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CLINICAL RESEARCH
Prevention and epidemiology

Weight and weight change and risk of atrial fibrillation: the HUNT study

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Aims Although obesity has been associated with risk of atrial fibrillation (AF), the associations of long-term obesity, recent obesity, and weight change with AF risk throughout adulthood are uncertain.

Methods and results An ambispective cohort study was conducted which included 15 214 individuals. The cohort was created from 2006 to 2008 (the baseline) and was followed for incident AF until 2015. Weight and height were directly measured at baseline. Data on previous weight and height were retrieved retrospectively from measurements conducted 10, 20, and 40 years prior to baseline. Average body mass index (BMI) over time and weight change was calculated. During follow-up, 1149 participants developed AF. The multivariable-adjusted hazard ratios were 1.2 (95% confidence interval 1.0–1.4) for average BMI 25.0–29.9 kg/m^2 and 1.6 (1.2–2.0) for average BMI ≥30 kg/m^2 when compared with normal weight. The association of average BMI with AF risk was only slightly attenuated after adjustment for most recent BMI. In contrast, current BMI was not strongly associated with the risk of AF after adjustment for average BMI earlier in life. Compared with stable BMI, both loss and gain in BMI were associated with increased AF risk. After adjustment for most recent BMI, the association of BMI gain with AF risk was largely unchanged, while the association of BMI loss with AF risk was weakened.

Conclusion Long-term obesity and BMI change are associated with AF risk. Obesity earlier in life and weight gain over time exert cumulative effects on AF development even after accounting for most recent BMI.

Keywords Atrial fibrillation • BMI • Weight • Weight change

Introduction

Obesity has reached epidemic proportions globally, with an estimated 38% of the world's adult population expected to be obese by 2030.[1] The last few decades have also witnessed a global rise in the incidence and prevalence of atrial fibrillation (AF), with an estimated 33.5 million people globally suffering from AF in 2010 and 5 million new cases expected to arise annually.[2] Atrial fibrillation increases mortality, morbidity, and reduces quality of life. Considering that prevention and treatment of AF are enormous medical and socioeconomic tasks, a deeper understanding of risk factors for AF is imperative.

Obesity has well-known associations with AF risk.[3,4] However, research using measurements of height and weight at a single point in time fails to assess the cumulative effect of obesity over the life course on AF development. Accordingly, little attention has been devoted to the impacts of long-term obesity and long-term weight change on AF development. Some previous studies have used

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self-reported prior body weight, in which individuals recalled their body weight earlier in life.[5,6] Self-reported current body weight is generally accurate,[7,8] but the accuracy of recall is imperfect and depends on current and past body mass index (BMI) values, changes in weight, end-digit preferences, and participants' current cognitive ability.[9] With regard to the diagnosis of AF, most prior studies have relied solely on administrative data without individual validation or verification.[5,10] This tends to lower the specificity of the AF diagnoses and introduce substantial misclassification.[11,12] Moreover, those few previous investigations with repeated measurements of body weight over time have been limited by small sample sizes,[5,10] short-time intervals between measurements,[6,10,13,14] and missing information on important covariates like comorbidity.[5,6,10,13]

In this large, population-based study, we investigated the cumulative effects of obesity and weight change on AF risk over four decades. We used repeated measurements of weight and height, relied on verified AF diagnoses and included information on a wide range of cardiovascular risk factors.

Methods

Study population

All 93 860 residents ≥20 years of age in Nord-Trøndelag County in Norway were invited to participate in the third HUNT study (HUNT-3) from October 2006 to June 2008. Of these, 50 804 participants (54%) answered questionnaires and underwent clinical examinations (baseline examinations). Holmen *et al.*[15] have described the HUNT study in more detail.

We excluded 1598 participants from the analysis who had a history of AF at baseline and 360 participants with missing values for baseline BMI.

Clinical examination

A clinical examination was conducted by trained nurses. Height and weight were measured barefoot and wearing light clothing; height was measured to the nearest centimetre and weight to the nearest 0.5 kg. Waist and hip circumferences were measured to the nearest centimetre with the participants standing erect and arms hanging relaxed.[15] Waist circumference (WC) was measured at the level of the umbilicus, and hip circumference was measured at the widest part of the hip/buttocks. Non-fasting blood samples were analysed for glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein.[15] Blood pressure was measured three times using a Dinamap 845XT (Critikon) based on oscillometry, with the arm resting on a table, and the average of the second and third measurement was used for analysis.[15]

Body mass index

Body mass index was calculated as body weight in kilograms divided by the squared value of height in metres, and divided into four categories: <18.5 kg/m^2 (underweight), 18.5 to 24.9 kg/m^2 (normal weight), 25 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).

Height and weight measurements were also available from a mandatory tuberculosis screening that was conducted between 1966 and 1969,[16] as well as the two previous rounds of the HUNT study; the HUNT-1 (1984–1986)[17] and HUNT-2 (1995–1997).[15] In all these studies, BMI was measured with similar methods to the HUNT-3 study. Among the 48 846 eligible participants in HUNT-3, 15 214 individuals had available information on previous height and weight from all the three previous measurements and were therefore eligible for the main analyses. Details about inclusions are provided in the Supplementary material online, *Figure S1*.

We denoted BMI at the four separate time points by the following terms: at HUNT-3 (2006–2008) as BMI_{07}, at HUNT-2 (1995–1997) as BMI_{96}, at HUNT-1 (1984–1986) as BMI_{85}, and at the tuberculosis screening (1966–1969) as BMI_{67} (Supplementary material online, *Figure S2*).

We utilized the following equations for further analyses:

1. Average BMI = $[(BMI_{67} \times time_{I-II}) + (BMI_{85} \times time_{II-III}) + (BMI_{96} \times time_{III-IV}) + (BMI_{07} \times time_{IV-})]/TotalTime$.
   where:
   $time_{I-II}$ = time from measurement I (i.e. in 1966–1969) to measurement II (i.e. in 1984–1986);
   $time_{II-III}$ = time from measurement II to measurement III (i.e. in 1995–1997);
   $time_{III-IV}$ = time from measurement III to measurement IV (i.e. in 2006–2008);
   $time_{IV-}$ = time from measurement IV to end of follow-up;
   Total Time = total time from measurement I to end of follow-up.
2. Average $BMI_{67-07} = [(BMI_{67} \times time_{I-II}) + (BMI_{85} \times time_{II-III}) + (BMI_{96} \times time_{III-IV}]/time_{I-IV}$
   where: $time_{I-IV}$ = time from measurement I to measurement IV.
3. Total BMI change = $\{[(BMI_{85} - BMI_{67}) \times time_{I-II}] + [(BMI_{96} - BMI_{85}) \times time_{II-III}] + [(BMI_{07} - BMI_{96}) \times time_{III-IV}]\}/time_{I-IV}$

We then analysed the effects of BMI change from BMI_{67} to BMI_{07} (total BMI change), from BMI_{67} to BMI_{85} (early BMI change), from BMI_{85} to BMI_{96} (middle BMI change), and from BMI_{96} to BMI_{07} (late BMI change) separately. We classified total, early, middle, and late BMI change into five categories: <-5 kg/m^2, ≥-5 to <-2.5 kg/m^2, ≥-2.5 to <2.5 kg/m^2, ≥2.5 to <5 kg/m^2, and ≥5 kg/m^2.

In addition, three distinctive BMI trajectories were identified based on group based trajectory modelling using the Stata Traj Plugin[18]: 'normal weight' (51.9% of the population), 'overweight' 40.4%, and 'obese' 7.7% (Supplementary material online, *Figure S3*). Detailed information on the process of trajectory modelling is provided in the Supplementary material online. Intra-individual BMI variability was calculated as the square root of the variance or the residual mean square,[19] from the four residuals from a participant-specific linear regression of the four BMI measurements, with participants' age as the independent variable.

Waist circumference and waist–hip ratio

Waist circumference and waist–hip ratio (WHR) measurements were available at HUNT-2 (1995–1997) and HUNT-3 (2006–2008).

We denote WC and WHR at the two time points by the following terms: at HUNT-3 (2006–2008): WC_{07} and WHR_{07}; at HUNT-2 (1995–1997): WC_{96} and WHR_{96}.

We utilized the following equations for the further analysis:

$$\text{Average waist circumference} = [(WC_{96} \times time_{III-IV}) + (WC_{07} \times time_{IV-})]/time_{III-end}.$$

$$\text{Average waist} - \text{hip ratio} = [(WHR_{96} \times time_{III-IV}) + (WHR_{07} \times time_{IV-})]/time_{III-end}.$$

where: $time_{III-end}$ = time from measurement III to end of follow-up.

Average WC was categorized according to the definition of abdominal obesity recommended by the Adult Treatment Panel[20]: ≤88 cm and >88 cm for women; ≤102 cm and >102 cm for men. Average WHR was also categorized according to the definition of abdominal obesity recommended by World Health Organization[21]: <0.85 and ≥0.85 for women; <0.90 and ≥0.90 for men. Waist circumference change was classified into five categories: <0 cm, ≥0 to <4 cm, ≥4 to <9 cm, ≥9 to <14 cm, and ≥14 cm. Waist–hip ratio change was classified into four categories: <0.03, ≥0.03 to <0.07, ≥0.07 to <0.11, and ≥0.11.

Atrial fibrillation

Atrial fibrillation diagnoses were retrieved from discharge registers at the two hospitals in Nord-Trøndelag County from the baseline examination until 30 November 2015. We used code I48 from the International Classification of Diseases Tenth Revision to screen for patients with possible AF. Medical records of these patients were then reviewed by a cardiologist (J.P.L.) and two specialists in internal medicine (M.V. and H.E.), and AF was adjudicated according to the electrocardiographic criteria recommended by the European Society of Cardiology (ESC).[22] Persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of haemodynamic instability (e.g. sepsis or non-cardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of the diagnosis, two physicians evaluated the available information separately. Only cases where both physicians concurred were regarded as AF. The rest were classified as possible AF and were not regarded as AF cases in the main analyses. The validation process is described in detail elsewhere.[11]

Covariates

Covariates were collected at HUNT-3. Smoking status was assessed as never, former, or current. We used self-reported alcohol consumption to classify individuals as abstainers, light drinkers (0 to 1 drinks per day), moderate drinkers (>1 but ≤2 drinks per day), or heavy drinkers (>2 drinks per day). Level of physical activity was self-reported; activity that did not make individuals sweat or cause laboured breathing was regarded as light (such as simple walking) and was otherwise considered hard (such as skiing, swimming, and working out). Physical activity was categorized into (i) inactivity (<3 h of light exercise per week or <1 h hard exercise), (ii) moderate activity (≥3 h of light exercise or 1–2 h of hard exercise per week), and (iii) high activity (≥3 h of hard physical activity per week). In addition, we used an alternative assessment of physical activity that incorporated the frequency, intensity, and duration of exercise.[23] Educational level was categorized as (i) primary and secondary school, (ii) vocational school and high school, (iii) junior college, (iv) undergraduate school, and (v) graduate school. Marital status was categorized as (i) unmarried, (ii) married, (iii) widow[er], (iv) divorced, (v) separated, (vi) live-in partner. Metabolic syndrome based on the International Diabetes Federation[24] was defined as the presence of elevated WC (≥102 cm for men, ≥88 cm for women) in addition to two or more of the following criteria: (i) increased non-fasting triglycerides (≥1.7 mmol/L), (ii) decreased HDL (<1.03 mmol/L for men, <1.29 mmol/L for women), (iii) increased blood pressure (≥130/85 mmHg) or use of blood pressure medication, (iv) increased non-fasting glucose (≥11.1 mmol/L) or diabetes diagnosis. Information on other chronic conditions was self-reported and included: (i) angina pectoris, (ii) stroke, (iii) asthma, (iv) osteoarthritis, (v) kidney disease, (vi) hyperthyroidism, (vii) fibromyalgia, (viii) rheumatoid arthritis, (ix) sarcoidosis, (x) ankylosing spondylitis, (xi) cancer, (xii) epilepsy, (xiii) osteoporosis, (xiv) chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, (xv) psoriasis, and (xvi) hypothyroidism. Information on history of acute myocardial infarction and heart failure was retrieved from hospital registers and diagnoses were reviewed by cardiologists.[25]

Statistical analyses

The main analysis included 15 214 individuals who had available information on BMI at four time points. Baseline characteristics were presented as means ± standard deviation for continuous variables and percentages for categorical variables. We also calculated the interquartile ranges of BMI values over time stratified by subsequent AF development.

Cox proportional regression models were used to assess the hazard ratio (HR) for AF for a given category of (i) average BMI (average BMI 18.5–24.9 kg/m^2 as the reference group), (ii) BMI change (change between -2.5 and 2.5 kg/m^2 as the reference group), (iii) BMI trajectory (normal weight trajectory as the reference group), (iv) BMI variability (the lowest variability between 0 and 1.07 kg/m^2 as the reference group), (v) average WC (average WC ≤88/102 cm women/men as the reference group), (vi) WC change (change between 0 and 4 cm as the reference group), (vii) average WHR (average WHR ≤0.85/0.90 women/men as the reference group), and (viii) WHR change (change between 0.03 and 0.07 as the reference group), respectively. Time was defined as days from inclusion to either incident AF or censoring due to death from other causes ($N = 2170$), emigration from the county ($N = 8$), or end of follow-up. We calculated HRs with their 95% confidence intervals (CIs). We included age, sex, height, smoking, educational level, marital status, physical activity, and alcohol consumption as potential confounders. In additional analyses, we also adjusted for metabolic status and chronic disorders. In the Cox model examining the effect of BMI change and BMI variability, we also adjusted for the slope of BMI to disentangle the effects of BMI fluctuations and BMI slope on AF development.[26] The correlation coefficients between BMI change and BMI slope are presented in Supplementary material online, *Figure S4*.

To examine whether past or recent BMI was a more important risk factor of AF, we calculated the relative risks according to categories of $BMI_{67\text{-}07}$ (i.e. average BMI from 1967 until baseline), with and without adjustment for the most recent BMI (BMI_{07}), respectively. We did not use the total average BMI (i.e. average BMI from 1967 until the end of follow-up), because the total average BMI included BMI_{07} itself and thus they were highly correlated with each other (Supplementary material online, *Figure S5*). We also calculated the relative risks for the four time points separately (Supplementary material online, *Table S1*). Similarly, we additionally adjusted for the most recent BMI to calculate HRs among different categories of BMI change.

The proportional hazards assumption was tested by comparing -ln-ln survival curves and by performing tests on Schoenfeld residuals for each covariate. We found no violations of the proportionality assumption.

To assess effect modification, we conducted analyses stratified by age, sex, and central obesity (WC ≥102/88 cm for men/women), respectively.

In sensitivity analyses, we regarded possible or single-episode AF during follow-up as events. To address the possibility of reverse causation as an explanation for the observed associations, we excluded the first 2 years of follow-up and repeated the analyses. In addition, we repeated our analyses by adjusting for alternative assessment of physical activity (i.e. the product of the frequency, intensity, and duration of exercises) instead of aforementioned categories of physical activity. Considering that hypertension is a potential consequence of obesity and is strongly associated with AF, we compared models with and without adjustment for hypertension. Lastly, to examine the possibility of survival bias, we used multivariable-adjusted logistic regression models to assess the cross-sectional associations of BMI at baseline, average BMI, and BMI change with risk of prevalent AF at baseline.

All statistical analyses were conducted using Stata 14.2 for Windows (StataCorp LP, College Station, TX, USA) and R 3.5.2 for Windows.

Results

Table 1 presents descriptive characteristics of the population ($n = 15\,214$) that had available information on BMI at the four time points. Mean BMI increased gradually with time. During a median

Table 1 Characteristics of the study population

Age at HUNT-3 (years)	66.6 (9.5)
Female, *n* (%)	8743 (57.5)
BMI_{67} (kg/m^2)	23.2 (3.1)
BMI_{85} (kg/m^2)	24.7 (3.3)
BMI_{96} (kg/m^2)	26.7 (3.8)
BMI_{07} (kg/m^2)	27.6 (4.2)
SBP (mmHg)	138.0 (19.6)
DBP (mmHg)	75.1 (11.4)
Total cholesterol (mmol/L)	5.8 (1.1)
HDL cholesterol (mmol/L)	1.4 (0.4)
Triglycerides (mmol/L)	1.7 (0.9)
Diabetes mellitus, *n* (%)	1054 (6.9)
Current smoker, *n* (%)	2292 (15.7)
Heavy drinkers, *n* (%)	216 (1.5)
University, *n* (%)	975 (6.6)
Physically inactive, *n* (%)	2992 (20.2)
Unmarried, *n* (%)	839 (5.5)

Values are presented as mean ± standard deviation or number (percentages). BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

follow-up of 8.0 years (114 511 person-years), 1149 (7.6%) participants developed AF.

Average body mass index and atrial fibrillation risk

The multivariable-adjusted HRs were 1.2 (95% CI 1.0–1.4) for average BMI 25.0–29.9 kg/m^2 and 1.6 (95% CI 1.2–2.0) for average BMI ≥30 kg/m^2 when compared with those having a normal weight (*Table 2*). The risk was lowest among those with an averaged BMI <18.5 kg/m^2. The relative risks were similar after additional adjustment for metabolic status and chronic disorders (*Table 2*).

We examined the relative importance of the most recent BMI and that of the average of the former BMI values. Average BMI earlier in life was associated with AF risk in the overweight (HR 1.2, 95% CI 1.0–1.5) and obese (HR 1.6, 95% CI 1.1–2.2) group compared with the normal weight group, even after adjustment for BMI at the beginning of follow-up (*Table 2*). In contrast, current BMI was not strongly associated with the risk of AF after adjustment for average BMI earlier in life (*Take home figure*).

When we calculated the relative risks for the four time points separately, the overweight and obesity groups had higher HRs compared with the normal weight group at each time point, respectively (Supplementary material online, *Table S1*).

Body mass index change and risk of atrial fibrillation

The box plots showed BMI increased over the follow-up, regardless of the subsequent AF status (Supplementary material online, *Figure S6*). However, the interquartile range of BMI in the AF development group was higher than that in the AF-free group over time.

Compared with stable BMI, both loss and gain in BMI were associated with increased AF risk (*Table 3*). For the total BMI change, there was an almost three-fold increase in AF risk among those with a BMI gain of more than 5.0 kg/m^2 compared with those with a stable BMI (i.e. change between 2.5 and -2.5 kg/m^2). For early, middle, and late BMI gain, a BMI gain of more than 5 kg/m^2 also showed a considerably higher AF risk compared with a stable BMI. The relative risks for late-period BMI gain were higher than that for the early- and middle-period BMI gain. The results were similar after additional adjustment for chronic disorders and the most recent BMI, respectively (results not shown). *Figure 1* shows relative risks of AF and BMI change (from measurement I to measurement IV) with and without adjustment for the most recent BMI. After adjustment for the most recent BMI, the association of BMI gain with AF risk was largely unchanged, while the association of BMI loss with AF risk was considerably weakened.

Body mass index trajectory, body mass index variability, waist circumference, waist–hip ratio, and risk of atrial fibrillation

Incident AF risk was highest in the obese trajectory group (HR 1.9, 95% CI 1.5–2.4), when compared with the normal weight trajectory group, followed by the overweight trajectory group (HR 1.2, 95% CI 1.0–1.4) (Supplementary material online, *Table S2*).

Participants with the highest degree of weight variability showed higher AF risk compared with those with the lowest weight variability (HR 1.5, 95% CI 1.2–1.8) (Supplementary material online, *Table S2*).

Averaged WC >88/102 cm for women/men was associated with higher AF risk (HR 1.2, 95% CI 1.1–1.4) compared with averaged WC ≤88/102 cm for women/men. The effects disappeared after additional adjustment for BMI (Supplementary material online, *Table S3*). Average WHR was not strongly associated with AF risk (Supplementary material online, *Table S3*). Neither WC change nor WHR change was strongly associated with AF risk (Supplementary material online, *Tables S4* and *S5*).

The role of hypertension

Among hypertensive participants, 44.1% took antihypertensive medication. Compared with participants with long-term lower BMI, those with long-term BMI ≥30 kg/m^2 were more likely to have hypertension and to take antihypertensive medication (Supplementary material online, *Figure S7*). Similarly, with comparison with participants who did not develop AF, those who developed AF were more likely to have hypertension and use antihypertensive medication. However, when we examined the effect of adjustment for hypertension, our results were little changed (results not shown).

Stratified analyses and sensitivity analyses

In stratified analyses, the relative risks for AF tended to be higher for individuals younger than 65 years than for those who were older by categories of average BMI (Supplementary material online, *Table S6*). For BMI change, the relative risks for AF were lower for individuals younger than 65 years than for those who were older (Supplementary material online, *Table S6*). The relative risks for AF were generally similar between women and men by categories of

Table 2 Hazard ratios for atrial fibrillation by categories of average body mass index until end of follow-up and by categories of average body mass index until the HUNT-3 measurement

BMI (kg/m^2)	Events	Person-years	Incidence rate[a]	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI
Average BMI from measurement I to end of follow-up									
<18.5	2	386	5.2	0.8	(0.2–3.0)	0.6	(0.1–4.0)	0.6	(0.1–4.1)
18.5–24.9	467	61 952	7.5	1	(Ref.)	1	(Ref.)	1	(Ref.)
25.0–29.9	555	44 725	12.4	1.2	(1.1–1.4)	1.2	(1.0–1.4)	1.1	(1.0–1.3)
≥30.0	125	7448	16.8	1.6	(1.3–2.0)	1.6	(1.2–2.0)	1.4	(1.0–1.8)
BMI (kg/m^2)	**Events**	**Person-years**	**Incidence rate[a]**	**HR[b]**	**95% CI**	**HR[c]**	**95% CI**	**HR[e]**	**95% CI**
Average BMI from measurement I to measurement IV									
<18.5	1	586	1.7	0.3	(0–2.3)	—	—	—	—
18.5–24.9	495	69 627	7.1	1	(Ref.)	1	(Ref.)	1	(Ref.)
25.0–29.9	537	38 540	13.9	1.3	(1.2–1.5)	1.3	(1.2–1.6)	1.2	(1.0–1.5)
≥30.0	116	5759	20.1	1.9	(1.6–2.4)	1.9	(1.4–2.4)	1.6	(1.1–2.2)

BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a]Incidence rate per 1000 persons-years.
[b]Adjusted for age, sex.
[c]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, and alcohol consumption.
[d]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, alcohol consumption, metabolic status, and chronic disorders.
[e]Adjusted for age, sex, height, smoking status, education, marital status, physical activity, alcohol consumption, and the most recent BMI (BMI_{07}).

average BMI and BMI change, respectively (Supplementary material online, *Table S7*). Neither was there statistical evidence for an interaction with central obesity (results not shown).

In sensitivity analyses, the results were consistent with the main analyses when possible or single-episode AF events were regarded as AF during follow-up (Supplementary material online, *Table S8*). There were 926 AF cases after the second year of follow-up. There was no decrease in the estimates after exclusion of the first 2 years of follow-up (Supplementary material online, *Table S8*). The cross-sectional associations of BMI with prevalent AF at baseline generally echoed the corresponding prospective associations (Supplementary material online, *Table S9*). The models where we adjusted for the frequency, intensity and duration of exercises instead of the categories of physical activity did not materially change the estimates (results not shown).

Discussion

In this large population-based study, long-term obesity and BMI change were associated with increased AF risk. Importantly, obesity earlier in life and BMI change exerted cumulative effects on AF development even after accounting for the most recent BMI. AF risk was increased not only among the obese but also among overweight individuals. A BMI gain of more than 5 kg/m^2 over 40 years was associated with an almost three-fold greater likelihood of AF development. A BMI gain in later life posed higher AF risk than that during an earlier period in life. Increased BMI variability was also associated with increased AF risk.

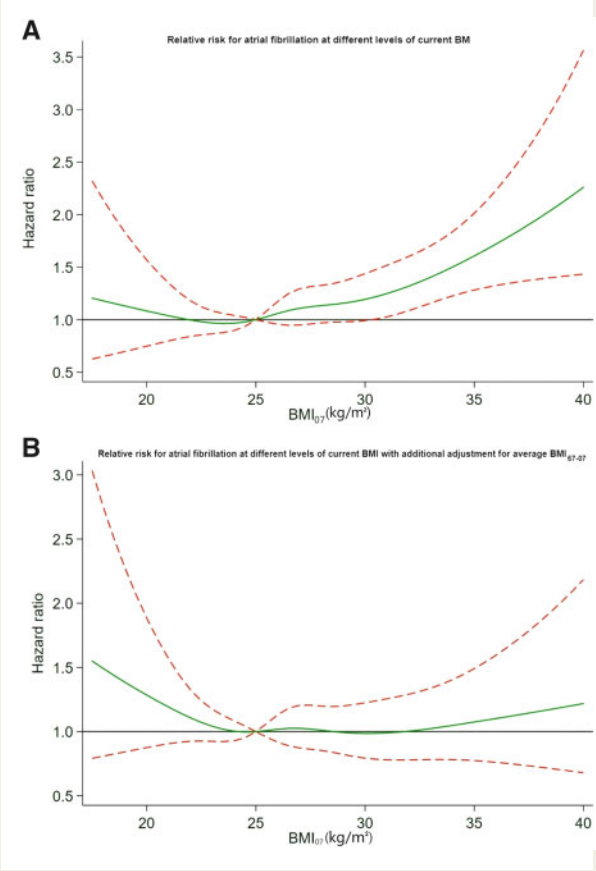
The cumulative effects of long-term obesity and weight change on AF have salient clinical and public health implications. According to 2016 ESC Guidelines for the management of AF,[27] identification and prevention of modifiable risk factors bring significant returns on investment in terms of AF management, number of lives saved and healthcare resources freed. Because obesity leads to AF over an extended period of time, our results highlight the particular importance of obesity prevention and treatment at younger ages to tackle the AF epidemic. Our findings also highlight the importance of considering weight history when assessing AF risk, rather than considering current weight status only.

The findings regarding the effects of long-term obesity are consistent with previous results on the effects of high BMI at a single point[28] and high long-term BMI[6,14] on AF development. To date, only one previous study with direct weight and height measurements has investigated cumulative effects of sustained weight on incident AF.[14] The study included 10 559 individuals with height and weight measurements at four time points (between 1987 and 1998) with a 15-year follow-up, and showed a 39% (95% CI 14–70%) increased AF risk in the long-term obese group compared with the non-obese group after controlling for the most recent BMI. However, the study had a relatively short-time window for repeated BMI measurements and chronic disorders were not ascertained.

Several potential mechanisms link sustained obesity and AF. Sustained obesity increases the risk and severity of left atrial enlargement,[29] atrial fibrosis,[29] electrical derangements of the atria,[29] impaired diastolic function,[30] inflammation,[31] and accumulation of pericardial fat, which are all key mechanisms in the pathogenesis of AF.[28,32] Sustained obesity is also associated with AF risk factors such as hypertension,[33] diabetes mellitus,[34] metabolic syndrome,[35] coronary artery disease,[36] and obstructive sleep apnoea,[28] which may contribute to atrial remodelling and the onset of AF.[28] Specifically, hypertension is a major risk factor for AF and is also strongly associated with obesity.[33] Our study showed that the proportion of hypertensive participants was highest among those with long-term obesity, and participants who developed AF were also more likely to have hypertension. Thus, hypertension might play a role in the pathway between obesity and AF, although our analyses did not support a major mediating effect for hypertension.

Our findings are in line with previous studies on the effect of weight gain on AF development,[5,6,10,13,37] which suggests that weight gain is associated with a 10–60% higher AF risk compared with stable body weight. Regarding weight loss, results from previous research are conflicting. In one prior study that included 14 219 participants with direct weight and height measurements,[13] 10-year weight loss was associated with a 50% higher AF risk compared with stable weight. However, this study only adjusted for prior cardiovascular disease as a chronic condition. Several other previous studies have failed to document a higher AF risk in association with weight loss.[5,6,10]

The effects of weight loss might be due to unmeasured confounding variables. Briefly, unintentional weight loss is part of the natural history of many diseases and a consequence of pre-existing chronic



Take home figure Hazard ratios of atrial fibrillation and body mass index at baseline adjusted for sex, age, height, smoking status, level of education, marital status, physical activity, and alcohol consumption (*A*) and additional adjustment for average body mass index up to baseline (*B*).

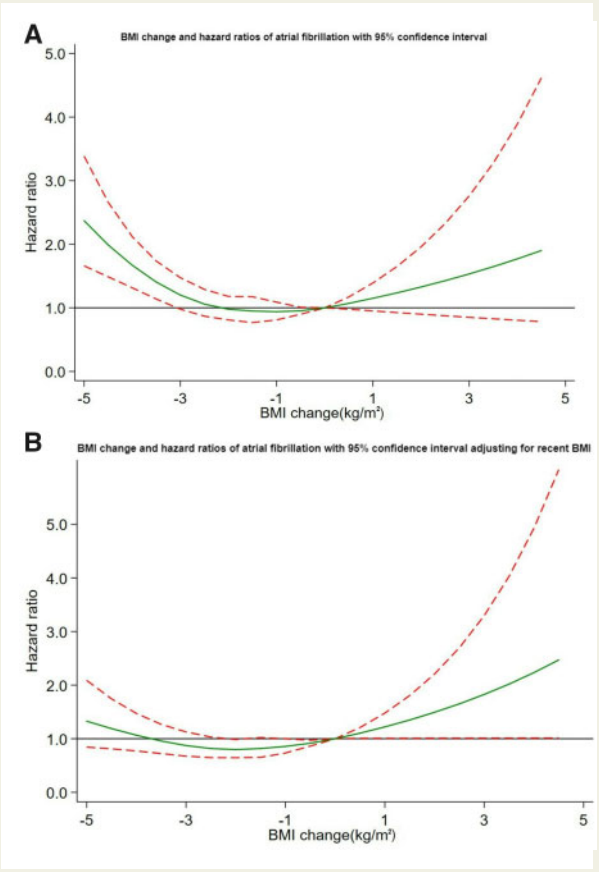


Figure 1 Hazard ratios of atrial fibrillation and body mass index change from measurement I to measurement IV, adjusted for sex, age, height, smoking status, level of education, marital status, physical activity, and alcohol consumption (*A*) and additional adjustment for the most recent body mass index (*B*).

Table 3 Hazard ratios for atrial fibrillation by categories of total, early, middle, and late body mass index change

BMI change (kg/m^2)	Whole period (1967–2007)	Early period (1967–1985)	Middle period (1985–1996)	Late period (1996–2007)
<-5	—	1.5 (0.5–4.6)	—	1.6 (0.8–2.9)
≥-5 to <-2.5	1.3 (0.3–5.4)	0.9 (0.6–1.3)	1.7 (1.0–3.1)	1.2 (0.9–1.5)
≥-2.5 to <2.5	(Ref.)	(Ref.)	(Ref.)	(Ref.)
≥2.5 to <5	1.1 (0.9–1.5)	1.1 (0.9–1.3)	0.9 (0.8–1.1)	1.0 (0.8–1.2)
≥5	2.6 (1.3–5.2)	1.3 (1.0–1.8)	1.1 (0.8–1.4)	1.5 (1.0–2.2)

Results were presented as hazard ratio (95% confidence interval).
Hazard ratios were adjusted for sex, age, smoking status, education, marital status, physical activity, alcohol consumption, and regression slope of BMI.
BMI, body mass index.

disorders,[38] which can distort the true association between body weight and AF risk. Since we could not distinguish the reasons for weight loss, we adjusted for a range of chronic conditions that are associated with unintentional weight loss. However, we cannot exclude the possibility that an occult disease might be associated with both unintentional weight loss and incident AF, which might cause a spurious association between weight loss and AF risk. Another issue is that the CIs of HRs were quite wide among individuals having experienced weight loss due to their relatively small numbers.

The effects of BMI variability on AF risk in our study tend to match previous research that found weight variability to be associated with risks of coronary heart disease and mortality.[26] However, no previous research has examined its effect on the onset of AF, although one previous study found that weight variability >5% was associated with a two-fold greater likelihood of recurrent AF.[39] One possible explanation for the adverse effects of weight variability may be its association with increased risks of hypertension[40] and metabolic syndrome,[41] which are reported to be risk factors for AF.[33,35] Furthermore, weight regain during weight cycling is associated with rapid adipose tissue growth and hyperplasia due to metabolic shifts favouring lipid storage,[42] and adipose tissue growth and hyperplasia is considered to be associated with AF risk.[28]

Additionally, we found that underweight was associated with reduced risk of AF. It has been suggested that underweight is associated with lower risk of hypertension, dyslipidaemia, and insulin resistance,[28] which may in turn reduce AF risk. The association between underweight and cardiovascular disease has been investigated extensively with conflicting results.[43,44] Research on the association of underweight with AF risk is still sparse, since most of studies investigating the association of obesity and AF have included underweight individuals with normal-weight due to the small sample size of the underweight individuals. One recent Korean nationwide population-based study showed that underweight was associated with increased risk of AF (HR 1.2, 95% CI 1.0–1.5).[45] However, this association could be due to unadjusted chronic diseases that confer higher risk of both underweight and AF. In our study, we were able to adjust for a broader spectrum of common chronic disorders than in this earlier study and we found no indication for an increased risk among the underweight participants after extensive adjustment for these disorders. In addition, a meta-analysis of 25 prospective studies on BMI and AF found no evidence of an increased risk with underweight.[3]

Study strengths and limitations

Our study population was stable (the net migration out of the county was 0.3% per year)[15] and homogeneous (less than 3% of the participants was non-Caucasian),[15] reducing the possibility of confounding by factors related to these characteristics. The exceptionally long-time window with repeated measurements of weight and height provided a unique opportunity to capture lifetime overweight and obesity, as opposed to most previous studies restricted to single measurements of BMI. The repeated measurements of weight and height allowed for the detection of weight change and weight variability over life course and quantifying their effects on AF development. The carefully supervised hospital information, register data, and validated AF as well as other cardiovascular events ensured virtually complete follow-up and minimized misclassification of incident AF. In addition, we included a wide range of covariates, including chronic disorders that may distort the associations between body weight and AF risk.

Apart from its strengths, our study also had several limitations. First, BMI does not differentiate between fat tissue and muscle mass, although we also had information on WC. Second, longitudinal data with exceptionally long-time windows are naturally subject to missing data at different time points,[46] which was also the case in the current study. The tuberculosis screening was conducted approximately 40 years before the baseline and was mandatory only for those who were at least 15 years old at that time.[16] Thus, a great proportion of the participants at baseline were simply too young to participate at the tuberculosis survey 40 years earlier. Since AF mainly occurs among the elderly,[47] the loss in statistical power was limited. Third, individuals with obesity may tend to have a higher detection rate of AF due to comorbidity demanding check-ups or hospitalizations, compared with non-obese counterparts. Thus, there may exist a higher detection rate for incident AF among obese than non-obese participants. Fourth, we had no information on intentional and unintentional weight loss. Fifth, the type of AF (paroxysmal vs. persistent) was not available to us. Sixth, we were not able to model BMI as a time-varying covariate because the follow-up for AF started at the last weight measurement (HUNT-3). We excluded participants with AF prior to the last measurement among those who attended HUNT-3, but the previous AF records from those who did not attend HUNT-3 were not available. However, we observed generally similar cross-sectional associations as had been observed for incident AF, providing assurance that substantial survival bias due to exclusion of those who had developed AF in the period up to HUNT-3 was unlikely. In addition, due to the strong age-dependency of AF, relatively few cases occurred prior to HUNT-3. Lastly, we were unable to use the echocardiographic data when investigating the association of BMI and AF risk, since in HUNT, echocardiographic data was available only in a small subset of healthy individuals ($n = 1296$), none of whom had hypertension or cardiovascular disease.[48] As reported previously, these echocardiographic examinations showed that higher BMI was associated with lower left ventricular (LV) function that LV strain was reduced by approximately 5% per 5 kg/m^2 increase in BMI, and that indexed LV mass was higher among those with higher BMI.[48]

Conclusions

In this population-based study with directly measured weight and height, long-term obesity, and weight change were associated with increased AF risk, even after accounting for current BMI. Our findings highlight the potential for population-wide weight control strategies to mitigate the emerging epidemic of AF.

Supplementary material

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

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