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ORIGINAL RESEARCH ARTICLE

Heart failure development in obesity: underlying risk factors and mechanistic pathways

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Abstract

Aims People with obesity are at risk for developing heart failure (HF), but little is known about the mechanistic pathways that link obesity with cardiac dysfunction.

Methods and results We included 2030 participants from the Swedish Obese Subjects study who received conventional obesity treatment. First-time detection of HF was obtained by cross-checking the study population with the Swedish National Patient Register and the Swedish Cause of Death Register. We also examined if atrial fibrillation and myocardial infarction as time-dependent variables could predict incident HF

The mean age of the study cohort was 48.7 years, and 28% were men. The mean body mass index at baseline was 40.1 kg/m^2 and remained stable during a median follow-up of 20.1 years. First-time diagnosis of HF occurred in 266 of patients and was related to male sex, increasing age, greater waist–hip ratio, hypertension, higher cholesterol, diabetes mellitus, and elevated free thyroxine in univariable analysis. Estimated glomerular filtration rate was negatively related to HF risk. In multivariable analysis, atrial fibrillation, which is related to HF with preserved ejection fraction (HFpEF), and myocardial infarction, which is linked to HF with reduced ejection fraction (HFrEF), were strongly associated with incident HF with sub-hazard ratios 3.75 (95% confidence interval: 2.72–5.18, $P < 0.001$) and 3.68 (95% confidence interval: 2.55–5.30, $P < 0.001$), respectively.

Conclusions Both atrial fibrillation and myocardial infarction as time-dependent variables were independently and strongly related to incident HF in people with excess body fat, suggesting two main obesity-related mechanistic pathways leading to either HFpEF or HFrEF.

Keywords Obesity; Heart failure; Risk factors; Atrial fibrillation; Myocardial infarction; Time-dependent variables

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Introduction

People with obesity are at increased risk for developing heart failure (HF),[1] which in turn is associated with impaired quality of life,[2] frequent hospitalizations,[3] and poor outcome.[4] In the US Framingham cohort,[5] the risk of HF increased by 5–7% for each increment of body mass index (BMI) (the weight in kilogrammes divided by the square of the height in metres). In that study, people with obesity (BMI $>$ 30 kg/m^2) had a twofold higher risk of developing HF compared with those with normal weight (BMI 20–25 kg/m^2).[5]

We have previously shown that weight loss induced by bariatric surgery is associated with reduced risk of incident cardiac failure among persons with obesity.[6] Further, this risk declined in parallel with a greater degree of weight loss. These findings strengthen the presumed causal association between obesity and incident HF. Still, little is known about the mechanistic pathways that link obesity with the development of impaired cardiac function.

The adverse effect of obesity on cardiac structure and function is likely to originate from a multitude of obesity-related comorbidities,[7] but the central pathways have not been elucidated. We hypothesized that

obesity-related risk factors such as hypertension, diabetes, dyslipidaemia, volume overload, and sleep apnoea would be likely to mediate a link between obesity and HF via two main mechanisms. First is by inducing microvascular disease leading to diastolic dysfunction reflected by atrial fibrillation (AF), and second is by causing macrovascular disease causing systolic dysfunction via myocardial infarction (MI).

When predicting the risk of HF, most studies consider only the importance of baseline risk factors.[8] However, many important predictors of cardiac dysfunction may change over time, and the detection of time-varying effects may provide important information on biological time patterns and pathophysiological mechanisms that otherwise would be missed. Further, among people with obesity who develop cardiac dysfunction, the proportion who acquire HF with preserved ejection fraction (HFpEF) as in contrast to the percentage of those who develop HF with reduced ejection fraction (HFrEF) has not been studied.

The Swedish Obese Subjects (SOS) study is an ongoing controlled intervention trial that compares the effects of bariatric surgery and conventional obesity care on morbidity and mortality.[9] The present study was limited to the SOS control group receiving conventional obesity care, in which the BMI remained stable during long-term follow-up.

Our goal was to investigate the association between baseline risk factors and the risk of HF among individuals in this population. We also studied if AF and MI as time-dependent variables could predict incident HF because these two conditions would reflect separate pathophysiological mechanisms.

Methods

Swedish Obese Subjects study

The ongoing prospective controlled SOS intervention study (NCT01479452), comparing the effects of weight loss by bariatric surgery and conventional obesity care, has previously been described in detail.[10] In brief, 4047 participants with obesity were enrolled at 25 surgical departments and at 480 primary health care centres between 1 September 1987 and 31 January 2001. The surgery group included 2010 individuals aged 37 to 60 years with aBMI $\geq$ 34 kg/m^2 for men and $\geq$ 38 kg/m^2 for women, who had expressed a preference for treatment with bariatric surgery. A matched control group of 2037 participants was created using an automatic matching programme and 18 matching variables (sex, age, weight, height, waist–hip ratio, blood pressure, serum cholesterol and triglycerides, smoking, diabetes, menopause, four psychosocial variables associated with risk for death, and two personality traits related to treatment preferences). Main exclusion criteria consisted of previous surgery for gastric ulcer, earlier bariatric surgery, malignancy $<$ 5 years, MI $<$ 6 months, bulimic eating pattern, drug or alcohol abuse, and psychiatric or cooperative problems that might render problems with compliance.

Present study subjects

The SOS obese control group comprised 2037 individuals receiving conventional obesity treatment and, in addition, three patients who were initially scheduled for surgery but changed their mind and had declined surgical intervention (n = 2040). For the purpose of the present study, we excluded those who had HF at baseline (n = 10), which resulted in a study group consisting of 2030 persons. All of these individuals were followed up and treated by primary health care centres. The treatment was not standardized and could range from basic diet recommendations to advanced counselling involving behaviour changes with respect to food intake, physical activity, and weight control. Follow-up visits were performed at 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years. Our study complied with the Declaration of Helsinki, and seven regional ethics review boards in Sweden approved the SOS study protocol. All participants gave written or oral consent.

Outcome

The main outcome of the present study was first-time detection of HF as a principal diagnosis among participants, by cross-checking the SOS database on obese control subjects with the Swedish National Patient Register[11] and the Swedish Cause of Death Register[12] for the following diagnosis codes: 428 (International Classification of Diseases-9 until 1996) and I50 (International Classification of Diseases-10 from 1997). Patients with HF as a secondary diagnosis were not included in the analysis. The Swedish health care system is nationalized and regulated by the Health and Medical Service Act. All Swedish citizens have a specific personal identity number that is recorded in connection with each health care contact, which makes it feasible to follow the interaction of the Swedish population with the health care system.[13] The National Patient Register has information on diagnoses for all inpatients in Sweden since 1987 and from all hospital-based outpatient visits since 2001. The Swedish Cause of Death Register, which originates from 1961, includes the presumed causes of death for all citizens registered in Sweden at the time of their death. In addition, we performed a clinical endpoint adjudication for the diagnosis of HF in a subgroup of patients (n = 108) by examining medical records for clinical history, electrocardiography, laboratory values, chest X-ray, and echocardiography when such examinations were available.

Previous medical history and baseline measurements

Self-reported information on previous leisure time physical activity, medication, smoking, and alcohol intake was obtained through a baseline questionnaire. Data on previous cardiovascular disease were obtained from the Swedish National Patient Register and based on the International Classification of Diseases ninth and tenth revisions (ICD-9/ICD-10) for AF: codes 427D/I48, for MI:codes 410/I21, I22; for intracerebral bleeding:codes 431/I61; for cerebral artery occlusion:codes 433, 434/I63, I65, and I66; and for acute non-defined stroke:codes 436/I64. Angina pectoris, peripheral *Proof.aspx* artery disease, transitory ischaemic attacks, and subarachnoid bleeding were not included in this definition.

At baseline and regular follow-up appointments, body weight was measured with electronic or calibrated scales. Other anthropometric measurements included waist circumference, waist–hip ratio, and sagittal diameter as assessments of abdominal obesity.[14] Blood samples were acquired and analysed by the Central Laboratory at Sahlgrenska University Hospital (accredited according to the international standard ISO 15189:2012) at baseline and after 2, 10, 15, and 20 years of follow-up. Hypertension was defined as systolic pressure $>$ 140 mmHg, or diastolic pressure $>$ 90 mmHg, or self-reported use of anti-hypertensive medication. Diabetes was defined as a fasting blood glucose level of at least 6.1 mmol per litre (110 mg per decilitre) or self-reported use of a prescribed antidiabetic medication. Estimation of glomerular filtration rate (eGFR) was achieved by using the equation provided by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[15]

Time-dependent variables

Time-dependent covariance occurs when a covariate changes over time during the follow-up period.[16] This is a fairly common phenomenon in clinical research. Such variables can be analysed with the Cox regression models to estimate their effect on survival time.[17] In the present study, we studied the ability of AF and MI as time-dependent variables to predict incident HF in both univariable and multivariable analyses.

Information on AF during follow-up was obtained by cross-checking the SOS database on obese control subjects with the Swedish National Patient Register for the following diagnosis codes: 427D (International Classification of Diseases-9 until 1996) and I48 (International Classification of Diseases-10 from 1997). In a similar manner, information on MI during follow-up was acquired by cross-checking the SOS database with the Swedish National Patient Register for the following diagnosis codes: 410 (International Classification of Diseases-9 until 1996), as well as I21 and I22 (International Classification of Diseases-10 from 1997).

Statistics

All statistical analyses were performed with the Stata statistical software (StataCorp, 2017. Stata Statistical Software: Release 15). Data are presented as mean values with standard deviations, medians with interquartile ranges, or as numbers and percentages as appropriate. Baseline comparisons between subgroups were performed with an unpaired *t*-test for normally distributed data, Mann–Whitney *U* test for non-parametric data, and Fisher's exact test for categorical data.

Participants were followed until the first-time *principal diagnosis* of HF, death, or 31 December 2016, at which point the National Patient Register and Cause of Death Register were complete and the registers were linked. Persons who reported a history of HF at baseline (n = 10) were excluded from all analyses resulting in a total study group of 2030 patients.

Cumulative incidence of HF was performed on a per protocol basis. Persons without HF who died [n = 317 (16%)] were treated as competing events. Those who emigrated [n = 24 (1.2%)], chose to undergo bariatric surgery [n = 285 (14)], or were alive at the end of follow-up [n = 1138 (56%)] were treated as censored observations. Differences in sex and various categories of age and BMI were assessed with a log-rank test.

Univariable and multivariable models were applied to obtain relative risk estimates expressed as sub-hazard ratios for preselected baseline risk factors considered traditional for HF according to the literature. In addition, analyses were performed including time-dependent variables (AF and MI) as predictors for incident HF. We report both unadjusted and adjusted results expressed as sub-hazard ratios. All statistical tests were two-tailed, and P values of less than 0.05 were considered statistically significant.

Results

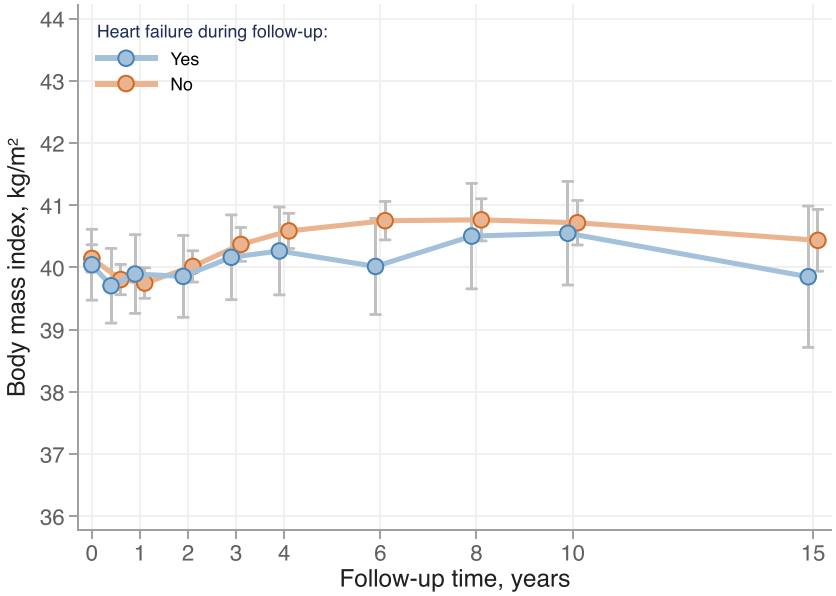
Among the 2030 participants in the present study, 266 developed HF and 1764 did not (*Table 1*). Patients with incident HF were more likely to be men, older, have a higher degree of abdominal fat, hypertension, dyslipidaemia, diabetes, higher levels of circulating free T4, and more often previous cardiovascular disease (*Table 1*). The baseline BMI of the total study group was 40.1 kg/m^2 and remained unchanged (40.1 kg/m^2) after a median follow-up of 20.1 (interquartile range 16.2–23.3) years (*Figure 1*). There were no significant differences in BMI between participants with or without HF at baseline

Table 1 Baseline characteristics of the total study group and for participants with and without incident heart failure

Variable	Total (n = 2030)	Heart failure (n = 266)	No heart failure (n = 1764)	P value
Male sex, n (%)	584 (29)	116 (44)	468 (27)	<0.001
Age (years)	48.7 ± 6.3	51.7 ± 6.2	48.2 ± 6.1	<0.001
Body weight (kg)	115 ± 17	116 ± 117	115 ± 17	0.317
Body mass index (kg/m^2)	40.1 ± 4.7	40.0 ± 4.7	40.1 ± 4.7	0.743
Waist circumference (cm)	120.2 ± 11.3	121.6 ± 10.8	120 ± 11.3	0.024
Waist–hip ratio	1.00 ± 0.1	1.00 ± 0.1	0.97 ± 0.1	<0.001
Sagittal diameter (cm)	27.4 ± 3.7	28.3 ± 3.8	27.2 ± 3.6	<0.001
Systolic BP (mmHg)	137.9 ± 17.9	143.2 ± 17.9	137.1 ± 17.8	<0.001
Diastolic BP (mmHg)	85.1 ± 10.7	87.5 ± 10.4	84.8 ± 10.6	<0.001
S-cholesterol (mmol/L)	5.6 ± 1.1	5.9 ± 1.1	5.6 ± 1.0	<0.001
S-HDL cholesterol (mmol/L)	1.4 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	0.140
S-Apolipoprotein B/A1 ratio	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.003
Blood glucose (mmol/L)	4.9 ± 1.8	5.2 ± 2.0	4.9 ± 1.8	0.019
S-Insulin (mU/L)	15.2 (0.12–6.89)	16.5 (11.4–23.6)	15.0 (10.5–22.3)	0.026
S-Free T4 (pmol/L)	15.7 ± 3.6	16.5 ± 4.9	15.6 ± 3.3	0.002
S-TSH (IU)	1.58 (1.02–2.35)	1.78 (1.10–2.62)	1.57 (1.01–2.34)	0.374
S-Creatinine (mmol/L)	69.5 ± 9.5	71 ± 12.1	69.3 ± 9.1	0.010
eGFR, CKD-EPI (mL/min/1.73 m^2)	95.3 ± 11.6	94.1 ± 12.8	95.5 ± 11.4	0.090
Year of inclusion (date)	1994.3 ± 3.5	1993.2 ± 3.3	1994.5 ± 3.4	<0.001
Leisure time physical activity, n (%)	1335 (66.1)	171 (64.3)	1,164 (66.4)	0.510
Hypertension, n (%)	1301 (63.8)	211 (79.3)	1,081 (61.4)	<0.001
Diabetes, n (%)	257 (12.7)	49 (18.4)	208 (11.8)	0.009
Smoking daily, n (%)	420 (20.8)	63 (23.7)	357 (20.3)	0.231
Alcohol (g/daily)	2.08 (0.12–6.89)	2.45 (0–9.15)	2.06 (0.20–6.63)	0.062
History of AF, n (%)	14 (0.7)	3 (1.1)	11 (0.6)	0.456
History of MI, n (%)	27 (1.3)	12 (4.5)	15 (0.9)	0.005
History of CVD, n (%)	47 (2.3)	14 (5.3)	33 (1.9)	0.017

AF, atrial fibrillation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (CKD-EPI model); MI, myocardial infarction. Values are presented as means ± standard deviations, medians (interquartile ranges), or numbers (percentages). P values denote comparisons between participants with and without incident heart failure.

Figure 1 Change in body mass index among participants with and without incident heart failure during 15 years of follow-up.



or during follow-up. More detailed baseline data for the control group have been presented in previous SOS publications.[18]

A few subjects had attained a BMI below the inclusion criterion when baseline measurements were performed. After the SOS surgical and control subjects had been

matched, there was a substantial delay until bariatric surgery could be performed (often more than 1 year), which explains why some control subjects had lost weight when baseline measurements were performed at around 4 weeks prior to intervention.[18]

Incidence of heart failure

A first-time diagnosis of HF as a *principal diagnosis* occurred in 266 of patients, and the clinical adjudication performed in a subsample of 108 patients confirmed that the HF diagnosis was correct in 103 (95%) of cases. Among 171 subjects, the HF diagnosis was registered within the context of hospitalization; in 62 cases, the syndrome was identified at an outpatient clinic; and in 33 persons, HF was detected under fatal conditions. The incidence rate for HF cases per 1000 patient years for the total study group was 7.19 [95% confidence interval (CI): 6.38–8.11 5.64]; for women, 5.64 (95% CI: 4.80–6.62); and for men, 11.2 (95% CI: 9.33–13.43.1). The unadjusted cumulative incidence rates were 2.9% (95% CI: 2.2–3.7%), 6.2% (95% CI: 5.2–7.3%), and 10.8% (95% CI: 9.5–12.4%) after 10, 15, and 20 years, respectively.

The risk of incident HF was higher in men compared with women (*Figure 2*), and the risk increased significantly along with age for both sexes (*Figure 3*). HF development was, on the other hand, not related to the degree of BMI in our study population, which was composed of individuals with overweight and obesity (Supporting Information, *Figure S1*). Self-reported use of conventional HF medication over time, including beta-blockers, agents acting on the renin–angiotensin–aldosterone system (angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers), and loop diuretics, increased significantly more among those with incident HF compared with those without (*Figure 4*).

Univariable and multivariable analyses

Univariable baseline predictors of incident HF in the total study population included male sex, increasing age, waist–hip ratio, hypertension, higher cholesterol, diabetes mellitus, and elevated free thyroxin, whereas eGFR was negatively related to HF risk (*Table 2*). Also, AF and MI as time-dependent covariates displayed strong univariable associations with incident HF (sub-hazard ratio 5.38, 95% CI: 4.06–7.14 and 5.54, 95% CI: 4.04–7.60, respectively). In multivariable analysis for the total study group, the baseline conditions that were independently associated with increased risk of HF included advancing age, waist–hip ratio, and free thyroxine. In this model, the sub-hazard ratios for AF and MI as time-dependent variables remained highly significant, 3.75 (95% CI: 2.72–5.18, $P < 0.001$) and 3.68 (95% CI: 2.55–5.30, $P < 0.001$), respectively. Smoking and alcohol intake at baseline were not related to development of HF, neither in univariable nor multivariable analysis. Age as a time-dependent variable was not significantly related to

Figure 2 Cumulative incidence of heart failure by sex during long-term follow-up.

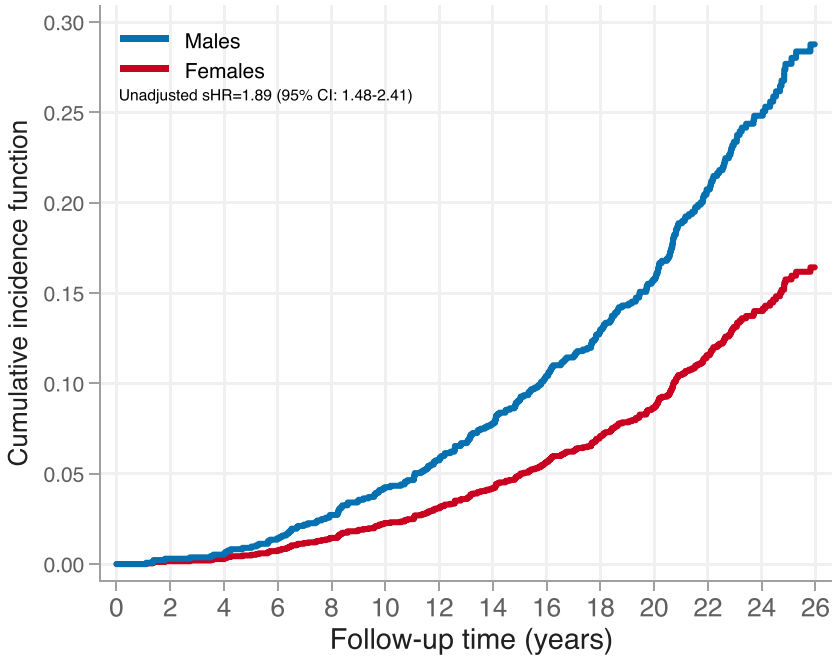


Figure 3 Cumulative incidence for heart failure in different age groups during long-term follow-up.

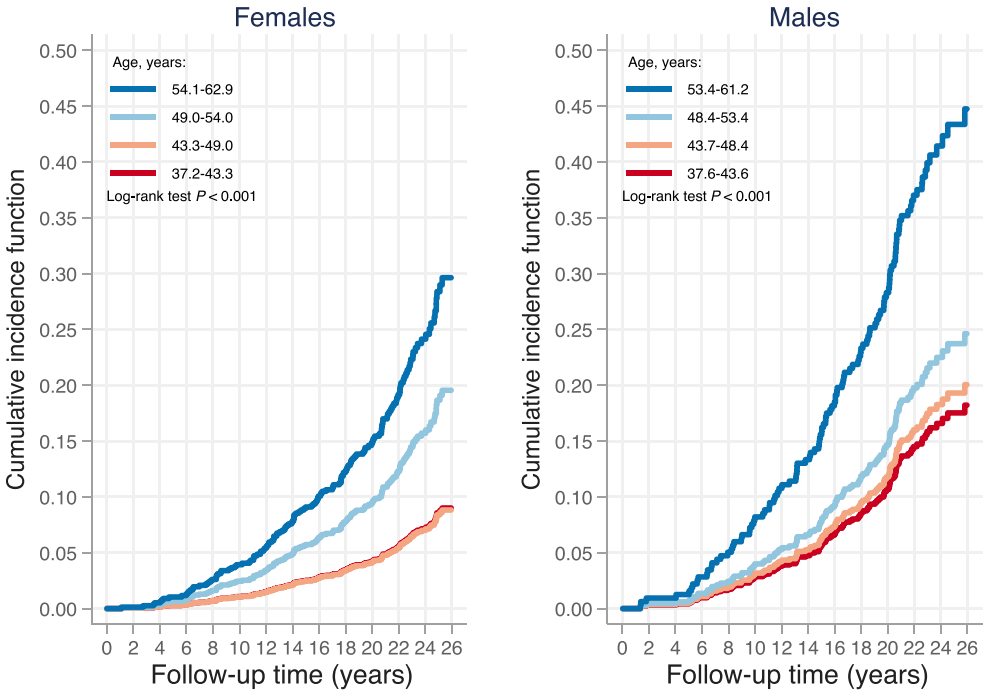


Figure 4 Cumulative incidence of self-reported use of conventional heart failure medications during follow-up.

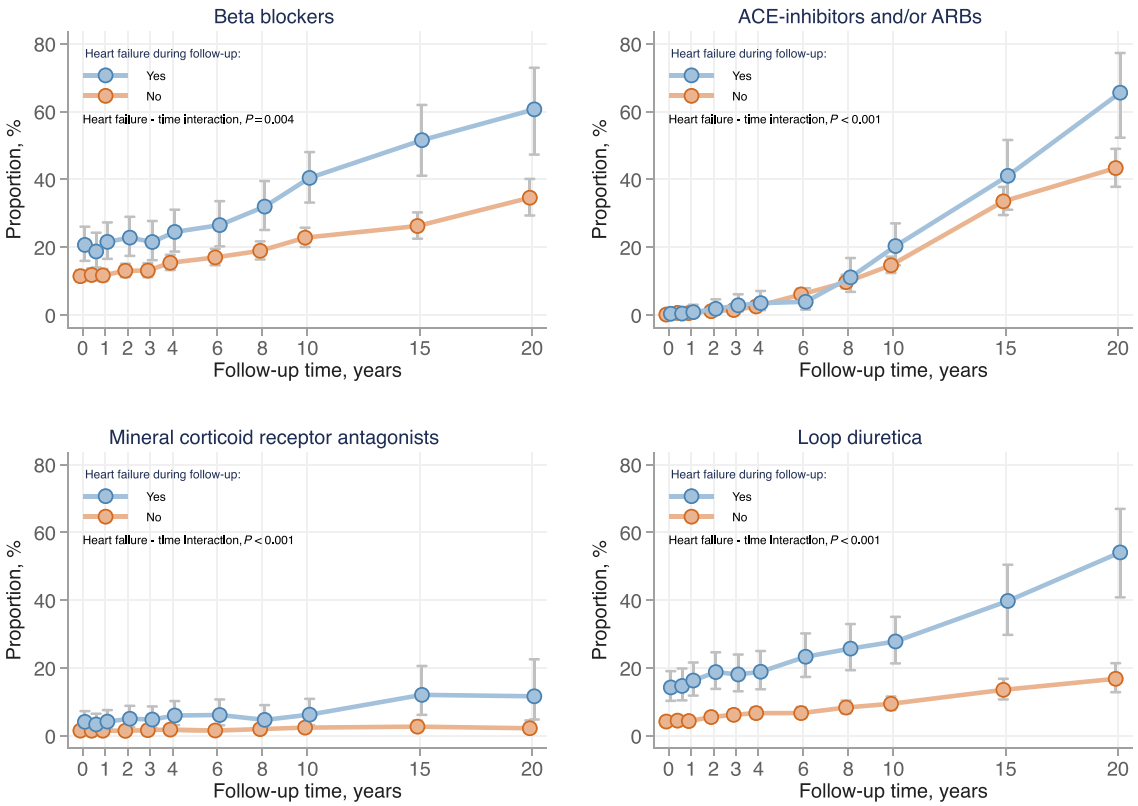


Table 2 Univariable and multivariable associations between selected baseline factors and risk of heart failure for the total study[a]

Variable	Total group univariable (n = 2030)	Total group multivariable (n = 2030)
Sex (men vs. women)	1.89 (1.48–2.41)***	1.29 (0.89–1.86)
Age (per 5 years)	1.51 (1.35–1.69)***	1.36 (1.18–1.55)***
Body mass index (per 5 kg/m^2)	1.02 (0.90–1.16)	1.02 (0.88–1.19)
Waist–hip ratio	1.50 (1.26–1.78)***	1.29 (1.02–1.62)*
Inclusion year	0.99 (0.95–1.03)	0.97 (0.93–1.01)
Leisure-time physical activity (yes vs.no)	0.87 (0.68–1.12)	0.86 (0.65–1.14)
Hypertension (yes vs. no)	2.04 (1.52–2.74)***	1.14 (0.83–1.57)
S-cholesterol (per mmol/L)	1.21 (1.09–1.35)***	1.05 (0.93–1.18)
Diabetes mellitus (yes vs. no)	1.70 (1.24–2.32)**	0.95 (0.66–1.39)
Free thyroxine (per 5 pmol/L)	1.35 (1.18–1.54)***	1.29 (1.10–1.51)***
Smoking (yes vs. no)	1.17 (0.88–1.55)	1.15 (0.83–1.59)
Alcohol intake (per 10 g daily)	1.16 (1.03–1.31)	1.01 (0.87–1.17)
eGFR (per 10 mL/min/1.73 m^2)	0.88 (0.79–0.97)*	0.92 (0.79–1.07)
Atrial fibrillation (time-dependent)	5.38 (4.06–7.14)***	3.75 (2.72–5.18)***
Myocardial infarction (time-dependent)	5.54 (4.04–7.60)***	3.68 (2.55–5.30)***

eGFR, estimated glomerular filtration rate.
[a]Values are given as sub-hazard ratios along with 95% confidence intervals in parenthesis.
*$P < 0.05$
**$P < 0.01$
***$P < 0.001$

outcome and therefore only included as a baseline covariate in our models.

In multivariable analyses stratified for sex and accounting for AF and MI (Supporting Information, *Table S1*), eGFR was independently and negatively related to HF risk for men and age and free thyroxine were independently and positively related to HF risk in women.

Discussion

The present study sheds light on underlying risk factors and potential mechanistic pathways related to the development of HF in obesity. Among 2030 patients with obesity free from HF at baseline, a total of 266 patients developed incident HF during a median follow-up of 20.1 years. Baseline variables that were independently associated with HF development were similar to that reported in previous publications[19] and included increasing age, male sex, abdominal obesity, hypertension, higher cholesterol levels, and diabetes, whereas superior renal function was associated with a reduction in incident HF. In addition, we observed that a higher free thyroxine level was a risk factor for HF in obesity, which is a novel finding.

When explanatory variables for HF risk do not change over time or when data are only collected at one time point as explanatory parameters, it is appropriate to use static variables to explain incident HF. Conversely, many important predictors of cardiac dysfunction may vary over time,[20] and if they are not accounted for, important information on time-related pathophysiological mechanisms may be missed. We applied AF and MI as time-dependent variables and found that they were strongly related to incident HF in both unadjusted and adjusted analysis. Once these time-dependent variables were accounted for, the relationship between hypertension and diabetes on the one side and incident HF on the other became non-significant. In a recent publication by Rosengren *et al*.[21] studying obesity in adolescence and long-term risk of early HF in men, both hypertension and diabetes demonstrated high multiple-adjusted hazard ratios for the risk of HF. Our findings, along with those of Rosengren *et al*., support our hypothesis that obesity-related hypertension and diabetes mediate the development of diastolic dysfunction reflected by AF, or systolic dysfunction caused by MI. Thus, it appears that AF and MI may reflect two different mechanistic pathways for the development of HF in people with obesity.

One mechanism by which obesity is likely to increase the risk for AF includes increased cardiac output and development of hypertension,[22] exerting increased preload and afterload on the left ventricle, leading to left ventricular hypertrophy.[23] Other harmful factors include diabetes,[24] obstructive sleep apnoea,[25] and systemic inflammation.[26] These risk factors are likely to cause excessive deposition of collagens, abnormal glycosylation of proteins, and crosslinking of collagen in the myocardium, which is supported by experimental and human studies.[27,28] This process leads to reduced diastolic compliance with increased left ventricular filling pressures and left atrial enlargement,[29] which in turn contributes to the development of AF and subsequent HF.[30] This is likely to be an important mechanistic pathway contributing to the development of HFpEF. In support of our assertion is a study by Sartipy *et al*., who found that AF was more common in patients with normal or high ejection fraction,[31] and

the paper by Paulus and Tschöpe,[32] in which they propose obesity-related comorbidities as drivers for myocardial remodelling and diastolic dysfunction through microvascular endothelial inflammation.

Another mechanistic pathway likely to cause HF in obesity, abdominal obesity in particular, is the development of cardiovascular risk factors leading to coronary heart disease and MI. Obesity is associated with atherosclerotic risk factors including hypertension, dyslipidaemia, and diabetes leading to atherosclerotic coronary plaque progression and coronary artery disease.[33–35] MI leads to tissue damage, which is replaced by a fibrotic scar and followed by left ventricular remodelling in the form of dilatation and declining systolic function and development of HF with reduced ejection fraction (HFrEF).

Obesity, especially abdominal obesity, is associated with various haemodynamic, neurohormonal and metabolic disturbances that affect cardiac structure and function.[36] Furthermore, epicardial fat may also contribute to both phenotypes through local effects on metabolism and inflammation.[37] In the present study, independent risk factors associated with the development of HF differed between women and men. This resonates with the proposals that obesity may be associated with distinct forms of HFpEF[32,38] and HFrEF[39] that differ between the sexes and may require specific treatment measures.[40]

Most epidemiological studies report that the incidence of HF remains fairly stable over time, but the prevalence is constantly rising,[41,42] which is probably related to an aging population and an improvement in HF survival. The obesity epidemic[43] and the contemporary diabetes epidemic[44] are frequently referred to as contributors to the steady incidence and rising prevalence of HF.[45,46] A high eGFR reflecting normal renal function was significantly protective of HF development, particularly in men. The cardiorenal syndrome, which implies renal dysfunction related to cardiac failure, is a common disorder and is independently associated with poor prognosis in patients with impaired diastolic or systolic heart function.[47]

It should be pointed out that BMI was not related to HF risk, neither in unadjusted nor in adjusted analysis. A likely explanation is that all study subjects had obesity, and therefore, the range of BMI was probably too limited to have an impact on HF risk. Also, smoking and alcohol intake did not display a significant link to incident HF, which is in contrast to the relation between these risk factors and cardiac dysfunction reported in previous studies.[48] We suspect that these may be false-negative findings (type II statistical error) due to a rather small sample size (n = 2030) compared with other larger epidemiological trials.[49] Also, a somewhat low frequency of smoking in the total study group (21%) and a moderate alcohol consumption among study participants (alcohol abuse was an exclusion criterion in the SOS study) may have contributed to the lack of association between these risk factors and incident HF. Conversely, abdominal obesity was associated with incident HF in both unadjusted and adjusted analysis, supporting an active role of visceral fat with respect to the development of HF, in particular HFpEF.[50]

Of notice is the relationship between increasing circulating levels of free thyroxine within normal reference values and incident HF among subjects with obesity in both unadjusted and adjusted analysis. This relationship, which has received little attention previously,[6] was apparent in the total study group and among women, in particular. Obesity has been shown to be associated with disturbances in thyroid function,[51] including higher free thyroxine levels within the normal range. This in turn might predispose to AF[52,53] and subsequent HF. Also, higher levels of free thyroxine could affect cardiac metabolism and energy homeostasis and contribute to impaired cardiac function.[54] The use of thyroid preparations was similar both in patients who developed HF and in those who did not and, therefore, unlikely to explain our findings. The relationship between elevated thyroxine levels within the normal range and incident HF in people with obesity deserves further research.

During follow-up, self-reported use of conventional HF medication including beta-blockers, agents acting on the renin–angiotensin–aldosterone system (angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers), and loop diuretics tended to increase in both groups, but to a greater degree in subjects with incident HF, which supports the validity of the diagnosis. The use of mineralocorticoid antagonists increased only in patients with HF diagnosis, but less than expected, which might reflect that many of the HF cases occurred early in the time course of the study before mineralocorticoid antagonists were introduced in guidelines as Class I, Level A treatment for HFrEF.[55] An increase in these medications could also to some degree be related to an aging obese population with increasing prevalence of hypertension and fluid retention unrelated to HF. In some cases, a loop diuretic could have been added to treat oedema related to lower extremity thrombosis[56] or lymphedema,[57] which are common comorbidities of obesity.

The proportion of obese people who acquire HFpEF opposite to those who develop HFrEF has not been studied specifically. Still, it is not unlikely that the percentages of these two HF phenotypes among subjects with obesity are similar to that observed in the general population.[58] Bursi *et al*. studied ejection fraction measured by echocardiography in 556 subjects with HF from the general population in the US Olmsted County and found that somewhat more than half of the patients had HFpEF.[59] In that study, patients who had HFpEF displayed a high mortality rate, which was comparable with that of patients with reduced ejection fraction. This in line with previous studies[60] and supports the importance of HF as a serious syndrome independent of underlying mechanism and ejection fraction.

In summary, obesity may lead to HF through two main different mechanistic pathways, both leading to impaired cardiac function. One of the pathways appears to result in HFpEF through myocardial fibrosis and cardiac stiffening triggering AF,[32] and the other seems to promote HFrEF via coronary atherosclerosis and MI resulting in left ventricular remodelling with impaired systolic function.[39] The strong relationship between incident HF, with AF on one side, and with MI on the other, supports these different mechanistic pathways. However, it is not unlikely that both mechanisms may operate together and reinforce each other to cause cardiac dysfunction in people with obesity.

Strengths and limitations of the study

The main strength of our study is a well-defined cohort, a prospective design, and long-term follow-up of study participants. On the other hand, the present study population was not selected randomly from the general population. Instead, participants had responded to advertisements in printed media regarding a weight loss study, in which they expressed a preference for conventional treatment. The control subjects in the SOS study were included based on an automatic matching programme to correspond to the population with obesity that was treated with bariatric surgery. Still, we feel that there is no reason to believe that our study group should differ largely from the obese population in general.

From an epidemiological standpoint, a study with 2030 participants and 266 events is not all that large. This may explain why, for example, diabetes, smoking, and alcohol consumption did not emerge as independent risk factors for incident HF as in other larger epidemiological studies. Thus, it is possible that these are false-negative findings (type II statistical errors). It is also possible that these obesity-related comorbidities mediate HF through AF and MI. Further, we did not have access to a matched control group from the general population, which would have enriched the study. Also, natriuretic peptides, such as N-terminal pro-brain natriuretic peptide, were not measured in the SOS study, which is a clear limitation, especially with respect to the predictive ability of our statistical models.

Neither HF nor AF were pre-specified endpoints in the SOS study; instead, these diagnoses were collected by crosslinking the SOS database with the National Patient Register on inpatient and outpatient diagnosis codes and for HF by crosslinking SOS data with the Swedish Cause of Death Register. Outpatient diagnoses of HF, AF, and MI were not available for the first 15 years of the study, but we expect that missing data are limited because these conditions are most often diagnosed in hospitalized patients. Further, the National Patient Register has been shown to be a powerful tool to study health-related outcomes in the Swedish populations, and the positive predictive values for HF (*principal diagnosis*), AF, and MI in this register have been found to be 88%, 97%, and 98%, respectively.[61] In another study examining the reliability of the National Patient Register, HF as a *principal diagnosis* was found to have a validity of 95%.[62] Further, the Cause of Death Register covers 99% of deaths in the Swedish population.[12] Although the National Patient Register does not cover primary care, it is unlikely that we missed many cases of AF because in Sweden, patients with this condition are customarily referred to a hospital for diagnostic work-up.

It would have been desirable to include more time-dependent variables to our statistical models, but collection of such data would have required better patient adherence to study visits, which was incomplete during long-term follow-up. Thus, due to missing data, we were not able to incorporate additional time-varying variables in our models. On the other hand, data on AF and MI retrieved from the National Patient Register were practically complete and, in our opinion, the most important time-dependent variables with respect to unravelling the pathophysiological mechanism leading to HF in obesity.

Conclusions

In the present study, we confirm that baseline variables including male sex, age, abdominal obesity, hypertension, higher cholesterol, and diabetes are all significant predictors of HF in people with obesity, whereas normal renal function exercises a protective effect on cardiac dysfunction. Notably, higher levels of circulating free thyroxine are linked to incident HF in obesity, particularly in women. Mechanisms by which excessive body fat accumulation causes HF fall into two categories. First is the development of diastolic dysfunction, which is reflected by AF, and second is the progress of systolic dysfunction, which is likely to be the result of MI. It is plausible that HFpEF and HFrEF occur at similar frequencies in relation to obesity, but both mechanisms may operate together, reinforcing each other to cause cardiac dysfunction in people with obesity.

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Conflict of interest

None of the authors has any conflicts of interest to declare with respect to the present study.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cumulative incidence for heart failure in different BMI categories during long-term follow-up.
Table S1. Univariable and multivariable associations between selected baseline factors and risk of heart failure for the total study group and for women and men separately.

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