR above the cutoff value. This difference was not seen for BMI. In men, the event rates of new-onset AF by increasing BMI quintiles were up to 9.5 per 1000 person-years. For WHR quintiles, the equivalent AF event rates were up to 9.8 per 1000 person-years. In women, the event rates of new-onset AF by increasing BMI quintiles were up to 6.8 per 1000 person-years. For WHR quintiles, the equivalent AF event rates were up to 6.8 per 1000 person-years. The cumulative hazard increased significantly among sex-specific quintiles of BMI and WHR, logrank $p < 0.001$ for all models (Fig. 3).

The new-onset AF risk gradually increased across the quintiles of body composition indices in both men and women and remained after adjusting for covariates (Table 1A and B, Fig. 4). Men in the highest BMI quintile had a 59% higher new-onset AF risk than those in the lowest quintile, HR: 1.59 (95% CI 1.32–1.91, *p for trend* <0.001). Women in the highest quintile had a 52% higher new-onset AF risk than those in the lowest quintile, HR: 1.52 (95% CI 1.23–1.88, *p for trend* <0.001). Furthermore, men in the highest WHR quintile had a 31% higher new-onset AF risk than those in the lowest quintile, HR: 1.31 (95% CI 1.09–1.57, *p for trend*: 0.01). However, no significant increase in new-onset AF risk was seen in those in the highest WHR quintile compared to those in the lowest quintile, HR: 1.12 (95% CI 0.90–1.41, *p for trend:* 0.17). No interaction was found for sex (*p*: 0.93).

Addition of WHR to the model for BMI per quintile yielded a HR of 1.54 (95% CI 1.26–1.89, p for trend <0.001) for men in the highest BMI quintile, comparable to that obtained from the model without WHR. In women,

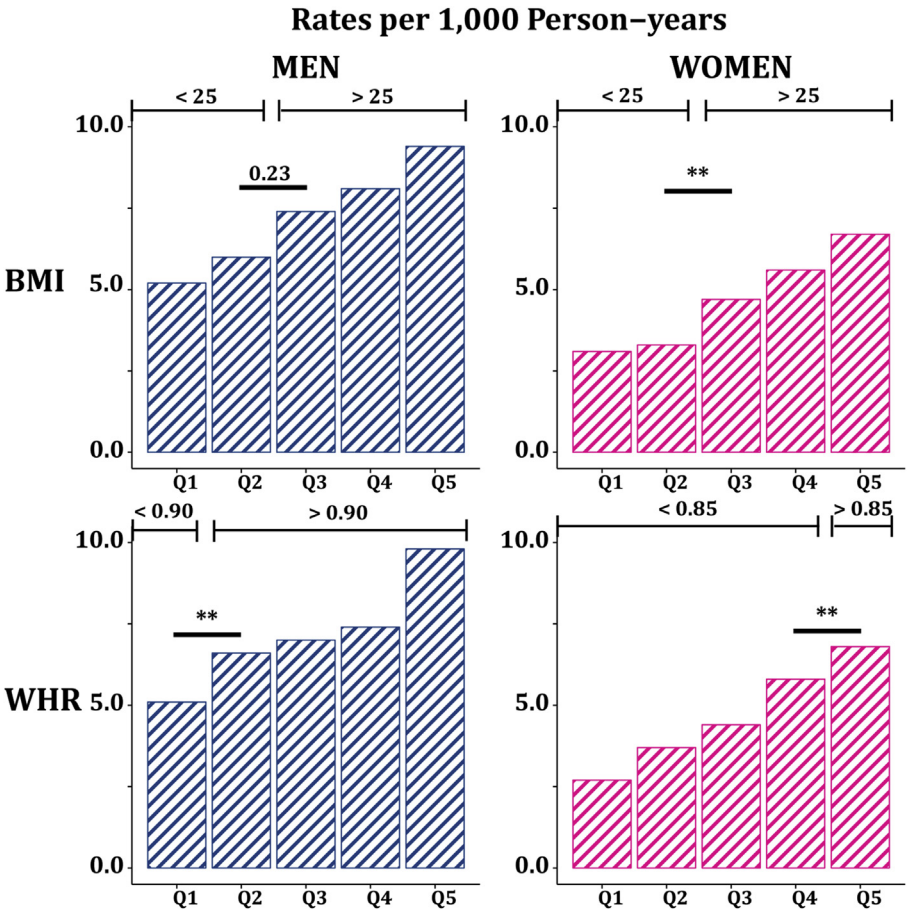

Figure 2 Sex-specific event rates of new-onset atrial fibrillation per 1000 person years by quintiles (Q) of adiposity indices and the sex-specific WHO cut-off values for overweight. Statistical significance was tested between quintiles around the WHO cut-off values for BMI and WHR indicating overweight.

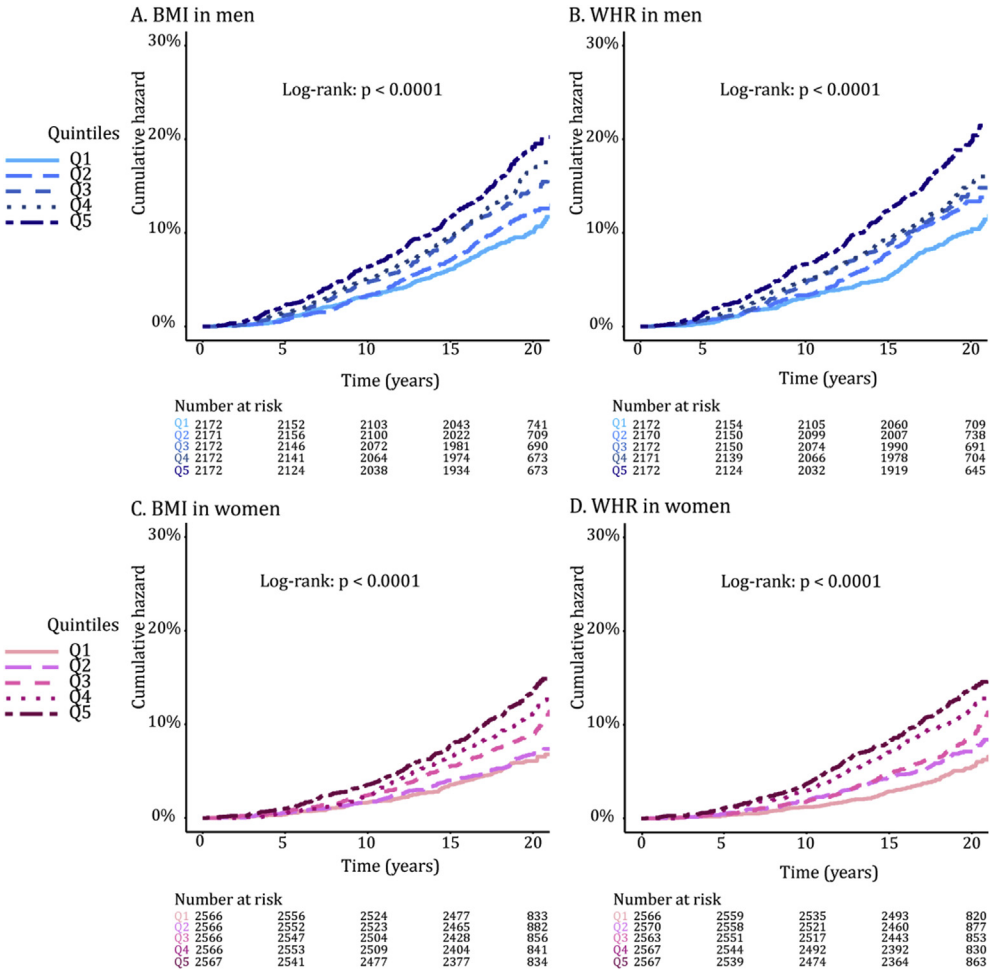

Figure 3 Sex-specific cumulative hazard ratios of new-onset atrial fibrillation by quintiles (Q) of adiposity indices.

however, the addition of WHR increased the risk of new-onset AF for those in the highest BMI quintile, HR of 1.55 (95% CI 1.25–1.93, p for trend <0.001).

Changes in body composition and new-onset AF

A total of 14,010 participants had a second health check and met the inclusion criteria. Participants who completed the second health check showed statistically significant difference, but not clinically relevant, on all baseline characteristics compared with the 9732 participants who only attended the first health check (Supplementary Table 3). Of the participants with a change in body composition, the majority increased to a more unfavorable body composition. The percentages of men and women with a changed BMI or WHR did not show difference when adjusted for the onset of AF (Supplementary Tables 4 and 5).

In men, an increased BMI was not associated with an increased new-onset AF risk, HR highest quartile (increase of >3 BMI units): 1.41 (95% CI 0.93–2.13, *p for trend*: 0.20), but it was associated with a significantly increased AF risk in women, HR highest quartile (increase of >3 BMI units): 1.58 (95% CI 1.09–2.28, *p for trend*: 0.01). Further, an increased WHR was not associated with an increased risk of new-onset AF both in men, HR highest quartile (increase of >0.05 WHR unit): 3.99 (95% CI 0.98–16.14, *p for trend*: 0.27), and in women, HR highest quartile (increase of >0.05 WHR unit): 1.90 (95% CI 0.60–5.98, *p for trend*: 0.38).

Additionally, a decreased BMI was not associated with a decreased new-onset AF risk in men, HR highest quartile (decrease of >3 BMI units): 3.58 (95% CI 0.89–14.46, *p for trend*: 0.59), and in women, HR highest quartile (>3 BMI units decrease): 0.66 (95% CI 0.38–1.13, *p for trend*: 0.85). A decreased WHR was not associated with a decreased new-onset AF risk in men, HR highest quartile (decrease of >0.05 WHR unit): 0.96 (95% CI 0.24–3.88, *p for trend*: 0.55), and in women, HR highest quartile (decrease of >0.05 WHR unit): 1.69 (95% CI 0.42–6.83, *p for trend*: 0.85).

Discussion

In this very large, prospective population study of middle-aged men and women, we found that body composition

Table 1A Unadjusted and adjusted hazard ratio for new-onset atrial fibrillation among 9454 men (1406 cases) per quintile of body composition. Models were adjusted for age, diabetes mellitus, systolic blood pressure thyroid disease and total cholesterol. Person-years calculated with corresponding follow-up duration. HR: hazard ratio, CI: confidence interval. Event rate was calculated as the rate of incident AF per 1000 person-years.

	Men					p-trend
	Weight (kg)					
	Q1 42.8–71.1	Q2 71.1–76.8	Q3 76.8–82.2	Q4 82.2–89.2	Q5 89.2–154	
Number	2174	2141	2190	2191	2176	
AF events	220	257	254	317	358	
Event rate	5.6	6.4	7.2	7.9	9.1	
Person years	39,610	38,731	39,617	39,153	38,450	
Model 1, unadjusted	1.00 (ref)	1.20 (1.00–1.44)	1.16 (0.97–1.39)	1.47 (1.24–1.75)	1.69 (1.43–2.00)	<0.001
Model 2, adjusted	1.00 (ref)	1.24 (1.03–1.49)	1.25 (1.03–1.50)	1.58 (1.32–1.89)	1.90 (1.59–2.25)	<0.001
	BMI (kg/m^2)					p-trend
	Q1 16.1–23.9	Q2 23.9–25.5	Q3 25.5–27.0	Q4 27.0–29.0	Q5 29.0–47.7	
Number	2171	2173	2172	2172	2172	
AF events	207	238	289	313	359	
Event rate	5.2	6.0	7.4	8.1	9.4	
Person years	39,621	39,483	38,987	38,835	38,379	
Model 1, unadjusted	1.00 (ref)	1.16 (0.96–1.39)	1.43 (1.19–1.71)	1.55 (1.30–1.85)	1.81 (1.52–2.15)	<0.001
Model 2, adjusted	1.00 (ref)	1.10 (0.91–1.34)	1.31 (1.09–1.58)	1.41 (1.17–1.69)	1.58 (1.32–1.89)	<0.001
	Waist (cm)					p-trend
	Q1 61.0–88.0	Q2 88.0–93.0	Q3 93.0–97.5	Q4 97.5–103.0	Q5 103.0–180.0	
Number	2149	2111	2231	2222	2154	
AF events	195	229	259	328	393	
Event rate	5.2	6.2	7.0	8.0	9.5	
Person years	39,413	38,336	40,403	39,752	37,566	
Model 1, unadjusted	1.00 (ref) (ref)	1.21 (1.00–1.47)	1.30 (1.08–1.56)	1.69 (1.41–2.01)	2.15 (1.81–2.56)	<0.001
Model 2, adjusted	1.00 (ref) (ref)	1.13 (0.92–1.37)	1.09 (0.90–1.32)	1.33 (1.10–1.60)	1.56 (1.30–1.87)	<0.001
	WHR					p-trend
	Q1 0.58–0.88	Q2 0.88–0.92	Q3 0.92–0.94	Q4 0.94–0.98	Q5 0.98–1.74	
Number	2171	2172	2172	2172	2171	
AF events	204	261	274	290	374	
Event rate	5.1	6.6	7.0	7.5	9.8	
Person years	39,664	39,400	39,118	38,944	38,188	
Model 1, unadjusted	1.00 (ref)	1.29 (1.08–1.55)	1.37 (1.14–1.64)	1.46 (1.22–1.74)	1.93 (1.63–2.29)	<0.001
Model 2, adjusted	1.00 (ref)	1.15 (0.95–1.39)	1.12 (0.93–1.35)	1.15 (0.95–1.38)	1.30 (1.08–1.55)	<0.001

increases the risk of developing new-onset AF, i.e., BMI increases the risk of AF in both men and women. Increased WHR significantly increases the risk of new-onset AF in men but not in women. These findings were supported by the absence of interaction of sex for the indexed measurements WHR and BMI. This discrepancy is explained by the absolute mean waist circumference, which is notably larger in men than in women, yielding a higher WHR in men. Importantly, BMI was similar in both men and women. Further, the absolute number of men with WHR above the cutoff value for obesity was considerably higher than that of women. Body fat in men was thus mainly distributed abdominally. This may reflect that a greater abdominal fat distribution, mainly consisting of visceral fat, is more unfavorable for the risk of AF than a more peripheral fat distribution, thus more subcutaneous fat. Further, an increased risk of developing new-onset AF was found in women when WHR was added to the multivariable model for BMI. This can be interpreted as an increased risk of developing new-onset AF in women with a high BMI is dependent on the body fat distribution. Thus, women with a high BMI and WHR, hence with probably more abdominal fat, have an increased AF risk compared to women with a high BMI and lower WHR, probably meaning more subcutaneous fat. In men, addition of WHR to the model for BMI yielded a comparable risk of developing new-onset AF. Finally, our data showed that a healthy body weight is associated with a lower incidence of new-onset AF.

These outcomes are partly in line with those reported in previous prospective cohort studies [12]. One unit BMI increment has been described to independently increase the risk of new-onset AF by 3–8% [4,19,20]. However, WHR was found to significantly increase the risk of new-onset AF, mainly driven by the cohort of Frost et al. [21]. The current analysis of the EPIC cohort contradicts this,

Table 1B Unadjusted and adjusted hazard ratio for new-onset atrial fibrillation 12,834 women (1100 cases) per quintile of body composition. Models were adjusted for age, diabetes mellitus, systolic blood pressure thyroid disease and total cholesterol. Person-years calculated with corresponding follow-up duration. HR: hazard ratio, CI: confidence interval. Event rate was calculated as the rate of incident AF per 1000 person-years.

	Women					p-trend
	Weight (kg)					
	Q1 36.0–58.4	Q2 58.4–63.6	Q3 63.6–68.8	Q4 68.8–76.4	Q5 76.4–139.2	
Number	2536	2646	2531	2587	2,54	
AF events	164	185	201	254	295	
Event rate	3.4	3.8	4.5	5.4	6.4	
Person years	46,865	48,845	46,545	47,316	46,152	
Model 1, unadjusted	1.00 (ref)	1.08 (0.88–1.34)	1.24 (1.01–1.52)	1.54 (1.27–1.88)	1.84 (1.52–2.23)	<0.001
Model 2, adjusted	1.00 (ref)	1.10 (0.88–1.37)	1.24 (1.00–1.54)	1.45 (1.18–1.78)	1.90 (1.55–2.33)	<0.001
	BMI (kg/m^2)					p-trend
	Q1 15.2–22.7	Q2 22.7–24.6	Q3 24.6–26.5	Q4 26.5–29.3	Q5 29.3–52.7	
Number	2566	2567	2566	2566	2567	
AF events	148	159	220	262	310	
Event rate	3.1	3.4	4.7	5.6	6.7	
Person years	47,445	47,490	47,163	46,906	46,591	
Model 1, unadjusted	1.00 (ref)	1.07 (0.86–1.34)	1.49 (1.21–1.84)	1.80 (1.47–2.20)	2.14 (1.76–2.61)	<0.001
Model 2, adjusted	1.00 (ref)	0.93 (0.73–1.17)	1.17 (0.94–1.45)	1.23 (0.99–1.52)	1.54 (1.25–1.89)	<0.001
	Waist (cm)					p-trend
	Q1 56.0–73.0	Q2 73.0–78.0	Q3 78.0–83.2	Q4 83.2–90.4	Q5 90.4–141.3	
Number	2551	2706	2458	2560	2571	
AF events	109	170	224	260	338	
Event rate	2.6	3.7	4.7	5.8	6.8	
Person years	47,423	50,061	45,153	46,746	46,432	
Model 1, unadjusted	1.00 (ref)	1.48 (1.17–1.88)	2.17 (1.72–2.72)	2.44 (1.95–3.05)	3.21 (2.59–3.98)	<0.001
Model 2, adjusted	1.00 (ref)	1.17 (0.91–1.51)	1.48 (1.16–1.88)	1.41 (1.11–1.79)	1.76 (1.39–2.22)	<0.001
	WHR					p-trend
	Q1 0.60–0.74	Q2 0.74–0.77	Q3 0.77–0.80	Q4 0.80–0.84	Q5 0.84–1.87	
Number	2566	2571	2563	2567	2567	
Person years	47,548	47,486	47,236	46,771	46,565	
AF events	130	175	207	271	317	
Event rate	2.7	3.7	4.4	5.8	6.8	
Model 1, unadjusted	1.00 (ref)	1.35 (1.07–1.70)	1.61 (1.29–2.00)	2.13 (1.73–2.63)	2.51 (2.04–3.07)	<0.001
Model 2, adjusted	1.00 (ref)	1.03 (0.81–1.30)	0.99 (0.80–1.26)	1.13 (0.91–1.42)	1.14 (0.91–1.42)	0.13

as it shows an increased risk in men but rejects WHR as risk stratification in women. In comparison, the participants from both cohorts were comparable depending on body composition measurements. However, the EPIC cohort was followed up for more than six years, and relatively more participants experienced new-onset AF. The latter was not consequently based on the longer follow-up duration, as events occurred evenly during follow-up.

Our results show an association in women between an increased BMI and an increased risk of new-onset AF, but this was not seen in men. Nor was a decrease in BMI associated with a decreased risk in both sexes. Anthropometric measurements may change more drastically over a longer duration, which would have gone undetected with a baseline and 3-year follow-up measurement. Subsequently, this should be considered when interpreting our findings. Of note, the LEGACY study, including patients with AF and a BMI $\geq$27 kg/m^2, found that 45.5% of patients, who lost $\geq$10% body weight, remained free of arrhythmia without antiarrhythmic drugs or ablation during follow-up, compared to 13.4% in patients, who lost <3% or gained weight [22]. Moreover, the ARREST-AF cohort study found that long-term freedom of AF after ablation was improved by weight management [23]. This underlines the role of regulating and sustaining a normal body weight on AF vulnerability.

Obesity induces atrial remodeling, an eminent process in AF pathophysiology [7]. Atrial remodeling can be caused by metabolic dysfunction, a low-grade inflammatory status, and atrial pressure overload, ascribed to a range of local and systemic metabolically active secretions of visceral fat [6,24,25]. Importantly, atrial remodeling is also caused by comorbidities such as hypertension and

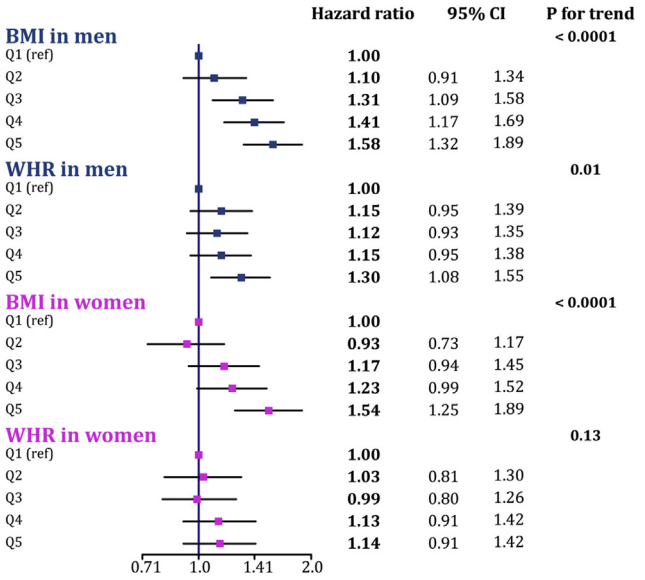

Figure 4 Sex-specific hazard ratios of new-onset atrial fibrillation among 9454 men (1406 cases) and 12,834 women (1100 cases) by quintiles of adiposity indices, adjusted for age, diabetes mellitus, systolic blood pressure, thyroid disease and total cholesterol. CI: confidence interval.

metabolic dysfunction [24]. The current analyses corrected for these comorbidities.

Limitations

First, case certainty was based on medication prescription specific for AF treatment, which has been validated before to be a good assessment of AF prevalence [14]. Importantly, we included patients using anticoagulants or digitalis, reducing the chance to wrongly include or exclude patients. However, of note, with this method, we may have included patients needing anticoagulants for other reasons and, on the other hand, excluded patients with AF without a prescription. Further, this may have led to exclusion of patients suffering from asymptomatic AF. ICD-10 hospital discharge codes were used to confirm AF incidence, which is an accepted method but limited by accurate registration of diagnosis and comorbidities. This may have underestimated the event rate of new-onset AF, concurrently that of important comorbidities. However, our results show a similar incidence as described in literature [1].

Second, overall, the entire EPIC Norfolk population was slightly overweight. As the obesity epidemic has only increased in the last decades, it can be expected that a consecutive generation may be more intensively exposed to risk factors to develop obesity and, consequently, its negative comorbidities [26].

Third, the current analysis is only able to confirm an association between body fat distribution and AF. Adjustments for many covariates known to elevate the risk for new-onset AF were made to assess the influence of body fat distribution. However, it cannot be ruled out that the increased risk of new-onset AF is indirectly based on the influence of mechanistic influence of obesity itself or on the concomitant risk profile, including CVD. Of note, animal studies have suggested a direct casual relation between obesity and new-onset AF [7,25]. Therefore, future studies should assess the causal role of visceral fat in AF pathophysiology in humans.

Conclusion

An increased body mass, described by BMI, is associated with an increased risk of developing new-onset AF in a dose-dependent manner. More abdominal fat distribution, described by WHR, is associated with an increased risk of developing new-onset AF in men but not in women. Our results indicate that more abdominal, likely mainly visceral, fat is associated with the risk of new-onset AF. Thus, future studies should assess the independent and causal role of visceral fat in AF pathophysiology and targets to alter the risk of new-onset AF.

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Appendix A. Supplementary data

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