Body mass index and mental health in young people

Predictors of early heart failure and cardiomyopathy

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The best and most beautiful things in the world cannot be
seen or even touched – they must be felt with the heart.

Helen Keller

To Grandma and Grandpa

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ABSTRACT

Background

Heart failure is a medical condition in which the heart muscle cannot maintain an adequate cardiac output, due to structural and/or functional impairment. It is a disorder with a major impact on quality of life and has a poor prognosis, comparable to those of many common forms of cancer. Heart failure among young people is rare, but in contrast to decreasing incidence rates overall, some studies have shown increasing rates among younger people. Accordingly, the rates of cardiomyopathy, which is often the condition underlying heart failure in the young, have more than doubled in Sweden during the last few decades, for unknown reasons. These increases in early heart failure and cardiomyopathy raise questions about the causes. One factor that coincides with this phenomenon is a marked rise in body weight and obesity among young people. At the same time, depression, anxiety, and hospitalizations for alcohol and drug use are becoming more frequent among young Swedes. Considering these coinciding trends, we hypothesized that being overweight and suffering from a mental illness at a young age are associated with an increased risk of future heart failure and cardiomyopathy.

Aim, subjects and methods

The overall aim of this thesis was to determine whether body mass index (BMI), nonpsychotic mental disorders, and stress resilience (susceptibility to stressful events) at a young age are associated with early heart failure and cardiomyopathy. We performed nationwide cohort studies using the Swedish Military Service Conscription Register and the Medical Birth Register. In Papers I-III, we obtained baseline data on 1.7 million young men who enlisted for mandatory military service in the period 1968–2005. Information on BMI, blood pressure, and medical history were extracted, along with test results of physical fitness, stress resilience, and cognitive ability. In Paper IV, we obtained information on BMI, smoking, and baseline disorders collected at the

first antenatal visit during pregnancy for 1.4 million women, in the period 1982–2014. By linking the data to the National Patient and Cause of Death registers, which is a unique possibility in Sweden thanks to our personal identification numbers, we identified cases of early heart failure and cardiomyopathy in these large population cohorts for a follow-up period of up to 46 years.

Results
We found that higher BMI in young people was associated with an increased risk of early heart failure and cardiomyopathy (Papers I, III, and IV). The increased risk was present already at BMI values that are considered mid- to high-normal for adolescent men (i.e., BMI 20–25), whereas, for cardiomyopathy, women of childbearing age had an elevated risk from BMI 25. The risk increased in line with increasing BMI, regardless of gender, such that severe obesity (i.e., BMI ≥35) was associated with a nine-fold increase in risk for early heart failure and cardiomyopathy among men, and a five-fold higher risk for cardiomyopathy among women. Furthermore, we found that nonpsychotic mental disorders in adolescent males, as well as low stress resilience, were associated with higher risk of early heart failure (Paper II).

Conclusions
Given the current trends towards increased body weight and mental illness among young people globally, physicians need to be aware of the potential future risk for increased numbers of heart failure and cardiomyopathy cases. The present findings emphasize the importance of weight control in youths, which is essential to curb the obesity epidemic and to prevent the consequences related to it**.** This should go hand in hand with intensified efforts to prevent mental illness in young people.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Hjärtsvikt är en allvarlig sjukdom, som innebär att hjärtat inte förmår att tillgodose kroppens organ med en tillräcklig blodvolym på ett funktionellt sätt. Sjukdomen kan ha stor inverkan på patienters livskvalitet med hög dödlighet i nivå med flera cancerdiagnoser. Hjärtsvikt är ovanligt hos unga, men i motsats till den sjunkande trenden man ser hos äldre, har nyare studier visat att hjärtsvikt ökar i den yngre befolkningen. Samtidigt har man noterat en fördubbling av antalet kardiomyopatier (hjärtmuskelsjukdomar) i Sverige under de senaste årtiondena, vilket är en vanlig bakomliggande orsak till hjärtsvikt hos unga. Det ökande antalet tidiga hjärtsviktsfall och kardiomyopatier väcker frågor kring möjliga orsaker. Parallellt med detta fenomen kommer årligen rapporter om att allt fler ungdomar är överviktiga och mår psykiskt dåligt. Vi ämnade därför undersöka om här finns ett samband.

Syfte, metod

Det övergripande syftet med denna avhandling var att studera om övervikt, psykisk ohälsa och låg stresstolerans hos unga medför en ökad risk för tidig hjärtsvikt och kardiomyopati. I detta syfte genomfördes populationsbaserade kohort-studier, där vi använde data från svenska nationella register. Detta gav oss unika möjligheter att kartlägga riskfaktorer i unga år. I artikel I–III erhöll vi information från värnpliktsregistret om 1,7 miljoner unga män som mönstrade in till den obligatoriska militärtjänstgöringen mellan 1968 och 2005. Detta innefattade uppgifter om kroppsmasseindex (BMI), blodtryck och sjukdomshistoria inklusive psykiatriska diagnoser, samt testresultat avseende fysisk kondition, muskelstyrka, kognitiv förmåga och stresstolerans. I artikel IV fokuserade vi på den kvinnliga populationen och erhöll information från det medicinska födelseregistret om BMI, rökning och sjukdomshistoria, vid första besöket i mödravården under tidig graviditet, för 1,4 miljoner kvinnor mellan 1982 och 2014. Genom att länka samman data med det nationella patientregistret och dödsorsaksregistret, vilket är möjligt genom våra unika svenska personnummer, kunde fall av hjärtsvikt och kardiomyopati identifieras under den upp till 46 år långa uppföljningstiden.

Resultat

Studierna visade att högt BMI hos unga är associerat med en ökad risk att utveckla tidig hjärtsvikt och kardiomyopati. Den ökade risken var uppenbar redan vid BMI i övre normalintervallet (BMI 20-25 kg/m^2) hos män i sena tonåren, medan unga kvinnor i fertil ålder hade en högre risk från och med BMI 25. En tydlig trend kunde urskiljas oavsett kön, där högre BMI medförde en gradvis ökad risk. Högst risk sågs vid fetma (BMI ≥35), motsvarande en

niofaldig ökad risk för tidig hjärtsvikt och kardiomyopati för män och en fem gånger ökad risk för kardiomyopati för kvinnor. Våra resultat visade också att psykisk sjukdom (exklusive psykossjukdom) och låg stresstolerans bland unga män är associerat med en ökad risk för framtida hjärtsvikt.

Slutsatser
Sammanfattningsvis tyder dessa studier på att övervikt och fetma, likväl som psykisk ohälsa och låg stresstolerans i unga år, kan medföra en ökad risk för att utveckla tidig hjärtsvikt och kardiomyopati. Detta kan komma att leda till allt fler kardiomyopatier och hjärtsviktsfall bland unga, vilket den medicinska professionen bör vara medveten om. Att fånga upp unga med övervikt och psykisk ohälsa ska därför vara av högsta prioritet med syfte att påbörja en snar intervention och förebygga framtida sjukdomsbörda.

LIST OF PAPERS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals:

I. Rosengren A, Åberg M, <u>Robertson J</u>, Waern M, Schaufelberger M, Kuhn G, Åberg D, Schiöler L, Torén K. Body weight in adolescence and long-term risk of heart failure in men in Sweden. *European Heart Journal. 2017;38(24):1926-1933.*

II. <u>Robertson J</u>, Schiöler L, Torén K, Söderberg M, Löve J, Waern M, Rosengren A, Åberg M. Mental disorders and stress resilience in adolescence and long-term risk of early heart failure among Swedish men.
International Journal of Cardiology. 2017;243:326-331.

III. <u>Robertson J</u>, Schaufelberger M, Lindgren M, Adiels M, Schiöler L, Torén K, McMurray J, Sattar N, Åberg M, Rosengren A. Higher body mass index in adolescence predicts cardiomyopathy risk in midlife: a long-term follow-up among Swedish men.
Circulation. 2019;140(2):117-125.

IV. <u>Robertson J</u>, Lindgren M, Schaufelberger M, Adiels M, Björck L, Lundberg CE, Sattar N, Rosengren A, Åberg M. Body mass index in young women and risk of cardiomyopathy: a long-term follow-up study in Sweden.
Submitted.

i

CONTENT

ABBREVIATIONS

BDNF	brain-derived neurotrophic factor
BMI	body mass index
CI	confidence interval
DNR	diary number
EF	ejection fraction
EPN	The Regional Ethical Review Board
ESC	European Society of Cardiology
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
ICD	International Classifications of Diseases
IQ	intelligence quotient
kg	kilogram
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
m	meter
NCDs	noncommunicable diseases
NO	nitrogen monoxide
PAR	population-attributable risk
PIN	personal identification number
PHYSBE	Physical Fitness and Brain - Epidemiological studies
Q1	quartile 1
Q3	quartile 3
SCAPIS	Swedish CArdioPulmonary bioImage Study
SD	standard deviation
SNS	sympathetic nervous system
W	Watts
W_{max}	maximum work capacity (Watts)
WHO	World Health Organization
VO_2 max	maximum oxygen consumption

INTRODUCTION

Heart failure and cardiomyopathy

Definition and prevalence

Heart failure is a medical condition in which the heart muscle cannot maintain an adequate cardiac output, due to structural and/or functional impairment. The shortage of blood-borne oxygen and nutrients leads to secondary organ malfunction in the kidneys, liver, central nervous system, peripheral muscles, and other organs. This may result in a variety of symptoms including fatigue, shortness of breath, and ankle swelling, and clinical signs such as jugular vein stasis, pulmonary crackles, and pitting edema (1). Heart failure is commonly classified by the left ventricular ejection fraction (EF), which is the proportion of left ventricular blood volume that is ejected in each heart beat (i.e., the end-diastolic volume minus the end-systolic volume divided by the end-diastolic volume). Normal EF is typically considered to be ≥50%. Heart failure with EF<40% is classified as heart failure with reduced EF (HFrEF), whereas EF≥50% is classified as heart failure with preserved EF (HFpEF). An EF in the range of 40%–50% forms a gray area, classified as mid-range (HFmrEF) (1). These subtypes differ with respect to etiology. HFrEF is more frequently associated with an ischemic etiology, while HFpEF correlates more with atrial fibrillation and hypertension. HFpEF is more commonly observed in the elderly and among women (1). The prognosis for heart failure is poor, being comparable to those of many common forms of cancer (2), and despite therapeutic advances, morbidity and mortality rates remain high. The prevalence depends on the definition applied, but it has been reported to be approximately 2% of the adult population in developed countries (3). In Sweden, the age-adjusted prevalence for patients in the age range of 19–99 years who have been hospitalized with heart failure increased from 1.73% in 1990 to a maximum of 2.13% in 1998, with a subsequent decrease to 1.99% in 2007 (4). However, in contrast to decreasing incidence rates overall, studies in Sweden and Denmark have found increasing rates among younger people (Figure 1) (5-7).
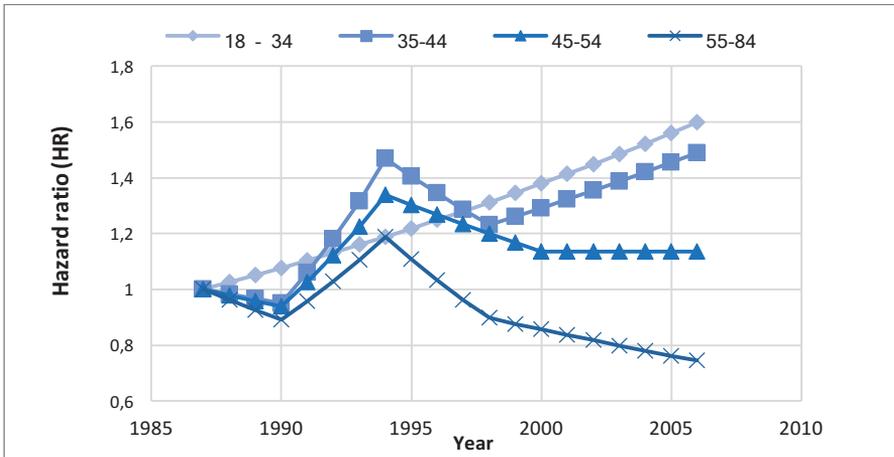
Figure 1. Incidence of first hospital admissions for heart failure by age category (years) in Sweden, for the period 1987-2006 (5). Reprinted with permission from Prof. Maria Schaufelberger.

While coronary heart disease and hypertension are the most frequent causes of heart failure in older patients, cardiomyopathy is a more common underlying condition in younger people with heart failure (Figure 2) (8). Concomitant with the rise of heart failure in the young, cardiomyopathy, as a disorder underlying heart failure, more than doubled between 1987 and 2006 in Sweden, for unknown reasons (5).
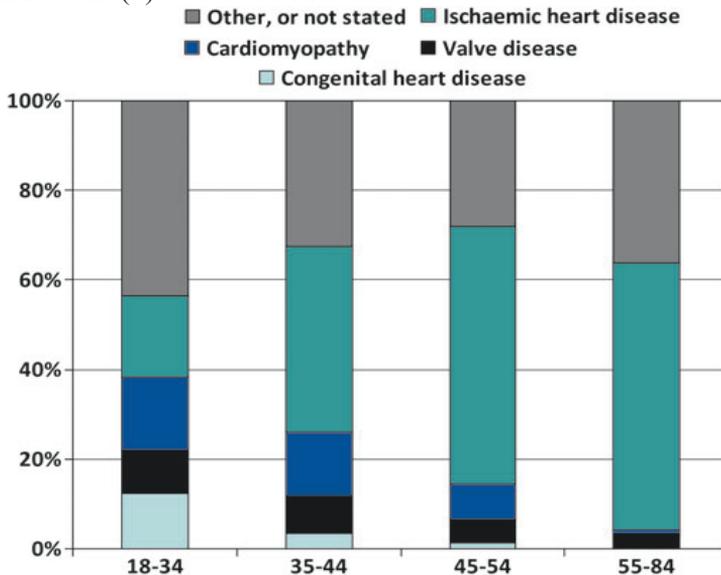
Figure 2. Comorbidity prevalence (%) of mutually exclusive diagnoses among patients with heart failure categorized by age group. Reprinted with permission (5). Barasa et al, Eur Heart J, page 27, 2014.

According to the latest classification from the European Society of Cardiology (ESC) in 2008 (9), cardiomyopathy is defined 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'*. The classification of cardiomyopathies has been a challenge owing to the extensive heterogeneity of these disorders. The ESC presented five categories of cardiomyopathy in 2008: dilated, hypertrophic, restrictive, arrythmogenic right ventricular, and unclassified, of which dilated and hypertrophic cardiomyopathies are the most common. Hypertrophic cardiomyopathy is genetically transmitted in most cases with a prevalence reported to be 0.2% (1 in 500 persons), whereas dilated cardiomyopathy is thought to be familial in 25% of the cases. The prevalence of dilated cardiomyopathy in the general population is not known, but has been suggested to be twice that of hypertrophic cardiomyopathy (i.e., 1 in 250 persons) (9, 10). Peripartum cardiomyopathy, which is a pregnancy-related disorder that resembles the dilated cardiomyopathy, occurs late in pregnancy or in the early puerperium, and thus, affects women only (11).

Overweight and obesity

Classification of adiposity status

Several anthropometric measures, such as body mass index (BMI), waist circumference, and waist-to-hip ratio, can be used to determine whether an individual is overweight or obese. During the 1990s, BMI (weight in kilograms (kg) divided by the square of the height in meters (m)) gradually became the universally accepted measure of the extent of being overweight, and recommended cutoff points have been established. Prior to this, the epidemiology of obesity was difficult to study, as the criteria applied differed between countries. According to the most recent classification of the World Health Organization (WHO) (12), underweight is defined as BMI <18.5, normal weight as 18.5–24.9, overweight as 25–29.9, and obesity as ≥30 kg/m^2. Overweight individuals can also be further stratified into pre-obese (BMI 25–29.9), obese class I (30–34.9), obese class II (35–39.9), and obese class III (≥40) (Table 1).

Table 1. Classification of BMI in adults as assigned by the WHO (12). Reprinted with permission (WHO Technical Report Series, volume 894, Table 2.1, page 9 (2000)).

Classification	BMI[a]	Associated health risks
Underweight	<18.5	Low (but increased risk of other clinical problems)
Normal range	18.5-24.9	Average
Overweight	>25	
Pre-obese	25-29.9	Increased
Obese class I	30-34.9	Moderately increased
Obese class II	35-39.9	Severely increased
Obese class III	≥40	Very severely increased

[a]*BMI values are age-independent and the same for both sexes according to the WHO.*

Notwithstanding the above, the BMI classification has been disputed on the basis that ethnic variations in body composition, such as varying levels of fatness and fat distribution at a given BMI, occur. For instance, Asians are known to differ from Caucasian populations in this context (13). For an accurate classification of overweight and obesity with respect to health risks, it has been proposed that the abdominal fat distribution, measured as waist circumference or waist-to-hip ratio, should be taken into account as a complementary measure to BMI (14). For absolute measurements of fat mass, magnetic resonance imaging can be applied (15), however, this modality is resource-intensive and rarely used to measure fatness in current clinical practice. In this thesis, we used BMI to define adiposity status, since other anthropometric measurements were not available in the registers from which we derived the data.

Prevalences of overweight and obesity

The global prevalences of overweight and obesity have increased markedly over the past decades. In 2016, 1.9 billion adults were overweight, with 650 million of these being obese, according to the WHO (16). This means that 39% of the world's adult population is overweight, and 13% is obese. Analyses of the Global Burden of Disease study data from 195 countries have revealed that the prevalence of obesity has doubled in more than 70 countries and has increased continuously in most other countries since 1980 (17). In 2015, the highest numbers of obese adults were living in the United States and China, whereas the highest numbers of obese children were in China and India. Although the trend towards increased obesity has started to decline in developed countries, it is likely to continue in developing countries (18). Thus, the widely held view of obesity, as a problem of high-income countries, should be revised (19). Sweden has a low prevalence of obesity compared to many other developed countries, however, according to the WHO, the age-standardized prevalence of overweight (BMI >25) among adults (>18 years

old), was 64% for men and 49% for women in 2016 (20). The neighboring Nordic countries had similar rates, whereas the corresponding prevalences for the US were 73% and 63% for men and women, respectively. Historically, studies of obesity trends in Sweden have given mixed results (21-31) (Table 2). National and regional studies have presented diverging patterns, probably due to variability in the rates and trends for different population groups and regions. According to a study with data from the Military Service Conscription Register of 1.5 million 18-year old men, the prevalences of moderate obesity (BMI>30) and, in particular, of severe obesity (BMI>35) increased dramatically from 1969 to 2005 (23). Increasing rates of overweight and obesity have also been noted for women of childbearing age in the period 1992–2010, with data on 116,000 individuals obtained from the Medical Birth Register (28). Additionally, the most recent report from the National Board of Health and Welfare showed continuing increases in the prevalence of maternal overweight to 26.4% and in maternal obesity to 15.1%, in 2017 (Figure 3) (32).

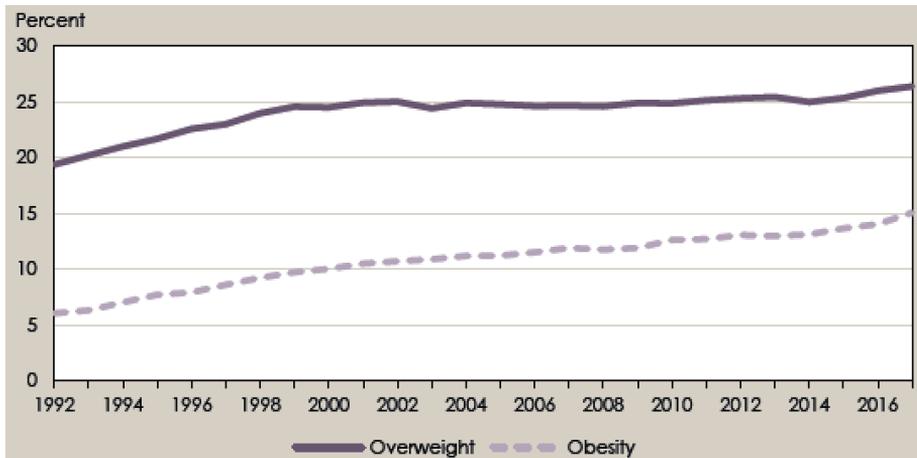*Figure 3. Prevalences (%) of overweight and obesity among birth-giving women at the first antenatal visit in Sweden, for the period 1992–2017. The solid line represents overweight women and the dashed line represents obese women. Reprinted unadjusted with permission from the National Board of Health and Welfare (32). Statistics on Pregnancies, Deliveries and Newborn Infants 2017, Diagram 2, page 2 (2019).*

Table 2. Overview of studies that have investigated the prevalences of overweight and obesity in Sweden.

Author	Year	Unit	Period or specific years studied	Location	Age (years)	Trend for men	Trend for women	Method used for data collection	Study population
Kark, Rasmussen (21)	2005	BMI	1970–2000	Sweden	17–20	Increase	–	Military Service Conscription Register. Measured height and weight.	n=1,500,000 (men only)
Berg et al (22)	2005	BMI	1985, 1990, 1995, 2002	Gothenburg, Sweden	25–64	Increase	Increase	Cross-sectional, population-based surveys. Measured height and weight.	n=5,600 (men/women)
Neovius et al (23)	2008	BMI	1969–2005	Sweden	17–20	Increase	–	Military Service Conscription Register. Measured height and weight.	n=1,580,000 (men only)
Lilja et al (24)	2008	BMI	1986, 1990, 1994, 1999, 2004	Northern Sweden	25–64	Increase	Increase	Cross-sectional population-based surveys. Measured height and weight.	n=8,900 (men/women)
Sundquist et al (25)	2010	BMI	2000/2001, 2004/2005	Sweden	16–84	Stability	Stability	Cross-sectional, population-based questionnaires. Self-reported height and weight.	n=20,900 (men/women)
Johansson et al (26)	2010	BMI	2004–2008	Sweden	16–84	Stability	Stability	Cross-sectional, population-based questionnaires. Self-reported height and weight.	n=41,000 (men/women)
Neovius et al (27)	2013	BMI	2002, 2006, 2010	Stockholm, Sweden	18–64	Increase	Increase	Cross-sectional, population-based questionnaires. Self-reported height and weight.	n=97,000 (men/women)
Chaparro et al (28)	2015	BMI	1992, 2000, 2010	Sweden	≥18	–	Increase	Medical Birth Register. Measured/self-reported height and weight.	n=116,122 (women only)
Molarius et al (29)	2016	BMI	2000, 2004, 2008, 2012	Mid-Sweden	25–74	Increase	Increase	Cross-sectional, population-based questionnaires. Self-reported height and weight.	n=106,000 (men/women)
Zhong et al (30)	2016	BMI	1963–2013	Gothenburg, Sweden	50	Increase	–	Cross-sectional, population-based surveys. Measured height and weight.	n=3,500 (men only)
Lissner et al (31)	2019	BMI	1968–2005	Sweden	18–19	Increase	–	Military Service Conscription Register. Measured height and weight.	n=1,540,532 (men only)

Causes of overweight and obesity

The increasing rates of overweight and obesity over the last decades are probably multifactorial in origin. The so-called 'Big Two' factors of food marketing practices (resulting in altered dietary patterns) and reduced physical activity have long been highlighted as important drivers of these trends (33). Changes in the food environment with increased availability of and lower prices for processed, energy-dense foods, along with major investments in the marketing of such food products have promoted overconsumption and weight gain (34). A study of Swedish patterns of consumption of processed and ultra-processed products, which are foods with low nutritional value but high energy density, highlighted a dramatic increase from 1960 to 2010 (35). The consumption of soft drinks and snack foods accounted for the most notable increase, with more than 300%. The intake of sugar-sweetened beverages has been found to increase particularly among children and adolescents in the last few decades, and this has played an important role in excess calorie intake and obesity (36). Physical activity, both recreational and occupational, is the main modifiable contributor to total energy consumption. The numbers of individuals who are employed in occupations that require physical activity of moderate intensity have decreased since 1960, with more people in occupations that involve sedentary tasks (37). Among young people, greater use of screen devices has been linked to obesity-related risk factors, including physical inactivity in a dose-response manner (38). Taken together, changes in dietary habits along with reduced physical activity appear to be the two main causes of the global obesity epidemic.

Apart from these two phenomena, several other factors have been postulated to contribute to weight gain. For instance, sleep deprivation has been associated with increased body weight, probably as a consequence of endocrine changes that increase hunger and stimulate appetite (39). The average duration of sleep has steadily decreased among children during the past several decades (40). Moreover, industrially produced substances have appeared at greater frequency in the food chain, and they constitute potential obesogenic factors that affect endocrine function (41). The ambient indoor temperature has also been discussed, since heating and air-conditioning devices encourage humans to spend more time than they did before in the thermoneutral zone, in which the body's energy consumption is at its lowest (42). Another factor that parallels the obesity epidemic is the declining rate of cigarette smoking (30). Weight gain is often a consequence of smoking cessation (43). In addition, the introduction and increased usage in recent decades of pharmaceutical drugs, such as antipsychotic agents (44) and oral contraceptives (45), are potential contributors, since weight gain is described as a possible side-effect of these treatments. Finally, maternal age has

increased (46), and the offspring of older mothers have been characterized as having higher BMI values (47). All of the abovementioned factors may affect people to varying degrees, given the strong heritability of obesity (48), with genes predisposing to adiposity in an unfavorable environment. Nevertheless, all of these factors are potential targets in order to prevent future obesity-related diseases.

Consequences of being overweight or obese

Overweight and obesity are major contributors to disability and mortality worldwide. Currently, the majority of the world's population live in countries where overweight and obesity kill more people than being underweight, and this is true for all high-income and most middle-income countries (16). In epidemiologic studies, obesity has been identified as a risk factor for many chronic disorders, such as cardiovascular diseases, diabetes mellitus (49), several cancers (50), autoimmune diseases (51), and osteoarthritis (52). Moreover, obesity among pregnant women, is related to adverse outcomes for both the mother and offspring (53), and there is support for the idea of intergenerational obesity transmission with maternal obesity (54). In turn, gaining excess weight already in childhood and adolescence is likely to result in a lifetime of being overweight or obese (55).

As described above, the traditionally accepted normal range of BMI designated by the WHO is rather broad, from 18.5 to 25 kg/m^2 (Table 1) (12). Studies that have investigated the optimal BMI values in adulthood with respect to the lowest mortality and morbidity risks have yielded somewhat different results within this BMI interval. In 2016, the Global BMI Mortality Collaboration attempted to estimate the association between the degree of overweight and mortality (56). Only never-smokers without previous disease who were still alive at least 5 years after recruitment were included in the analyses. All-cause mortality was found to be minimal for an adult BMI in the range of 20–24.9, whereas the mortality rate increased significantly both below and above this range. Findings from the Prospective Studies Collaboration have demonstrated that the lowest risk of overall mortality is for BMI 22.5–24.9 (57). In addition to an increased risk of mortality above this range, they reported a higher risk already at levels just below BMI 22.5. Of note, the increased mortality risk below BMI 22.5 was mainly associated with smoking, respiratory diseases, and lung cancer in this population of middle-aged persons (mean age at recruitment: 46 (SD 11) years). Taken together, these results indicate that mid-range BMI values within the conventional normal limits are advantageous in midlife, although whether this holds true also for younger adults is not well-established.

Mental health and stress

Mental health

Mental health problems have become more common among young people in high-income countries during the last decades (58). In Sweden, mental illness in youth increased dramatically during the 1990s. Compared to the 1980s, the proportion of young people with symptoms of anxiousness, nervousness, and angst increased three-fold. It was also more common for young people to be hospitalized with depression and anxiety (59). As mental illness at a young age became more frequent for unknown reasons, a governmental commission was set up to investigate this issue. Among several possible contributors, two factors fulfilled the criteria for potential main causes (60). First, an increased use of alcohol was noted, and early alcohol consumption has been found to predict subsequent major depressive disorder (61), especially among women (62). Second, the labor market showed higher rates of unemployment, and more young people were not part of the labor force due to schooling and other reasons (60). The labor market theory is supported by a study that used the information from ten European countries from 1983/1985 to 2002 to demonstrate an association between changes in the proportion of 15-year-olds with symptoms (feeling low, headache and difficulty getting to sleep) and changes in the proportion of 15–24-year-olds who were not in the labor force. The authors concluded that changes in the national labor market for young people contributed to the deterioration of mental health (63). During the early 2000s, the increase in mental illness among young people in Sweden has continued according to the National Board of Health and Welfare (Figure 4) (64), and the Swedish Agency for Youth and Civil Society (65). The consequences of mental illness in this age category are pernicious, including poorer quality of life and marginalization (66), as well as increased risk for cardiovascular diseases (67).
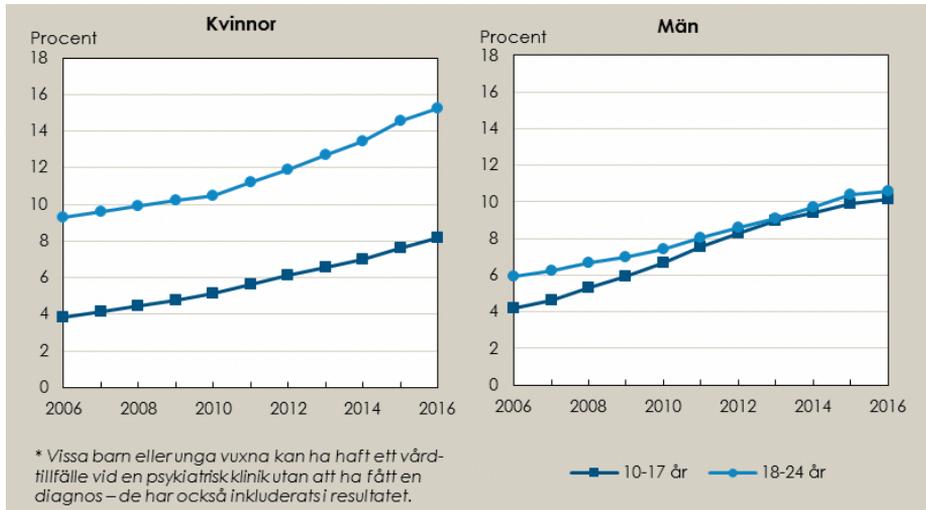
Figure 4. Prevalence (%) of children and young adults who had a hospital admission or specialist outpatient visit due to a mental disorder or who were picking up a prescription of psychotropic agents, during the period 2006–2016. Dark-blue line, 10–17 years of age; light-blue line, 18–24 years of age. Females are shown in the left panel, and males in the right panel. Reprinted unadjusted with permission from the National Board of Health and Welfare (64), Figure 1, page 9 (2017). Translation from the Swedish: Kvinnor, *women;* Män, *men;* år, *year; *Some children or young adults may have attended a psychiatric clinic without receiving a diagnosis – they are also included in the results.*

Stress

The concept of stress and its relationship to unfavorable health outcomes encompasses numerous factors from external stressors to potential reactions to stress. External stressors include work-related stress (68), unfavorable life events (69), and financial difficulties (70), while potential reactions to stress include psychological distress (71), depression (72), exhaustion (73), and sleep disorders (74). A Swedish study of 50-year-old men found that the proportion with self-reported permanent stress increased from 8.7% in 1973 to 19.2% in 2013 (30). In a Danish longitudinal study from 2009, in which more than 7,000 men and women were followed for a decade, high levels of self-reported stress were associated with adverse health behaviors, including smoking, physical inactivity, and higher alcohol intake, as well as use of antihypertensive medication and development of diabetes (75). The biological stress response, as initiated by stressors, is mediated by the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. In daily life, these systems respond to stressful events by releasing stress hormones. Thus, the HPA axis regulates cortisol release from the adrenal cortex and the SNS secretes catecholamines by nerves and the adrenal medulla. Whereas these responses may be protective in the short term, permanent activation of these pathways

has been shown to have damaging effects, leading to the development of diseases (76). There are inter-individual variations in the ability to cope with stress, termed 'stress resilience'. This is thought to be determined early in life by genetic predisposition (77) and childhood circumstances (78). On the one hand, high stress resilience entails healthy levels of psychological and physical functioning despite a disruptive event (79). On the other hand, low stress resilience in adolescence may predict a future burden of health issues and it has been associated with increased risk of several somatic conditions, such as type 2 diabetes (80), hypertension (81), stroke (82), and coronary heart disease (83).

Population-based cohort studies in Sweden

The term 'cohort' is often used to describe a designated group of persons that is followed over a period of time. In a cohort study, a part of the study population can be identified that has been or will be exposed to a factor that could increase the possibility of occurrence of illness or some other outcome (Figure 5). Mostly, such studies investigate etiological factors and are termed observational studies (84). In those studies, the investigator cannot decide which individuals get exposed to a risk; it is only possible to observe what happens over time.
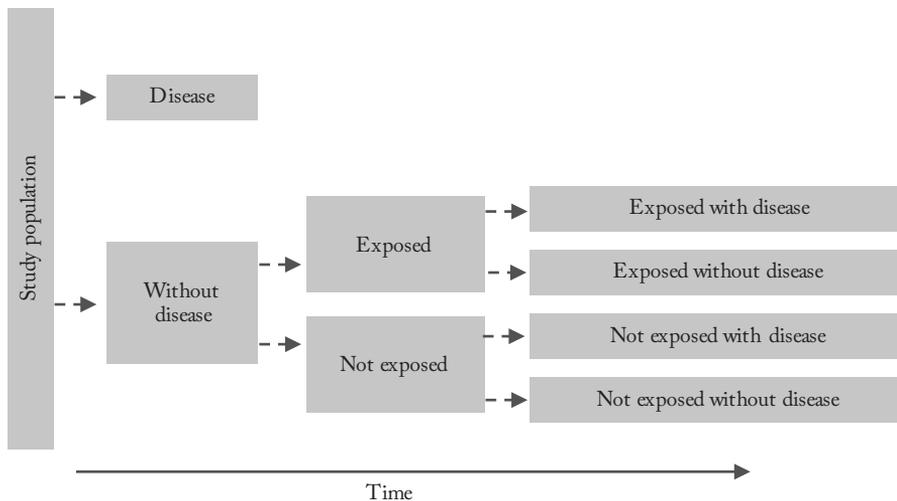
Figure 5. Flow chart of a cohort study (84). Reprinted with permission from John Wiley & Sons Ltd. Medical statistics, Figure 12.1, page 228, Copyright 2007.

Population-based studies are designed to answer research questions for defined populations. The answers should be generalizable to the whole population addressed in the study hypothesis, and not only to the individuals included in the study. Thus, an important issue is the selection of the included individuals, so as to achieve a representative population. In Sweden, there are unique possibilities to study risk factors among young people, with nationwide routines for documentation on specific occasions through the lifetime, for both men and women.

Studying the Swedish young male population

One occasion that previously affected the majority of all Swedish 18-year-old men was the mandatory enlistment in military service. The decision to introduce mandatory military service for all 18-year-old men in Sweden was taken in 1901, after which about 30,000 men per year started military training. Thereafter, the armed forces were upgraded during the two World Wars. In the 1950s, the number had increased to 50,000 men annually, and 1964 is considered as the year in which the Swedish Armed Forces peaked. At that time, detailed medical examinations of conscripts by a physician were introduced, along with an interview with a psychologist. The intake process for conscripts was extended to 2 days, allowing for more medical, physical, and psychological tests. Digitization of the test results started in 1968, and the database is complete from 1969. In the spring of 1980, the Swedish Air Force in Uppsala was the first to offer women military training, and in 1994 it became possible for women to undergo the same military training as men. Over the following years, the number of individuals in military training gradually decreased to about 41,500 individuals in 1990 and 16,500 in 2000 (Figure 6).

Figure 6. Numbers of enlisting Swedish conscripts for the period 1969–2005, of which some went through military training each year.

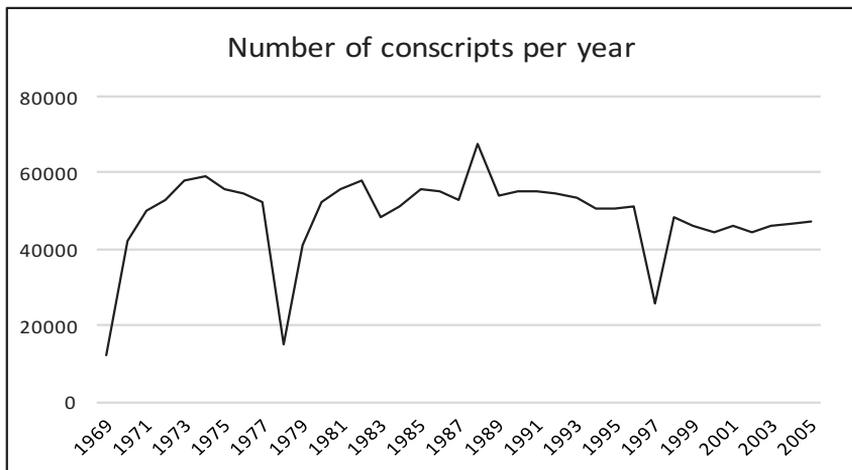In 2010, the mandatory peace-time conscription was abolished in favor of a voluntary recruitment system, and at the same time the process was rendered gender-neutral. However, to maintain military readiness, the Government of Sweden decided that the voluntary system had to be complemented by compulsory military service, so it reintroduced conscription-based recruitment in 2018. This means that approximately 4,000 18-year-olds of both sexes (about 4%) will be recruited for military training annually (affects Swedes born after 1999). These conscripts are selected from 13,000 young people who are asked to undergo a military assessment, based on individual motivation and interest. The aim is to encourage them either to become military professionals or, later, to join the military reserves (85).

Studying the Swedish young female population

An opportunity equivalent to the mandatory military conscription for men, does not exist for women in Sweden. However, a majority (>85%) of the Swedish female population gives birth at least once in life (86), at which point the woman will be registered at one of the antenatal clinics. The national maternal healthcare system was developed during the 1930s with the United Kingdom as a model. At first, only two visits were implemented during pregnancy, but this has been increased over time to the current system of scheduled visits on a more regular basis, including a parental education program (87). This enables the maternal healthcare system to embrace various aspects of health for women of childbearing age and their partners.

Knowledge gaps

In recent years, the increasing rates of heart failure and cardiomyopathy in the young have raised questions about possible causes. The reported divergent trends of heart failure incidence in younger and older people are of great concern. Given that heart failure, to date, is uncommon in young people, most studies have focused on the etiology and prognosis in older populations. There is a knowledge gap regarding these important aspects for younger age categories. An obvious factor that coincides with the increase in early heart failure and cardiomyopathy is the marked rise in the numbers of young people who are overweight or obese (23, 28). It is well-known that overweight and obesity can lead to adverse health issues including cardiovascular diseases (49), as well as, structural and functional changes in the heart (88). However, the long-term effects of adiposity in early adulthood have not been thoroughly studied. Younger age at onset may result in a longer duration of adiposity throughout life, which may increase obesity-related morbidity. Most of the studies that have investigated adolescent overweightness, have used the entire normal range of BMI (BMI 18.5-25) as the reference group (89-93), and

therefore, they have only examined the risk for persons with BMI >25. The availability of Swedish registers makes it possible to create study populations that are sufficiently large to enable analyses of BMI values both within and beyond the normal range, despite relatively low rates of heart failure and cardiomyopathy events among young people. In particular, cases of cardiomyopathy are rare, and risk factors for this condition are scarcely explored, even more so in females. Whereas an association between body weight in middle-aged women and risk of developing heart failure has been reported recently in a Swedish study (94), no studies have, to our knowledge, investigated body weight in young women and men and the risk for cardiomyopathy including the different subtypes of the disease.

Along with the increasing incidence of overweightness, the numbers of young people who suffer from depression, anxiety, and substance abuse are on the rise in Sweden (59, 65). There is evidence of increased risk of cardiovascular illness in persons with psychiatric disorders (67, 95), and a possible link between major depression and heart failure has been proposed (96). Furthermore, psychological stress, as well as difficulties in coping with stressful events, are associated with unfavorable health outcomes, including cardiovascular diseases (72, 81). However, whether or not the presence of nonpsychotic mental disorders and low stress resilience already in adolescence contributes to an increased risk of heart failure in adulthood remains unclear.

Considering these aspects, we hypothesized that the increasing rates of obesity and mental illness in young people are associated with the concomitant increase in persons being diagnosed with heart failure and cardiomyopathy in the Swedish population. As part of filling the existing gaps in knowledge, our epidemiologic investigations of exposures in early adult life may allow for the detection of potential associations. Historically, risk factors and an unhealthy lifestyle in young people have been difficult to capture, since most studies with older participants provide limited information on risk factors early in life, combined with the usually low participation rates among young people in population-based surveys. In this context, the Military Service Conscription Register and the Medical Birth Register contribute as valuable sources of epidemiological knowledge.

AIMS

The overall aim of this thesis was to investigate whether BMI and mental health in young people predict the risk of heart failure and cardiomyopathy in adulthood.

The specific aims of the individual papers were:

I.   To study the relation between BMI in young men and risk for early hospitalization with heart failure.

II.   To study whether nonpsychotic mental disorders and low stress resilience in young men are associated with increased risk of early heart failure.

III.   To study whether overweight and obesity among men in late adolescence predict the risk for cardiomyopathy in midlife.

IV.   To study overweight and obesity in young women as risk factors for cardiomyopathy in midlife.

SUBJECTS AND METHODS

National population registers

All Swedish residents are registered with a unique ten-digit personal identification number (PIN) at birth or immigration since 1947. This number is used extensively in public administration, such as education, migration, issuing of passports, and in the routine healthcare, as well as in medical research, where it can be used as the linkage tool between registers (97). The national registers utilized in the four papers of this thesis are outlined below (Table 3).

Table 3. National population and health registers utilized in the papers of this thesis.

Register	Paper I	Paper II	Paper III	Paper IV
The Military Service Conscription Register	✓	✓	✓	
The Medical Birth Register				✓
The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)	✓	✓	✓	✓
The National Patient Register	✓	✓	✓	✓
The Cause of Death Register	✓		✓	✓

The Military Service Conscription Register (Papers I–III)

The Swedish Military Service Conscription Register was established in 1952, with digitization of the data from 1968. Up until the abolishment of the mandatory military service, all Swedish men in the age range of 18–24 years were obliged to enlist in military service according to Swedish law. Exemption from enlistment was only granted for imprisonment, severe medical conditions or physical disabilities, with these exemptions usually limited to 2%–3% annually. After Year 2000, exemptions could also be permitted after a written application to the National Service Administration, which became more common until compulsory conscription was formally abandoned in 2010.

The Medical Birth Register (Paper IV)

The Swedish Medical Birth Register was established in 1973 at the request of the Swedish parliament. All healthcare providers have to report information from the medical records regarding the prenatal, delivery and neonatal care to the register, resulting in an estimated coverage of 99% (98). To date, the number of infants born annually has varied between 84,000 and 122,000 (99). While modifications to the content and to the methods of data collection have

been made over the years, the basic structure of the register remains. During the first 10 years, it was based on information from standardized forms, so-called 'Medical Birth Reports' (*Medicinskt födelsemeddelande*), which were written by secretaries at the obstetric clinics. These reports were identical in form throughout almost all the counties of Sweden, with the main purpose being to establish communication between the delivery unit, the antenatal center, and the pediatric healthcare. In 1982, this was replaced by three medical records that covered antenatal care of the mother, delivery, and pediatric examination of the infant. A new procedure with check boxes for several serious conditions replaced the previous notations with International Classifications of Diseases (ICD) codes for specific diseases during pregnancy. Across all the years, valid information on height is available for about 80% of the women and early pregnancy weight data are available for about 70% of the women (98).

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) (Papers I–IV)

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), with 80% national coverage, has been administered by Statistics Sweden since 1990 (100). It contains data for the labor market and the educational sector. The database is updated annually at year end for all residents registered in Sweden who are 16 years or older. For the work of this thesis, we obtained information on parental educational level for conscripts in Papers I–III, as an indicator of socioeconomic status, since most of the men were 18–19 years of age at conscription and had not yet completed their own education. For conscription examinations before LISA was established in 1990, the highest parental education achieved (Paper I) or the first parental education registered (Papers II and III) as of 1990 or later was utilized. In Paper IV, we obtained information on the individual educational level for each woman. For deliveries before LISA was established, the first registered education level as of 1990 or later was used.

The National Patient Register (Papers I–IV)

The national health system in Sweden is publicly funded and provides specialist and hospital care at low cost to all inhabitants. At outpatient visits or upon hospital discharge, each patient receives at least one diagnostic code (according to the ICD), which is recorded in the Swedish National Patient Register (101). There was a gradual increase in coverage of inpatient data from 1970 to 1986, and the dataset is considered to be complete from 1987. Outpatient visits were included from Year 2001. Primary care data are not included.

The register has been validated in several studies. A review conducted in 2011 found a high positive predicted value of 85%–95% for the majority of the diagnoses included (102). The proportion of valid diagnoses was described as being higher for patients with severe forms of disease. In a validation study of the heart failure diagnoses (103), 82% of the registered cases were classified as having been correctly diagnosed, according to the European Society of Cardiology (ESC) definition from 1995. Echocardiographic examination increased the validity to 88%. The validity was noticeably higher among patients who were treated at an internal medicine (86%) or cardiology (91%) department, and when heart failure was the principal diagnosis (95%). A recent validation study of cardiomyopathy diagnoses in the National Hospital Register conducted by our research group comprised more than 600 cases (mean age 58.9 (SD 15.5) years; 68.2% men) in western Sweden over a period of 20 years (104). Records for all patients with a cardiomyopathy diagnosis, as reported to the National Hospital Register, were identified in the local discharge registers in three hospitals, with different catchment areas, and validated according to the criteria determined by the ESC in 2008 (9). The accuracy rates were: 85.5% for dilated cardiomyopathy; 87.5% for hypertrophic cardiomyopathy; and 100% for other cardiomyopathies. There was no significant trend over time, and there was more or less uniform use of echocardiography for the investigation of suspected cardiomyopathy throughout the study period (on average, 94.6% of cases), except for the first 2 years (1989–1990).

The Cause of Death Register (Papers I, III, IV)

The Cause of Death Register holds information on all deceased Swedish residents, classified according to the ICD (105). When there is a death, a physician has to submit a medical death certificate to the National Board of Health and Welfare within 3 weeks. The information is thereafter recorded in the Cause of Death Register, which contains data from every year since 1952. The quality of the register and accuracy of death causes for cardiovascular diseases have been reported as being high (106).

Study populations

The study cohorts in this thesis are derived from the Military Service Conscription Register (Papers I–III) and the Medical Birth Register (Paper IV). The Conscription Register data were extracted from Statistics Sweden on two occasions, whereby the data in Paper I were received and modified by our research group in the first round. The data in the second extract was further modified to eliminate incorrect registrations of individuals, resulting in different initial study samples in Paper I, as compared to Papers II and III.

Figure 7 shows an overview of the exclusion criteria used for the cohorts in the different papers and the final numbers of participants.

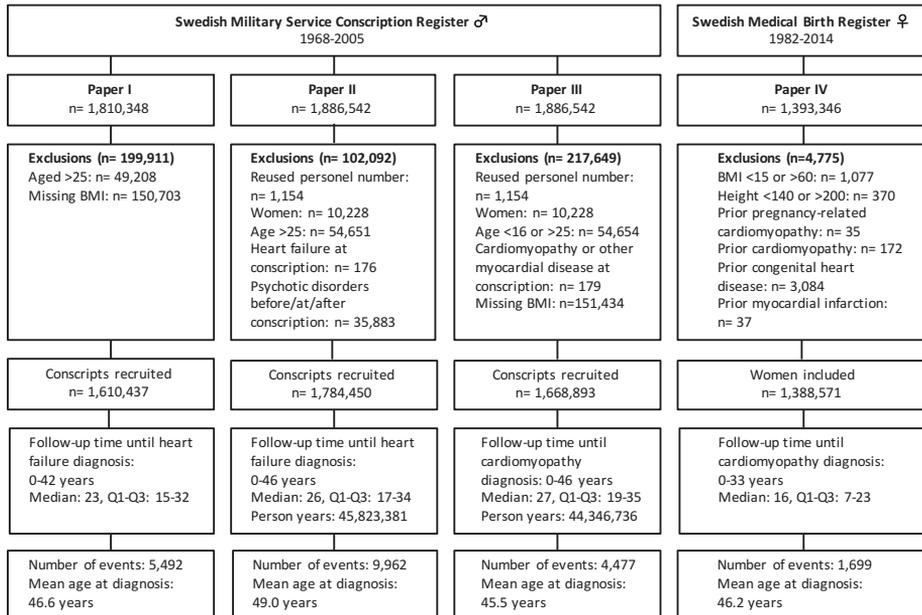| Swedish Military Service Conscription Register ♂ 1968-2005			Swedish Medical Birth Register ♀ 1982-2014
Paper I n= 1,810,348	**Paper II** n= 1,886,542	**Paper III** n= 1,886,542	**Paper IV** n= 1,393,346
Exclusions (n= 199,911) Aged >25: n= 49,208 Missing BMI: n= 150,703	**Exclusions (n= 102,092)** Reused personel number: n= 1,154 Women: n= 10,228 Age >25: n= 54,651 Heart failure at conscription: n= 176 Psychotic disorders before/at/after conscription: n= 35,883	**Exclusions (n= 217,649)** Reused personel number: n= 1,154 Women: n= 10,228 Age <16 or >25: n= 54,654 Cardiomyopathy or other myocardial disease at conscription: n= 179 Missing BMI: n=151,434	**Exclusions (n=4,775)** BMI <15 or >60: n= 1,077 Height <140 or >200: n= 370 Prior pregnancy-related cardiomyopathy: n= 35 Prior cardiomyopathy: n= 172 Prior congenital heart disease: n= 3,084 Prior myocardial infarction: n= 37
Conscripts recruited n= 1,610,437	Conscripts recruited n= 1,784,450	Conscripts recruited n= 1,668,893	Women included n= 1,388,571
Follow-up time until heart failure diagnosis: 0-42 years Median: 23, Q1-Q3: 15-32	Follow-up time until heart failure diagnosis: 0-46 years Median: 26, Q1-Q3: 17-34 Person years: 45,823,381	Follow-up time until cardiomyopathy diagnosis: 0-46 years Median: 27, Q1-Q3: 19-35 Person years: 44,346,736	Follow-up time until cardiomyopathy diagnosis: 0-33 years Median: 16, Q1-Q3: 7-23
Number of events: 5,492 Mean age at diagnosis: 46.6 years	Number of events: 9,962 Mean age at diagnosis: 49.0 years	Number of events: 4,477 Mean age at diagnosis: 45.5 years	Number of events: 1,699 Mean age at diagnosis: 46.2 years

Figure 7. Overview of included and excluded participants in Papers I–IV.

Methods (Papers I–III)

Enlistment to military service took place at six conscription centres around Sweden during the study period (Figure 8). A standardized 2-day protocol was used for assessment of suitability for military service, which included physical and psychological evaluations (Figure 9).

Assessment at conscription

Conscripts were initially seen by a nurse, who performed a somatic assessment that included measurements of weight and height, sight and color vision testing, and a hearing test, along with recording of the medical history (Figure 9). Weight (kg) was measured by use of analogue or digital scales, and height (m) was measured by use of a wall-mounted stadiometer, with light

Figure 8. Military conscript test centers in Sweden during the study period.

clothing and without shoes. BMI was calculated (kg/m^2), and the conscripts were classified as being underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9), or obese (≥30). Heart rate and blood pressure were measured in recumbent men after a resting period of 5–10 minutes.
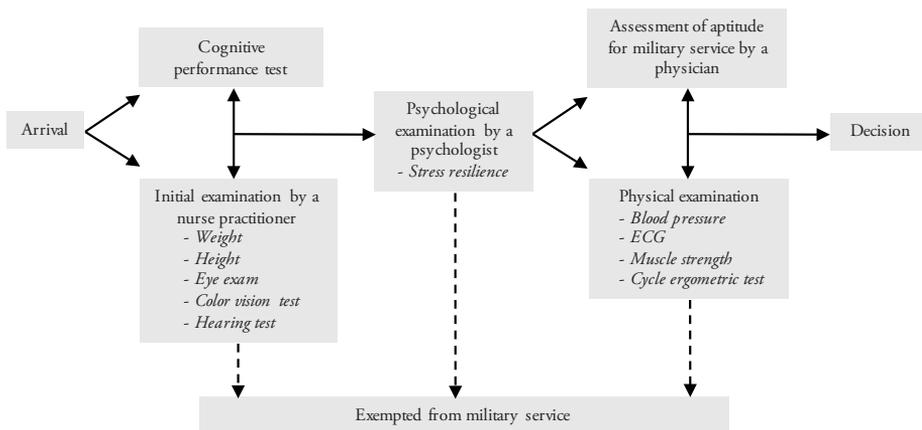
Figure 9. Overview of the conscription flow chart (Papers I–III) (107). Adapted from Pliktverkets handboksserie. Reprinted with permission from Rekryteringsmyndigheten.

Conscripts with somatic or psychiatric conditions were registered with ICD diagnostic codes by a physician. This was based on expression of symptoms and/or self-reported medical history. For the purpose of Paper II, psychiatric disorders were categorized into groups, as described in Table 4.

Table 4. Overview of diagnostic codes for nonpsychotic and psychotic mental disorders at conscription according to the International Classification of Diseases (ICD).

Diagnosis	ICD–8	ICD–9	ICD–10
Depressive/neurotic disorders	296.0, 296.2, 298.0, 300.0–9, 305, 307	298.0, 300.0–9, 306, 308, 309, 311	F32-F34, F38-F48
Personality disorders	301	301	F60–F69
Alcohol use disorders	291, 303	291, 303, 305.0	F10
Substance use disorders	294.3, 304	292, 304, 305.1–8	F11–F19
Schizophrenia[a]	295	295	F20, F21, F25
Other non-affective psychoses[a]	297.0–9, 298.2–3, 298.9	297, 298.2–4, 298.8–9	F22-F24, F28-F29
Bipolar disorders[a]	296.1, 296.3, 298.1	296.0, 296.2–5, 298.1	F30-F31

[a]*Psychotic mental disorders for exclusion purposes only.*

Cognitive performance test

At the beginning of the enlistment procedure, all individuals performed a cognitive test in four parts, covering different aspects of cognitive function: logical performance; verbal test of synonyms and opposites; test of visuospatial/geometric perception; and technical/mechanical skills, including the solving of mathematical/physics problems (108). The logical test measured the ability to understand written instructions and apply them to a problem-solving task. The verbal test examined the ability to execute concept discrimination (removal of the right word from a set) before 1980, and thereafter, the capability to select a correct synonym or antonym from a given set of words. Before 1980, the visuospatial test contained questions about 2D-puzzles, while after 1980, the test evaluated the capacity to identify the correct 3D-image from 2D-drawings (metal folding). The technical/mechanical test comprised problem-solving tasks that required knowledge of basic mathematics and physics. The scores from each test were weighted equally and summed to give a measure of general cognitive performance. The combined test score was translated to a nine-graded normally distributed scale (nine indicating high cognitive ability). Since no raw data were electronically recorded before 1996, we have used the nine-graded scale in the present papers. A study of a comparable cognitive test, used in the military enlistment in

Denmark, reported a high test validity, which was not undermined by motivational influences related to attitude towards military service (109).

Test of stress resilience

The purpose of the 25-minute psychological examination was to assess the ability to cope with wartime stress, and it can be used as a measure of stress resilience. The test was performed by a certified psychologist, using a written manual in a semi-structured interview. Questions regarding predisposition to anxiety, ability to control nervousness, and stress tolerance were always included, while other individual questions varied. Subjects relevant to everyday life, such as interests, recreational activities, psychological motivation, social skills, and emotional stability were supposed to be discussed (110). The obtained answers were summarized in a stress resilience score on a scale of 1 to 9, with higher scores indicate better functioning. It was not possible to avoid military service by scoring low on the test, so there should be no incentive to underperform. However, low stress resilience resulted in a higher probability of being assigned to a military support duty (shorter training period), while high stress resilience was required for more challenging military service positions, and for later officer training (111). The inter-rater reliability between psychologists at different test centers has been suggested to be high, with a value of 0.85 (112). The stress resilience score has also been validated against the army service records of final performance grades at the end of the military training period and has shown satisfactory conformity (111). In Paper II, stress resilience was trichotomized into low (1–3), moderate (4–6), and high (7–9).

Physical fitness tests

The fitness test contained two components: cardiorespiratory fitness and muscle strength. To test cardiorespiratory fitness, conscripts underwent a maximal bicycle ergometry test. First, a normal resting electrocardiogram was obtained, and this was followed by 5 minutes of submaximal training at 75–175 Watts (W), depending on body weight. The work resistance was then increased by 25 W/min, while the conscripts tried to maintain 60–70 revolutions per minute until failure due to exhaustion. The final work rate (W_{max}) was recorded and divided by the body weight, W_{max}/kg. This measure generated a better correlation with maximum oxygen consumption (VO_2 max) (correlation coefficient approximately 0.9) than with predicted VO_2 max (correlation coefficient approximately 0.6–0.7) (113, 114), which is another variable of fitness available in the dataset. The value in W_{max}/kg was then converted into a score between 1 and 9 on a non-normally distributed scale.

Isometric muscle strength, utilized in Papers I and III, was a combined result of three strength tests: knee extension (weighted 1.3×); elbow flexion (weighted 0.8×); and hand grip (using a tensiometer; weighted 1.7×) (115). The test results were merged into one estimate, given in kiloponds (before 1979) or Newtons (after 1979), and converted into a nine-graded scale.

Methods (Paper IV)

In Paper IV, data were obtained from the initial routine maternal care visits during the first or second pregnancy, as registered in the Medical Birth Register for the period 1982–2014, including 99% of all births in Sweden (98), and representing >85% of all Swedish women (86). The most common first-time visit to an antenatal care clinic was after ten full weeks of pregnancy. About 90% of the women had an initial visit before 12 full weeks, and only a few women had the initial visit before the end of Week 8 (98).

Initial antenatal visit to maternal healthcare

At the first antenatal visit, data on age, smoking habits, medical drug use, and medical diagnoses, among other variables, were registered. Between 1983 and 1989, pre-pregnancy weight was calculated by subtracting the gestational weight gain from the weight at delivery. As weight could only be recorded with two digits, all the women who weighed ≥100 kg were recorded as weighing 99 kg. During 1990 and 1991, data on weight were not collected. From 1992 onwards, early pregnancy weight was measured/self-reported during the first antenatal visit (98). Since weight gain during the first trimester has previously been demonstrated to be very low, at only 0.5–2.0 kg (116-118), this measurement was considered suitable as the pre-pregnancy weight.

Main exposures and outcomes (Papers I–IV)

An overview of the thesis framework, including the main exposures and outcomes of the papers, is provided in Table 5.

Table 5. Overview of the thesis framework.

Paper	Gender	Exposure	Outcome

I	Men	BMI	Heart failure
			  Congenital heart disease and valvulopathies
			  Coronary heart disease and/or diabetes
			  and/or hypertension
			  Cardiomyopathy
			  Other

II	Men	Nonpsychotic mental disorders, Stress resilience	Heart failure

III	Men	BMI	Cardiomyopathy
			  Dilated
			  Hypertrophic
			  Alcohol/drug-induced
			  Other

IV	Women	BMI	Cardiomyopathy
			  Dilated
			  Hypertrophic
			  Alcohol/drug-induced
			  Pregnancy-related
			  Other

Ascertainment of outcomes and comorbidities

Heart failure and cardiomyopathy, as well as comorbidities, were identified by the ICD diagnostic codes in the National Patient Register (Papers I–IV) and the Cause of Death Register (Papers I, III, and IV). ICD-8 was used for the period 1968–1986, ICD-9 for the period 1987–1996, and ICD-10 from 1997 onwards. At outpatient visits or upon discharge from the hospital, patients received one principal diagnosis and, if applicable, one or several secondary diagnoses. In Papers I–II, heart failure in any diagnostic position at discharge was accepted, since patients may have suffered from and received another primary diagnosis. In Paper I, a hierarchal classification of heart failure, previously described by our group (5), was used to distinguish between different etiological origins: a) congenital heart disease and valvulopathies; b) coronary heart disease and/or diabetes and/or hypertension; c) cardiomyopathy; and d) other causes. In Papers III and IV, cardiomyopathy diagnoses were defined as described in Table 6.

Table 6. Overview of the diagnostic codes for the studied outcomes and comorbidities, according to the International Classification of Diseases (ICD).

Diagnosis	ICD-8	ICD-9	ICD-10
Acute myocardial infarction	410	410	I21
Alcohol use disorders	291, 303	291, 303, 305.0	F10
Any coronary heart disease	410–414	410–414	I20–I25
Atrial fibrillation	427.92	427D	I48
Cardiomyopathy	425	425	I42, I43
Dilated	425.09	425E	I42.0
Hypertrophic	425.00	425B	I42.1–2
Alcohol/drug-induced	–	425F, 425X[b]	I42.6, I42.7–9[b]
Peripartum	–[a]	–[a]	O90.3
Other	425.08	425A, 425D, 425H, 425W, 425X[c]	I42.3–5, I42.7–9[c], I43.0
Congenital heart disease	746, 747	745–747	Q20–Q28, Q87, Q89
Diabetes	250	250	E10–E14
Heart failure	427.00, 427.10	428	I50
Hypertension	401–405	401–405	I10–I15
Stroke, hemorrhagic	431	431	I61
Stroke, ischemic	433, 434, 436	433, 434, 436	I63, I64
Substance use disorders	294.3, 304	292, 304, 305.1–8	F11–F19
Valvular disease	394–396, 398, 424	394–398, 424	I05–I09, I33–I39

[a]*A diagnostic code for peripartum cardiomyopathy only exists in ICD-10. Further identification of pregnancy-related cardiomyopathies is described in the Methods section of Paper IV.*
[b]*If prior alcohol/substance use disorder occurred (see Methods sections in Papers III and IV).*
[c]*If no prior alcohol/substance use disorder occurred (see Methods sections in Papers III and IV).*

Statistical analyses

Statistical analyses were performed using SAS, ver. 9.4 (SAS Institute, Cary, NC), and R, ver. 3.2.2, 3.4.2, and 3.6.0 (http://www.R-project.org).

For descriptive statistics, continuous variables are presented as means with standard deviations, except for follow-up time, which is presented as the median with interquartile interval. Categorical variables are expressed as frequencies and percentages. To calculate incidence rates, expressed as cases per 100,000 observation years, and their corresponding confidence intervals (CIs), we used Poisson regression. Cox proportional hazards regression analyses were used to examine if BMI (Papers I, III, and IV), nonpsychotic disorders (Paper II), and stress resilience (Paper II) were associated with subsequent heart failure (Papers I, II) and cardiomyopathy (Papers III, IV). The

BMI range of 18.5–19.9 was used as the reference group for men in Papers I and III, while BMI 20–22.49 was used as the reference for women in Paper IV, who in general were a decade older than the men at baseline. The absence of a mental disorder, and the presence of high stress resilience were used as reference groups in Paper II. The follow-up period started at the date of conscription (Papers I–III) or antenatal visit (Paper IV), and individuals were followed until one of the events listed in Table 7 occurred. The study participants in Papers III and IV were also censored in the case of an acute myocardial infarction, so as to avoid misclassifications, and in Paper IV, additionally, if a pregnancy-related cardiomyopathy occurred. Since women are at risk of a pregnancy-related cardiomyopathy only around pregnancy, which constitutes a short period of the follow-up time, those cases were censored and excluded from the analyses. Furthermore, a sensitivity analysis was performed in Paper III, in which death was treated as a competing event.

Table 7. Overview of events that resulted in end of follow-up, as used in the papers.

Followed until	Paper(s)
Acute myocardial infarction	III–IV
Death	I–IV
Emigration out of Sweden	I–III
End of follow-up (December 31, 2010)	I
End of follow-up (December 31, 2014)	II–IV
First cardiomyopathy diagnosis	III, IV
First heart failure hospitalization	I, II
Pregnancy-related cardiomyopathy	IV

For each study, Cox proportional hazards regression models were set up using varying covariate adjustments. We refrained from adjusting for comorbidities that occurred during the follow-up period, since they may act as mediators in the pathway towards heart failure rather than as confounders. The proportional hazards assumptions were tested using plots based on weighted residuals (119). Variables that did not fulfil the assumption of proportional hazards, except for diastolic blood pressure in Paper I, were stratified, and accordingly, assumptions of proportional hazards were fulfilled in all the final models. Diastolic blood pressure showed non-proportional signs, however, the effect on BMI in further analyses were negligible and the variable could therefore be left unmodified. Spline plots were generated with BMI as a restricted cubic spline in Papers I, III, and IV. Population-attributable risk (PAR), which is the association of a specific risk factor with a specific disease as a proportion of all risk factors for that disease, was calculated according to a method described by Natarajan (120), using the hazard ratios from the Cox proportional hazards regressions (Papers I and II).

Ethical considerations

The potential risks for the participants in the papers of this thesis mainly concern personal integrity. All data linkages were performed by Statistics Sweden and the National Board of Health and Welfare. Before data delivery, the national personal identification numbers were replaced with study identification numbers. Thus, the data was completely decoded and anonymized to the researchers. The Regional Ethical Review Board in Gothenburg approved all the studies (Table 8) and waived the need for consent, indicating that the benefits of the collected data and the studies being performed outweighed potential risks related to integrity intrusion. The studies conform to the guidelines stated in the Declaration of Helsinki.

Table 8. Ethical approvals.

	Ethical Review Board (EPN)	Diary number (DNR)
Paper I	Gothenburg	162–05, 567–15
Paper II	Gothenburg	462–14, 567–15
Paper III	Gothenburg	462–14, 567–15
Paper IV	Gothenburg	103–15

The Swedish Military Service Conscription Register and the Medical Birth Register provide a unique opportunity to study two large populations from early in life until heart failure or cardiomyopathy diagnosis, and elucidate the future risks of high BMI and mental illness at a young age. The findings and conclusions from our studies are difficult to obtain using other study designs.

RESULTS

Association between BMI in late adolescence and risk of early heart failure (Paper I)

In Paper I, we investigated the relationship between BMI in young men and long-term risk of early hospitalization with heart failure in adulthood.

Of the 1.6 million men who were included in the study, 80% were of normal weight (BMI 18.5–24.9), 10% were overweight (BMI 25–29.9), and 2.3% were obese (BMI ≥30). Among the obese men, more than one in five was classified as severely obese (BMI ≥35), constituting 0.5% of the total number of conscripts. Regarding the prevalences of moderate and severe obesity during the conscription period of 1968–2005, the percentages were very low in the early 1970s (0.8% and 0.1%, respectively), but increased significantly over the following 30 years to 3.8% and 1.3%, respectively. Moreover, within the obesity category, we found an increase in the percentage of severely obese subjects: from 14% in the 1970s to 26% in the period 2000–2005 (Figure 10).

Figure 10. Prevalences (%) of moderate (BMI 30–34.9) and severe (BMI ≥35) obesity in young men at their military conscription examination in the period 1968–2005 (n=1,610,437).

In general, the obese subjects had poorer fitness level, poorer cognitive capacity, and their parents more often had a lower level of education, as compared to the normal-weight subjects. In contrasted, the obese subjects performed to a higher level in the muscle strength test (Figure 11).
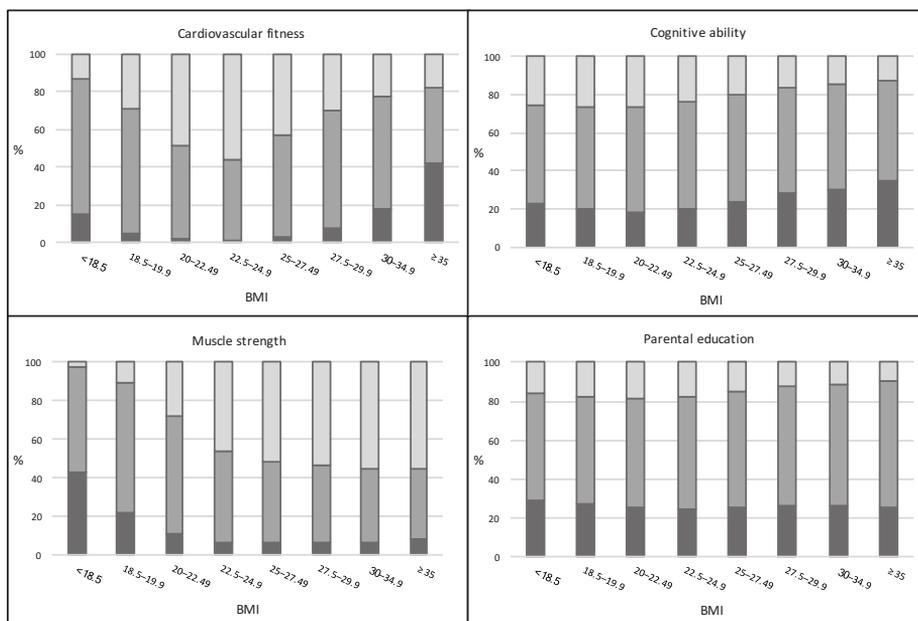
Figure 11. Baseline data on cardiovascular fitness, cognitive ability, muscle strength, and parental education for young men at their military conscription examination, in the period 1968–2005, divided according to BMI category. Bar color scheme: dark-gray, low level; medium-gray, moderate level; and light-gray, high level.

We identified approximately 5,500 hospitalized cases of heart failure (principal or secondary discharge diagnosis) during the up to 42 years of follow-up. Censoring was made due to death for 36,715 (2.3%) individuals, and due to emigration for 61,578 (3.8%) individuals. The oldest participants included in the study had reached the age of 60 years by the end of the follow-up, which is why all cases were considered as early heart failure. Men who had a higher BMI value received the diagnosis at a younger mean age than those with a normal BMI value. Heart failure with underlying coronary heart disease, and/or diabetes, and/or hypertension was the most commonly observed condition, constituting 50% of the cases, whereas cardiomyopathy accounted for 15%, and congenital heart disease or valvular disease accounted for 13% of the cases. One-fourth of the cases did not have an additional diagnosis registered either before or at the time of index event.

The lowest risk for heart failure was present at BMI 20, with a steep linear increase in risk as the BMI increased. Compared to the reference group (BMI 18.5–19.9), the increased risk was seen already at mid-normal BMI (20–22.49) (hazard ratio (HR) 1.22 (95% CI 1.10–1.35) (Figure 12), after adjustment for age, year of conscription, baseline comorbidities, parental education, systolic and diastolic blood pressure, IQ, muscle strength, and fitness. The highest risk

for heart failure was seen for BMI ≥35 (HR 9.21 (6.57–12.92)). Moreover, for every unit increase in BMI, the risk of heart failure risk increased by 16%.
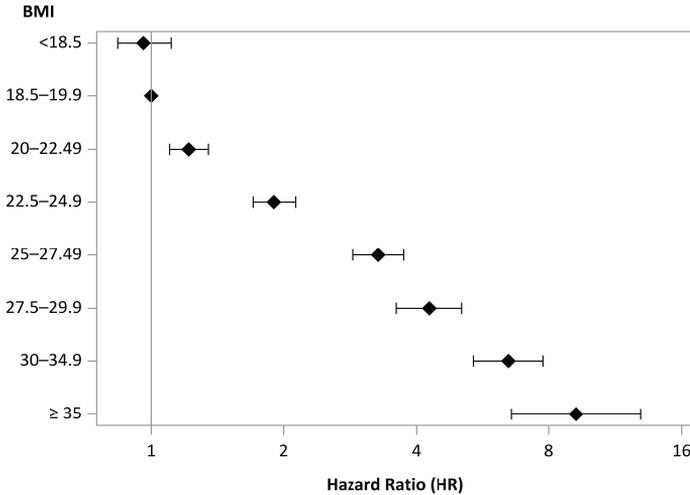

Figure 12. Association between body mass index in late adolescence and risk of hospitalization for heart failure as the principal or secondary discharge diagnosis. Adjusted for age, year of conscription, baseline comorbidities, parental education, systolic and diastolic blood pressure, IQ, muscle strength, and fitness.

Sensitivity analysis of conscripts with missing BMI

A sensitivity analysis of the 150,703 conscripts with missing BMI values, showed that the majority of the missed values were seen in the later conscription years (Figure 13), and they were represented at all the test centers. About 91% of conscripts with missing BMI were 18 or 19 years of age, which is similar to the total study population (96%).
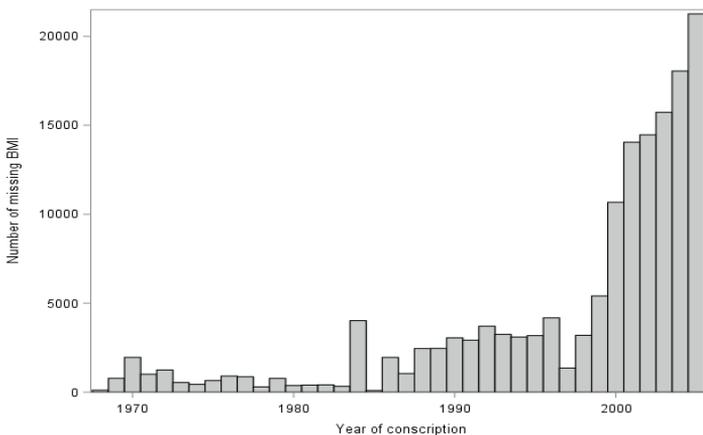

Figure 13. Conscripts with missing BMI upon examination in the period of 1968–2005.

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Most of conscripts with missing BMI did not have data on weight or height registered, and information on their cardiorespiratory fitness and muscle strength was lacking. Approximately 81,000 of them were also missing a value for cognitive performance. However, among conscripts with missing BMI and a registered score for cognitive performance, the proportion of conscripts with low IQ was higher than in the total study population (51.0% vs. 20.2%) (Table 9).

Table 9. Characteristics of the conscripts with missing BMI (n=150,703), as compared to the total study population[a] (n=1,610,437).

	Low, % (n)	Moderate, % (n)	High, % (n)	Missing, n
Cardiorespiratory fitness				
Conscripts with missing BMI	9.2 (343)	69.2 (2,587)	21.6 (809)	146,964
Total study population[a]	3.9 (46,119)	53.6 (632,261)	42.5 (501,053)	431,004
Muscle strength				
Conscripts with missing BMI	19.6 (1,052)	52.6 (2,821)	27.8 (1,489)	145,341
Total study population[a]	14.0 (223,805)	56.5 (902,648)	29.5 (470,795)	13,189
IQ				
Conscripts with missing BMI	51.0 (35,682)	37.8 (26,421)	11.3 (7,893)	80,707
Total study population[a]	20.2 (323,083)	54.8 (874,906)	25.0 (398,923)	13,525
Parental education				
Conscripts with missing BMI	15.7 (22,753)	63.8 (92,328)	20.5 (29,731)	5,891
Total study population[a]	25.9 (399,768)	56.6 (871,726)	17.5 (269,406)	69,537

[a]*Excluding conscripts with missing BMI values.*

Association between nonpsychotic mental disorder and stress resilience in late adolescence and risk of early heart failure (Paper II)

In Paper II, we investigated whether having a nonpsychotic mental disorder and low stress resilience in late adolescence were associated with increased risk of early heart failure.

At enlistment to military service during the period 1968–2005, we identified almost 75,000 out of 1.8 million conscripts (mean age, 18.3 (SD 0.7) years), who were diagnosed with a nonpsychotic mental disorder at the conscription

examination (based on symptoms and/or self-reported medical history; hospital discharge diagnoses were not included) (Table 4). The most common forms were depressive or neurotic disorders (77%), followed by alcohol or substance use disorders (22%), and personality disorders (14%). There has been a decreasing trend of conscripts with a nonpsychotic mental disorder over time from 9.1% in the late 1970s to 0.7% at the beginning of the 2000s (Table 10).

Table 10. Numbers of conscripts diagnosed with a nonpsychotic mental disorder at the conscription examination, per decade in the period of 1968–2005.

Decade	Nonpsychotic mental disorder, n (%)	No mental disorder, n (%)	Total, n
1968-1970	4,898 (9.1)	49,039 (90.9)	53,937
1971-1980	37,805 (7.8)	445,871 (92.2)	483,676
1981-1990	21,638 (4.0)	524,194 (96.0)	545,832
1991-2000	8,637 (1.8)	464,135 (98.2)	472,772
2001-2005	1,544 (0.7)	226,689 (99.3)	228,233
Total	74,522	1,709,928	1,784,450

Conscripts who were diagnosed with a nonpsychotic mental disorder had poorer fitness level, lower cognitive ability, and lower stress resilience than those with no mental disorder. Stress resilience was trichotomized as low (1–3), moderate (4–6), and high (7–9). High stress resilience was related to higher physical fitness level as well as greater cognitive ability. It was also more common to have highly educated parents in this group. Across all the years, the mean BMI among conscripts with nonpsychotic mental disorders was 21.4 compared to 21.9 among those without a mental disorder. Division of the conscription years into decades revealed no time trend regarding BMI difference between the two groups (Table 11).

Table 11. Mean BMI (SD) at baseline among conscripts with and without a nonpsychotic mental disorder, divided by decades for the period 1968–2005.

Decade	Nonpsychotic mental disorder, mean BMI (SD)	No mental disorder, mean BMI (SD)
1968-1970	20.6 (2.6)	20.9 (2.5)
1971-1980	21.2 (2.9)	21.4 (2.7)
1981-1990	21.8 (3.4)	21.8 (2.8)
1991-2000	22.2 (3.5)	22.4 (3.2)
2001-2005	22.6 (3.4)	22.9 (3.7)
Missing BMI	6,668/74,522= 8.9%	139,598/1,709,928= 8.2%

We identified close to 10,000 unique cases with hospitalization due to heart failure during the up to 46 years of follow-up. The presence of a nonpsychotic mental disorder in youth resulted in a 36% increased risk for subsequent early

heart failure (HR 1.36 (1.25–1.47)) when adjusting for age, year of conscription, test center, comorbidities at baseline, BMI, systolic and diastolic blood pressure, fitness, intelligence quotient (IQ), and parental education. Subjects with a nonpsychotic mental disorder in adolescence were diagnosed with heart failure at an older age than subjects with no mental disorder (50.9 vs 48.8 years).

Among the included conscripts, 320,622 (18%) had low stress resilience, 934,969 (52%) had moderate stress resilience, and 346,462 (19%) had high stress resilience. High stress resilience was used as reference in the analyses. Low stress resilience increased the risk of early heart failure by 41% compared to high stress resilience (HR 1.41 (1.30–1.53)) in the fully-adjusted model (Table 12).

Table 12. Hazard ratios (HR) and 95% confidence intervals (CI) for stress resilience among adolescent men in relation to risk of early heart failure.

	Events/population	Low (1–3)	Moderate (4–6)	High (7–9)
Model 1[a]	9,003/1,601,538	2.09 (1.96–2.23)	1.27 (1.20–1.35)	1 (reference)
Model 2[b]	6,588/1,139,212	1.41 (1.30–1.53)	1.05 (0.98–1.12)	1 (reference)

[a]*Adjusted for age at conscription, conscription year, and test center.*
[b]*Adjusted for age at conscription, conscription year, test center, comorbidities at baseline, BMI, systolic and diastolic blood pressure, concomitant nonpsychotic mental disorders, fitness, IQ, and parental education.*

Association between BMI in late adolescence and risk of cardiomyopathy (Paper III)

In Paper III, we investigated whether being overweight or obese in late adolescence predicted the risk for cardiomyopathy in midlife.

We identified almost 4,500 cases of cardiomyopathy during a follow-up of a maximum of 46 years after conscription. Of these, 2,631 were diagnosed with a dilated cardiomyopathy, 673 with a hypertrophic cardiomyopathy, 480 with an alcohol/drug-induced cardiomyopathy, and 538 with unspecified or specified less-common forms of cardiomyopathy. The mean age at diagnosis was 45.5 (SD 9.3) years for all the subjects, whereas a higher BMI resulted in a gradually younger age at onset to a minimum of 40.6 (SD 8.6) years for BMI ≥35.

For dilated cardiomyopathy, the incidence rate was 5.0 cases/100,000 observation years at BMI 18.5–19.9, as compared to 24.7 cases/100,000 observation years at BMI ≥35. The corresponding incidence rates were 1.2 and 2.1 for hypertrophic cardiomyopathy, 1.1 and 4.1 for alcohol/drug-induced

cardiomyopathy, and 1.0 and 1.4 for other cardiomyopathies, respectively. In line with this, Cox proportional hazards regression analyses showed that higher BMI in youth was strongly associated with increased risk of cardiomyopathy, particularly the dilated form. The increased risk for dilated cardiomyopathy started at high-normal BMI levels (BMI 22.5–24.9) with HR 1.56 (1.32–1.85), adjusted for age, year of conscription, test center, and baseline comorbidities, systolic and diastolic blood pressure, fitness, muscle strength, parental education, and alcohol or substance use disorder. At BMI ≥35, the risk was nine-fold higher than that in the reference group (BMI 18.5–19.9). For each unit increment in BMI, the risk increased by: 15% for dilated cardiomyopathy (HR 1.15 (1.13–1.17)); 11% for hypertrophic cardiomyopathy (HR 1.11 (1.07–1.16)); and 11% for alcohol/drug-induced cardiomyopathy (HR 1.11 (1.06–1.17)). Spline plots were generated to present visually the effect of BMI on risk for cardiomyopathy (Figure 14).
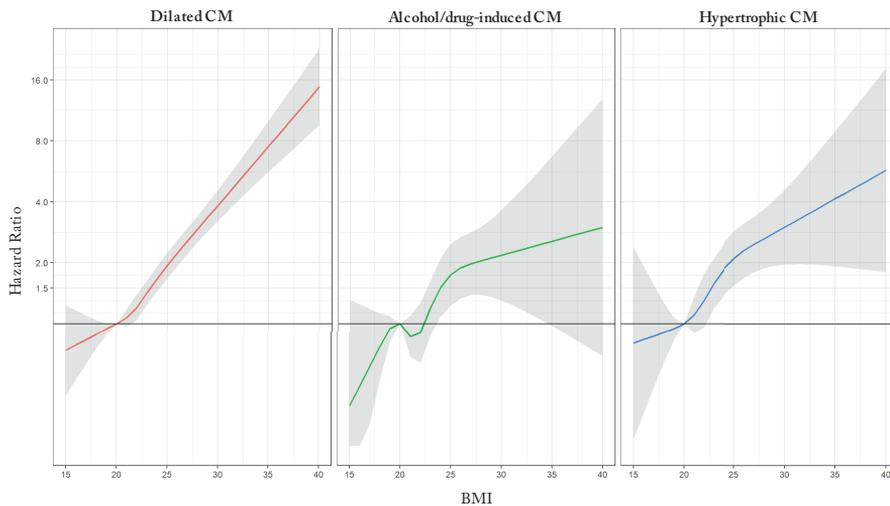

Figure 14. Spline plots presenting the effect of BMI in late adolescent men on risk for dilated cardiomyopathy (CM), alcohol/drug-induced cardiomyopathy, and hypertrophic cardiomyopathy. The model was adjusted for age, conscription year (as a spline with knots at 5% (1971), 35% (1982), 65% (1992), and 95% (2004)), test center, baseline comorbidities (diabetes mellitus, hypertension, congenital heart disease), systolic and diastolic blood pressure, fitness, muscle strength, parental education, and alcohol or substance use disorder (n=773,679). The plots were generated with BMI as a restricted cubic spline with degree 3 and 4 knots placed at 5% (BMI 18.0), 35% (BMI 20.5), 65% (BMI 22.4), and 95% (BMI 27.5), with BMI 20 as reference. Reprinted with permission. Robertson et al, Circulation 2019, page 122.

Association between BMI and risk of cardiomyopathy in young women (Paper IV)

In Paper IV, we investigated whether for young women being overweight or obese was associated with future cardiomyopathy.

The study cohort comprised nearly 1.4 million women of childbearing age (mean age, 27.9 (SD 4.9) years), with BMI registered at the first antenatal visit in the Swedish Medical Birth Register, for the period 1982–2014. First-time pregnancies constituted 78.4% of the cohort, whereas the remaining women were pregnant for the second time. About 69% of the women were of normal weight (BMI 18.5–24.9), 20% were overweight (BMI 25–29.9), and 7.5% were obese (BMI ≥30). Among the obese women, one out of four was classified as severely obese (BMI ≥35), representing 1.9% of the total study population (Figure 15).
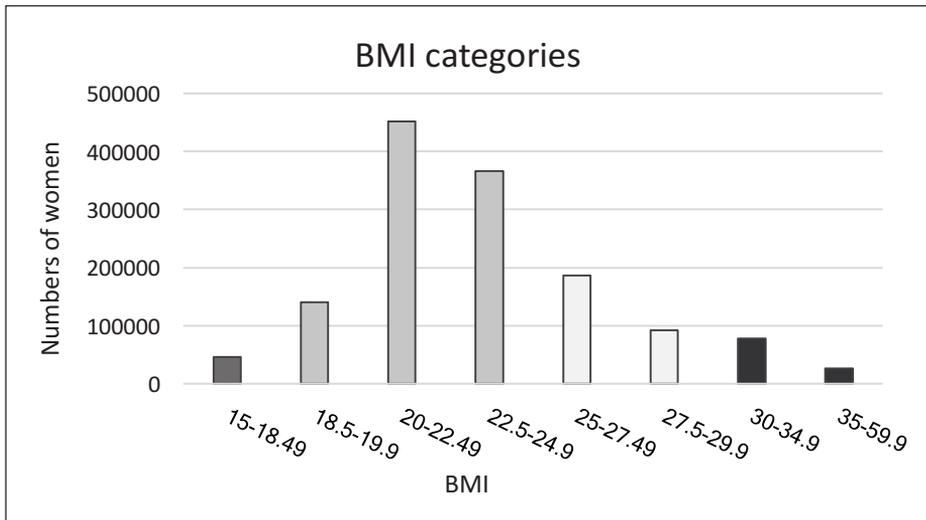

Figure 15. Numbers of women of childbearing age in the Medical Birth Register, for the period 1982–2014, divided according to BMI category (normal range, BMI 18.5–24.9; overweight, BMI ≥25; obese, BMI ≥30).

Comorbidities at baseline were rare in this relatively young study population, however, diabetes (0.59%) and hypertension (0.41%) were the most common. Approximately 15% of all the included women were smokers, and the proportion of women with high education level (>12 years of studies) was higher with midrange BMI.

We identified a total of 1,699 individual cases of cardiomyopathy, which could be divided into five categories: a) dilated cardiomyopathy (n=481); b) hypertrophic cardiomyopathy (n=246); c) alcohol/drug-induced cardiomyopathy (n=61); d) pregnancy-related cardiomyopathy (n=374); and e) other forms of cardiomyopathy (n=509). Pregnancy-related cardiomyopathy was diagnosed within 90 days before delivery and up to 180 days postpartum. Since the risk for this disorder is only around pregnancies and not during the entire follow-up period, women with pregnancy-related cardiomyopathy were censored at the date of diagnosis and not included as events in the analyses. Women who were registered with both dilated and hypertrophic cardiomyopathy at different times during the follow-up (1.6%) were categorized as having an indeterminable cardiomyopathy, and they were not included in any of the five main categories. The lowest risk for future cardiomyopathy was found at BMI 21 in young women. The risk increased gradually as BMI increased, particularly for the cases of dilated cardiomyopathy, for whom there was an almost five-fold increase in risk (HR 4.71 (2.81–7.89)) among the severely obese (BMI ≥35) in the fully-adjusted model (adjusted for age, year, parity, comorbidities at baseline, smoking, and education) (Figure 16).
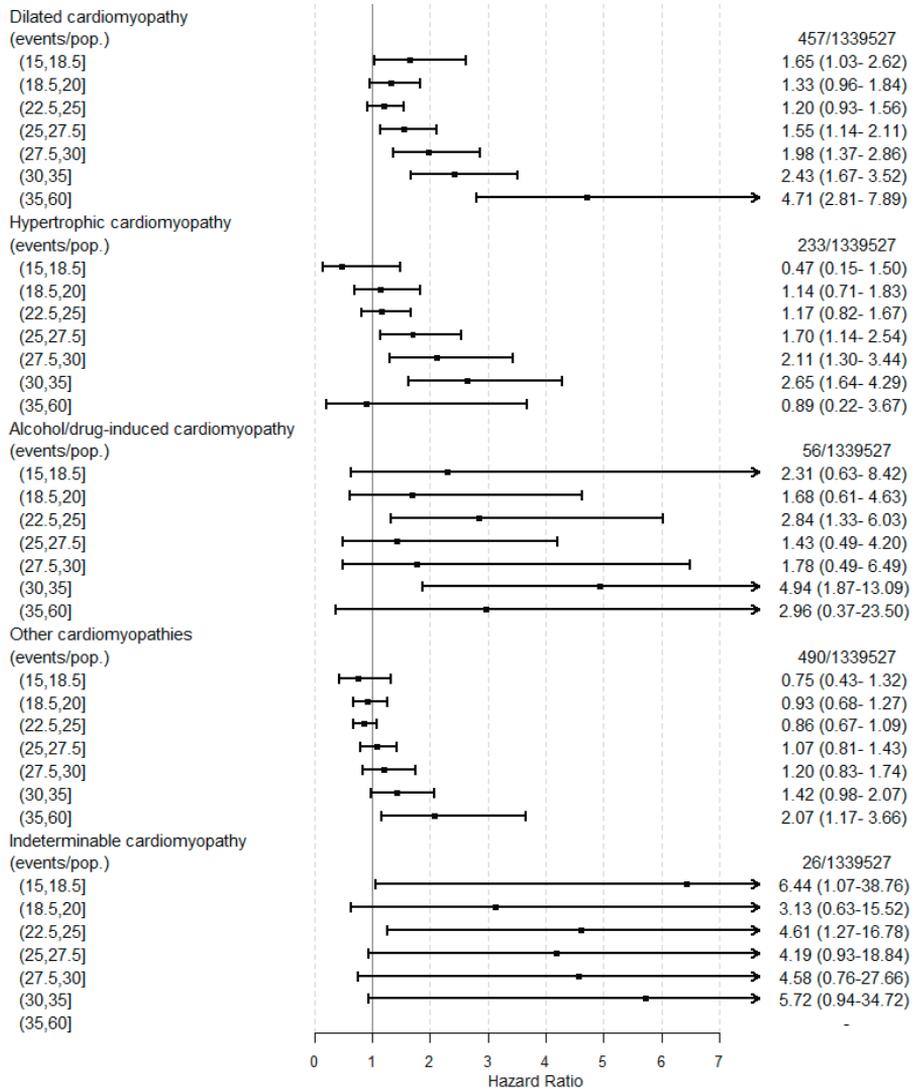
Figure 16. Hazard ratios (HR) and 95% confidence intervals (CIs) by BMI category,
demonstrating the effect of BMI in young women on risk for future cardiomyopathy.
The model is adjusted for age, year, parity, comorbidities at baseline, smoking, and
education (n=1,339,527).

DISCUSSION

Findings and implications

BMI, early heart failure and cardiomyopathy

In our cohort studies, we found an association between BMI at a young age and early heart failure among men, as well as between BMI at a young age and cardiomyopathy in midlife among both sexes. Obesity as a risk factor for heart failure has been described previously (121, 122). An association between BMI in middle-aged, but not in elderly, women and heart failure has been reported in a Swedish study (94). In addition, BMI change during puberty has, independently of childhood BMI, been associated with risk of heart failure (123). A causal relationship between BMI in young people and heart failure cannot be verified from our observational data. However, there is supporting evidence in the literature for the linkage between overweight early in life and heart failure.

First, the development of obesity at a young age, as opposed to obesity later in life, is of particular concern due to early clustering and long-time exposure of cardiovascular risk factors, such as type 2 diabetes, hypertension, and dyslipidemia (92). As tracking of overweight and obesity from childhood to adulthood is common (55), these risk factors are likely to emerge. Second, apart from predisposition to cardiovascular risk factors, BMI has been stated to be independently associated with heart failure. Data from the Framingham Heart Study showed that an increased risk for heart failure remained in the analyses after adjustment for known risk factors. In that study, about 11% of the cases of heart failure in men and 14% in women were attributed to obesity alone. Furthermore, every unit of increment in BMI resulted in an increased risk for heart failure, by 5% for men, and 7% for women (122). In our study, we found a corresponding stepwise increase in risk by 16% for every unit increase in BMI, which is noticeably higher. However, statistical models, in which adjustments for all risk factors are made, may underestimate the true risk of adiposity in association with heart failure. To avoid such underestimation, we refrained from adjusting for follow-up comorbidities, such as coronary heart disease, diabetes mellitus, and hypertension in this thesis. These conditions are, in themselves, strongly associated with higher BMI and constitute steps in the pathway towards heart failure.

In addition to the increased risk of heart failure related to higher BMI, we found an increased risk for cardiomyopathies starting already at high-normal levels of BMI (22.5–24.9), particularly with respect to dilated cardiomyopathy.

Whether or not obesity is specifically associated with cardiomyopathy is a matter of debate. However, most studies have not been able to achieve a long follow-up time, which explains why the effects on the myocardium of longer-duration obesity have not been analyzed (124). In this thesis, we followed the study populations for up to 33 (Paper IV) and 46 years (Paper III), respectively, which enabled us to establish a long-term association between obesity and cardiomyopathy.

It has previously been proposed that the cardiovascular risks linked to obesity go beyond the development of atherosclerosis (93). To meet the increased metabolic demand that comes with excess body weight, the circulating blood volume and cardiac output increase, leading to an elevated hemodynamic load with chamber dilation and hypertrophy over time. Additional mechanisms that potentially link obesity to cardiac structural and functional abnormalities include neurohormonal activation and increased oxidative stress. Myocardial lipotoxicity, a process in which excess fatty acid and triglycerides accumulate in cardiac myocytes, is also known to cause cellular dysfunction and apoptosis. All these factors may result in left ventricular remodeling, cardiac fibrosis, and impaired systolic, as well as diastolic function (125, 126). Along with increased body mass and visceral adiposity, it has been suggested that changes in adipose tissue biology play a major role in the development of heart failure, since expanding fat deposits drive the evolution of a pro-inflammatory condition. This involves an increased secretion of adipocyte-derived molecules, for instance resistin (127), leptin, neprilysin, and aldosterone (128), which induce an inflammatory response leading to cardiac fibrosis and microvascular abnormalities. In the Framingham Offspring Study, resistin was associated with heart failure independently of ischemic heart disease (127). Moreover, higher leptin levels have been found in patients with heart failure (129), and have been proposed to promote cardiac hypertrophy and remodeling (130). Furthermore, results from the Multi-Ethnic Study of Atherosclerosis showed that the inflammatory biomarkers interleukin-6 and C-reactive protein may be important mediators of the association between obesity and heart failure (131). Taken together, our findings indicate an association between BMI and early heart failure and cardiomyopathy, which is further supported by studies that have investigated different pathophysiological pathways. Although the mechanisms are not fully understood, a multifaceted interplay of the factors mentioned above, among others, is likely to contribute to the development of obesity-related heart failure and cardiomyopathy.

The optimal level of BMI in young adulthood

For young men, we found an increased risk of heart failure and cardiomyopathy with BMI 20–22.49, and 22.5–24.9, respectively, as

compared to BMI 18.5–19.9. The corresponding BMI with increased risk for cardiomyopathy in women, who were in general 10 years older at baseline, was 25–27.49, as compared to BMI 20–22.49. Thus, adolescent men appear to have an increased risk of heart failure and cardiomyopathy at BMI-levels within the normal range (18.5–25), according to the WHO (Table 1) (12). Most studies investigating the association between adolescent adiposity and future cardiovascular disease or mortality, refer to the entire normal range (BMI 18.5–25) as a single reference group (89-93), and study only the risk with BMI>25. With respect to our present results, and in accordance with a recently published study on Israeli adolescents (132), it appears that the currently accepted normal range may underestimate the true risk associated with being overweight in young adulthood. The Israeli study identified an increased risk of death from coronary heart disease in middle-age with mid-normal BMI (20–22.49) in adolescence as compared to low BMI (17.5–19.9), which accords with our results in Paper I. A significantly elevated risk of death from all cardiovascular causes started already at BMI values >20.3. Accordingly, there is need for further research on overweightness in young adulthood, to elucidate if the established normal range of BMI is applicable to young people or if a future adjustment of the recommended optimal BMI level would be beneficial for cardiovascular health later in life.

Mental health, stress resilience and early heart failure

It is well-known that patients who are diagnosed with schizophrenia and other psychotic disorders have increased cardiovascular morbidity and mortality (133-135). In Paper II, we investigated whether nonpsychotic mental disorders in adolescence, which constitute the major increase in psychiatric illness today (59), were also associated with risk of heart failure. Indeed, we found a strong association between nonpsychotic mental disorders in late adolescence and risk of future heart failure.

The linkage between nonpsychotic mental disorders and cardiovascular disease is not clearly understood. However, mentally ill patients of both sexes have increased risk of cardiovascular risk factors, particularly diabetes, hyperlipidemia, and obesity (95). They are also more likely to embrace an unhealthy lifestyle, including poor dietary habits, physical inactivity, and smoking (136). Importantly, patients with mental disorders suffer from later and lower detection rates of cardiovascular risk factors (95), which makes them more vulnerable. In line with this, we found that individuals with a nonpsychotic mental disorder in adolescence were diagnosed with heart failure at a later stage than mentally healthy adolescents. This can, of course, also be explained in part by the decreasing prevalence of nonpsychotic mental disorders at conscription over time, which resulted in a higher percentage of

mentally ill adolescents in the earlier study period and, thereby, a longer follow-up time for those individuals in general. Another aspect of interest is that people with psychosocial problems are less likely to adhere to medical and behavioral guidelines, which may promote disease development (137). Taken together, mentally ill patients of both sexes may have several unfavorable factors with respect to cardiovascular health, including heavier burden of cardiovascular risk factors, unhealthy lifestyle, patient's and/or doctor's delay, as well as reduced medical compliance.

We found a 26% increased risk for future heart failure associated with a depressive or neurotic disorder in late adolescence, even after adjustment for BMI, blood pressure, comorbidities, fitness, and IQ. Accordingly, a study of individuals with major depression and anxiety found that the increased risk for heart failure persisted after adjustment for established cardiovascular risk factors, such as smoking, type 2 diabetes, hypertension, hyperlipidemia, and obesity (96). This indicates an independent relationship, and several theories of possible biological pathways have been put forward. First, shared hereditary factors have been identified in depression and heart disease in a twin study (138), suggesting a genetic overlap. Second, mentally ill patients have higher circulating levels of pro-inflammatory cytokines (139), and there is a growing body of evidence to suggest that systemic inflammation plays a major role in the pathogenesis of heart failure (140). Moreover, endothelial dysfunction is seen among depressed individuals, and this leads to decreased excretion of nitrogen monoxide (NO) and vasoconstriction (139). Other mechanisms induced by depression include: elevated platelet activity, HPA axis dysfunction, decreased heart rate variability, neurohormonal and autonomic dysfunctions (elevated levels of catecholamines and cortisol), and lower levels of brain-derived neurotrophic factor (BDNF) (139). Thus, multiple pathways, beyond the well-recognized risk factors, are suggested to be important players in the association between mental illness and heart failure.

Another finding in Paper II was that low stress resilience entailed a 41% increased risk for heart failure, as compared to high stress resilience. It can be assumed that stress resilience measured in late adolescence reflects the ability of the individual to deal with stressful events during life. Compromised stress resilience in youth may therefore result in higher levels of stress in adulthood, which promotes the development of several cardiovascular risk factors, such as type 2 diabetes and hypertension (75, 80, 81). The long-term effects of stress may also include detrimental health-related behaviors, like reduced physical activity, smoking and excessive alcohol consumption (75), all of which are cardiovascular risk factors (141, 142). In line with this, a recent study has shown that low stress resilience in adolescence is associated with higher risk of using addictive substances in adulthood (143). With this in mind, young

men who have a limited ability to handle stress potentially constitute a vulnerable group with a long-term risk of unfavorable health outcomes.

In summary, based on our results, along with previously described clinical findings and shared pathophysiological pathways, young patients with nonpsychotic mental disorders and low stress resilience should receive particular attention in order to prevent future somatic disease burden. Since a nationwide dataset corresponding to the Military Service Conscription Register with information on female adolescents is not in place, we were not able to study the effects of nonpsychotic mental disorders and low stress resilience in adolescent women. While we believe that our findings are applicable to the female population, further research is needed to confirm this.

Methodological considerations

In this thesis, we have embraced a cohort design based on national registers. Coupling the information from high-quality nationwide registers facilitates large population-based prospective studies with long-term follow-up periods spanning several decades. This enabled us to obtain high numbers of study participants with almost complete follow-up.

Previous studies that have investigated the influence of different levels of BMI on heart failure have used relatively small study samples (93, 122). This has limited the possibility to narrow the BMI intervals and to detect differences also within the broad established BMI categories. As a result, BMI 25 has often been used as the cut-off, above which the risk has been shown to increase. Our population-based studies were large enough to distinguish BMI subgroups within the normal, overweight, and obese ranges. We found an increased risk for heart failure already at BMI 20–22.49, and for cardiomyopathy at BMI 22.5–24.9, as compared to BMI 18.5–19.9 among adolescent men. These findings suggest that the current approach, using a BMI threshold of 25 in young adulthood, may lead to an underestimation of the true risk for heart failure and cardiomyopathy associated with elevated BMI. Thus, an adjustment of the recommended optimal BMI level for young people is likely to be beneficial with respect to cardiovascular health.

Regarding the relationship between mental disorders and cardiovascular disease, including heart failure, previously conducted longitudinal studies have focused primarily on individuals who were diagnosed with psychotic disorders (134) or with depression or anxiety (96). Moreover, most of those studies relied on self-reported questionnaires of mental health and had rather short follow-up periods. In Paper II, we used a broader approach and investigated the impact on heart failure risk of a wide range of professionally diagnosed mental

disorders in youth, including more unusual conditions such as personality disorders and alcohol or substance use disorders. This was possible due to the large sample size and the long follow-up period over several decades.

Confounding

The inherent major limitation of an observational cohort study is that the associations detected between exposure and outcome do not necessarily imply a causal relationship. Associations may be explained by another factor that is related to both the exposure of a risk factor and the outcome, which is called confounding and this commonly occurs in epidemiological comparisons. Confounding can result in both under- and over-estimations of the true effect (144). To be designated as a confounder, a variable must: have an association with the disease (be a risk factor); be associated with the exposure (unequally distributed between the exposed and non-exposed groups); and not be an effect of the exposure (not part of the causal pathway) (Figure 17) (145).
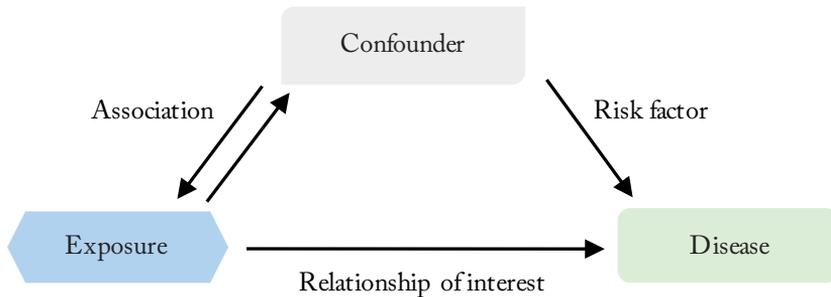

Figure 17. Criteria for a confounder. Reprinted with permission (145). Jager et al, Kidney Int, page 257, 2008.

In our analyses, we have adjusted for possible confounders, such as age at conscription, conscription year, test center (Papers I–III), age at antenatal visit, year, parity (Paper IV), and comorbidities at baseline (Papers I–IV). In the conscription register studies (Papers I–III), we have also adjusted for baseline physical fitness, muscle strength, IQ, and parental education. In Paper IV, using data from the Medical Birth Register, we have added education level and baseline smoking as covariates. A limitation with our papers, as with other register-based studies, is the scarce access to information on other potential confounders, such as exposures during follow-up. Residual confounding of unmeasured exposures should, therefore, not be forgotten. To establish causal relationships between environmental factors and disease, Mendelian randomization studies have become widely used to overcome potential confounding and reverse causation. A recent report with this study design, investigating the association between adiposity and heart failure, using a

genetic variant associated with obesity, provided evidence to indicate a causal relationship (146). In this context, future studies on BMI and cardiomyopathy are warranted.

Selection bias

Besides confounding, selection bias has to be considered in observational cohort studies. Selection bias arises from the selection of study subjects or from factors that have impacts on study participation (144), which may lead to a non-representative sample of the population intended to be analyzed. The use of Swedish national high-quality registers with comprehensive coverage enables the inclusion of mainly unselected populations.

For the purposes of Papers I–III, we used the Military Service Conscription Register with data obtained during the mandatory enlistment to military service for all Swedish 18-year-old males. In Papers I and III, we included all young men with valid information on BMI. A sensitivity analysis of those men with missing BMI values showed that the majority enlisted during the last five conscription years included in the papers. Therefore, in most of the cases, it is not likely that disease development had started at the end of follow-up, so we believe that this did not affect the results. In Paper II, we included all the enlisting men, except for those with a psychotic disorder before, at or after conscription. In the early study period, only a few men were exempted from enlistment, mostly for serious reasons. However, this changed over the years with the increasing practice of excusing young men from military service for other reasons than before. We found a decreasing prevalence of nonpsychotic mental disorders over time, which we believe can be explained by this increasing practice of excusing men with adverse medical diagnoses. As a result, mentally ill young men, with more serious effects on psychosocial functioning, may have been granted an exemption, and thus, were not included in our analyses. A selection bias towards healthier conscripts may have affected the external validity and contributed to more conservative risk estimates in Paper II.

In Paper IV, we included all the birth-giving women in Sweden, which has been reported to be >85% of Swedish women during the study period (86). As involuntary childlessness is more common among obese women (147), there is a possibility that there was a selection bias towards leaner subjects. This may have promoted an underestimation of cardiomyopathy incidence. However, obesity accounts for only a fraction of all cases of involuntary infertility. Since the overwhelming majority of Swedish women do give birth and almost all of them are included in the Swedish Medical Birth Register (99%) (98), the study

population can be considered to be satisfactorily representative of all women in Sweden during the study period.

Other selection biases as a result of loss of follow-up in Papers I–IV are considered to be minimal, as population-based registers with high coverage enable almost complete follow-up. There is a theoretical possibility that early-onset obesity, mental illness, and low stress resilience, all of which entail higher risks of early death, prevent study participants from being diagnosed with future heart failure or cardiomyopathy. However, since the numbers of deaths are very few in these young cohorts, this is not thought to have affected our results.

Information bias

Besides confounding and selection bias, it is important to evaluate the possibility of information bias, due to misclassifications of the exposure being measured or of the outcome (144). In this thesis, the exposures were BMI, nonpsychotic mental disorders, and stress resilience in young age groups.

At the time of mandatory enlistment to military service in Sweden, it must have been inevitable to elude men who lacked motivation and who knowingly underperformed in the tests, in the hope of being granted an exemption. This is particularly important to consider in studies that use test results for physical fitness or cognitive performance during conscription, as exposures. While each of these tests is not validated in this regard, a Danish study of a comparable cognitive test at conscription, demonstrated that motivational influences related to attitude towards military service did not affect the test validity (109). In Papers I and III of this thesis, BMI, as the main exposure, was calculated from standardized measurements of weight and height, which are difficult to manipulate, why we believe that attitude issues have not affected our results. Moreover, the associations that we found between BMI and heart failure and cardiomyopathy were only slightly attenuated when adjustments were made for fitness, strength, and IQ in the analyses. Furthermore, in Paper IV, body weight was measured in most cases. Measured anthropometric values have been demonstrated to have a higher accuracy rate than self-reported values, since bodily perception tends to underestimate true BMI (148). People are prone to underestimating their weight and overestimating their height (149). Since height was partly self-reported in Paper IV, this may have caused an underestimation of the BMI values in some cases.

In Paper II, nonpsychotic mental disorders were identified and registered according to ICD-codes by the physicians at enlistment. Despite this professional procedure, it has been demonstrated that for conscripts with a

history of psychiatric hospitalizations before conscription, only one in five was diagnosed with a mental disorder at conscription (67). This relatively low diagnostic rate may be explained by either recovery or a failure to report symptoms, and this could have resulted in more conservative results. In Paper II, stress resilience was assessed by military-trained certified psychologists using a standardized written manual to assure uniform assessments (110). It has been argued that this procedure offers a more precise measure than one based on self-reported questionnaires, since more extensive information about psychological status can be revealed in a personal encounter (110). In addition, the rate of inter-rater reliability between psychologists at different test centers has been reported to be high (112). Despite this, attitudes towards military service may have caused misclassifications if conscripts consciously tried to answer questions in an excessively negative way with the goal of avoiding military training or increasing their chances to serve as non-commissioned officers (shorter training period). However, validations of the stress resilience score at enlistment against subsequent records of military performance and leadership proficiency have shown a high level of precision for the assessment (111, 150). Whether or not the stress resilience capacity can also be applied in everyday life is, of course, an interesting topic. Although it was originally designed to be an indicator of ability to function psychologically in a demanding environment, such as military troop life or in the extreme situation of armed combat, the result is based on skills (such as teamwork and responsibility) that may be beneficial for achieving success in both the military and in the labor market. Therefore, there is reason to believe that the stress resilience score is applicable to stressful events in a life-course perspective. Accordingly, conscripts who scored higher on the test, have been postulated to be more successful in the labor market later in life (110), which strengthens the test validity.

Regarding information bias due to misclassification of the outcomes, we consider the possibility of this happening to be very low. The validity of heart failure and cardiomyopathy diagnoses in the Swedish National Patient Register has been reported as high (103, 104), as described earlier in the Methods section. Since all cases in the papers are considered to have been early incidents, with patients aged <65 years (mean ages at diagnosis, 46.6, 49.0, 45.9, and 46.2 years, respectively), we believe that the clinicians had a strong incitement to perform thorough investigations in order to ascertain the correct diagnosis among these young patients. To assure a heart failure diagnosis in Papers I and II, we included only hospitalized cases from the National Hospital Register. As diagnoses of heart failure listed in the Cause of Death Register may be uncertain or unconfirmed, they were not included. However, cardiomyopathy diagnoses in the Cause of Death Register are assumed to have

been certified with an autopsy, and thus, this register was utilized in Papers III and IV, together with the National Patient Register.

Gender aspects

Papers I–III included only young men, as the military enlistment was mandatory only for adolescent males during the study period. There were about 10,000 women in the register during that period, but we considered them not to be representative of the Swedish female population, and they were therefore excluded from the analyses. In Paper IV, to complete the picture with regard to gender, we decided to investigate whether our finding of an association between BMI and cardiomyopathy in males was also valid for women. As corresponding register data for women in late adolescence do not exist, we obtained information on women of childbearing age from the Swedish Medical Birth Register.

Our findings allow us to conclude that elevated BMI in young people increases the risk of future cardiomyopathy, regardless of gender (Papers III, IV). Furthermore, the association between body weight and heart failure in young men that we found in Paper I, has recently been demonstrated by our research group to apply to young women (151). Sex differences in cardiovascular diseases are well-known. First, cardiovascular disease differs in its clinical presentation depending on sex (152). Second, it has been shown that men have a 2-fold higher risk than women for incident myocardial infarction after adjustment for age and established risk factors (153). However, although men had a higher risk throughout life, the incidence rate ratios declined with age (3.64 (95% CI, 2.85–4.65), 2.00 (1.76–2.28), and 1.66 (1.42–1.95) for age groups 35–54, 55–74, and 75–94 years, respectively). Adjustment for systolic blood pressure, diabetes, BMI, and physical activity did not influence these results. Women with heart failure diverge from men in several ways; they are generally older at onset, and they more often suffer from hypertension, diabetes, and atrial fibrillation, whereas they are less likely to have ischemic heart disease (154). Of note, women with a myocardial infarction have a higher relative risk of heart failure than their male counterparts (155). Between 1990 and 2000, the age-adjusted prevalence of hospitalized patients with heart failure in Sweden increased from 1.70% to 2.13% for men, and from 1.77% to 2.14% for women. Subsequently, the prevalence decreased to 2.03% for men and 1.93% for women in 2007 (4). This difference may be explained by divergent mortality trends, where, in particular, the prognosis among younger men aged 35–64 years has improved more than it has for women (156). The more prominent decrease in case fatality among men is probably a result of the progress made in the treatment of myocardial infarctions (157), in combination

with the successful reduction of cardiovascular risk factors during the last decades (158). Regarding cardiomyopathies, the prevalence has been reported to be higher among males, especially for dilated cardiomyopathy (159-162), which is in line with the incidence rates found in our studies (Papers III, IV). Our results indicate a somewhat more equal sex distribution of hypertrophic cardiomyopathy, as supported by previous research (159, 161, 162). Whereas studies of alcoholic cardiomyopathy have been inconclusive (163, 164), we found higher incidence rates of alcohol/drug-induced cardiomyopathies among men than among women.

When examining the BMI threshold, above which the risk of heart failure and cardiomyopathy started to rise, the threshold for women was higher than that for the men. Women had an increased risk of cardiomyopathy at BMI values in the range of 25–27.49, which is a level that is considered to be overweight, as compared to BMI 20–22.49 (Paper IV). The men in Paper III, on the other hand, had an increased risk already at BMI 22.5–24.9 (values within the normal range) compared to BMI 18.5–19.9. Apart from the obvious 10-year difference in mean age with older women at baseline in Paper IV (28 vs. 18 years for the men in Paper III), previous studies have similarly demonstrated a higher risk for men regarding diabetes (165) and mortality (166) for a given BMI, than for women. Therefore, our findings accord with the already observed sex differences with respect to the relationship between overweightness and adverse health outcomes.

Strengths and limitations

The exquisite opportunity to link national population-based registers in Sweden is made possible by the unique personal identification number assigned to all Swedish residents. The datasets utilized in this thesis were originally collected for administrative reasons rather than for research, which may result in lack of information on variables or on confounders of interest. The quality of the collection methods has also been beyond our control. However, as discussed above, the methods used to gather information on the exposures and outcomes in the present studies are well-established, which means that the chance of a significant information bias in these cohorts must be regarded as very low. The datasets enabled us to acquire information on large representative populations spanning decades. The Military Service Conscription Register and the Medical Birth Register are exceptional in providing data on BMI for a majority of the young adult population, which is the main strength in Papers I, III, and IV. There is a possibility that mildly elevated BMI in early adult-life reflect high muscle mass rather than adiposity, which, however, we believe is unlikely to be the case with very high BMI.

Moreover, the results were only slightly attenuated when adjustment was made for muscle strength in the analyses of the men. In our study of women (Paper IV), the weight measured at the first antenatal visit (very early in pregnancy) was considered to be equal to pre-pregnancy weight, since only minor weight gain occurs during the first trimester (116-118). Anthropometric variables other than BMI, such as waist circumference and waist-to-hip ratio, were unfortunately not available in any of the datasets.

From the Military Service Conscription Register, it was also possible to obtain information on psychiatric disorders and stress resilience among all 18-year-old men enlisting in Sweden (Paper II). The psychiatric disorders were diagnosed by physicians, and stress resilience was assessed by certified psychologists, which ensured a professional evaluation of the conscripts. Despite the limitation that details of the stress resilience test are labeled as military secrets by Swedish law and not available for research purposes, it was possible to receive a large amount of information on adolescent stress resilience scores. This enabled us to investigate stress resilience in youth, in accordance with one of the study aims.

Study generalizability in Papers I–III was limited by age, sex, and ethnicity. Thus, the results may not be representative of other populations or of women. However, the gender aspect regarding cardiomyopathies was taken into account in Paper IV. As it was not possible to assess systematically the effect of ethnicity, due to the lack of detailed data, the increased immigration that occurred during the study periods could not be taken into account.

Follow-up via the National Patient and Cause of Death registers provided identification of a high number of heart failure and cardiomyopathy cases. Although the diagnoses in the National Patient Register have been collected only for administrative reasons, as previously described, and are not formally validated, studies have reported a high validity of both heart failure and cardiomyopathy (103, 104). It is unlikely that the strong associations presented in this thesis are due to misclassifications of these disorders. Since the overall rates of cardiomyopathies are very low, this large and long-term dataset was required to obtain sufficient statistical precision. We are not aware of other similar datasets that are large enough for a comparison study.

Finally, we were not able to study potential significant exposures in adulthood during the follow-up period, such as weight change, smoking habits, diet, physical activity, alcohol consumption, and substance abuse. Thus, the ways in which subsequent weight gain contributes to the development of heart failure and cardiomyopathy could not be elucidated from our data. However,

it is reasonable to believe that increased weight in young age persists, and even increases, throughout the lifetime (55).

Implications and clinical significance

The papers in this thesis present the impact of BMI, mental health, and stress resilience at a young age on future risk of heart failure and cardiomyopathy. The studies are among the first to report that even mid- to high-normal BMI (BMI 20–24.9) in young age predicts the risk of early heart failure and cardiomyopathy. Our findings highlight the potential long-term consequences of overweightness and mental illness. Thus, when young people bring their lifestyle habits and morbidity patterns into the later stages of life, in which heart failure is common, heart failure may evolve as a major threat to health worldwide.

BMI is nowadays recognized worldwide as a standard measurement of adiposity status. To date, a BMI of 25, which is the boundary between normal weight and overweight, has often been used as a cutoff point in studies of morbidity and mortality risks. The findings in this thesis indicate that the current approach with a BMI threshold of 25 in young adulthood may lead to an underestimation of the true risk for future somatic disease burden. Accordingly, an adjustment of the recommended optimal BMI level for young people may be beneficial with respect to cardiovascular health. Further studies on adolescent women and on other cardiovascular outcomes are needed in this regard.

To manage the challenges associated with the increasing proportion of overweight and obesity among young people, certain interventions are urgently needed. First, once established, overweight and obesity are much harder to combat. As a preventive strategy, greater emphasis should be placed on the maintenance of a healthy body weight from an early age. Second, children and adolescents are more susceptible to food marketing than adults, indicating that the extensive exposure to unhealthy food and beverage products needs to be regulated. Using targeted taxation to reduce consumption, particularly of sugar-sweetened drinks, has decreased purchases of such products outside Sweden (167). In addition, subsidizing healthier foods has tended to modify dietary behavior in favor of promoted groceries (168). However, such interventions are politically controversial. Third, physical activity prescribed by health professionals, preventively or for the treatment of a disease, is another action with potentially beneficial results. Introducing daily school-based physical activities during all nine mandatory school years in Sweden could be a way to reach all children and adolescents. This has also been associated with improved eligibility for upper secondary school and mean

grade score in boys in a Swedish study (169). The building of environments that promote physical activity, such as accessible bicycle and walking paths, playgrounds, appealing stairs, safe environments for walking and bicycling, and attractive school yards, may be important in preventing weight gain. Moreover, such actions may prove to be valuable in reducing and preventing mental illness among young people, as well.

Utilization and communication of research results

Physicians in clinical practice need to be aware of the increasing rates of heart failure and cardiomyopathy in young persons. The present thesis contributes with new knowledge about the impact of higher BMI and mental illness in young people on the risk for future disease development. To communicate our results to clinicians, in addition to publications in academic journals, we have presented our findings at international academic conferences visited by health professionals. The results have also been highlighted on public radio[1], and in daily newspapers[2]. Moreover, we plan to publish a summary of the results as a popular Science report in journals that are read by a high number of physicians, such as *Läkartidningen*. We believe that our results have the potential to attract attention, as they relate to a vital issue of public interest with possibilities for prevention. Active communication of the findings to policy-makers will hopefully mean that our results can be used for improved decision making and for the implementation of forceful societal actions. This is important towards achieving the third Sustainable Development Goal set by the United Nations General Assembly, in which it is stated that noncommunicable diseases, including obesity, as well as mental diseases, should be reduced up to Year 2030. Thus, identifying exposed young people and helping them to achieve weight control and mental well-being should be prioritized. Such efforts are likely to result in a reduced somatic disease burden later in life, including heart failure and cardiomyopathy.

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[1]*Vetenskapsradion, Sveriges Radio, June 17, 2016; July 17, 2019*
[2]*Göteborgs-Posten, June 5, 2019; July 17, 2019; Expressen, June 17, 2016; Forskning & Framsteg, June 16, 2016.*

CONCLUSIONS

Our findings indicate that even a slightly increased BMI in young age is associated with:

- An increased risk of early heart failure in men, which is a condition that is becoming more frequent among young people. Since the global prevalence of overweight and obesity is increasing, including a growing number of people with severe obesity, health interventions to ensure weight control early in life should be prioritized by the medical profession.

- An increased risk of early cardiomyopathy, which is an increasingly common disorder underlying heart failure in younger patients. This was seen in both men and women, and for dilated cardiomyopathy, in particular, which is the most frequently observed form of cardiomyopathy. The already marked importance of weight control at a young age is further strengthened by these findings. In addition, the results provide more evidence for obesity being a potentially important cause of adverse cardiac remodeling that is independent of clinically evident ischemic heart disease.

Our findings also suggest that nonpsychotic mental disorders, as well as low stress resilience in late adolescence are associated with:

- An increased risk of early heart failure in men. This association may be explained by the higher risk of cardiovascular risk factors and lower likelihood of adherence to medical and behavioral guidelines among mentally ill patients, as well as by possibly shared biological and hereditary pathways. Adolescent individuals with low stress resilience, which determines the ability to deal with stressful events during life, may constitute a potentially vulnerable group with respect to future somatic disease burden. Thus, identifying young people who are coping with these mental difficulties should go hand in hand with the management of overweight and obesity.

FUTURE PERSPECTIVES

This thesis contributes with new knowledge about how BMI and mental health early in life influence the risk of developing heart failure and cardiomyopathy in midlife. Heart failure among young people appears to be on the rise (5). This is a trend that clinicians need to be aware of together with an awareness of the etiologies behind, in order to prevent future disease burden. We found that even mildly elevated levels of BMI in young age were associated with early heart failure and cardiomyopathy. To improve our understanding of the effect of adiposity on the heart, further research is needed. Possible targets are the potential pathophysiological pathways, of which metabolic disturbances and hormonal dysregulation are interesting. Moreover, our findings suggest that young men with nonpsychotic mental disorders or low stress resilience are at increased risk of future heart failure, which can probably be applied to other unfavorable cardiovascular health outcomes. Further research is needed, regarding both sexes, to ascertain whether early preventive efforts for individuals with mental illness and compromised stress resilience, can improve subsequent behavioral patterns and reduce the associated somatic morbidities.

In this thesis, we investigated overweight, obesity, and mental illness among young people in relation to future disease burden. Information on adolescent men was obtained from the conscription data in the Military Service Conscription Register. An equal compulsory opportunity, from which information on adolescent females is available, is not currently available. However, there is an increasing participation of young Swedish women in contemporary military conscription, and this may offer possibilities to investigate exposures also in female adolescents in the future. Furthermore, since we did not have information regarding subsequent weight changes during the life-course, we were not able to study the weight gain or loss that occurred in adulthood. It would, of course, be interesting to analyze the impact of longitudinal trends of overweight and obesity on the heart. Although there is a tradition of providing nationwide registers with information on large populations in Sweden, BMI data are not collected to the extent that they are collected during the military conscription, at any time later in life. Since cardiomyopathies are rare disorders, a large dataset is required in order to obtain sufficient precision to be able to analyze how changes in BMI, and other exposures during life, influence the development of the condition. A long follow-up is also needed in this context, as there may be a long latency period from exposure to disease development. Hopefully, in the future, population-based cohorts will become available to overcome such difficulties. A recently collected data source, which potentially could be linked to the Military Service Conscription Register and the Medical Birth Register, is the Swedish

CardioPulmonary bioImage Study (SCAPIS) cohort of 30,000 middle-aged men and women (age range, 50–64 years) with information on risk factors for cardiovascular disease, such as BMI, smoking, blood pressure, serum levels of cholesterol, triglycerides, and measurements of markers of disease progress (e.g. coronary and carotid plaques). Taken together, the well-established tradition in Sweden of collecting data into national registers provides unique materials and study settings. This tradition should be maintained to foster even greater possibilities in future epidemiological research studies.

RELATED PUBLICATIONS NOT INCLUDED IN THIS THESIS

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