


ORIGINAL RESEARCH

Body Mass Index in Adolescence and Long-Term Risk of Early Incident Atrial Fibrillation and Subsequent Mortality, Heart Failure, and Ischemic Stroke

Demir Djekic , MD, PhD; Martin Lindgren, MD, PhD; N. David Åberg , MD, PhD; Maria Åberg, MD, PhD; Espen Fengsrud , MD, PhD; Dritan Poci , MD, PhD; Martin Adiels , MS, PhD; Annika Rosengren , MD, PhD

BACKGROUND: We sought to determine the role of obesity in adolescent men on development of atrial fibrillation (AF) and subsequent associated clinical outcomes in subjects diagnosed with AF.

METHODS AND RESULTS: We conducted a nationwide, register-based, cohort study of 1 704 467 men (mean age, 18.3±0.75 years) enrolled in compulsory military service in Sweden from 1969 through 2005. Height and weight, blood pressure, fitness, muscle strength, intelligence quotient, and medical disorders were recorded at baseline. Records obtained from the National Inpatient Registry and the Cause of Death Register were used to determine incidence and clinical outcomes of AF. During a median follow-up of 32 years (interquartile range, 24–41 years), 36 693 cases (mean age at diagnosis, 52.4±10.6 years) of AF were recorded. The multivariable-adjusted hazard ratio (HR) for AF increased from 1.06 (95% CI, 1.03–1.10) in individuals with body mass index (BMI) of 20.0 to <22.5 kg/m² to 3.72 (95% CI, 2.44–5.66) among men with BMI of 40.0 to 50.0 kg/m², compared with those with BMI of 18.5 to <20.0 kg/m². During a median follow-up of ≈6 years in patients diagnosed with AF, we identified 3767 deaths, 3251 cases of incident heart failure, and 921 cases of ischemic stroke. The multivariable-adjusted HRs for all-cause mortality, incident heart failure, and ischemic stroke in AF-diagnosed men with baseline BMI >30 kg/m² compared with those with BMI <20 kg/m² were 2.86 (95% CI, 2.30–3.56), 3.42 (95% CI, 2.50–4.68), and 2.34 (95% CI, 1.52–3.61), respectively.

CONCLUSIONS: Increasing BMI in adolescent men is strongly associated with early AF, and with subsequent worse clinical outcomes in those diagnosed with AF with respect to all-cause mortality, incident heart failure, and ischemic stroke.

Key Words: adolescence and ischemic stroke ■ atrial fibrillation ■ body mass index ■ heart failure ■ mortality

Obesity is a complex metabolic condition defined as an excessive accumulation of body fat and is associated with a range of disorders, including cardiovascular disease.^{1–4} Individuals with a body mass index (BMI) of >30 kg/m² are classified as obese, those with a BMI of 35 to >40 kg/m² are classified as severely obese, and those with a BMI of >40 kg/m² are classified as morbidly obese.

In 2016, >650 million individuals, equivalent to 12% of the world's population, were estimated to be obese.⁵

The prevalence of obesity has approximately tripled during the past 50 years, and it is anticipated that by 2025, 33 of 53 European countries will reach an obesity prevalence exceeding 20%, with increasing rates in children and adolescents.^{5–7} In Swedish adolescent men, the prevalence of severe and morbid obesity increased from 0.1% in 1969 to 1974 to 1.1% in 1996 to 2005.⁸ Accordingly, with unprecedented numbers of young people overweight and obese, there is an urgent need to address the long-term consequences.

Correspondence to: Demir Djekic, MD, PhD, Department of Cardiology, Sahlgrenska University Hospital/Östra, Diagnosvägen 11, 416 85 Gothenburg, Sweden. Email: demir.djekic@vgregion.se

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CLINICAL PERSPECTIVE

What Is New?

- In adolescent men, increased risk of future atrial fibrillation (AF) started already at low-normal body mass index and continued to increase with increasing body mass index.
- Adolescent men with severe or morbid obesity, corresponding to body mass index levels $>35\text{ kg/m}^2$, had a 3- to 4-fold increased risk of AF in early adulthood (mean age at diagnosis, 43.4 years).
- The risk for all-cause mortality, heart failure, and ischemic stroke among men diagnosed with AF in adulthood was strongly associated with body mass index in adolescence.

What Are the Clinical Implications?

- Assessment of long-standing and early-onset obesity among men diagnosed with AF could help to identify individuals with a particularly high risk of clinical outcomes, such as all-cause mortality, heart failure, and ischemic stroke.
- A more vigilant monitoring of obese individuals may be warranted in patients with AF, and these issues should be addressed in future randomized studies.

Nonstandard Abbreviations and Acronyms

IS	ischemic stroke
W_{\max}	maximum work capacity

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults worldwide, with 43.6 million diagnosed in 2016, equivalent to a prevalence of 2% to 4%, and is more common in elderly individuals and in men.⁹ Individuals with AF are at a 1.5- to 3.5-fold risk of death, with about 21% of those deaths attributed to heart failure (HF) and ischemic stroke (IS).^{9–12} Studies have shown lower rates of all-cause mortality in obese subjects with AF, a phenomenon known as the “obesity paradox.”^{13,14} The observed obesity paradox that emerged from these studies may potentially be related to an older and sicker study population. Recent data from a prospective cohort of middle-aged patients with AF did not show obesity to be associated with higher risk of poor clinical outcomes.¹⁵ Other studies have suggested both overweight and obesity as a risk factor for death and a composite end point of IS, thromboembolism, and death, but not for HF or IS alone, in patients with AF.¹⁶ Accordingly, there is a need for

further studies in this area, in particular among those diagnosed already when young, where a double burden of early obesity and AF may theoretically be more harmful than AF alone.

In this long-term cohort study, we aimed to establish the relationship of BMI in adolescence with later diagnosis of AF using a nationwide register of men enrolled in compulsory military service in Sweden. A further goal was to determine the influence of adolescent overweight and obesity on clinical outcomes in individuals later diagnosed with AF.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Data of conscripts ($n=1\,918\,466$) into military service from 1969 through 2005 were drawn from the Swedish Military Service Conscript Register (Figure S1). Military service was mandatory in Sweden until 2005, except for prison inmates, those with severe medical conditions, or those with functional disability ($\approx 2\%–3\%$ annually). The personal identity number was reused for some enlistees; these were excluded ($n=1154$). Women ($n=10\,228$), men aged <15 and >40 years ($n=14\,204$), and those with missing BMI data ($n=188\,274$) were excluded from the analysis. We also excluded a limited number of subjects with BMI $>50\text{ kg/m}^2$ ($n=139$) because there might have been errors in registering their weight or height.

All military conscripts underwent a 2-day assessment at 1 of 6 centers in Sweden.² The assessment protocols were performed according to standard procedures and included measures of weight, height, and blood pressure and evaluation of cognition, cardiorespiratory fitness, and muscle strength. A global intelligence score (intelligence quotient [IQ]) was obtained from the cognitive evaluations and used as a proxy for general cognitive ability. The test results were standardized and transformed to Standard Nine (stanine) scores 1 to 9.

A bicycle ergometric test was performed to evaluate cardiorespiratory fitness. Briefly, 5 minutes of submaximal exercise was performed at work rate of 75 to 175 W, depending on the body weight.¹⁷ The work rate was continuously increased by 25 W/min until limited by exhaustion. The final work rate (maximum work capacity [W_{\max}]) was recorded and divided by kilograms (W_{\max}/kg). This measure was used because W_{\max}/kg yielded a better correlation with maximum oxygen consumption (correlation coefficient of ≈ 0.9) than the predicted maximum oxygen consumption (correlation coefficient

of 0.6–0.7).¹⁸ The resulting value (W_{\max}/kg) served as a measure of cardiorespiratory fitness. W_{\max}/kg was recorded as raw data for the conscription in years 1972 through 2005. No raw data were recorded for the conscripts performing at the lowest 3 fitness levels (=stanines) in years 2000 through 2005. For the rest of the years, these conscripts were categorized into the lowest fitness group.² From 1969 through 1971, raw data were not recorded, but the values of W_{\max}/kg were converted to 9 levels that served as a measure of fitness. Isometric muscle strength was measured by hand grip, elbow flexion, and knee extension. Weighted values were integrated into an overall estimate in kiloponds until April 1, 1979, and in Newtons after that date.¹⁹ Test results were standardized against data from previous years, resulting in scores from 1 to 9 (low to high).

The Longitudinal Integration Database for Health Insurance and Labour Market was used to obtain data about the highest completed level of parental education, available for 80% of the study population and stratified into ≤ 9 , 10 to 12, and >12 years.

Outcomes

Data were obtained from the Swedish National Inpatient Registry, recording hospital inpatient and outpatient visits or discharge. The coverage of inpatient discharge increased during the period from 1970 through 1986 and is complete since 1987, with outpatient visits recorded from 2001. AF cases and clinical outcomes (IS and HF) after a recorded case of AF were identified according to the *International Classification of Diseases, Eighth Revision (ICD-8)*, *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Classification of Diseases, Tenth Revision (ICD-10)*, and linked to the Hospital Register and Cause of Death Register through the Swedish 12-digit personal identity number with diagnoses coded as in both main and secondary diagnosis (Table S1). We were unable to differentiate between various subtypes of AF, such as paroxysmal, persistent, or permanent AF as well as atrial flutter.

Statistical Analysis

Enlistee records were reviewed from date of conscription until an initial AF diagnosis, death, emigration, or December 31, 2019, whichever occurred first (14–50 years). Men with a registered AF diagnosis during follow-up formed a subcohort that was followed up with respect to clinical outcomes, including all-cause mortality, HF, and IS.

Unadjusted incidence rates and 95% Poisson CIs (exact) were calculated. Cox regression was used to estimate the association of BMI in adolescence with risk of future AF. To not underestimate the true risk

associated with high adolescent BMI, we did not adjust for interim diagnoses of comorbidities, such as hypertension and diabetes, conditions that are strongly associated with elevated BMI and involved in the pathophysiological mechanism of AF. BMI was classified as <18.5 , 18.5 to <20.0 , 20.0 to <22.5 , 22.5 to <25.0 , 25.0 to <27.5 , 27.5 to <30.0 , 30.0 to <35.0 , 35 to <40.0 , and 40.0 to 50.0 kg/m^2 . For Cox regressions of BMI and subsequent clinical outcomes, BMI “normal” reference was set at $<20.0\text{ kg/m}^2$, contrasting to the more traditional definition of normal BMI of 18.5 to 20 kg/m^2 ⁵ because of the near-continuous increase in risk of AF from low BMI values observed in prior analyses from this cohort.²⁰

Subjects who developed AF were followed up until a clinical cardiovascular outcome of death, HF, or IS. Incidence rates and corresponding 95% CIs for clinical events were calculated with Poisson regression. Cox regression was used to estimate the association of adolescent BMI with future hospitalization for clinical outcomes in patients with AF. This analysis included fewer subject groups with BMI <20.0 (reference), 20.0 to <25.0 , 25.0 to <30.0 , and $>30.0\text{ kg/m}^2$, because relatively few clinical outcomes developed in those exhibiting the most extreme obesity.

Systolic blood pressure was stratified into 100 to 119, 120 to 125, 126 to 130, 131 to 138, and 139 to 180 mmHg, and diastolic blood pressure was stratified as 40 to 59, 60 to 65, 66 to 70, 71 to 76, and 77 to 100 mmHg. Cardiorespiratory fitness was categorized as low,^{1–4} moderate,^{5–7} or high,^{8,9} and muscle strength was categorized as low,^{1–3} moderate,^{4–6} or high.^{7–9} Parental education was classified as ≤ 9 , 10 to 12, or >12 years.

Differences among conscription centers, conscription years, and age at conscription were adjusted for as potential confounders. Spline plots were produced with BMI as a restricted cubic spline with knots placed at 5% (18.1 kg/m^2), 35% (19.9 kg/m^2), 65% (23.2 kg/m^2), and 95% (27.2 kg/m^2). Year of conscription was included in the spline with knots placed at 5% (1972), 35% (1979), 65% (1994), and 95% (2002). Effects of interactions of BMI with other variables on the incidence of AF were tested with BMI as a continuous variable. Systolic and diastolic blood pressure, cardiorespiratory fitness, muscle strength, parent education, baseline diabetes, hypertension, and congenital heart disease were analyzed as factors. The unadjusted models are presented in Figures S2 through S5.

Random forest, a robust and nonparametric machine learning statistical method that optimizes predictive accuracy by fitting an ensemble of trees, was used to study the interactions among baseline risk factors on clinical outcomes in patients with AF.²¹ Finally, to aid interpretation of the random forest results, partial dependence plots were produced to show the interaction

effects among the most important cardiovascular risk factors.

Data were prepared with SAS version 9.4 (SAS Institute, Cary, NC), and statistical analyses were conducted using R software version 3.4.2 (dplyr, moonBook, ggplot, caret, rms, plotmo, and survival packages; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Approval

The regional ethical review board of Gothenburg approved the study (registration number 567-15), which conformed to the principles outlined in the Declaration of Helsinki. Informed consent was not required because data were not collected for a research purpose.

RESULTS

Study Population and Follow-Up

Table 1 shows the characteristics of the 1 704 467 men in the study (mean age, 18.3 ± 0.75 years) after exclusions (Figure S1); 8.1% were underweight (BMI $<18.5 \text{ kg/m}^2$), 79.5% were normal weight (BMI 18.5 – $<25 \text{ kg/m}^2$), 10.0% were overweight (BMI 25 to $<30 \text{ kg/m}^2$), 1.8% were obese, 0.4% were severely obese, and 0.1% were morbidly obese (Table 1). There were no major differences in age or height among the BMI categories of the subjects. Systolic and diastolic blood pressure increased slightly with BMI. The proportion of subjects with low cardiorespiratory fitness, muscle strength, and IQ was higher in obese, compared with normal weight, men. Few comorbidities were present at baseline, but in the 2 most obese categories, 1% to 2% were diagnosed with hypertension already at conscription.

During a median follow-up of 32 years, 36 693 men were registered with a diagnosis of AF (Table S2). The number of AF cases in the total cohort was 68 per 100 000 observed person-years, increasing from 61 per 100 000 person-years in those with BMI of 18.5 to $<20 \text{ kg/m}^2$ to 131 per 100 000 person-years in the BMI group of 40 to 50 kg/m^2 (Table S2). The median age of AF diagnosis in the total cohort was 52.4 years, decreasing from a median of 54 years at AF diagnosis for those with BMI of 18.5 kg/m^2 to 43.4 years in the BMI group of 40 to 50 kg/m^2 .

Risk of AF

The cumulative incidence rate of AF after a maximum 50-year follow-up until December 31, 2019, was 20% among men fulfilling criteria for obesity at baseline, 12.4% in overweight men, and 8.3% in those with BMI 20 to $<25 \text{ kg/m}^2$, compared with 6.5% in men with BMI $<20 \text{ kg/m}^2$ (Figure 1A).

Compared with the BMI reference of 18.5 to $<20.0 \text{ kg/m}^2$, the adjusted risk for AF at low-normal BMI levels of 20.0 to $<22.5 \text{ kg/m}^2$ was hazard ratio (HR) of 1.06 (95% CI, 1.03–1.10) and this increased gradually to 3.72 (95% CI, 2.44–5.66) at BMI of 40 to 50 kg/m^2 (Figure 1B and Table 2). The multivariable-adjusted HR showed a 6.4% higher risk of AF (HR, 1.064 [95% CI, 1.059–1.068]) for each kg/m^2 increase in BMI.

In the multivariable-adjusted models, age, year of conscription, systolic blood pressure, cardiorespiratory fitness, IQ, and baseline comorbidities were independent predictors of AF (Table S3). There were significant negative interactions between BMI and IQ (ie, the effect of high BMI on risk of AF was attenuated in subjects with high compared with low IQ). In contrast, we found positive interactions between BMI and muscle strength and adult congenital heart disease (namely, the effect of high BMI on the risk of AF was increased in subjects with higher muscle strength or in those with adult congenital heart disease) (Table S3).

Event Rates and Risk of Clinical Outcomes in Subjects With AF

Among men diagnosed with AF ($n=36 693$), there were 3767 deaths, representing 13.2 cases per 1000 person-years (Table S4), increasing from 13.0 per 1000 person-years in subjects with BMI $<20 \text{ kg/m}^2$ to 22.6 per 1000 person-years for BMI $>30 \text{ kg/m}^2$. Similarly, 3251 men developed HF, and 921 developed IS (Table S4). The number of cases per 1000 person-years was 11.7 for HF and 3.4 for IS in those with AF. The figures per 1000 person-years in subjects with a BMI $<20 \text{ kg/m}^2$ were 11.8 for HF and 3.6 for IS compared with 19.2 and 5.4, respectively, for BMI $>30 \text{ kg/m}^2$.

All-cause mortality after a maximum 10-year follow-up after AF index diagnosis was 19.1% in obese subjects, 16.8% in overweight subjects, and 11.4% in those with BMI 20 to $<25 \text{ kg/m}^2$, compared with 11.7% in men with BMI $<20 \text{ kg/m}^2$. The corresponding cumulative incidence of HF was 12.2% in obese subjects, 8.7% in overweight subjects, and 5.1% in those with BMI 20 to $<25 \text{ kg/m}^2$, compared with 5.2% in men with BMI $<20 \text{ kg/m}^2$; and for IS, the values were 4.8%, 3.8%, 3.0%, and 3.2%, respectively.

The risk for all-cause mortality, incident HF, and IS gradually increased with increasing BMI levels in subjects diagnosed with AF (Figure 2). The multivariable-adjusted HR for all-cause mortality was 2.86 (95% CI, 2.30–3.56) in individuals with BMI $>30 \text{ kg/m}^2$ in adolescence compared with those having BMI levels $<20 \text{ kg/m}^2$ (Table 3), with an 8.8% higher risk of all-cause mortality per BMI unit. Obese and overweight subjects showed a significantly higher multivariable-adjusted HR for incident HF (HR, 3.42 [95% CI, 2.50–4.68] and HR, 2.17 [95% CI, 1.73–2.72], respectively) compared

Table 1. Baseline Characteristics of Study Population Relative to BMI

Characteristic	BMI <18.5 kg/m ²	BMI 18.5–<20.0 kg/m ²	BMI 20.0–<22.5 kg/m ²	BMI 22.5–<25.0 kg/m ²	BMI 25.0–<27.5 kg/m ²	BMI 27.5–<30.0 kg/m ²	BMI 30.0–<35.0 kg/m ²	BMI 35.0–<40.0 kg/m ²	BMI 40.0–50.0 kg/m ²
All	1 704 467 (100)	307 135 (18.0)	687 070 (40.3)	362 485 (21.3)	126 193 (7.4)	44 592 (2.6)	30 800 (1.8)	62 444 (0.4)	1302 (0.1)
Men, n (%)	1 704 467 (100)	307 135 (18.0)	687 070 (40.3)	362 485 (21.3)	126 193 (7.4)	44 592 (2.6)	30 800 (1.8)	62 444 (0.4)	1302 (0.1)
Age, mean (SD), y	18.3 (0.8)	18.3 (0.7)	18.3 (0.7)	18.4 (0.9)	18.4 (1.0)	18.4 (0.9)	18.4 (0.8)	18.4 (0.8)	18.4 (0.9)
Height, mean (SD), cm	179 (6.6)	179 (6.6)	179 (6.5)	179 (6.6)	179 (6.6)	179 (6.8)	179 (6.8)	180 (6.8)	179 (7.0)
Weight, mean (SD), kg	70.4 (11.1)	62.2 (4.8)	68.3 (5.4)	75.6 (6.0)	83.5 (6.6)	91.8 (7.4)	102.6 (9.1)	118.8 (10.0)	135.9 (11.9)
BMI, mean (SD), kg/m ²	21.9 (3.1)	19.3 (0.4)	21.2 (0.7)	23.6 (0.7)	26.1 (0.7)	28.6 (0.7)	31.9 (1.4)	36.8 (1.4)	42.4 (2.1)
Systolic BP, mean (SD), mmHg	128.5 (11.1)	126.6 (10.9)	128.2 (10.9)	129.9 (10.9)	131.3 (10.9)	132.5 (11.3)	133.9 (11.1)	136.2 (11.7)	137.9 (13.7)
Diastolic BP, mean (SD), mmHg	67.6 (9.9)	67.3 (9.7)	67.4 (9.8)	67.7 (9.9)	68.5 (10.1)	69.3 (10.4)	70.5 (10.6)	72.6 (11.0)	74.3 (12.2)
W _{max} , mean (SD)	251.7 (96.5)	225.3 (95.3)	254.8 (94.8)	276.6 (91.8)	278.8 (88.9)	275.8 (84.9)	272.8 (82.9)	267.7 (83.8)	256.5 (83.9)
W _{max} /kg, mean (SD)	3.2 (1.8)	3.0 (1.9)	3.7 (1.4)	3.7 (1.2)	3.4 (1.1)	3.0 (0.9)	2.7 (0.82)	2.3 (0.7)	1.9 (0.6)
Cardiorespiratory fitness, n (%)									
Low (1–4)	258 951 (15.8)	42 847 (32.5)	69 133 (10.4)	36 212 (10.4)	23 620 (19.6)	14 797 (35.0)	15 040 (53.9)	33 32 (72.4)	615 (82.8)
Moderate (5–6)	799 867 (48.7)	170 421 (57.2)	320 911 (48.2)	150 854 (43.1)	55 917 (46.3)	18 186 (43.0)	87 57 (31.4)	82 3 (17.9)	77 (10.4)
High (7–9)	583 072 (35.5)	15 094 (11.5)	276 043 (41.4)	162 622 (46.5)	41 167 (34.1)	9 291 (22.0)	4 094 (14.7)	448 (9.7)	51 (6.9)
Muscle strength, n (%)									
Low (1–3)	235 891 (14.1)	67 079 (43.6)	73 146 (10.8)	23 255 (6.5)	7 992 (6.5)	3 003 (6.9)	2 086 (7.1)	419 (8.1)	114 (12.4)
Moderate (4–6)	946 216 (56.5)	203 875 (67.4)	416 908 (61.6)	170 486 (47.8)	52 006 (42.0)	17 485 (40.1)	11 129 (37.8)	18 79 (36.2)	332 (36.1)
High (7–9)	491 679 (29.4)	3867 (2.9)	186 638 (27.6)	162 753 (45.7)	63 898 (51.57)	23 166 (53.1)	16 232 (55.1)	2897 (55.8)	475 (51.6)
IQ, n (%)									
Low (1–3)	340 882 (20.4)	30 658 (22.6)	124 952 (18.5)	70 930 (19.9)	29 928 (24.2)	12 359 (28.3)	9 107 (30.7)	19 31 (34.6)	422 (39.0)
Moderate (4–6)	915 535 (54.7)	70 704 (52.1)	370 363 (54.8)	199 738 (56.1)	69 491 (56.2)	24 004 (55.0)	16 258 (54.8)	29 46 (52.8)	546 (50.5)
High (7–9)	417 656 (25.0)	34 319 (25.3)	180 851 (26.8)	85 372 (24.0)	24 279 (19.6)	7 250 (16.6)	4 318 (14.6)	708 (12.7)	114 (10.5)
Parental education, n (%)									
≤9y	226 062 (16.2)	20 849 (19.1)	89 673 (15.9)	45 515 (15.2)	16 277 (15.6)	5 902 (15.9)	3 903 (15.2)	7 31 (13.9)	172 (15.4)
10–12y	865 245 (62.1)	66 138 (60.7)	343 571 (61.0)	189 310 (63.0)	68 948 (65.9)	25 177 (68.0)	18 081 (70.4)	38 83 (73.5)	803 (71.9)
>12y	301 594 (21.7)	21 946 (20.2)	129 807 (23.1)	65 610 (21.8)	19 377 (18.5)	5 955 (16.1)	3 683 (14.4)	6 65 (12.6)	142 (12.7)
Diagnosis at baseline, n (%)									
ACh	2469 (0.2)	235 (0.2)	937 (0.1)	543 (0.2)	187 (0.2)	75 (0.2)	58 (0.2)	10 (0.2)	1 (0.1)
Diabetes	1331 (0.1)	89 (0.1)	532 (0.1)	341 (0.1)	116 (0.1)	29 (0.1)	24 (0.1)	11 (0.2)	0 (0.0)
Hypertension	2825 (0.2)	115 (0.1)	860 (0.1)	654 (0.2)	376 (0.3)	229 (0.5)	223 (0.7)	77 (1.3)	23 (1.8)

ACh indicates adult congenital heart disease; BMI, body mass index; BP, blood pressure; IQ, intelligence quotient; and W_{max}, maximum work capacity.

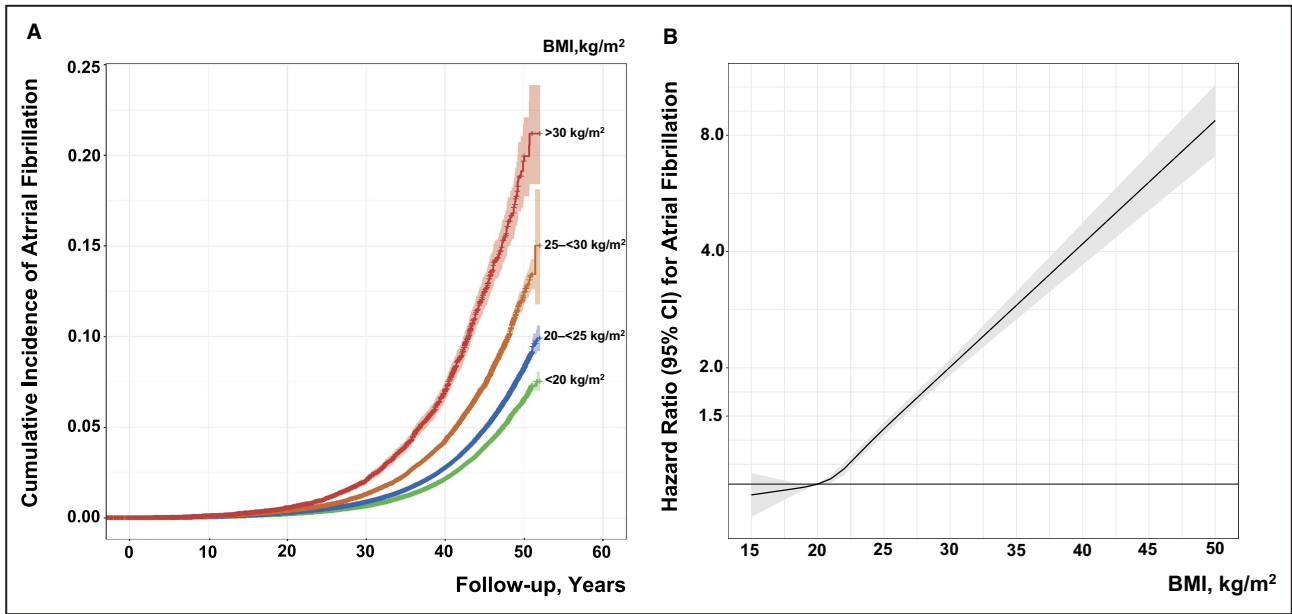


Figure 1. A, Cumulative incidence of atrial fibrillation with respect to body mass index (BMI) group. B, Association of BMI at conscription into military service with risk of early-onset atrial fibrillation. The model was adjusted for age, conscription year as a spline with knots at 5%, 25%, 75%, and 95% (1972, 1979, 1994, and 2002), test center, systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and baseline comorbidities (diabetes, hypertension, and adult congenital heart disease) (n=1 287 197). BMI of 15 to 50 kg/m² was modeled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (18.1, 19.9, 23.2, and 27.2 kg/m²) with BMI of 20 kg/m² as reference.

with subjects with BMI levels <math><20\text{ kg/m}^2</math>. In similarly adjusted models, those subjects with AF with BMI >math>30\text{ kg/m}^2</math> at baseline exhibited a higher risk of developing IS (HR, 2.34 [95% CI, 1.52–3.61]) compared with those with BMI levels <math><20\text{ kg/m}^2</math>.

To visualize the complex interaction effects of BMI with the most important risk factors, we constructed 3-dimensional partial dependence plots. We found the

interaction effects between BMI and IQ and systolic and diastolic blood pressure on all-cause mortality and incident HF (Figure 3). The probability of all-cause mortality in subjects with AF gradually increased with lower IQ, and higher systolic and diastolic blood pressure (Figure 3A). Similar trends were observed for incident HF (Figure 3B); however, for subjects with high BMI levels, the probability for incident HF was high,

Table 2. HRs (95% CIs) for AF Relative to BMI Group

Variable	Model 1*	Model 2†	Model 3‡	Model 4§
Events/population	36 693/1 704 466	36 275/1 614 868	36 126/1 587 607	24 897/1 297 909
BMI <math><18.5\text{ kg/m}^2</math>	0.94 (0.90–0.98)	0.94 (0.90–0.98)	0.99 (0.95–1.04)	1.00 (0.95–1.06)
BMI $18.5\text{--}20.0\text{ kg/m}^2$	1.00	1.00	1.00	1.00
BMI $20.0\text{--}22.5\text{ kg/m}^2$	1.15 (1.12–1.19)	1.14 (1.11–1.18)	1.09 (1.05–1.12)	1.06 (1.03–1.10)
BMI $22.5\text{--}25.0\text{ kg/m}^2$	1.43 (1.39–1.48)	1.41 (1.36–1.46)	1.29 (1.24–1.33)	1.23 (1.18–1.28)
BMI $25.0\text{--}27.5\text{ kg/m}^2$	1.74 (1.66–1.81)	1.69 (1.62–1.77)	1.55 (1.48–1.62)	1.45 (1.37–1.54)
BMI $27.5\text{--}30.0\text{ kg/m}^2$	2.28 (2.14–2.42)	2.19 (2.06–2.33)	2.03 (1.91–2.16)	1.87 (1.73–2.02)
BMI $30.0\text{--}35.0\text{ kg/m}^2$	2.91 (2.71–3.11)	2.76 (2.58–2.96)	2.56 (2.39–2.75)	2.39 (2.19–2.61)
BMI $35.0\text{--}40.0\text{ kg/m}^2$	3.75 (3.24–4.33)	3.64 (3.14–4.22)	3.41 (2.93–3.97)	2.80 (2.30–3.40)
BMI $40.0\text{--}50.0\text{ kg/m}^2$	4.70 (3.44–6.41)	4.39 (3.13–6.15)	4.30 (3.05–6.06)	3.72 (2.44–5.66)
Per unit BMI	1.083 (1.080–1.087)	1.080 (1.077–1.084)	1.071 (1.068–1.075)	1.064 (1.059–1.068)

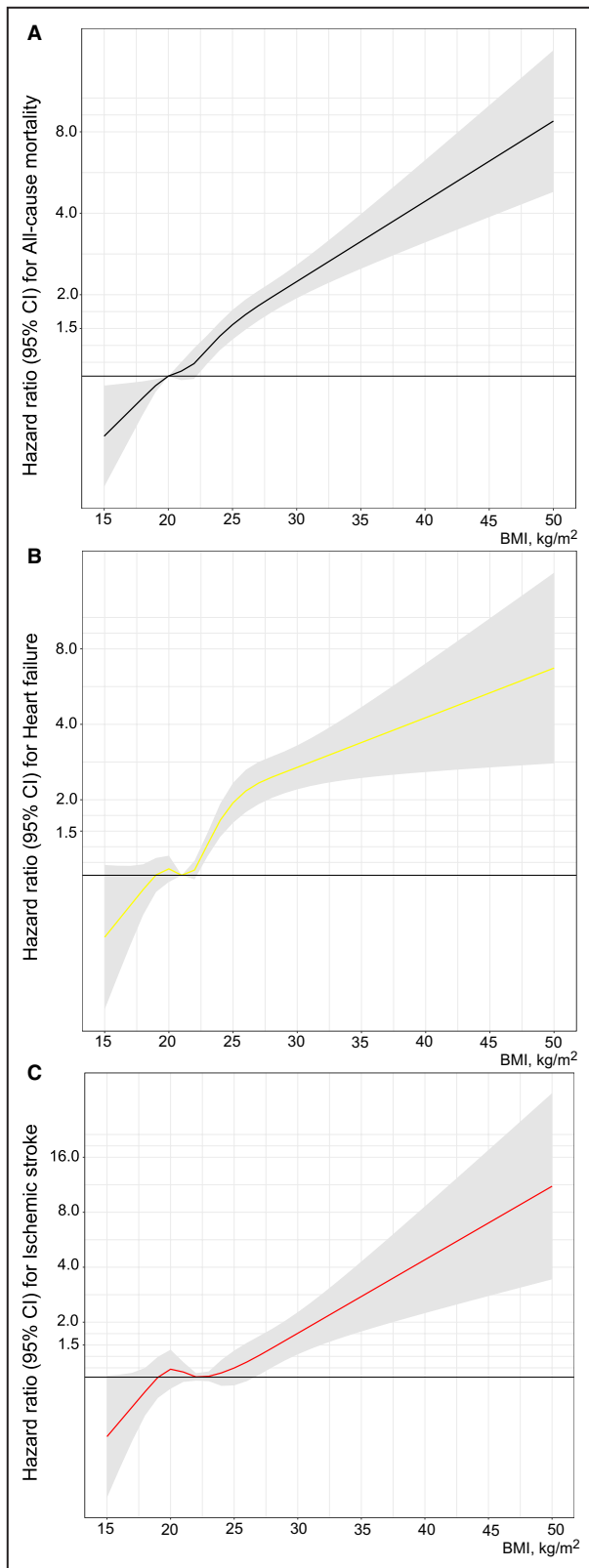
The HRs were derived from Cox regressions (Methods) with different models of adjustments as follows. AF indicates atrial fibrillation; BMI, body mass index; and HR, hazard ratio.

*Model 1 adjusted for age at conscription, conscription year, and test center.

†Model 2 as model 1, additionally adjusted for systolic and diastolic blood pressure at baseline, and baseline comorbidities diabetes, hypertension, and adult congenital heart disease.

‡Model 3 as model 2, additionally adjusted for cardiorespiratory fitness and muscle strength.

§Model 4 as model 3, additionally adjusted for parental education and intelligence quotient.



independent of IQ and blood pressure. There were no significant interactions among BMI and risk factors on IS (data not shown).

Figure 2. Association of adolescent body mass index (BMI) diagnosed with atrial fibrillation with mortality and clinical outcome in early adulthood.

Risk of all-cause mortality (A), heart failure (B), and ischemic stroke (C) in patients with atrial fibrillation relative to BMI. The models were adjusted for age, conscription year as a spline with knots at 5%, 25%, 75%, and 95% (years 1970, 1972, 1982, and 1992), test center, systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and baseline comorbidities (diabetes, hypertension, and congenital heart disease). BMI of 15 to 50 kg/m² was modeled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (18.1, 20.0, 23.5, and 28.0 kg/m²) with BMI of 20 kg/m² as reference for all-cause mortality, 21 kg/m² for heart failure, and 22.5 kg/m² for ischemic stroke.

DISCUSSION

In this large nationwide long-term study, elevated BMI in adolescence was associated with increased risk of AF in adulthood in comparatively young men. An increased risk was observed already at mildly elevated BMI within the normal range, with a 3- to 4-fold increase in risk among men with severe or morbid obesity, corresponding to BMI levels >35 kg/m², suggesting a causal role of adiposity on pathophysiological processes leading to AF. In addition, our data also suggest that adolescent obesity is prognostic of poorer outcomes in subjects later diagnosed with AF with respect to all-cause mortality, HF, and IS. Investigating the true association of obesity with AF is challenging because of the complex interactions of obesity with other factors associated with AF, such as poor diet, low physical activity, hypertension, diabetes, smoking, elevated blood lipids, and sleep apnea.⁹ However, young obese individuals may not have accumulated these risk factors to the same extent as older cohorts, and the present study cohort accordingly provides a valuable opportunity to investigate the impact of obesity per se on AF. We found that age, year of conscription, systolic blood pressure, cardiorespiratory fitness, IQ, and baseline comorbidities, such as hypertension and adult congenital heart disease, in adolescence were additional factors associated with development of AF in adulthood, but the relationship with BMI in adolescence persisted independent of these factors and comorbidities.

An increased risk of AF in obese subjects has been a consistent finding of several register- and population-based prospective cohort studies.^{16,20,22,23} In the prospective Danish Diet, Cancer, and Health Study of 47 589 randomly selected participants aged 50 to 64 years followed up for 5.7 years, 553 subjects developed AF or flutter.¹⁶ The adjusted HR for AF in obese, compared with normal weight, men was 2.35 (95% CI, 1.70–3.25), with each SD increment of BMI significantly related to incident AF (HR, 1.08). A prospective study from Sweden of 4021 subjects aged 60 years, with a

Table 3. HRs (95% CIs) for Clinical Outcomes in Patients With AF Relative to BMI Group

Variable	Model 1*	Model 2†	Model 3‡	Model 4§
All-cause mortality				
Events/population, n	3767/36 459	3742 /36 041	3735/35 892	2145/24 757
BMI <20.0kg/m ²	1.00	1.00	1.00	1.00
BMI 20–<25.0kg/m ²	1.01 (0.93–1.09)	1.01 (0.93–1.09)	1.25 (1.15–1.35)	1.26 (1.13–1.41)
BMI 25–<30.0kg/m ²	1.62 (1.46–1.80)	1.60 (1.43–1.78)	2.02 (1.80–2.26)	2.11 (1.81–2.45)
BMI ≥30kg/m ²	2.12 (1.82–2.49)	2.10 (1.79–2.47)	2.50 (2.12–2.97)	2.86 (2.30–3.56)
Per unit BMI	1.063 (1.053–1.072)	1.063 (1.053–1.072)	1.081 (1.071–1.091)	1.088 (1.074–1.010)
Heart failure				
Events/population, n	1648/34 534	1629/34 131	1626/33 983	956/23 568
BMI <20.0kg/m ²	1.00	1.00	1.00	1.00
BMI 20–<25.0kg/m ²	1.08 (0.96–1.22)	1.08 (0.95–1.22)	1.28 (1.12–1.46)	1.22 (1.03–1.45)
BMI 25–<30.0kg/m ²	1.87 (1.59–2.19)	1.86 (1.58–2.19)	2.28 (1.92–2.71)	2.17 (1.73–2.72)
BMI ≥30kg/m ²	3.04 (2.44–3.79)	2.88 (2.29–3.63)	3.40 (2.68–4.32)	3.42 (2.50–4.68)
Per unit BMI	1.085 (1.071–1.099)	1.083 (1.068–1.098)	1.099 (1.084–1.114)	1.104 (1.084–1.125)
Ischemic stroke				
Events/population, n	921/35 025	917/34 616	916/34 468	550/ 23846
BMI <20.0kg/m ²	1.00	1.00	1.00	1.00
BMI 20–<25.0kg/m ²	0.95 (0.82–1.11)	0.93 (0.80–1.08)	1.08 (0.92–1.27)	1.09 (0.88–1.34)
BMI 25–<30.0kg/m ²	1.21 (0.97–1.52)	1.15 (0.91–1.44)	1.37 (1.07–1.74)	1.29 (0.93–1.78)
BMI ≥30kg/m ²	1.88 (1.36–2.60)	1.74 (1.25–2.43)	1.99 (1.40–2.81)	2.34 (1.52–3.61)
Per unit BMI	1.040 (1.021–1.061)	1.034 (1.014–1.055)	1.052 (1.031–1.074)	1.058 (1.030–1.086)

The HRs were derived from Cox regressions (Methods) with different models of adjustments as follows. AF indicates atrial fibrillation; BMI, body mass index; and HR, hazard ratio.

*Model 1 adjusted for age at conscription, conscription year, and test center.

†Model 2 as model 1, additionally adjusted for systolic and diastolic blood pressure at baseline, and baseline comorbidities diabetes, hypertension, adult congenital heart disease, and heart failure.

‡Model 3 as model 2, additionally adjusted for cardiorespiratory fitness and muscle strength.

§Model 4 as model 3, additionally adjusted for parental education and intelligence quotient.

mean follow-up of 13.6 years and 285 cases of incident AF, revealed obesity to be associated with an ≈2-fold risk of AF, regardless of whether metabolic syndrome was present or not.²²

A previous study of the present cohort, followed up for a median of 26 years with 9777 cases of incident AF, showed an ≈2-fold risk of hospitalizations for AF among men who were obese in adolescence compared with those with BMI 20 kg/m².²⁰ However, with a longer follow-up and addition of outpatient cases, and analysis of important post-AF outcomes, we were able to follow the severely obese category, relevant to the current obesity pandemic with severe and morbid obesity increasing worldwide.

Accordingly, there is a need to address how the issue should be addressed. To the best of our knowledge, the present study of ≈1.7 million subjects with a median follow-up of 32 years and 36 693 cases of incident AF is the largest, with the longest follow-up and the highest number of identified AF outcomes. The cumulative incidence of 20% among obese subjects was high, also in absolute terms, and approaching that of lifetime risk (about 25%), whereas the men of the

present study were much younger.²⁴ We found an increased risk of AF starting at normal BMI levels in adolescence and ≈3- and 4-fold risks of incident AF in the severely and morbidly obese subjects, respectively, compared with normal weight subjects. The European Society of Cardiology 2020 guidelines pertaining to AF recommend screening for AF in individuals aged ≥65 years and in patients with hypertension, and it should be considered in those with obstructive sleep apnea, but not in obese subjects.⁹ Our data generate questions to be further addressed in randomized trials: whether screening for AF in severely and morbidly obese subjects may increase survival or prevent HF or stroke in this group. In a previous study from the MESA (Multi-Ethnic Study of Atherosclerosis), the relationship between BMI and development of AF was J shaped.²⁵ The nearly linear association in the present study may be explained by the fact that we measured weight and height in adolescence, and not in adulthood; hence, the association may differ, with a stronger relationship among younger people, to that seen in adulthood.

The mechanisms by which obesity may lead to the development of AF are complex and not completely

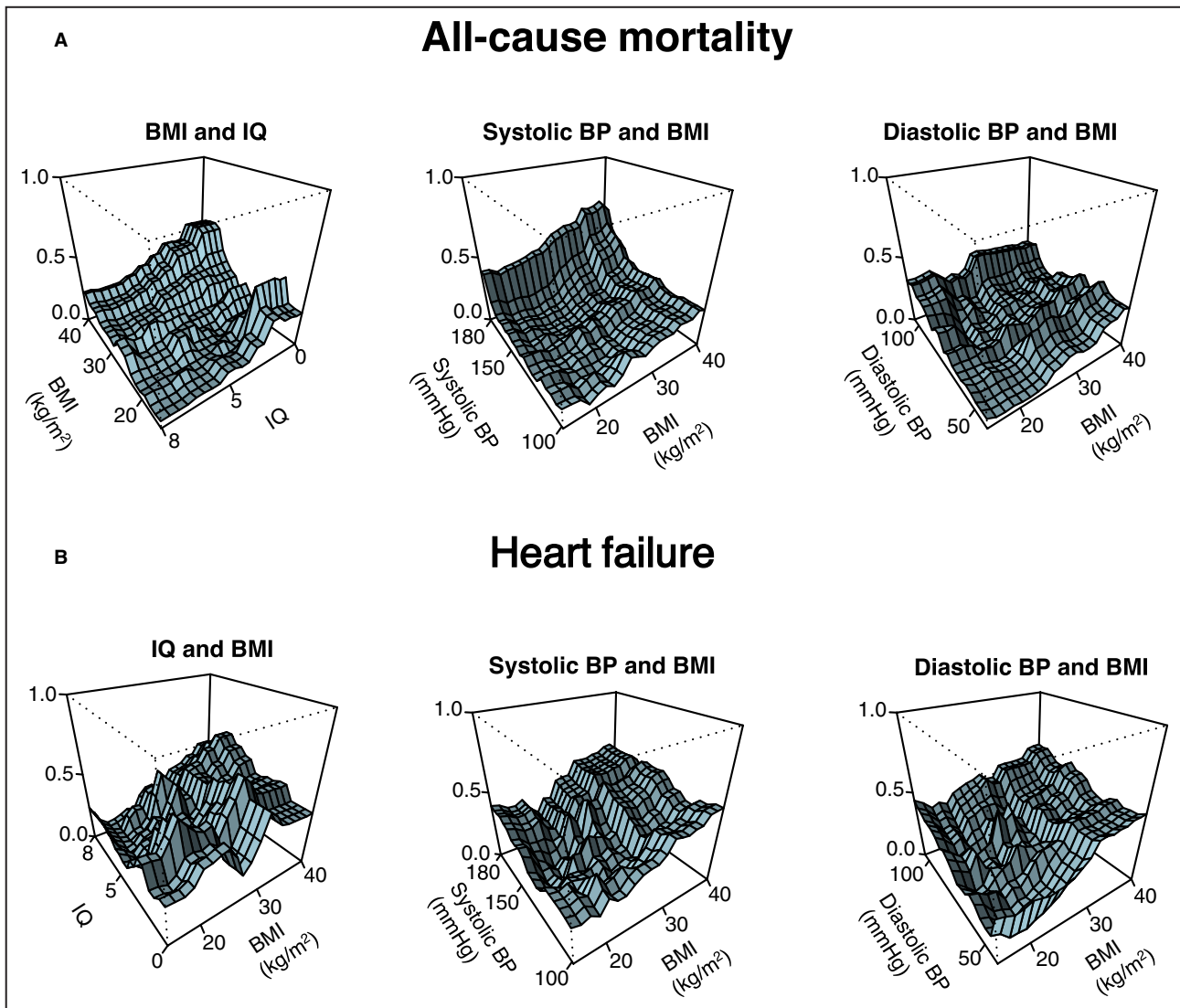


Figure 3. Three-dimensional partial dependence plots generated from the random forest models.

Graphical visualization of the most important interactions between body mass index (BMI) and risk factors (x_1 and x_2 axis) on all-cause mortality (A) and incident heart failure (B) (y axis). The y axis denotes probability of all-cause mortality or incident heart failure. A, Intelligence quotient (IQ) is in the reverse direction from high to low. BP indicates blood pressure.

understood. Obese individuals may be susceptible to AF via alterations in hemodynamics and cardiac structures, such as increased blood volume and increased stroke volume, eventually causing elevation in left atrial pressure, increase in left ventricular wall stress, and left ventricular remodeling and diastolic dysfunction that may trigger AF.²⁶ An excessive accumulation of adipose tissue may result in release of proinflammatory cytokines and oxidative stress and excess deposition of epicardial fat, contributing to left atrial enlargement and left ventricular diastolic dysfunction and remodeling, including collagen deposition and fibrosis.²⁶

Individuals with AF are at 1.5- to 3.5-fold risk of death compared with those with sinus rhythm.^{9,10,12} A prospective study of Japanese men (n=4045) showed

that common causes of death among patients with AF were malignancy (23.1%), infection/sepsis (17.3%), or HF (14.5%), with stroke-related mortality at 6.5%.¹¹ However, the impact of obesity on death in relation to other comorbidities in patients with AF has not been extensively studied. Further on, in subgroup analyses of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study, 304 deaths occurred in 2492 subjects (mean age, 66.4 years at baseline; 35.7% obese) who were followed up for a mean of 3 years. Obese subjects with AF showed higher rates of all-cause mortality, but not of stroke; however, the adjusted HR for all-cause mortality was not significantly associated with obesity.²⁷ In a second subgroup analysis, a Cox regression analysis adjusted only for those baseline variables

that differed significantly revealed a significant inverse relationship between obesity and all-cause mortality.¹³ Findings of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) randomized trial subgroup analysis of 17 913 subjects (mean age, 69.4 years; 40.0% obese) were similar, with a median follow-up of 1.8 years, 1229 deaths, and 465 strokes or systemic emboli. In multivariable adjusted models, obesity in those with AF was associated with lower risk of all-cause mortality, but not of stroke or systemic embolism.¹⁴ Findings from these 2 studies were compatible with a potential obesity paradox, indicating that obese subjects with AF are “protected” from cardiovascular outcomes, but where this effect is mainly attributable to older and sicker individuals being included. Investigating the association between AF and HF might be complex, as the 2 conditions often overlap.²⁸

Findings of observational prospective studies have differed from subgroup analyses of randomized trials that suggest an obesity paradox. In a recent prospective study of 1956 patients (mean age, 73.8 years; 37.2% obese) with AF receiving anticoagulants, and a median follow-up of 3 years, observing 255 deaths and 45 strokes, obesity was not associated with all-cause mortality or stroke. This contrasts to the findings of the prospective observational Danish Diet, Cancer and Health study (aged 50–64 years at baseline; $n=57\,053$), where the subcohort with AF ($n=3135$; followed up for a median 4.9 years) had a significant association for obesity with a composite end point of IS, thromboembolism, and death, even after adjustment for CHA₂DS₂-VASc (HR, 1.36 [95% CI, 1.11–1.65]). However, obesity was not significantly associated with IS or HF alone.

Our data gained from a median follow-up of ≈ 6 years of 37 000 subjects with AF suggest that obesity in adolescence is associated with an ≈ 3 -fold risk of all-cause mortality, 3.5-fold risk of incident HF, and 2.5-fold risk of incident IS. In addition, the probability for all-cause mortality gradually increased with lower IQ and higher blood pressure levels, whereas the probability for incident HF was high in subjects with high BMI levels independent of blood pressure. We believe these findings are novel and suggest that the question of whether more rigorous monitoring of obese subjects with AF may improve prognosis and survival should be addressed in future trials. For example, otherwise healthy men aged <65 years with AF would normally not be considered for anticoagulant therapy; our findings might indicate a potential beneficial effect that might be explored in a clinical trial.

STRENGTHS AND LIMITATIONS

Strengths of the present study include a large sample size with a high number of AF cases, long-term follow-up, and the population-based study design comprising

a cohort largely representative of the male adolescent population of Sweden. In addition, we investigated the association of BMI in early adolescence with clinical outcomes in patients diagnosed with AF.

There are limitations to our study that should be addressed. First, we used BMI as a proxy for overweight and obesity. Mildly elevated BMI may reflect high muscle mass, not adiposity, but this is unlikely to be the case when BMI is extremely high. Second, our data and statistical analysis did not account for variation of BMI over time, which might have introduced a time-related bias. This has been demonstrated in a previous study in which a decrease in BMI over time was associated with lower rates of AF.²⁹ However, it should also be addressed that obesity in adolescence may cause irreversible changes in cardiac structures strongly associated with AF, such as left atrial enlargement. This has been shown in a previous study investigating changes in cardiac geometric structures before and after bariatric surgery in 38 adolescents.³⁰ Indeed, there were no changes in the dimension of left atrium or the left ventricle, which might suggest that obesity in adolescence is a crucial determinant of AF irrespective of changes in weight during adulthood.³¹

Third, our homogeneous study population with respect to sex and ethnicity precludes the generalizability of results to women and to populations of other ethnicities. Age-adjusted incidence, prevalence, and life-time risk of AF are lower in women compared with men and varies with race and ethnicity. Fourth, another inherent limitation is the inability to account or adjust for the development of comorbid medical diagnoses. One might hypothesize that the conpendium of risk factors that closely track with obesity and morbid obesity explain the development of AF, as opposed to a direct causal role of elevated adolescent BMI levels. This might suggest BMI is a mere marker of downstream risk factors (eg, type 2 diabetes, obstructive sleep apnea, and essential hypertension), which predispose to AF. Still, given the young age of the cohort at baseline, it is more likely that high BMI exerts an effect on future AF through these intermediary factors, which would likely not have developed in the absence of an elevated BMI, or at least not to the same extent. In addition, we were unable to include potential lifestyle risk factors, such as smoking, diet, alcohol consumption, and physical activity occurring during follow-up as potential mediating factors, nor did we have information on adult BMI. Fifth, we were unable to differentiate between AF and atrial flutter and various subtypes of AF, such as paroxysmal, persistent, or permanent AF. Finally, lack of data on oral anticoagulant use is a limitation as we cannot exclude that body weight might impact on the use of anticoagulants and subsequent AF-related strokes.

CONCLUSIONS

Severe and morbid obesity in adolescence in men is strongly associated to development of AF in early adulthood. Documented obesity in adolescence in men later diagnosed with AF is associated with higher risk of all-cause mortality, incident HF, and IS. Increasing obesity prevalence in the young is likely to lead to increasing rates of early AF, with markedly elevated risk of poor outcomes.

ARTICLE INFORMATION

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Affiliations

Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden (D.D., M.L., A.R.); Cardiology unit, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden (D.D., M.L., M.A., A.R.); Department of Internal Medicine, Institute of Medicine, The Sahlgrenska Academy, University of Gothenburg, Sweden (N.D.Å.); Department of Acute Medicine and Geriatrics (SU/Sahlgrenska), Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden (N.D.Å.); School of Public Health and Community Medicine/Primary Health Care, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden (M.Å.); Region Västra Götaland, Regionhälsan, Gothenburg, Sweden (M.Å.); Department of Cardiology, Örebro University, Örebro, Sweden Faculty of Medicine and Health, Örebro University, Örebro, Sweden (E.F.); and Department of Clinical Physiology, Institute of Medicine at the Sahlgrenska Academy, Sahlgrenska University Hospital, Gothenburg, Sweden (D.P.).

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Disclosures

None.

Supplemental Material

Table S1–S4
Figure S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. ICD codes of Atrial Fibrillation, baseline comorbidities and clinical outcomes

Diagnosis	ICD 8	ICD 9	ICD 10
Atrial fibrillation	42792	427D	I48.0-I48.9
Diabetes mellitus	250	250	E10-E14
Hypertension	401-405	401-405	I10-I15
ACH	746-747	745-747	Q2, Q332, Q871E, Q872, Q874, Q878, Q90, Q96
Heart failure	42700	428A, 428B, 428X	I50.0-I50.9
Ischemic stroke	433,00, 433,99 434,00, 434,99 435,00, 435,99 436,00, 436,99	433A, 433B 433C, 433D 433W, 433X 434A, 434B 434X, 436X	I63.0-I63.9

International classification of diseases (ICD), ACH (adult congenital heart disease)

Table S2. Event rates for atrial fibrillation relative to body mass index group

	All	BMI <18.5 kg/m ²	BMI 18.5–<20.0 kg/m ²	BMI 20.0–<22.5 kg/m ²	BMI 22.5–<25.0 kg/m ²	BMI 25.0–<27.5 kg/m ²	BMI 27.5–<30.0 kg/m ²	BMI 30.0–<35.0 kg/m ²	BMI 35.0–<40.0 kg/m ²	BMI 40.0–50.0 kg/m ²
n (%)	1704467 (100)	138645 (8.1)	307135 (18.0)	687070 (40.3)	362485 (21.3)	126193 (7.4)	44592 (2.6)	30800 (1.8)	6244 (0.4)	1302 (0.1)
Events, n (%)	36693 (100)	2871 (7.8)	6228 (16.9)	14176 (38.6)	7967 (21.7)	3008 (8.2)	1260 (3.4)	953 (2.6)	190 (0.5)	40 (0.1)
Cases per 100 000 observed person years (CI)	68 (67–69)	61 (59–63)	61 (59–62)	65 (63–66)	73 (71–74)	82 (79–85)	100 (94–105)	114 (107–121)	122 (105–140)	131 (93–178)
Age at diagnosis, year(SD)	52.4 (10.6)	54.0 (10.3)	53.6 (10.3)	52.5 (10.6)	51.7 (10.7)	51.1 (10.8)	50.7 (10.6)	50.4 (10.3)	48.3 (10.6)	43.4 (10.3)
Median follow up time, y (IQR)	32 (24–41)	36 (26–45)	34 (26–44)	33 (25–41)	31 (22–39)	29 (21–38)	28 (21–37)	26 (19–35)	24 (18–32)	22 (17–30)
Person-years of follow-up	53704092	4699225	10186471	21882960	10972929	3679934	1262415	834324	155266	30569

BMI= body mass index; CI= Confidence intervals, IQR= Interquartile range, SD= Standard deviation.

Table S3. Hazard Ratios (95% CIs) for Atrial Fibrillation by cardiovascular risk factors

	Multivariable adjusted Model
Events/population, n	24897/1297909
Age	1.11(1.09-1.13)
P-value interaction	0.80
Center	1.00(0.99-1.01)
P-value interaction	0.10
Year	1.01(1.01-1.02)
P-value interaction	0.32
Systolic blood pressure	
100–119 mmHg	1
120–125 mmHg	1.07(1.03-1.11)
126–130 mmHg	1.10(1.06-1.15)
131–138 mmHg	1.08(1.04-1.13)
139–180 mmHg	1.20(1.15-1.25)
P-value interaction	0.23
Diastolic blood pressure	
40–59 mmHg	1
60–65 mmHg	0.99(0.95-1.04)
66–70 mmHg	1.00(0.96-1.05)
71–76 mmHg	1.00(0.95-1.04)
77–100 mmHg	1.03(0.99-1.08)
P-value interaction	0.73
Cardiorespiratory fitness	
High (8-9)	1
Moderate (5-7)	1.03 (0.99-1.07)
Low (1-4)	1.17(1.12-1.22)
P-value interaction	0.06
Muscle strength	
High (8-9)	1
Moderate (5-7)	0.91(0.82-1.01)
Low (1-4)	0.93(0.83-1.05)
P-value interaction	0.004
Parental education	
High (8-9)	1
Moderate (5-7)	1.04(0.99-1.08)
Low (1-4)	1.02(0.96-1.06)
P-value interaction	0.27
IQ	
High (8-9)	1
Moderate (5-7)	1.04 (1.01-1.07)
Low (1-4)	1.14(1.09-1.18)
P-value interaction	0.006
Baseline comorbidities	
Diabetes	1.50(0.95-2.35)
P-value interaction	0.33
Hypertension	1.55(1.24-1.95)
P-value interaction	0.46
GUCh	5.99(4.89-7.34)
P-value interaction	0.0004

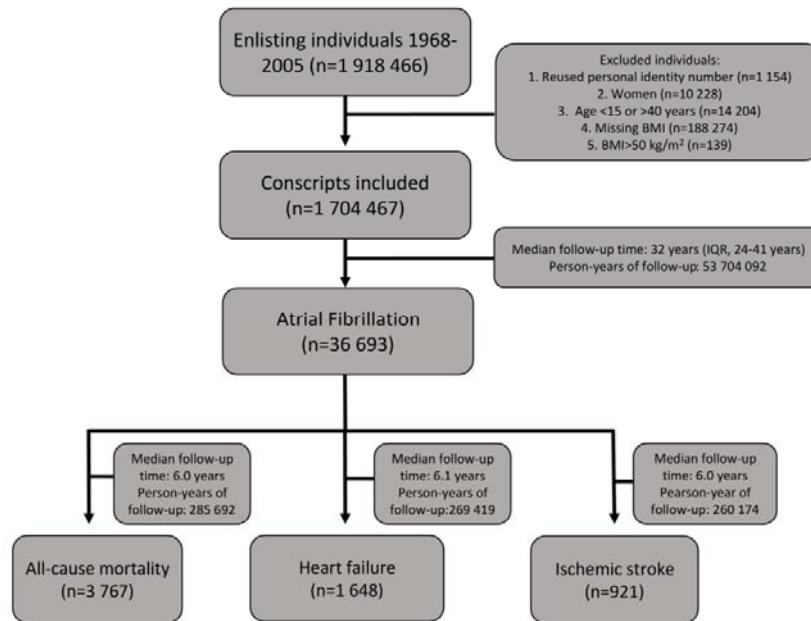
Hazard ratios were derived by Cox regressions (methods), and interactions by use of BMI as continuous variable (methods).

Table S4. Event rates for clinical outcomes in patients with atrial fibrillation relative to body mass index group

	All	BMI<20.0 kg/m ²	BMI 20– <25.0 kg/m ²	BMI 25– <30.0 kg/m ²	BMI ≥30 kg/m ²
All-cause mortality					
total n (%)	36459 (100)	9037(24.8)	22006 (60.4)	4244 (11.6)	1172 (3.2)
Events, n (%)	3767 (100)	917 (24.3)	2083 (55.3)	578 (15.3)	189 (5.0)
Cases per 1000 observed person years (CI)	13.2 (12.8– 13.6)	13.0 (12.1– 13.8)	11.9 (11.4– 12.5)	18.0 (16.6– 19.6)	22.6 (19.5– 26.0)
Age at death, y (SD)	58.6(7.4)	59.3(7.4)	58.7(7.4)	57.9(7.5)	56.1(8.1)
Median follow up time, y (IQR)	6.0 (2.4– 12.0)	6.7 (2.9–12.1)	6.7 (2.8–12.5)	6.5 (2.8–12.4)	6.7 (3.3–11.6)
Person-years of follow up	285692	70724	174543	32051	8373
Heart Failure					
Total n (%)	34534 (100)	8592 (24.9)	20966 (60.7)	3919 (11.3)	1057 (3.1)
Events, n (%)	3251 (100)	808 (24.9)	1818 (55.9)	475 (14.6)	150 (4.6)
Cases per 1000 observed person years (CI)	11.7 (11.3– 12.2)	11.8 (11.0– 12.6)	10.7 (10.2– 11.2)	15.5 (14.2– 17.0)	19.2 (16.2– 22.5)
Age of diagnosis, y(SD)	57.4(7.6)	57.6(8.3)	57.7(7.3)	56.8(7.7)	55.2(7.5)
Median follow up time, y IQR)	6.1 (2.5– 11.7)	6.2 (2.5–11.5)	6.2 (2.5–11.8)	6.0 (2.4–11.6)	5.9 (2.8–10.9)
Person-years of follow up	269419	66920	165627	29526	7345
Ischaemic Stroke					
Total n (%)	35025 (100)	8641 (24.7)	21183 (60.5)	4078 (11.6)	1123 (3.2)
Events, n (%)	921(100)	242 (26.3)	522 (56.7)	114 (12.4)	43 (4.7)
Cases per 1000 observed person years (CI)	3.4 (3.1–3.6)	3.6 (3.1–4.0)	3.1 (2.8–3.4)	3.7 (3.1–4.5)	5.4(3.9–7.3)
Age at diagnosis, y(SD)	61.2(6.8)	59.3(3.2)	58.2(6.9)	56.5(7.3)	54.3(8.2)
Median follow up time, y(IQR)	6.0 (2.4– 11.5)	6.1 (2.4–11.3)	6.1 (2.4–11.6)	5.7 (2.2–11.1)	5.7 (2.7–10.4)
Person-years of follow up	260174	67834	168028	30761	7980

BMI= body mass index; CI= Confidence intervals, IQR= Interquartile range, SD= Standard deviation.

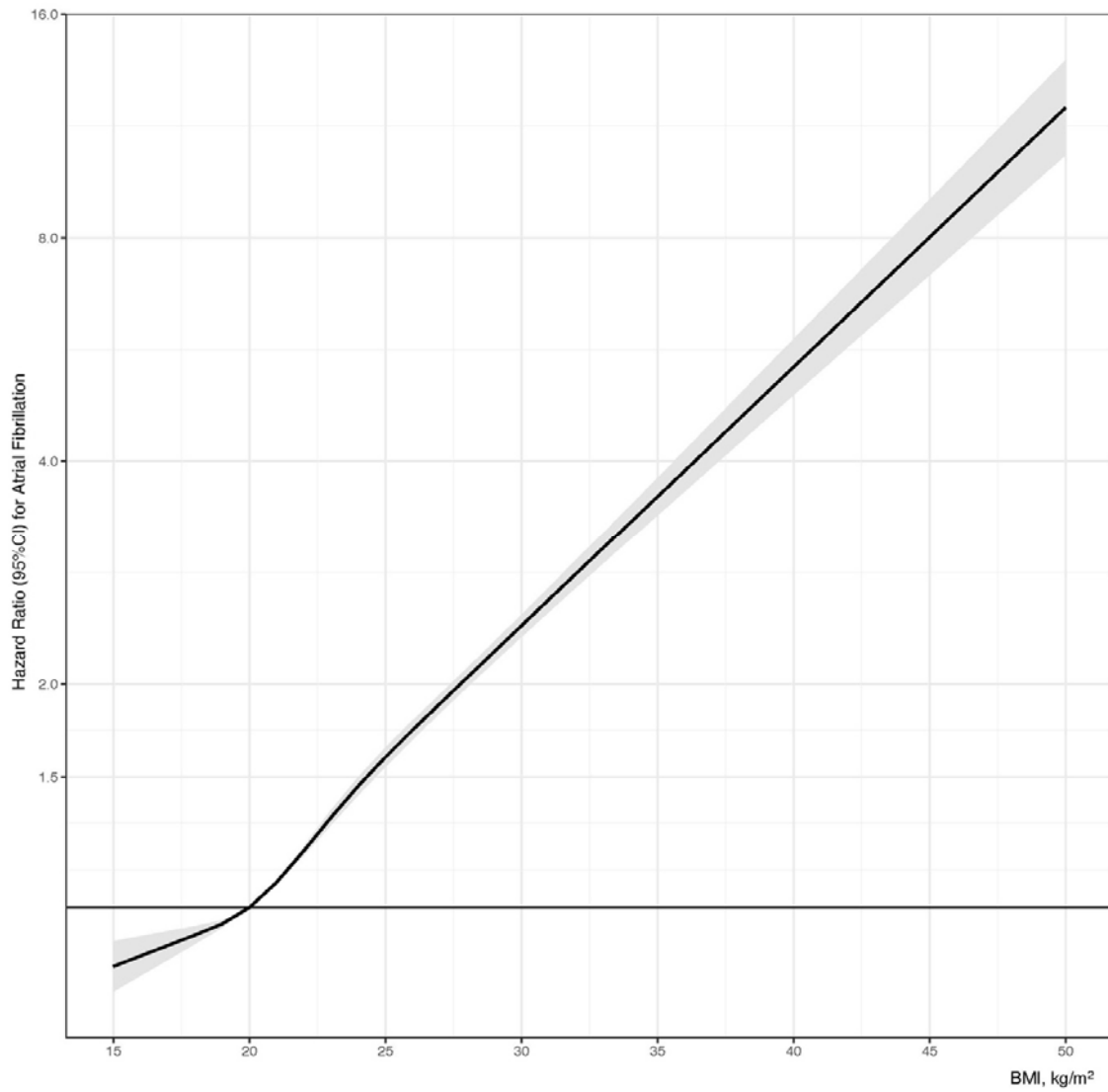
Figure S1. Study flowchart



The flow chart is in accordance with the STROBE criteria.

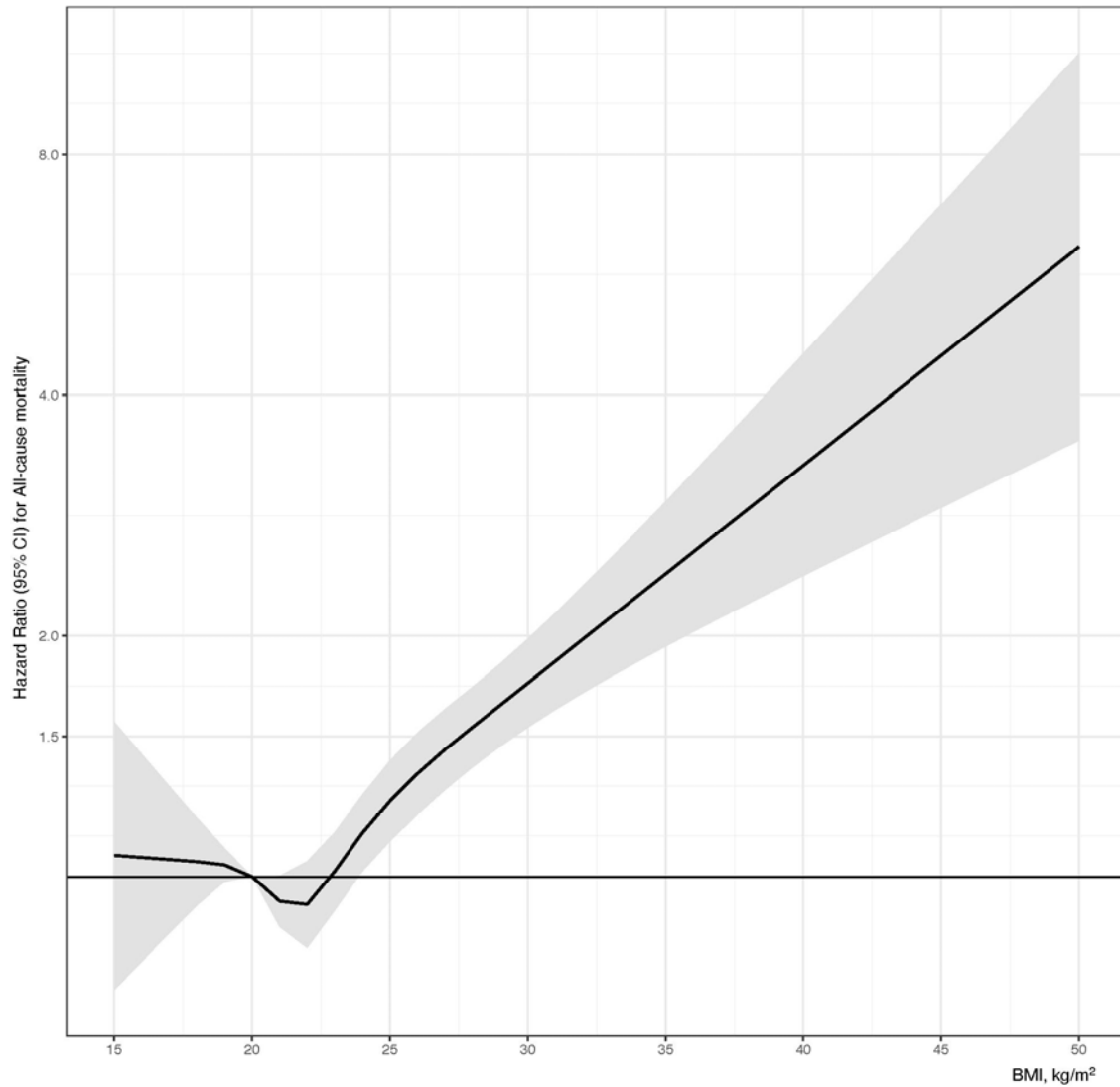
BMI; Body mass index.

Figure S2. Association between body mass index (BMI) at conscription and risk for Atrial Fibrillation



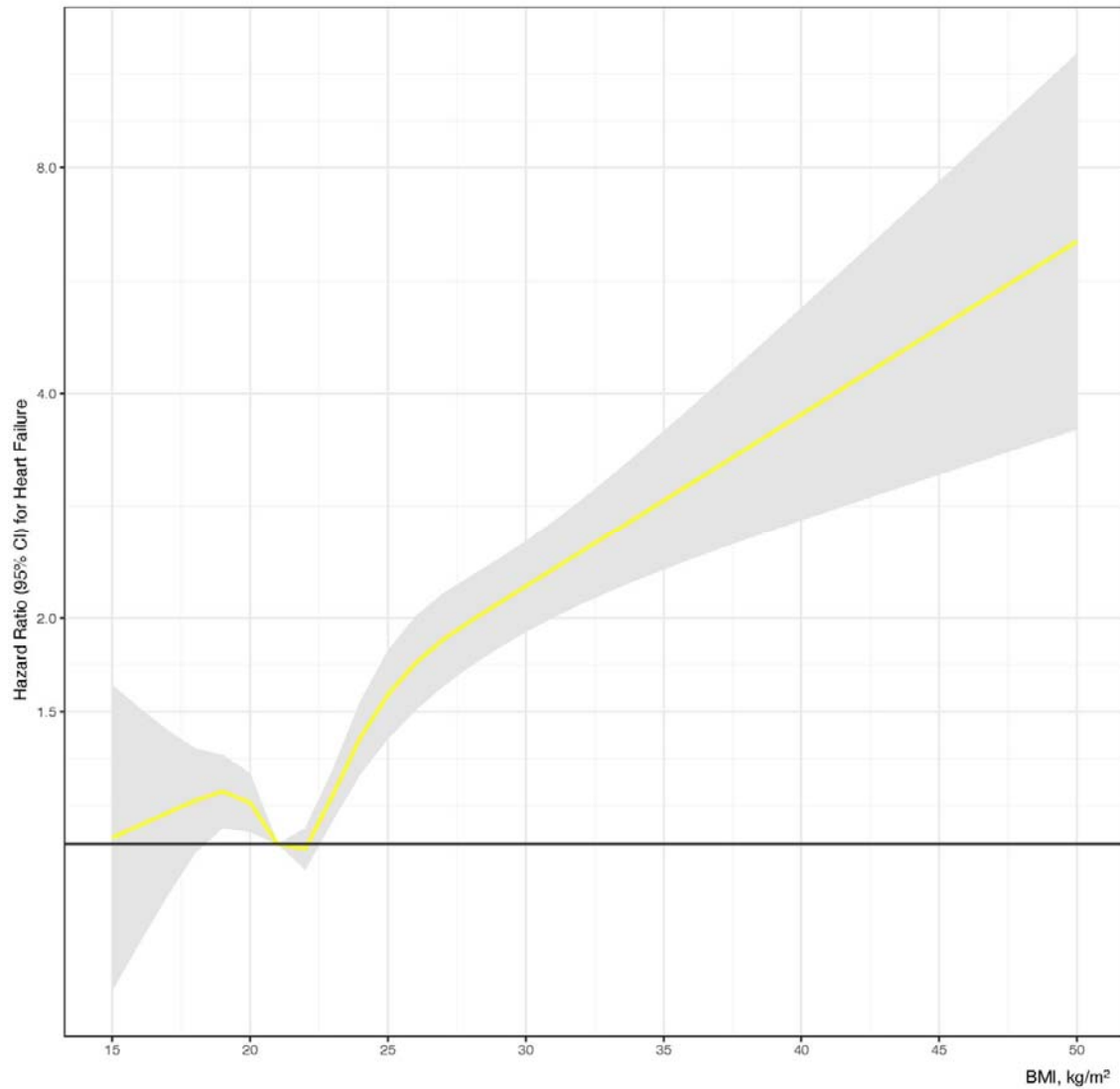
The model was unadjusted (n= 1704467). BMI was restricted to BMI between 15 and 50 kg/m² and modelled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (i.e., 18.1, 19.9, 23.2, and 27.2 kg/m²), with BMI of 20 kg/m² as reference.

Figure S3. Association between body mass index (BMI) at conscription and risk for all-cause mortality in patients diagnosed with Atrial Fibrillation



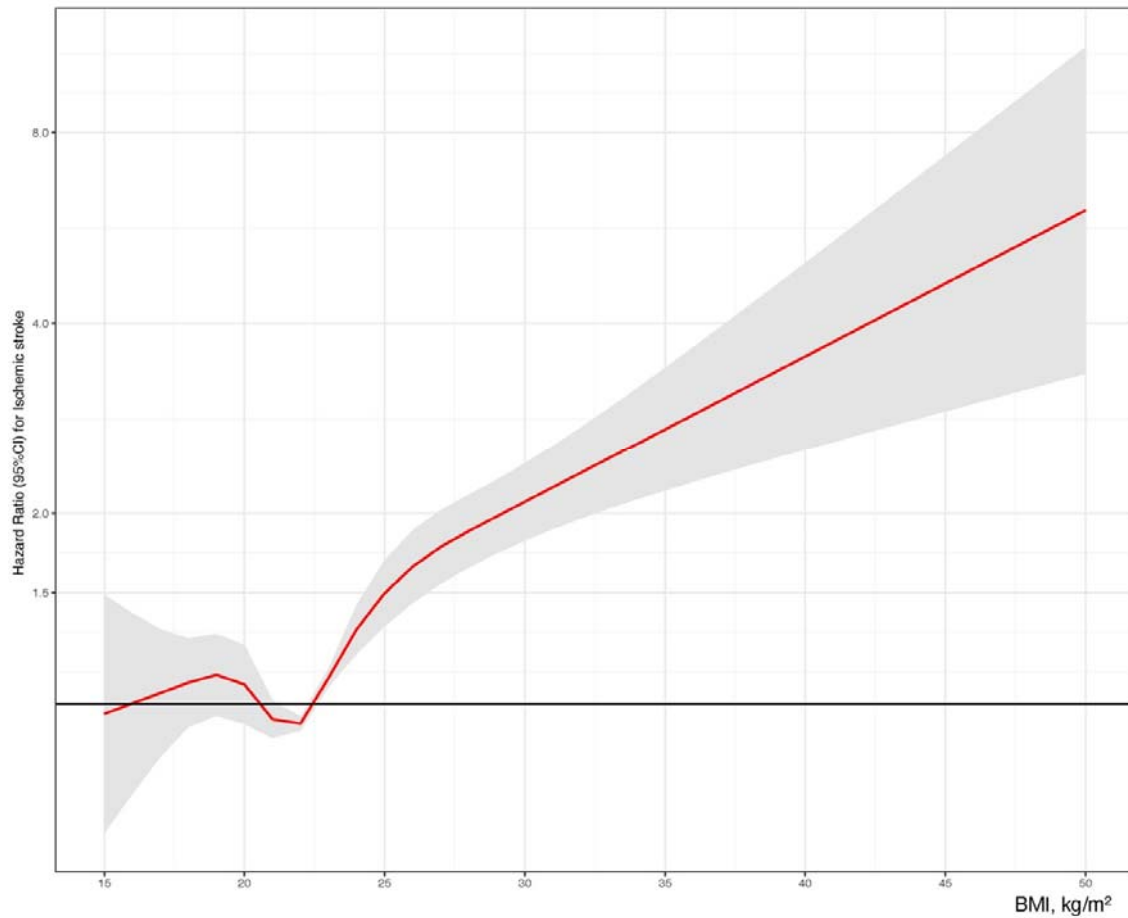
The model was unadjusted (n=36445). BMI was restricted to BMI between 15 and 50 kg/m² and modelled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (ie, 18.1, 20.0, 23.2, and 27.2 kg/m²), with BMI of 20 kg/m² as reference.

Figure S4. Association between body mass index (BMI) at conscription and risk for Heart failure (HF) in patients diagnosed with Atrial fibrillation (AF)



The model was unadjusted (n=34534). BMI was restricted to BMI between 15 and 50 kg/m² and modelled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (ie, 18.0, 20.0, 23.4, and 27.8 kg/m²), with BMI of 22 kg/m² as reference.

Figure S5. Association between body mass index (BMI) at conscription and risk for Ischemic stroke (IS) in patients diagnosed with Atrial fibrillation



The model was unadjusted (n=35 013). BMI was restricted to BMI between 15 and 50 kg/m² and modelled as a restricted cubic spline with knots at 5%, 25%, 75%, and 95% (ie, 18.1, 20.0, 23.5, and 28.1 kg/m²), with BMI of 22.5 kg/m² as reference.