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Higher Body Mass Index in Adolescence Predicts Cardiomyopathy Risk in Midlife

Long-Term Follow-Up Among Swedish Men

Josefina Robertson, MD
Maria Schaufelberger, MD, PhD
Martin Lindgren, MD, PhD
Martin Adiels, PhD
Linus Schiöler, PhD
Kjell Torén, MD, PhD
John McMurray, MD, PhD
Naveed Sattar, MD, PhD
Maria Åberg, MD, PhD
Annika Rosengren, MD, PhD

BACKGROUND: Modifiable lifestyle factors in relation to risk for cardiomyopathy, a common and increasing cause of heart failure in the young, have not been widely studied. We sought to investigate a potential link between obesity, a recognized predictor of early heart failure, in adolescence and being diagnosed with cardiomyopathy in adulthood.

METHODS: This was a nationwide register-based prospective cohort study of 1 668 893 adolescent men (mean age, 18.3 years; SD, 0.7 years) who enlisted for compulsory military service from 1969 to 2005. At baseline, body mass index (BMI), blood pressure, and medical disorders were registered, along with test results for fitness and muscle strength. Cardiomyopathy diagnoses were identified from the National Hospital Register and Cause of Death Register during an up to 46-year follow-up and divided into categories: dilated, hypertrophic, alcohol/drug-induced, and other. Hazard ratios were calculated with Cox proportional hazards models.

RESULTS: During follow-up (median, 27 years; Q1–Q3, 19–35 years), 4477 cases of cardiomyopathy were identified, of which 2631 (59%) were dilated, 673 (15%) were hypertrophic, and 480 (11%) were alcohol/drug-induced. Increasing BMI was strongly associated with elevated risk of cardiomyopathy, especially dilated, starting at levels considered normal (BMI, 22.5–<25 kg/m^2; hazard ratio, 1.38 [95% CI, 1.22–1.57]), adjusted for age, year, center, and baseline comorbidities, and with a >8-fold increased risk at BMI ≥35 kg/m^2 compared with BMI of 18.5 to <20 kg/m^2. For each 1-unit increase in BMI, similarly adjusted hazard ratios were 1.15 (95% CI, 1.14–1.17) for dilated cardiomyopathy, 1.09 (95% CI, 1.06–1.12) for hypertrophic cardiomyopathy, and 1.10 (1.06–1.13) for alcohol/drug-induced cardiomyopathy.

CONCLUSIONS: Even mildly elevated body weight in late adolescence may contribute to being diagnosed with cardiomyopathy in adulthood. The already marked importance of weight control in youth is further strengthened by these findings, as well as greater evidence for obesity as a potential important cause of adverse cardiac remodeling that is independent of clinically evident ischemic heart disease.

Key Words: adolescent ■ cardiomyopathies ■ obesity ■ overweight ■ population groups

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Clinical Perspective

What Is New?

- Cardiomyopathies have often been seen as mostly genetic in origin, and potentially modifiable causes have not been widely studied.
- We followed up a large number of adolescent men, some of whom were subsequently diagnosed with cardiomyopathy, and identified a strong link to overweight and obesity.

What Are the Clinical Implications?

- Given the overall increase in body weight in young people globally, physicians need to be aware of an increased risk for cardiomyopathy.
- The already marked importance of weight control in youth is further strengthened by these findings, as well as more evidence for obesity as a potential important cause of adverse cardiac remodeling that is independent of clinically evident ischemic heart disease.

Heart failure among young people is rare, but in contrast to decreasing incidence rates overall, some studies have found increasing rates among younger people.[1,2] Although coronary heart disease and hypertension are the most frequent causes of heart failure in older patients, cardiomyopathy is a more common underlying condition in the young. The incidence of hospitalizations for heart failure associated with cardiomyopathy in Sweden more than doubled from 1987 to 2006.[1]

The classification of cardiomyopathy is challenging because of the marked heterogeneity and differences in definitions over the years. The latest classification from the European Society of Cardiology,[3] from 2008, defines cardiomyopathy as "a myocardial disease in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality." Five categories are presented; dilated, hypertrophic, restrictive, arrhythmogenic right ventricular, and unclassified cardiomyopathy. In a validation study of cardiomyopathy diagnoses in the Swedish National Hospital Register, dilated cardiomyopathy was the most common diagnosis (67%), followed by hypertrophic cardiomyopathy (16%), whereas other types were rare.[4] Modifiable causes listed for dilated cardiomyopathy include myocarditis, drugs, alcohol, endocrine disorders, and nutritional deficiencies,[3] with ≈25% estimated to have genetic causes resulting from specific genetic defects linked to cardiac muscle development.[5] Hypertrophic cardiomyopathy is mostly a familial dominant inheritable disease,[6] with obesity and athletic training listed as potential acquired causes.[3]

A strong link has been identified between adolescent obesity and early heart failure.[7] Given the overall increase in body weight in young people in Sweden[8] and globally,[9] coinciding with the rise in individuals being diagnosed with cardiomyopathy in the Swedish population, we hypothesized that there might be an association between adiposity (as measured by body mass index [BMI]) and cardiomyopathy. We identified only 1 previous study that investigated this potential link.[10] In this study, a range of early cardiovascular deaths were analyzed, among which 121 were rated as being from cardiomyopathies, with a 4-fold increase in risk of death attributed to cardiomyopathy among obese adolescents relative to those with a BMI from 18.5 to <22 kg/m^2. The obese category had only 6 deaths, however, and the validity of the diagnosis was not specified. Accordingly, it was not possible to investigate either the association with severe obesity, which forms an increasing proportion among the overweight,[11] or the association with obesity on specific cardiomyopathies. Diagnoses of different types of cardiomyopathy in the Swedish National Hospital Register have been shown to be accurate in at least 85% of cases.[4] In the present study, we set out to investigate the risk of specific types of cardiomyopathy across categories of BMI in late adolescence.

METHODS

The raw data for our estimates are potentially identifiable, and access to those data is restricted. Researchers wishing to access the individual-level data need to apply for permission through a Research Ethics Board and from the primary data owners: the Swedish National Board of Health and Welfare, Statistics Sweden, and the Swedish Military Service Conscription Register.

Study Population

A cohort of young individuals who enlisted for military service between 1969 and 2005 was extracted from the Swedish Military Service Conscription Register (n=1 886 542). Except for those in prison and those with severe medical conditions or functional disabilities (2%–3% annually), this was compulsory until 2005. Women enlisting during this period were excluded from the study (n=10 228). After exclusions, mainly men with missing height or weight data (n=151 434), 1 668 893 conscripts were included in the study (Figure I in the online-only Data Supplement).

All men underwent standardized examinations at 6 centers, which included measurement of weight, height, and blood pressure and recording of medical conditions. A psychologist evaluated psychiatric symptoms, including alcohol and drug abuse disorders, during a structured interview; if present, the psychiatric symptoms were evaluated by a physician and coded according to the *International Classification of Diseases*. Cardiorespiratory fitness was evaluated by a bicycle ergometric test, with the final work rate (Wmax) divided by

body weight. Raw data of Wmax per kilogram were available for the conscription years 1972 to 2005. For the first years (1969–1971), raw data were not recorded into data files, but the values of Wmax per kilogram were directly converted into 9 levels that were digitized and served as a measure of fitness.[12–14] For conscription years 2000 to 2005, no raw data were recorded from conscripts performing the lowest 3 levels of fitness; thus, these levels were missing during this period. Isometric muscle strength was measured by knee extension, elbow flexion, and hand grip.[12] Weighted values were integrated into an overall estimate in kilopond (until April 1, 1979) or Newton (after April 1, 1979). Test results were standardized against data from previous years, resulting in scores from 1 to 9 (low to high). Information on highest achieved parental education was derived from the longitudinal integration database for health insurance and labor market studies (Swedish acronym LISA). It includes all registered inhabitants from the age of 16 years (80% coverage) and is divided into 7 levels: <9 years, pre–high school education of 9 years, high school education, university (<2 years), university (≥2 years), postgraduate education, and postgraduate research training.

Outcomes

The universal healthcare system in Sweden offers specialist hospital inpatient and outpatient care at low cost to all citizens. Data from visits or discharges are recorded in the Swedish National Hospital Register. Inpatient discharge data coverage increased gradually during the period of 1970 to 1986 and is complete from 1987, with outpatient visits complete from 2001. Cardiomyopathy cases, according to the *International Classification of Diseases* revisions 8 through 10, were identified through linkage to the Hospital Register and Cause of Death Register (Methods and Table I in the online-only Data Supplement). Primary care data were not included in this study. Cardiomyopathy diagnoses were categorized as dilated cardiomyopathy, hypertrophic cardiomyopathy, alcohol/drug-induced cardiomyopathy, and other cardiomyopathies (composed of less common forms). Cardiomyopathies with a prior myocardial infarction were considered heart disease of ischemic origin, censored at the date of diagnosis, and excluded from all analyses.

Statistical Analysis

Data were prepared with SAS version 9.4 (SAS Institute, Cary, NC), and statistical calculations were performed with R version 3.4.2 (http://www.R-project.org). The follow-up period started at the date of conscription (baseline) and ended on December 31, 2014 (maximum, 9–46 years). Subjects were followed up until a first cardiomyopathy diagnosis, death, emigration, myocardial infarction, or end of follow-up (December 31, 2014), whichever occurred first. Incidence rates and corresponding 95% CIs were calculated with Poisson regression. Cox proportional hazards models were used to estimate cause-specific hazard ratios to assess the influence of BMI and presumptive predictors for cardiomyopathy. To avoid underestimating the true risk associated with high adolescent BMI, we refrained from adjusting for follow-up comorbidities such as coronary heart disease, diabetes mellitus, or hypertension, conditions that are strongly associated with an elevated BMI and constitute steps in the pathway toward heart failure. A sensitivity analysis was performed to study competing risk in which death was treated as a competing event. We used the Fine-Gray method for competing risk and coded fatal cardiomyopathy events as cardiomyopathy events rather than deaths. BMI was categorized into 8 groups (<18.5, 18.5–<20, 20–<22.5, 22.5–<25, 25–<27.5, 27.5–<30, 30–<35, and ≥35 kg/m^2). Systolic and diastolic blood pressures were each categorized into 5 groups (systolic: 100–119, 120–125, 126–130, 131–138, and 139–180 mm Hg; diastolic: 40–59, 60–65, 66–70, 71–76, and 77–100 mm Hg). Categorical variables were conscription test center, cardiorespiratory fitness, overall muscle strength, and parental education. Cardiorespiratory fitness was trichotomized as low (1–4), moderate (5–7), or high (8 and 9) and muscle strength as low (1–3), moderate (4–6), or high (7–9). Parental education was defined as low (pre–high school, ≤9 years), medium (high school, 10–12 years), or high (university and higher, >12 years). Differences among regions, examination years, and age at conscription were considered potential confounders, and we adjusted for them. Alcohol-induced cardiomyopathy is a well-known condition,[15] and alcohol/substance use disorders in adolescence were therefore included in the model. The proportionality assumption was tested with tests based on weighted residuals,[16] and the models were stratified for variables not fulfilling the proportionality criteria. Thus, the final models were stratified for year of conscription. Spline plots were generated with BMI as a restricted cubic spline with degree 3 and 4 knots placed at 5% (18.0 kg/m^2), 35% (20.5 kg/m^2), 65% (22.4 kg/m^2), and 95% (27.5 kg/m^2). Year of conscription was included in the spline with knots placed at 5% (1971), 35% (1982), 65% (1992), and 95% (2004). Interactions between BMI and other variables were tested in the BMI range >20 kg/m^2 with BMI as a continuous variable. Systolic and diastolic blood pressures, cardiorespiratory fitness, and muscle strength were tested as continuous variables, and alcohol/substance use disorder was tested as a factor of 2 levels.

The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved the study, and the investigation conforms to the principles outlined in the Declaration of Helsinki.

RESULTS

Study Population and Follow-Up

Of the 1 668 893 conscripts in the study (96% who were 18 or 19 years of age; mean, 18.3 years; SD, 0.7 year), 4477 were diagnosed with cardiomyopathy during follow-up (median, 27 years; quartile 1–3, 19–35 years; 44 346 736 person-years; Figure I in the online-only Data Supplement). The most common form was dilated cardiomyopathy (59%, n=2631). There were 673 cases of hypertrophic cardiomyopathy and 480 cases of alcohol/drug-induced cardiomyopathy (15% and 11%, respectively). Only 4 cases of dilated, none of the hypertrophic, and 11 of the alcohol/drug-induced cardiomyopathies were diagnosed from the death registry alone, without prior hospitalization. Baseline data by BMI categories

are shown in Table 1; 79.6% of the men were normal weight (BMI, 18.5–<25 kg/m^2), 10.0% were overweight (BMI, 25–<30 kg/m^2), and 2.2% were obese, of whom 7383 (0.4% of the study population) had a BMI of ≥35 kg/m^2. Blood pressure increased with increasing body weight. Cardiorespiratory fitness was highest in men with midrange BMI, whereas high muscle strength was much more common in obese compared with lean men. Overall, a low proportion (0.9%) of conscripts was identified with alcohol/substance use disorders.

Risk for Cardiomyopathy

Individuals with higher BMI were diagnosed with a cardiomyopathy at a younger age compared with their leaner peers (Table 2). For each of the studied outcomes, the number of events, incidence rates per 100 000 observation years, and their corresponding confidence intervals by categories of BMI are presented in Table 2. Incidence rates for all categories of cardiomyopathies were slightly J-shaped, ranging from a low of 4.7 cases of dilated cardiomyopathy per 100 000 person years in men with BMI of 20 to <22.5 kg/m^2 to 24.7 for BMI ≥35 kg/m^2; for hypertrophic cardiomyopathy, from a low of 1.2 among men with a BMI of 18.5≤BMI<20 to 3.3 among men with BMI 30≤BMI<35 kg/m^2; for alcohol/drug-induced cardiomyopathy, from 0.9 among men with BMI 20 to <22.5 kg/m^2 to 4.1 in the highest BMI category; and for other cardiomyopathies, from 1.0 with a BMI of 18.5≤BMI<20 to 3.1 among men with BMI 30≤BMI<35 kg/m^2. The highest BMI category (BMI 35 kg/m^2 and over) held very few cases for some categories. In comparison, corresponding rates were considerably higher for acute myocardial infarction at 45.8 to 88.3 and for heart failure at 8.0 to 48.8 (Table II in the online-only Data Supplement).

Starting at high-normal levels of BMI (22.5–<25 kg/m^2), the risk of dilated cardiomyopathy increased in a linear fashion compared with the BMI reference

Table 1. Baseline Characteristics by BMI Category

	All	BMI<18.5 kg/m^2	18.5 kg/m^2 ≤BMI<20 kg/m^2	20 kg/m^2 ≤BMI<22.5 kg/m^2	22.5 kg/m^2 ≤BMI<25 kg/m^2	25 kg/m^2 ≤BMI<27.5 kg/m^2	27.5 kg/m^2 ≤BMI<30 kg/m^2	30 kg/m^2 ≤BMI<35 kg/m^2	35 kg/m^2 ≤BMI
Men, n (% of total)	1 668 893 (100)	134 753 (8.1)	300 610 (18.0)	673 394 (40.3)	355 486 (21.3)	123 438 (7.4)	43 654 (2.6)	30 175 (1.8)	7383 (0.4)
Age, y	18.3 (0.7)	18.3 (0.6)	18.3 (0.6)	18.3 (0.6)	18.3 (0.7)	18.4 (0.8)	18.4 (0.8)	18.3 (0.8)	18.3 (0.7)
BMI, kg/m^2	21.9 (3.0)	17.7 (0.67)	19.3 (0.42)	21.2 (0.71)	23.5 (0.69)	26.1 (0.73)	28.6 (0.68)	31.9 (1.36)	37.8 (2.66)
Systolic BP, mm Hg	129 (10.9)	126 (10.7)	127 (10.7)	128 (10.7)	130 (10.7)	131 (10.7)	133 (11.1)	134 (11.0)	136 (11.4)
Diastolic BP, mm Hg	67.6 (9.8)	67.4 (9.6)	67.2 (9.6)	67.3 (9.7)	67.7 (9.8)	68.4 (10.0)	69.3 (10.3)	70.4 (10.5)	72.6 (10.9)
Cardiorespiratory fitness, % (n)									
Low (1–4)	13.5 (166 393)	33.5 (32 314)	17.4 (39 598)	9.0 (46 079)	7.8 (20 443)	14.4 (12 165)	27.2 (7354)	43.5 (6924)	62.7 (1516)
Moderate (5–7)	58.7 (722 393)	59.3 (57 153)	64.2 (145 725)	57.8 (297 356)	56.2 (147 846)	60.8 (51 395)	56.5 (15 286)	43.8 (6971)	27.3 (661)
High (8, 9)	27.8 (341 927)	7.2 (6885)	18.4 (41 842)	33.2(170 793)	36.0 (94 720)	24.9 (21 013)	16.3 (4400)	12.8 (2032)	10.0 (242)
Muscle strength, % (n)									
Low (1–3)	13.8 (150 192)	43.2 (39 568)	21.7 (43 854)	10.4 (45 573)	6.0 (13 692)	5.8 (4504)	6.3 (1711)	5.9 (1062)	6.6 (228)
Moderate (4–6)	57.6 (627 097)	54.2 (49 627)	68.4 (138 565)	62.9 (276 925)	48.6 (110 557)	41.9 (32 801)	39.4 (10 721)	37.1 (6723)	34.3 (1178)
High (7–9)	28.6 (311 834)	2.6 (2398)	10.0 (20 176)	26.8 (117 765)	45.4 (103 440)	52.3 (40 941)	54.3 (14 773)	57.0 (10 315)	59.0 (2026)
Parental education, % (n)									
Pre–high school (1, 2)	28.2 (455 404)	31.5 (40 687)	29.4 (84 993)	27.5 (179 273)	27.1 (93 219)	28.4 (34 012)	29.6 (12 536)	29.5 (8634)	28.4 (2050)
High school (3, 4)	43.5 (701 303)	42.3 (54 610)	42.3 (122 334)	42.7 (278 340)	44.1 (152 026)	46.2 (55 241)	48.2 (20 378)	49.8 (14 573)	52.7 (3801)
University or higher (5–7)	28.3 (455 631)	26.1 (33 699)	28.3 (81 990)	29.7 (193 492)	28.8 (99 300)	25.4 (30 314)	22.2 (9396)	20.8 (6080)	18.9 (1360)
Alcohol/substance use disorder, % (n)	0.9 (14 449)	1.0 (1391)	1.0 (2872)	0.8 (5550)	0.8 (2871)	0.8 (1043)	0.9 (396)	0.8 (256)	0.9 (70)

Values are mean (SD) for continuous variables. BMI indicates body mass index; and BP, blood pressure.

Table 2. Event Rates per 100 000 Observation-Years for Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy, Alcohol/Drug–Induced Cardiomyopathy, and Other Cardiomyopathies by BMI Category

	All	BMI<18.5 kg/m²	18.5 kg/m² ≤BMI<20 kg/m²	20 kg/m² ≤BMI<22.5 kg/m²	22.5 kg/m² ≤BMI<25 kg/m²	25 kg/m² ≤BMI<27.5 kg/m²	27.5 kg/m² ≤BMI<30 kg/m²	30 kg/m² ≤BMI<35 kg/m²	35 kg/m²≤BMI
Men, n (% of total)	1 668 893 (100)	134 753 (8.1)	300 610 (18.0)	673 394 (40.3)	355 486 (21.3)	123 438 (7.4)	43 654 (2.6)	30 175 (1.8)	7383 (0.4)
Age at cardiomyopathy diagnosis (SD), y	45.5 (9.3)	46.4 (9.0)	46.9 (9.0)	46.3 (9.4)	44.9 (9.5)	44.3 (9.0)	43.4 (9.2)	42.6 (9.2)	40.6 (8.6)
Follow-up time, median (Q1, Q3)	27 (19, 35)	30 (21, 38)	29 (20, 37)	27 (19, 35)	25 (18, 33)	24 (16, 32)	23 (15, 31)	21 (14, 29)	18 (12, 26)
Dilated cardiomyopathy									
Events, n (%)	2631 (0.16)	223 (0.17)	427 (0.14)	861 (0.13)	542 (0.15)	277 (0.22)	145 (0.33)	120 (0.40)	36 (0.49)
Cases per 100 000 observation-y (95% CI)	5.9 (5.7–6.2)	5.7 (5.0–6.5)	5.0 (4.6–5.5)	4.7 (4.4–5.1)	6.0 (5.5–6.5)	9.3 (8.2–10.4)	14.2 (12.0–16.7)	18.0 (14.9–21.5)	24.7 (17.3–34.2)
Hypertrophic cardiomyopathy									
Events, n (%)	673 (0.04)	50 (0.04)	101 (0.03)	248 (0.04)	152 (0.04)	72 (0.06)	25 (0.06)	22 (0.07)	3 (0.04)
Cases per 100 000 observation-y (95% CI)	1.5 (1.4–1.6)	1.3 (1.0–1.7)	1.2 (1.0–1.4)	1.4 (1.2–1.5)	1.7 (1.4–2.0)	2.4 (1.9–3.0)	2.4 (1.6–3.6)	3.3 (2.1–5.0)	2.1 (0.4–6.0)
Alcohol/drug-induced cardiomyopathy									
Events, n (%)	480 (0.03)	45 (0.03)	89 (0.03)	172 (0.03)	106 (0.03)	35 (0.03)	16 (0.04)	11 (0.04)	6 (0.08)
Cases per 100 000 observation-y (95% CI)	1.1 (1.0–1.2)	1.2 (0.8–1.5)	1.1 (0.8–1.3)	0.9 (0.8–1.1)	1.2 (1.0–1.4)	1.2 (0.8–1.6)	1.6 (0.9–2.5)	1.6 (0.8–2.9)	4.1 (1.5–9.0)
Other cardiomyopathies									
Events, n (%)	538 (0.03)	49 (0.04)	88 (0.03)	195 (0.03)	125 (0.04)	37 (0.03)	21 (0.05)	21 (0.07)	2 (0.03)
Cases per 100 000 observation-y (95% CI)	1.2 (1.1–1.3)	1.3 (0.9–1.7)	1.0 (0.8–1.3)	1.1 (0.9–1.2)	1.4 (1.2–1.6)	1.2 (0.9–1.7)	2.1 (1.3–3.1)	3.1 (1.9–4.8)	1.4 (0.2–5.0)

BMI indicates body mass index; Q1, quartile 1; and Q3, quartile 3.

of 18.5 to <20 kg/m² (Figure and Table 3), with a >8-fold increased risk at BMI ≥35 kg/m². For each 1-unit increase in BMI, the hazard ratio for dilated cardiomyopathy, adjusted for age at conscription, conscription year, test center, and baseline comorbidities, was 1.15 (95% CI, 1.14–1.17), for hypertrophic cardiomyopathy was 1.09 (95% CI, 1.06–1.12), and for alcohol/drug-induced cardiomyopathy was 1.10 (95% CI, 1.06–1.13; Table 3). Hazard ratios were largely similar in multiple-adjusted models additionally adjusted for systolic and diastolic blood pressures, cardiorespiratory fitness, muscle strength, parental education, and alcohol/substance use disorders, based on fewer events because of missing data for some variables (Table 3 and Figure II in the online-only Data Supplement). The hazard ratios did not change materially when we studied competing risk in which death was treated as a competing event (Table III in the online-only Data Supplement). Corresponding rates for acute myocardial infarction and heart failure are presented in Table IV and Figure III in the online-only Data Supplement. The relationships between BMI and dilated cardiomyopathy (nonischemic heart muscle disease) and between BMI and a diagnosis of cardiomyopathy with a prior myocardial infarction are shown in Figure IV in the online-only Data Supplement.

We found a graded association between diastolic blood pressure and dilated cardiomyopathy (Tables V and VI in the online-only Data Supplement). However, no association was found between blood pressure and hypertrophic cardiomyopathy. Low cardiorespiratory fitness and low muscle strength were associated with increased risk of both dilated cardiomyopathy and alcohol/drug-induced cardiomyopathy. There was a >7-fold increased risk for a subsequent alcohol/drug-induced cardiomyopathy associated with an alcohol/substance use disorder in adolescence (Table VI in the online-only Data Supplement).

DISCUSSION

In this prospective cohort study of almost 1.7 million young men, elevated BMI in adolescence was associated with the development of cardiomyopathy in adulthood, with a steadily increasing risk from high-normal values and up to 8-fold increase for dilated cardiomyopathy at BMI ≥35 kg/m². Other types of cardiomyopathies were also more

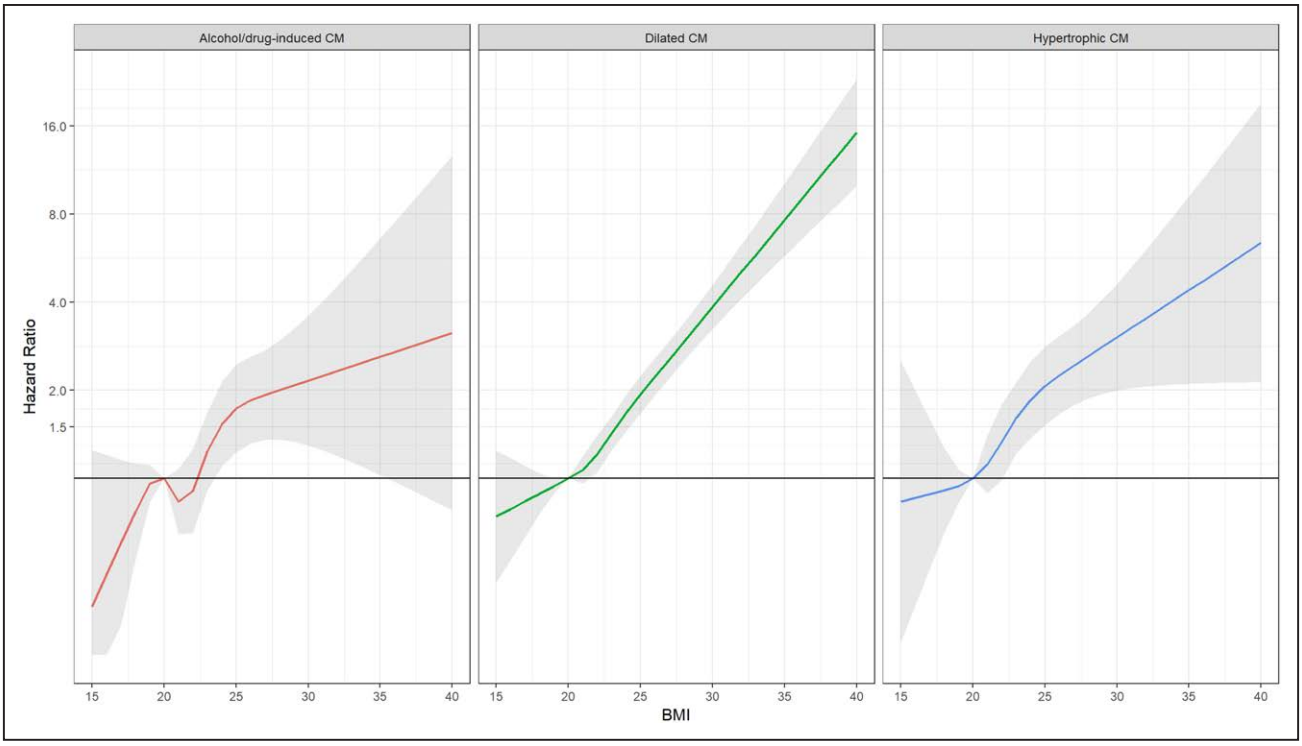

Figure. Association between body mass index (BMI) at conscription and risk for cardiomyopathy (CM).
The model was adjusted for age, conscription year (as a spline with knots at 5%, 35%, 65%, and 95%, ie, 1971, 1982, 1992, and 2004), test center, and baseline comorbidities (diabetes mellitus, hypertension, congenital heart disease), systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and alcohol or substance use disorder (n=773 679). BMI was restricted to BMI between 15 and 40 kg/m^2 and modeled as a restricted cubic spline with knots at 5%, 35%, 65%, and 95% (ie, 18.0, 20.5, 22.4, and 27.5 kg/m^2), with BMI of 20 kg/m^2 as reference. The unadjusted model is presented in Figure II in the online-only Data Supplement.

common in the obese and overweight categories. Additional factors measured in adolescence that were associated with long-term increased risk of cardiomyopathy were low cardiorespiratory fitness and low muscle strength, although associations with BMI were independent of them.

Cardiomyopathies are a heterogeneous group of disorders that are difficult to define and delimit, and compared with other cardiovascular disorders, they are relatively rare. Dilated cardiomyopathy is the most prevalent type,[17] but the validity of a diagnosis of general or specific forms of cardiomyopathy needs to be established. In a recent study from our group in which we validated hospital diagnoses of cardiomyopathy against predefined criteria and the use of echocardiography was nearly 100% throughout the study period, diagnoses of dilated cardiomyopathy, hypertrophic cardiomyopathy, and other cardiomyopathies were found to be accurate in 86%, 88%, and 100% of cases, respectively.[4] Although that study included 3 hospitals in different settings, in 3 cities, and in an unselected population covering a large part of western Sweden, there were no significant changes in accuracy between the hospitals or over the extended study period of 20 years. Furthermore, of the individuals with dilated and alcohol-associated cardiomyopathies in the present study, 69% were diagnosed with heart failure at some point, but the absence of a heart failure diagnosis does not exclude the presence of symptoms, and clinical heart failure is not a prerequisite for a diagnosis of cardiomyopathy. Men with a diagnosis of hypertrophic cardiomyopathy received a diagnosis of heart failure much less often (11%), whereas among men without a diagnosis of cardiomyopathy, only 0.8% were diagnosed with heart failure.

Few studies have described the epidemiology of cardiomyopathies,[17–20] and risk factors for these disorders remain a largely unexplored field. The present cohort study adds to the literature by investigating BMI in late adolescence and identifying a large number of cardiomyopathy cases over an extended follow-up. This provides an opportunity to identify adolescent men who are at an elevated risk not only for cardiomyopathy but also for a range of other disorders associated with obesity,[10] particularly because cardiovascular risk factors, including overweight and obesity, tend to cluster and track from childhood into adulthood.[21,22] The 1 existing relevant study that we identified,[10] based on a cohort of 2.3 million Israeli adolescents and identifying 121 deaths attributed to cardiomyopathies, also found a graded increase in risk with increasing BMI. This study, however, was not powered to investigate specific forms of cardiomyopathy or the association with severe obesity, or BMI ≥35 kg/m^2, which forms an increasing proportion among the overweight in Sweden.[11] We found an 8-fold increase in risk for dilated cardiomyopathy at BMI ≥35 kg/m^2.

Table 3. Hazard Ratios (95% CIs) for Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy, Alcohol/Drug-Induced Cardiomyopathy, and Other Cardiomyopathies by BMI Category

	Dilated Cardiomyopathy	Hypertrophic Cardiomyopathy	Alcohol/Drug-Induced Cardiomyopathy	Other Cardiomyopathies
Model 1*				
Events/population, n	2631/1 668 781	673/1 668 781	480/1 668 781	538/1 668 781
BMI<18.5 kg/m^2	1.07 (0.91–1.26)	1.04 (0.74–1.46)	1.04 (0.73–1.49)	1.19 (0.84–1.68)
18.5 kg/m^2≤BMI<20 kg/m^2	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
20 kg/m^2≤BMI<22.5 kg/m^2	1.01 (0.90–1.13)	1.20 (0.95–1.51)	0.97 (0.75–1.26)	1.06 (0.83–1.37)
22.5 kg/m^2≤BMI<25 kg/m^2	1.38 (1.22–1.57)	1.55 (1.21–2.00)	1.31 (0.99–1.74)	1.41 (1.07–1.85)
25 kg/m^2≤BMI<27.5 kg/m^2	2.26 (1.94–2.63)	2.31 (1.70–3.12)	1.40 (0.95–2.07)	1.28 (0.87–1.89)
27.5 kg/m^2≤BMI<30 kg/m^2	3.65 (3.02–4.41)	2.41 (1.55–3.74)	2.00 (1.17–3.41)	2.17 (1.35–3.50)
30 kg/m^2≤BMI<35 kg/m^2	5.03 (4.10–6.17)	3.39 (2.13–5.40)	2.34 (1.25–4.39)	3.40 (2.11–5.50)
35 kg/m^2≤BMI	8.11 (5.76–11.43)	2.28 (0.72–7.22)	7.22 (3.14–16.58)	1.55 (0.38–6.33)
Per unit BMI†	1.15 (1.14–1.17)	1.09 (1.06–1.12)	1.10 (1.06–1.13)	1.08 (1.05–1.12)
Model 2‡				
Events/population, n	1553/773 805	360/773 805	280/773 805	292/773 805
BMI<18.5 kg/m^2	0.85 (0.69–1.06)	1.02 (0.64–1.61)	0.77 (0.48–1.24)	1.08 (0.67–1.75)
18.5 kg/m^2≤BMI<20 kg/m^2	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
20 kg/m^2≤BMI<22.5 kg/m^2	1.13 (0.97–1.31)	1.31 (0.96–1.81)	0.95 (0.68–1.32)	0.97 (0.69–1.36)
22.5 kg/m^2≤BMI<25 kg/m^2	1.56 (1.32–1.85)	1.75 (1.22–2.51)	1.66 (1.15–2.41)	1.24 (0.84–1.83)
25 kg/m^2≤BMI<27.5 kg/m^2	2.35 (1.90–2.89)	3.06 (2.00–4.68)	1.60 (0.94–2.75)	1.09 (0.63–1.91)
27.5 kg/m^2≤BMI<30 kg/m^2	3.13 (2.36–4.16)	3.03 (1.60–5.75)	2.20 (1.03–4.70)	2.32 (1.21–4.43)
30 kg/m^2≤BMI<35 kg/m^2	4.91 (3.64–6.61)	3.17 (1.42–7.07)	1.96 (0.70–5.49)	3.38 (1.68–6.81)
35 kg/m^2≤BMI	9.35 (5.60–15.62)	3.28 (0.45–23.90)	9.56 (2.91–31.37)	4.67 (1.12–19.48)
Per unit BMI†	1.15 (1.13–1.17)	1.11 (1.07–1.16)	1.11 (1.06–1.17)	1.11 (1.07–1.17)

BMI indicates body mass index.

*Model 1 adjusted for age at conscription, conscription year, test center, and baseline comorbidities (diabetes mellitus, hypertension, congenital heart disease).

†Calculated for BMI >20 kg/m^2.

‡Model 2 additionally adjusted for systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and alcohol or substance use disorder.

Globally, the rising trends in children's and adolescents' BMIs have plateaued in many high-income countries,[9] but levels remain disturbingly high, and accordingly, this could herald a future global epidemic of obesity-related heart conditions in the young and middle-aged.

Estimating the association between obesity and cardiovascular risk is complicated because of the strong association between elevated body weight and other cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemias.[23] Young people might not yet have accumulated these risk factors, and accordingly, they are an optimal study population in this regard. Childhood obesity has, however, independently been associated with significant changes in myocardial geometry and function,[24] which has been further strengthened in a study of obesity genes in young adults,[25] indicating an early onset of potentially unfavorable alterations in the myocardium that are independent of other cardiovascular risk factors. In this study, we found that the risk of cardiomyopathy started to increase at levels of adolescent BMI at the upper normal level, which is in accordance with recent findings with respect to early heart failure[7] and is supported by the findings by Twig et al.[10] In studies of people with severe obesity, cardiomyopathy has been identified as a complication,[26,27] with severity and duration of obesity recognized as essential determinants of alterations in cardiac performance and morphology.[28] The development and progression of myocardial remodeling in obese subjects are predisposed by multiple mechanisms, including hemodynamic alterations such as increased blood volume and cardiac output, leading to left ventricular hypertrophy and dilation. Indeed, obesity appears to be an underrecognized driver of adverse cardiac remodeling and heart failure, as recently argued.[29] Altered lipid metabolism, including overactivity of adipocyte cell–signaling molecules such as aldosterone, neprilysin, and leptin,[30] inflammation, and oxidative stress, has been described as contributing to these effects, potentially resulting in cardiac fibrosis

and impaired diastolic and systolic function.[31] All the specific categories of cardiomyopathy that we identified showed an association with body weight, although that association is strongest for dilated cardiomyopathy. How increasing BMI causes the observed associations cannot be answered from these data. Although part of the answer may relate to myocardial effects of excess fat, this would not be expected to increase the risk for true hypertrophic cardiomyopathy, which is a hereditary condition in most cases. Instead it may be that elevated BMI leads to hypertrophy as a result of increased left ventricular wall stress related to volume and pressure overload, caused by hypertension, blood volume expansion, and increased myocardial work. In these ways, higher BMI might lead to earlier symptomatic expression and therefore a diagnosis of cardiomyopathy (and exacerbate other deficits in cardiac function, leading to premature decompensation). It is also known that obesity and alcohol intake synergize to increase risks of several complications such as liver diseases,[32] and the same may be true for cardiomyopathy. Because alcohol abuse and substance abuse are important independent reversible causes of myocardial dysfunction,[15] we treated them as a separate group, but even so, there was still a strong association with overweight and obesity.

Associations between blood pressure in adolescence and cardiomyopathy were either nonsignificant or weak. The positive association between elevated diastolic blood pressure and risk of dilated cardiomyopathy was much less strong than that found for BMI and was notably absent for hypertrophic cardiomyopathy. Although further development with respect to hypertension during follow-up is not known, this indicates that the hypertrophy was likely not caused by hypertension, a distinction that is sometimes difficult to make in clinical practice. Except for BMI, hypertrophic cardiomyopathy did not have identifiable risk factors to the same extent as the other categories, probably because of the strong genetic component associated with this type of cardiomyopathy.[3]

Strengths and Limitations

Strengths of this study include the large sample size (>1.6 million participants), the prospective population-based design, and the fact that the study population is largely representative of the male general population in these age categories in Sweden during the study period. A large number of cases of cardiomyopathies were recorded during an extended follow-up. Recent data from a validation study by our group showed that the cardiomyopathy diagnoses in the National Hospital Register, during a period overlapping that of the present study, have a high validity with a diagnostic accuracy of >85%, with no change in diagnostic accuracy over the 20-year study period and with a more or less uniform use of echocardiography in the investigation of suspected cardiomyopathy throughout these years.

There are also some limitations to our study. We used BMI as an indicator of overweight and obesity. Mildly elevated BMI in youth may reflect high muscle mass, not adiposity, which, however, is unlikely to be the case when BMI is very high. We also observed increasing risks from high-normal BMI, and when we adjusted for muscle strength, the association between BMI and cardiomyopathy was only slightly attenuated. Other measurements such as waist circumference, waist-to-hip ratio, or any other anthropometric variable beyond BMI were not available in the data set. The study population was homogeneous with respect to age, sex, and ethnicity, which limits the generalizability to women and to other populations. Immigration increased over the period, but the effect of ethnicity could not be systematically assessed because of a lack of detailed data. Furthermore, the diagnostic criteria for cardiomyopathy have changed over time. Limited diagnostic criteria over the initial follow-up indicate that some patients with cardiomyopathy according to the 2008 guidelines might not have been identified. In addition, we were unable to study some other potentially important exposures such as weight gain or loss, smoking habits, diet, physical activity, occupation, alcohol consumption, and substance abuse during follow-up. Hence, there is no way to know if subsequent weight changes would affect the risk.

CONCLUSIONS

This cohort study adds to the literature by identifying elevated BMI in adolescence to be associated with a diagnosis of cardiomyopathy in adulthood, especially dilated cardiomyopathy. The already marked importance of weight control in youth is further strengthened by these findings, as well as greater evidence for obesity as a potential important cause of adverse cardiac remodeling that is independent of clinically evident ischemic heart disease.

ARTICLE INFORMATION

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Correspondence

Annika Rosengren, MD, PhD, Department of Medicine, Sahlgrenska University, Hospital/Östra, SE 416 85 Göteborg, Sweden. Email annika.rosengren@gu.se

Affiliations

Department of Public Health and Community Medicine/Primary Health Care (J.R., M.A.), Department of Molecular and Clinical Medicine (M.S., M.L., M.A., A.R.), and Section of Occupational and Environmental Medicine, Department of Public Health and Community Medicine (L.S., K.T.), Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden. Sahlgrenska University Hospital, Gothenburg, Sweden (J.R., M.S., M.L., A.R.). British Heart Foundation Cardiovascular Research Centre (J.M.) and Institute of Cardiovascular and Medical Sciences (N.S.), University of Glasgow. Department of Cardiology, Western Infirmary, Glasgow, UK (J.M.).

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Disclosures

None.

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