Body weight in adolescence and long-term risk of early heart failure in adulthood among men in Sweden

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Aims	To study the relation between body mass index (BMI) in young men and risk of early hospitalization with heart failure.
Methods and results	In a prospective cohort study, men from the Swedish Conscript Registry investigated 1968–2005 (n = 1 610 437; mean age, 18.6 years were followed 5–42 years (median, 23.0 years; interquartile range, 15.0–32.0), 5492 first hospitalizations for heart failure occurred (mean age at diagnosis, 46.6 (SD 8.0) years). Compared with men with a body mass index (BMI) of 18.5–20.0 kg/m^2, men with a BMI 20.0–22.5 kg/m^2 had an hazard ratio (HR) of 1.22 (95% CI, 1.10–1.35), after adjustment for age, year of conscription, comorbidities at baseline, parental education, blood pressure, IQ, muscle strength, and fitness. The risk rose incrementally with increasing BMI such that men with a BMI of 30–35 kg/m^2 had an adjusted HR of 6.47 (95% CI, 5.39–7.77) and those with a BMI of $\geq$35 kg/m^2 had an HR of 9.21 (95% CI, 6.57–12.92). The multiple-adjusted risk of heart failure per 1 unit increase in BMI ranged from 1.06 (95% CI, 1.02–1.11) in heart failure associated with valvular disease to 1.20 (95% CI, 1.18–1.22) for cases associated with coronary heart disease, diabetes, or hypertension.
Conclusion	We found a steeply rising risk of early heart failure detectable already at a normal body weight, increasing nearly 10-fold in the highest weight category. Given the current obesity epidemic, heart failure in the young may increase substantially in the future and physicians need to be aware of this.
Keywords	Heart failure • Adolescence • Hospital admission • Epidemiology

Heart failure, with a prognosis worse than that of many common forms of cancer,[1] predominantly afflicts the elderly. However, we have recently documented an increasing incidence of heart failure in Sweden among persons younger than 45 years, while there was a fall among those aged 55 years and older.[2]

An obvious factor that coincides with the increase in heart failure among the young is a marked rise in body weight and obesity[3] in Sweden and elsewhere. Obesity is a recognized risk factor for heart failure,[4] starting at a high-normal or slightly elevated body mass index (BMI).[5] In a study of Danish male conscripts,[6] high BMI was associated with increased risk of heart failure but because there were only 106 cases the effect of body weight across a wide range could not be studied.

The Swedish registry of conscripts contains anthropometric data on >1.5 million young men. Through linkage to the Swedish national inpatient registry (IPR), we evaluated all cases of

hospitalizations for heart failure in relation to their BMI over an extended period.

Methods and statistics

Participants

In a prospective cohort study, we used data from the Swedish Conscript registry.[7−9] Until recently, Swedish law required that all 18-year-old Swedish men enlist. Exemptions were granted only for men serving time in prison, or with severe chronic medical or mental conditions (∼2−3% each year). From 1968 to 2005, all enlisted men ($n = 1\,810\,348$) underwent standardized physical and cognitive examinations at six conscription centres, where they were seen by a psychologist and a physician. After excluding men enlisting late (aged $\geq$25 years) ($n = 49\,208$) and men with missing BMI ($n = 150\,703$), 1 610 437 men were included. The Ethics Committee of the University of Gothenburg approved the study.

Swedish military service conscription register data and covariates from other sources

The 2-day examination involved measurement of weight, height, and blood pressure in the supine position after 5−10 min of rest. Height (m) was measured by use of wall-mounted stadiometers, and weight (kg) was measured by use of analogue or digital scales. Body mass index was calculated as weight/height[2]. Cardiovascular fitness was assessed using cycle ergometry.[7] The cognitive performance tests and fitness tests[8,9] are described in Supplementary material online.

The longitudinal integration database for health insurance and labour market studies (Swedish acronym LISA) held by Statistics Sweden provided information on parental education (80% coverage).

Follow-up procedures

Sweden has a universal healthcare system that provides low-cost hospital care to all citizens. Data from the Swedish Military Service Conscription Register was linked to the Swedish inpatient and death registries through the Swedish personal identification number.

Definition of heart failure and comorbidities

Because a large proportion of patients with heart failure had other primary discharge diagnoses (e.g. cardiomyopathy or congenital heart disease), a first-ever heart failure diagnosis code in any position was accepted. The *International Classification of Diseases, Eighth Revision* (ICD-8) was in use from 1968 to 1986, the ICD-9 from 1987 to 1996, and the ICD-10 since 1997. We defined heart failure by 427,00 and 427,10 for ICD-8, 428 for ICD-9, and I50 for ICD-10.

Diagnoses for concomitant or pre-existing comorbidity were included up to the point of the heart failure discharge diagnosis and are listed in the Supplement. We assigned mutually exclusive causes of heart failure in the following hierarchical order[2]: (i) congenital heart disease and valvulopathies, (ii) coronary heart disease (CHD) and/or diabetes and/or hypertension, (iii) cardiomyopathy, and (iv) other causes.

Statistical analysis

Incidence rates and corresponding 95% confidence intervals were calculated using Poisson regression. We used Cox proportional hazards models to assess the influence of BMI at the time of conscription and potential confounders on a first hospitalization for heart failure. Subjects were followed from the date of conscription until the time of (i) first heart failure hospitalization, (ii) death, (iii) emigration, or (iv) the end of follow-up (31 December 2010) (minimum, 5 years; maximum, 42 years at the time of the last follow-up). To avoid underestimating the true risk associated with high adolescent BMI, we refrained from adjusting for follow-up comorbidities such as CHD, diabetes, or hypertension, conditions which in themselves are strongly associated with an elevated BMI and constitute steps in the pathway toward heart failure. The proportional hazard assumptions were investigated using tests and plots based on weighted residuals.[10] Diabetes and cardiovascular fitness showed signs of non-proportional hazards; hence, we stratified the models for these variables where applicable. Diastolic blood pressure also showed signs of non-proportional hazards, but further investigation by stratifying on quintiles or modelling its interaction with time showed a negligible effect on the estimates of BMI. Therefore, diastolic blood pressure was used in the models without any remedial measures. The year of conscription was modelled as a cubic restricted spline with four knots placed at the 5th, 35th, 65th, and 95th percentiles.[11] We used the same approach in the analysis of BMI, where BMI was constrained to be linear in log hazard at a BMI of <18 and >27.5 kg/m^{2}. Age at conscription was modelled as a categorical variable. To examine how strength, fitness, and IQ at the age of 18 years would impact the association between BMI and risk of heart failure in adulthood, we included these variables as covariates. Muscular strength, IQ, fitness stanines, and parental education were trichotomized as low (1−3), medium (4−6), and high (7−9). Due to the large number of observations, the *P*-values were very small (in all analyses when the 95% confidence interval was separated from 1, the *P*-values were <0.0001) and are therefore not reported.

Population-attributable risk, or the association of a specific risk factor with a specific disease as a proportion of all risk factors for that disease, was calculated using the method described by Natarajan.[12] using the hazard ratios from the Cox proportional hazard regression models.

Statistical calculations were performed with SAS version 9.4 (SAS Institute, Cary, NC), with the exception of model checking, which was performed with R version 3.2.2 (http://www.R-project.org).

Results

Study population

Of the 1 610 437 men in the study (mean BMI, 21.9 kg/m^{2}; standard deviation [SD], 3.1), 79.6% were of normal weight (BMI of 18.5−25.0 kg/m^{2}), 10.0% were overweight (BMI of 25−30 kg/m^{2}), and only 2.3% were obese ($n = 36\,608$, of which 7723 had a BMI of $\geq$35.0 kg/m^{2}) (*Table 1*). Baseline data for fitness, muscular strength, IQ, parental education, diagnoses at baseline and during follow-up are shown in Supplementary material online, Table S1.

Table I Baseline characteristics, age at first heart failure discharge, incidence of heart failure and of heart failure from mutually exclusive associated conditions by body mass index category by body mass index category in 1 610 437 male conscripts

	All n = 1 610 437 (100%)	BMI < 18.50 n = 130 423 (8.1%)	BMI 18.50–19.99 n = 289 857 (18.0%)	BMI 20.00–22.49 n = 648 830 (40.3%)	BMI 22.50–24.99 n = 342 960 (21.3%)	BMI 25.00–27.49 n = 119 469 (7.4%)	BMI 27.50–29.99 n = 42 290 (2.6%)	BMI 30.00–34.99 n = 29 385 (1.8%)	BMI ≥ 35.00 n = 7223 (0.4%)
Number of men (% of total)									
Age (years)	18.3 (0.7)	18.3 (0.6)	18.3 (0.6)	18.3 (0.6)	18.4 (0.8)	18.4 (0.8)	18.3 (0.8)	18.3 (0.8)	18.3 (0.7)
Height, mean (SD)	1.79 (0.07)	1.80 (0.07)	1.79 (0.07)	1.79 (0.07)	1.79 (0.07)	1.79 (0.07)	1.79 (0.07)	1.79 (0.07)	1.79 (0.07)
Weight, mean (SD)	70.5 (11.0)	57.1 (4.9)	62.3 (4.8)	68.3 (5.4)	75.6 (6.0)	83.6 (6.6)	91.9 (7.4)	102.6 (9.1)	121.2 (11.4)
BMI, mean (SD)	21.9 (3.1)	17.7 (0.7)	19.3 (0.4)	21.2 (0.7)	23.5 (0.7)	26.1 (0.7)	28.6 (0.7)	31.9 (1.4)	37.8 (2.7)
Systolic BP, mean (SD)	128.5 (10.9)	125.6 (10.7)	126.7 (10.7)	128.2 (10.7)	129.9 (10.7)	131.3 (10.7)	132.5 (11.1)	133.9 (11.0)	136.3 (11.4)
Diastolic BP, mean (SD)	67.7 (9.7)	67.5 (9.5)	67.4 (9.6)	67.4 (9.7)	67.8 (9.8)	68.5 (10.0)	69.3 (10.3)	70.8 (10.6)	72.6 (10.9)
Age at heart failure diagnosis	46.6 (8.0)	47.4 (7.7)	47.2 (7.8)	46.9 (8.1)	46.3 (8.1)	46.4 (7.3)	46.4	44.5 (8.6)	42.8 (8.1)
Heart failure as a main diagnosis, n	2576	209	392	819	537	298	132	143	46
Cases per 100 000 observation years (95% CI)	6.94 (6.68–7.22)	6.31 (5.51–7.23)	5.47 (4.96–6.04)	5.39 (5.04–5.78)	7.17 (6.59–7.80)	12.09 (10.79–13.55)	15.81 (13.33–18.75)	26.40 (22.41–31.10)	39.85 (29.85–53.20)
Heart failure in any diagnostic position, n	5493	468	861	1781	1160	601	282	266	74
Cases per 100 000 observation years (95% CI)	14.81 (14.42–15.20)	14.14 (12.92–15.48)	12.03 (11.25–12.86)	11.72 (11.19–12.28)	15.50 (14.63–16.42)	24.40 (22.53–26.43)	33.81 (30.08–37.99)	49.15 (43.59–55.43)	64.18 (51.10–80.60)
Heart failure with congenital or acquired valvular disease, n	704	77	132	257	146	48	25	16	3
Cases per 100 000 observation years (95% CI)	1.90 (1.76–2.04)	2.33 (1.86–2.91)	1.84 (1.55–2.19)	1.69 (1.50–1.91)	1.95 (1.66–2.29)	1.95 (1.47–2.59)	3.00 (2.03–4.44)	2.96 (1.81–4.83)	2.60 (0.84–8.07)
Heart failure with CHD, diabetes, or hypertension, n	2731	201	384	791	596	357	177	179	46
Cases per 100 000 observation years (95% CI)	7.36 (7.09–7.64)	6.07 (5.29–6.97)	5.36 (4.85–5.93) 5.21	5.21 (4.86–5.58)	7.96 (7.35–8.63)	14.49 (13.07–16.08)	21.22 (18.31–24.59)	33.08 (28.57–38.30)	39.89 (29.88–53.26)
Heart failure with cardiomyopathy, n	803	81	142	285	153	73	33	25	11
Cases per 100 000 observation years (95% CI)	2.16 (2.02–2.32)	2.45 (1.97–3.04)	1.98 (1.68–2.34)	1.88 (1.67–2.11)	2.04 (1.74–2.40)	2.96 (2.36–3.73)	3.96 (2.81–5.56)	4.62 (3.12–6.84)	9.54 (5.28–17.23)
Heart failure, any other cause, n	1255	109	203	448	265	123	47	46	14
Cases per 100 000 observation years (95% CI)	3.38 (3.20–3.57)	3.29 (2.73–3.97)	2.84 (2.47–3.25)	2.95 (2.69–3.23)	3.54 (3.14–3.99)	4.99 (4.18–5.96)	5.63 (4.23–7.50)	8.50 (6.37–11.35)	12.14 (7.19–20.50)

Hospitalizations for heart failure

During follow-up lasting 5−42 years (median, 23.0 years; interquartile range, 15.0−32.0), we identified 5492 incident cases of heart failure (defined as a principal or secondary discharge diagnosis of heart failure) at a mean age of 46.6 years (SD, 8.0). *Figure 1* shows a slightly J-shaped association between BMI and heart failure. The lowest risk was present at a BMI of ~20 kg/m^2, and a steep linear increase occurred with increasing body weight.

Of the 5492 cases, 704 (12.8%) were associated with congenital or acquired valvular disease; 2731 (49.7%) with CHD, diabetes, or hypertension; and 803 (14.6%) with cardiomyopathy. One fourth of the cases (1255, 22.9%) did not have a registered associated diagnosis prior to, or concomitant with, the diagnosis of heart failure. For all categories, including cases with a principal diagnosis of heart failure ($n = 2576$) the two lowest normal weight categories had the lowest incidence (*Table 1*). For heart failure overall, these two categories had a risk of 12.03 and 11.72 per 100 000 person-years, respectively, increasing to 64.18 among men with baseline BMI of ≥35 kg/m^2. Supplementary material online, Figures S1A−E, shows associations between BMI at the time of conscription and heart failure as a principal diagnosis, or associated with specific causes.

Using low-normal weight (BMI of 18.5−20.0 kg/m^2) as the reference category, a moderate increase in risk was discernible at a slightly elevated normal weight (*Table 2*). Compared with men with low-normal weight men with a BMI 20.0−22.5 kg/m^2 had an hazard ratio (HR) of 1.22 (95% CI, 1.10−1.35), after adjustment for age and year of conscription, comorbidities at baseline, parental education, systolic and diastolic blood pressure, IQ, muscle strength, and fitness. Men with a BMI of 22.5−25.0 kg/m^2 had a corresponding adjusted HR of 1.90 (1.70−2.13). Hazard ratio for successively increasing BMI rose incrementally such that the HR for a BMI of 30−35 kg/m^2 was 6.47 (5.39−7.77), while that for a BMI of ≥35 kg/m^2 was 9.21 (6.57−12.92). The population-attributable

risk for a BMI of ≥22.5 vs. <22.5 kg/m^2 was 24.0% (95% CI, 21.4%−26.5%) in the fully adjusted model.

Cases associated with CHD, diabetes, or hypertension demonstrated very high multiple-adjusted HRs of 11.38 (9.01−14.38) for a BMI of 30 to <35 kg/m^2 and 14.75 (9.64−22.59) for a BMI of ≥35 kg/m^2. For heart failure associated with cardiomyopathy, risk increased to a multiple-adjusted HR of 6.86 (2.93−16.02) for a BMI of ≥35 kg/m^2. The fully adjusted population-attributable risk for a BMI of ≥22.5 vs. <22.5 kg/m^2 ranged from 9.7 (2.8−17.0), for heart failure associated with valvular disease, to 33.4 (29.7−37.0) for heart failure associated with CHD, diabetes, or hypertension. Associations were similar for heart failure as a main diagnosis (Supplementary material online, Table S2), but less strong for acute myocardial infarction, stroke, cardiovascular death, and all-cause mortality. *Table 3* shows the HRs associated with heart failure per 1-unit increase in BMI in men with BMI of ≥20 kg/m^2, with multiple-adjusted estimates ranging from 1.06 (1.02−1.11) (valvular disease) to 1.20 (1.18−1.22) (CHD, diabetes, or hypertension).

Discussion

The present data set enabled us to investigate the association between body weight across a wide range and early heart failure. We documented an increase in risk that was almost 10-fold among the very obese, and detectable already at body weight levels that are considered to be normal. The effect was broadly similar across our predefined categories of heart failure, and for heart failure as a main diagnosis.

Body weight is increasing in Sweden.[13] Recent estimates of obesity, which are fairly typical for Europe, are ~4% of those <20 years of age and just <20% of adults,[14] with considerably higher estimates of obesity found in other Western countries, such as the USA. In a study of the present cohort of adolescent men, the prevalence of moderate obesity (BMI 30.0−34.9 kg/m^2) almost quintupled from the early 1970s and over the next 35 years, while the prevalence of BMI ≥35 kg/m^2 increased 10-fold.[3]

We found that risk of heart failure started to increase at body weights that are normal and considered desirable (BMI of 22.5−25.0 kg/m^2). Most studies use a cut-off of 25 kg/m^2, which will underestimate the risk of heart failure associated with elevated weight. Although high body weight has long been linked to cardiomegaly, cardiomyopathy, and sudden death,[15] these conditions were thought only to be associated with severe obesity. However, Kenchaiah et al.[16] demonstrated that the risk of heart failure began to increase at much lower BMI levels, with a 5% and 7% increase in the risk per 1-unit BMI increase men and women, respectively, who were middle-aged or older. Our estimate (16% per 1-unit BMI increase) is markedly higher.

The mechanisms linking obesity to cardiac structural and functional abnormalities are not well understood. A complex interplay exists between body weight and haemodynamic, neurohormonal, and metabolic factors as well as inflammation and oxidative stress.[17−20] These factors contribute to the development of cardiac hypertrophy, interstitial fibrosis,[17] and other forms of cardiac dysfunction.[18−20] Bariatric surgery reportedly dramatically reverses the disturbances in left ventricular function.[21] Importantly, obesity early in life is not only associated with cardiometabolic risk factors[22]
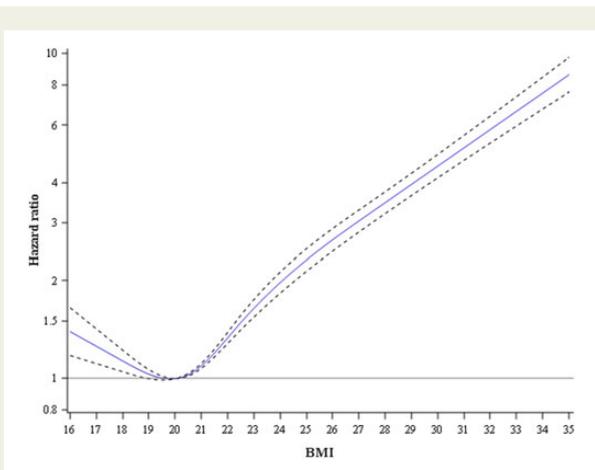
Figure 1 Association between body mass index at conscription and risk of hospitalization with a principal or secondary discharge diagnosis of heart failure. Adjusted for age at conscription, period, baseline comorbidities, and parental education. The number of events and men in different BMI categories are shown in *Table 1*.

Table 2 Hazard ratios for heart failure and mutually exclusive associated conditions of heart failure[a] by body mass index category[b], and population-attributable risks for a body mass index of ≥22.5 vs. <22.5 kg/m²

BMI category	Hazard ratio (95% CI) *P*-value		
	Model 1	**Model 2**	**Model 3**
Heart failure hospitalization (events/population)	5492/1 610 352	4794/1 454 228	3791/1 116 880
<18.5	1.08 (0.96−1.21)	1.09 (0.96−1.23)	0.96 (0.84−1.11)
18.5 to <20.0 (reference)	1.00	1.00	1.00
20.0 to <22.5	1.08 (1.00−1.17)	1.07 (0.98−1.17)	1.22 (1.10−1.35)
22.5 to <25.0	1.59 (1.46−1.74)	1.58 (1.43−1.73)	1.90 (1.70−2.13)
25.0 to <27.5	2.70 (2.43−3.00)	2.58 (2.31−2.89)	3.28 (2.88−3.74)
27.5 to <30.0	4.00 (3.50−4.58)	3.74 (3.23−4.32)	4.27 (3.60−5.07)
30.0 to <35.0	6.48 (5.64−7.45)	5.59 (4.80−6.52)	6.47 (5.39−7.77)
≥35.0	10.38 (8.16−13.20)	7.62 (5.78−10.06)	9.21 (6.57−12.92)
Population-attributable risk, % (95% confidence interval)[a]	22.6 (20.6−24.7)	21.9 (19.7−24.2)	24.0 (21.4−26.5)
Heart failure hospitalization with congenital heart disease/valvulopathy (events/population)	704/1 610 352	625/1 454 228	462/1 116 ,880
<18.5	1.15 (0.87−1.52)	1.30 (0.96−1.75)	1.06 (0.74−1.52)
18.5 to <20.0 (reference)	1.00	1.00	1.00
20.0 to <22.5	1.03 (0.83−1.27)	1.11 (0.88−1.39)	1.11 (0.85−1.44)
22.5 to <25.0	1.30 (1.03−1.65)	1.43 (1.11−1.84)	1.38 (1.01−1.88)
25.0 to <27.5	1.43 (1.02−1.99)	1.55 (1.09−2.20)	1.68 (1.12−2.54)
27.5 to <30.0	2.33 (1.52−3.58)	2.28 (1.44−3.63)	2.30 (1.33−3.98)
30.0 to <35.0	2.63 (1.56−4.43)	2.66 (1.54−4.60)	1.78 (0.81−3.91)
≥35.0	3.00 (0.95−9.44)	1.04 (0.14−7.50)	1.54 (0.21−11.26)
Population-attributable risk, % (95% CI)[a]	9.6 (4.3−15.3)	10.1 (4.3−16.3)	9.7 (2.8−17.0)
Heart failure hospitalization with CHD, diabetes, or hypertension (events/population)	2731/1 610 352	2357/1 454 228	1900/1 116 880
<18.5	1.02 (0.86−1.21)	1.00 (0.83−1.21)	0.93 (0.75−1.15)
18.5 to <20.0 (reference)	1.00	1.00	1.00
20.0 to <22.5	1.09 (0.97−1.24)	1.07 (0.94−1.22)	1.32 (1.14−1.54)
22.5 to <25.0	1.90 (1.67−2.16)	1.83 (1.60−2.11)	2.43 (2.07−2.86)
25.0 to <27.5	3.74 (3.24−4.33)	3.50 (2.99−4.10)	4.95 (4.13−5.92)
27.5 to <30.0	5.93 (4.96−7.09)	5.35 (4.40−6.49)	6.81 (5.43−8.54)
30.0 to <35.0	10.37 (8.67−12.40)	8.68 (7.12−10.59)	11.38 (9.01−14.38)
≥35.0	15.55 (11.39−21.23)	10.44 (7.25−15.03)	14.75 (9.64−22.59)
Population-attributable risk, % (95% CI)[a]	31.7 (28.7−34.6)	30.6 (27.4−33.9)	33.4 (29.7−37.0)
Heart failure hospitalization with cardiomyopathy (events/population)	803/1 610 352	726/1 454 228	569/1 116 880
<18.5	1.18 (0.90−1.55)	1.26 (0.95−1.67)	1.07 (0.76−1.49)
18.5 to <20.0 (reference)	1.00	1.00	1.00
20.0 to <22.5	1.01 (0.83−1.24)	0.97 (0.79−1.20)	1.11 (0.87−1.41)
22.5 to <25.0	1.18 (0.94−1.49)	1.12 (0.88−1.43)	1.32 (0.99−1.74)
25.0 to <27.5	1.82 (1.37−2.41)	1.64 (1.21−2.22)	1.76 (1.23−2.52)
27.5 to <30.0	2.56 (1.75−3.74)	2.39 (1.61−3.56)	2.25 (1.37−3.68)
30.0 to <35.0	3.24 (2.11−4.97)	2.53 (1.57−4.07)	2.26 (1.22−4.17)
≥35.0	7.88 (4.25−14.60)	6.96 (3.63−13.36)	6.86 (2.93−16.02)
Population-attributable risk, % (95% CI)[a]	12.1 (6.8−17.5)	10.1 (4.5−16.0)	10.4 (4.0−17.2)
Heart failure hospitalization, all other (events/population)	1255/1 610 352	1086/1 454 228	860/1 116 880
<18.5	1.08 (0.86−1.37)	1.00 (0.77−1.29)	0.92 (0.68−1.25)
18.5 to <20.0 (reference)	1.00	1.00	1.00
20.0 to <22.5	1.14 (0.96−1.34)	1.11 (0.93−1.33)	1.18 (0.96−1.44)

Table 2 *Continued*

BMI category	Hazard ratio (95% CI) P-value		
	Model 1	Model 2	Model 3
22.5 to <25.0	1.50 (1.25–1.80)	1.53 (1.26–1.87)	1.74 (1.38–2.18)
25.0 to <27.5	2.26 (1.80–2.83)	2.26 (1.77–2.88)	2.65 (2.01–3.49)
27.5 to <30.0	2.70 (1.97–3.72)	2.73 (1.94–3.82)	2.79 (1.86–4.19)
30.0 to <35.0	4.49 (3.26–6.19)	4.17 (2.93–5.95)	4.63 (3.04–7.07)
≥35.0	7.91 (4.59–13.62)	6.85 (3.70–12.70)	6.68 (2.90–15.39)
Population-attributable risk, % (95% CI)[a]	16.7 (12.5–21.1)	17.7 (13.1–22.5)	19.3 (13.9–24.8)

Model 1: Adjusted for age at conscription, conscription year, test center, and comorbidities at baseline.
Model 2: Additionally adjusted for parental education, systolic and diastolic blood pressure.
Model 3: Additionally adjusted for IQ, muscle strength, and fitness.
[a] Mutually exclusive causes of heart failure were assigned in the following hierarchical order: (i) congenital heart disease and valvulopathies, (ii) coronary heart disease (CHD) and/or diabetes and/or hypertension, (iii) cardiomyopathy, and (iv) other causes (Supplementary material online, Appendix p. 5).
[b] Incidence rates are given in *Table 1*.

Table 3 **Adjusted hazard ratios associated with heart failure and mutually exclusive associated conditions of heart failure[a] per 1-unit increase in BMI in men with a BMI of ≥20 kg/m² [b]**

	HR per 1-kg/m² increase (95% CI)		
	Model 1	Model 2	Model 3
Heart failure in any diagnostic position (events/population)	4163/1 190 092	3650/1 076 443	2910/825 376
	1.17 (1.16–1.18)	1.15 (1.14–1.16)	1.16 (1.15–1.17)
Heart failure as a main diagnosis (events/population)	1975/1 190 092	1730/1 076 443	1378/825 376
	1.18 (1.17–1.19)	1.17 (1.15–1.18)	1.18 (1.16–1.20)
Heart failure with congenital or acquired valvular disease (events/population)	495/1 190 092	448/1 076 443	327/825 376
	1.09 (1.06–1.12)	1.08 (1.04–1.11)	1.06 (1.02–1.11)
Heart failure with CHD, diabetes, or hypertension (events/population)	2145/1 190 092	1860/1 076 443	1515/825 376
	1.20 (1.19–1.22)	1.19 (1.17–1.20)	1.20 (1.18–1.22)
Heart failure with cardiomyopathy (events/population)	580/1 190 092	517/1 076 443	412/825 376
	1.13 (1.10–1.15)	1.11 (1.09–1.14)	1.09 (1.06–1.13)
Heart failure, any other cause (events/population)	943/1 190 092	825/1 076 443	656/825 376
	1.13 (1.11–1.15)	1.13 (1.10–1.15)	1.13 (1.10–1.16)

Models 1–3: adjustments as for *Table 2*.
[a] See *Table 2* footnote.
[b] Incidence rates are given in *Table 1*.

but also with impaired cardiovascular structure and function.[23] Even so, the greatest population burden of heart failure among the young and middle-aged is driven by the high-normal weight or overweight categories because these categories are the most highly represented.

The association between body weight and heart failure was strongest in patients with conditions well known to be associated with heart failure (CHD, diabetes, or hypertension) and weakest, but still highly significant, in patients with valvular disease. There was also a strong association for heart failure attributed to cardiomyopathy, although this is a highly heterogeneous condition.[24]

With respect to limitations to our findings, diagnoses of heart failure, and other conditions were collected for administrative reasons, cases were not formally validated, and there was no data on cardiac

function or other clinical characteristics. Nonetheless, a hospital diagnosis of heart failure in Sweden has been shown to have high validity, particularly as a main diagnosis,[25] and so have other major cardiovascular diagnoses.[26] In our study, risk estimates were similar regardless of whether cases were assigned a primary diagnosis or not. In a recent unpublished validation study that we performed on 964 hospital records with a discharge diagnosis of heart failure (mean age 78 years) the diagnosis was definite or probable in 94.4%, the most common reason for assigning a probable and not definite diagnosis being that an echocardiography had not been done. This would apply in very few cases below the age of 65, where a careful evaluation of any case of suspected heart failure would be mandatory. Accordingly, it is unlikely that the strong association that we found would be due to misclassification of heart failure.

A second limitation is the lack of information on subsequent weight development, and on other risk factors in adult life such as dyslipidaemia. A mildly elevated weight at the age of 18 years might be a marker of an increased risk of developing subsequent obesity.[27] The extent to which weight gain in adulthood contributes to the development of early heart failure cannot be established from our data. A third limitation was that the findings of the present study are limited to Swedish men and may not be applicable to women or to other settings. The main strength of the present study is the uniquely large number of cases occurring at a young age.

In conclusion, we found a steep increase in the risk of early heart failure associated with increasing body weight starting at levels that are considered normal. Given the global trend in adolescent overweight and obesity, early heart failure might well become a major threat worldwide, an aspect that has not received much attention in current prevention guidelines.[28] The strong association that we found between body weight and early heart failure serves to underline the urgent need for global action to curb the obesity epidemic.

Supplementary material

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

Authors' contributions

L. S. performed statistical analysis; A. R., M. Å., K. T. handled funding and supervision; M. Å. acquired the data; A. R., M. Å., K. T. conceived and designed the research; A. R., J. R., M. Å., K. T., L. S. drafted the manuscript; M. S., M. W., D. Å., G. K., L. S. made critical revision of the manuscript for key intellectual content.

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CARDIOVASCULAR FLASHLIGHT

Extensive cardiac infiltration in acute T-cell lymphoblastic leukemia: occult extra-medullary relapse and remission after salvage chemotherapy

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A 38-year-old man was admitted with vasculitic rash and horizontal diplopia 9 months post allogenic stem cell transplantation for T-cell acute lymphoblastic leukemia (ALL). Magnetic resonance (MR) of the orbits showed enlarged extra-ocular muscles and an echocardiogram, to exclude cardiac embolic sources, showed bi-ventricular hypertrophy and speckled myocardium. A 12-lead ECG showed diffuse T-wave inversion (*Panel 1A*). A cardiovascular MR (CMR) showed preserved bi-ventricular systolic function, septal left ventricular (LV) hypertrophy (max 21 mm, normal <12mm) (*Panel 1B*) with increased LV mass (88 g/m^2, normal 48–77 g/m^2). Multiple areas of myocardial and pericardial infiltration ($n = 9$, largest 18×50mm) were noted on advanced tissue characterisation, showing markedly increased T1 values on native T1 mapping, and non-enhancing after contrast administration (*Panel 1C* and *D*, white arrows). The CMR findings raised the suspicion of acute
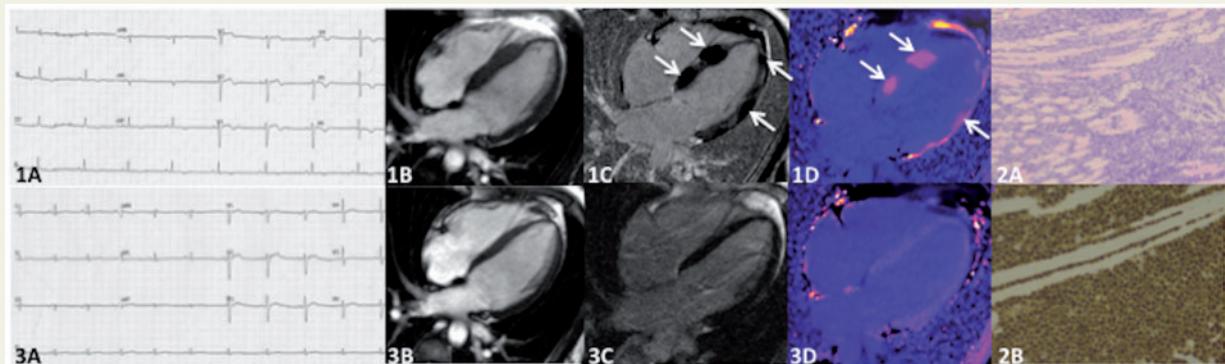
cardiac involvement of ALL. A MR-guided biopsy of the swollen ocular left rectus muscle confirmed the diagnosis of relapsed acute T-cell ALL (*Panel 2A* and *B*), further supported by evidence of 0.09% T-lymphoblasts on bone marrow flow cytometry and low-level central nervous system (CNS) disease on lumbar puncture. As all the investigations confirmed acute multi-organ ALL relapse (heart, extra-ocular muscles, bone marrow, and CNS), systemic chemotherapy with *nelarabine*, and intra-thecal cytosine *arabinoside* were started. Diplopia rapidly improved, and a repeat orbit MR 14 days after commencement of chemotherapy showed complete resolution of extra-ocular muscle enlargement. A 1-month repeat CMR to assess cardiac response demonstrated complete resolution of all nodular lesions with normalization of LV wall thickness (10 mm) and mass (60 g/m^2) (*Panel 3B*, *C*, and *D*), and of the widespread T-wave inversion on ECG (*Panel 3A*).