Body weight, body size and early cardiovascular disease

Epidemiological studies using Swedish registries

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"There are three types of lies: lies, damned lies and statistics"

Benjamin Disraeli (1804–1881), British Prime Minster

!The origin of this quote has been disputed.

To my loving family and the cat. Thank you for all the love and support.

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ABSTRACT

Background: Obesity is a known risk factor for cardiovascular morbidity and mortality, as well as for atrial fibrillation and heart failure. While overweight and obesity have become increasingly more common in Sweden and worldwide during the past decades, there have also been an increase of some cardiovascular diseases (CVD) among men and women younger than 45 years old in Sweden. Significant weight loss has several beneficial effects on these conditions. Bariatric surgery has shown to induce great weight loss and to improve cardiac function.

Aims and methods: The aim of this thesis was to investigate trends in mean body mass index (BMI), overweight and obesity in young women during past decades. Thereto, we sought to estimate the impact of body size, body weight and obesity on the risk of early CVD and mortality in young women and in obese patients with and without surgical treatment for obesity, and compare that risk with the Swedish total population. All studies included in this thesis are population-based trend- and cohort-studies, and are based on data from Swedish national registries. In Study I–III, the study populations were derived from the Medical Birth Register and included all women in Sweden who gave birth between 1982 and 2014. In Study IV–V, the Patient Register was used to create cohorts including all individuals diagnosed with obesity, with and without bariatric surgery, between 2000 and 2011 and between 2001 and 2013. Logistic regression models were used to analyze the relationship between BMI and socioeconomic status. To analyze the relationship between BMI, obesity, obesity surgery and morbidity and mortality in CVD, Kaplan-Meier curves, Cox regression, Poisson regression, and logistic regression were applied.

Results: The incidence of obesity has significantly increased among young women since 1982. This increase was observed in all levels of education and in all counties in Sweden. An increased body weight and body size early in life is strongly associated with an increased risk of early heart failure and atrial fibrillation among women. There was a linear relationship between BMI measured early in life and an increasing risk of developing early heart failure, starting already at BMI 22.5–25, among women. The risk of heart failure and acute myocardial infarction (AMI) was markedly reduced among patients with a diagnosis of obesity who had undergone obesity surgery compared with patients with a diagnosis of obesity who had not undergone such surgery. Within 3 years of follow-up, they also had a reduced risk of cardiovascular-related and all-cause mortality, but not during 3–10 years of follow-up. Obesity surgery did not seem to affect the risk of developing ischemic stroke to the same extent. Compared with the total population, patients with a diagnosis of obesity who have undergone obesity surgery have the same risk of AMI during 10 years of follow-up. They also had a similar risk of developing ischemic stroke during the first three years, after which the risk increased again.

Conclusions: Given the strong associations identified between an elevated body size and BMI early in life and increased risk of atrial fibrillation and heart failure, along with increased risk of heart failure, AMI, and premature death among patients with obesity, the illuminated increase in obesity among young first time-mothers will most likely cause a rice in serious health problems in Sweden the following decades.

Keywords: epidemiology, body mass index, obesity, bariatric surgery, gastric bypass, cardiovascular disease, mortality

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Fetma är en känd riskfaktor för kardiovaskulär sjuklighet och dödlighet, liksom för förmaksflimmer och hjärtsvikt. Samtidigt som övervikt och fetma har blivit allt vanligare i Sverige och världen över under de senaste decennierna, har det också skett en ökning av förekomsten av vissa hjärt-kärlsjukdomar bland män och kvinnor yngre än 45 år i Sverige. En betydande viktminskning har ett flertal fördelaktiga effekter på dessa tillstånd. Fetmakirurgi har visats inducera en signifikant viktminskning och förbättrad hjärtfunktion.

Metoder: Syftet med denna avhandling var att undersöka trender i kroppsmasse index (body mass index [BMI]), övervikt och fetma under de senaste decennierna. Därtill var syftet att estimera påverkan av kroppsyta, kroppsvikt och fetma på förtida sjuklighet och dödlighet i hjärt-kärlsjukdomar bland unga kvinnor och bland patienter med fetma, med och utan fetmakirurgi, samt att jämföra den risken med den svenska befolkningens. Studierna som inkluderas i avhandlingen är populations-baserade trend- och kohortstudier, och bygger på data ifrån svenska nationella register. I Studie I–III skapades studiepopulationerna utifrån medicinska födelseregistret och inkluderade alla kvinnor i Sverige som fött barn mellan 1982 och 2014. I Studie IV–V användes patientregistret för att skapa kohorter med alla individer som fått en fetmadiagnos med och utan fetmakirurgi, mellan åren 2000–2011 samt mellan åren 2001–2013. För att analysera sambandet mellan BMI och socioekonomisk status användes logistiska regressionsmodeller. För att analysera sambandet mellan BMI, fetma, fetmakirurgi och insjuknande och dödlighet i hjärt-kärlsjukdomar tillämpades Kaplan-Meier kurvor, Coxregression, Poisson-regression, samt logistisk-regression.

Resultat: Förekomsten av fetma har ökat avsevärt bland unga kvinnor sedan 1982. Denna ökning observerades i alla utbildningsnivåer och i alla län i Sverige. En ökad kroppsvikt och kroppsyta mätt tidigt i livet är starkt förknippat med en ökad risk för tidig hjärtsvikt och flimmer bland kvinnor. Det fanns ett linjärt samband mellan BMI mätt tidigt i livet och en ökande risk för att utveckla tidig hjärtsvikt bland kvinnor. Den förhöjda risken började redan vid BMI 22.5–25. Risken för hjärtsvikt och hjärtinfarkt var kraftigt reducerad för patienter med en fetmadiagnos som hade genomgått fetmakirurgi jämfört med patienter med en fetmadiagnos som inte genomgått sådan kirurgi. Inom tre års uppföljning så hade de även minskad risk för kardiovaskulärrelaterad och all typ av dödlighet, men inte under 3–10 års

uppföljning. Fetmakirurgi verkade inte påverka risken att insjukna i ischemisk stroke i lika stor utsträckning. Jämfört med totalbefolkningen så har patienter med en fetmadiagnos som har genomgått fetmakirurgi samma risk att drabbas av hjärtinfarkt under 10 års uppföljning. På kort sikt hade de även liknande risk att insjukna i ischemisk stroke, därefter ökade risken återigen.

Slutsatser: Givet den starka association som identifierats mellan ett högt BMI och kroppsyta tidigt i livet och senare ökad risk för hjärtsvikt och flimmer samt mellan fetma och tidigt insjuknande i hjärtsvikt, hjärtinfarkt och förtida död, så kommer den ökning av fetma och grav fetma som identifierats bland unga kvinnor sedan 1982 och framåt på sikt sannolikt medföra en ökning i allvarliga hälsoproblem.

LIST OF PAPERS

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

I. Lundberg CE, Ryd M, Adiels M, Rosengren A, & Björck L. Social inequalities and trends in pre-pregnancy body mass index in Swedish women.
Under review.

II. Lundberg CE, Adiels M, Björck L, & Rosengren A. Young women, body size and risk of atrial fibrillation.
European Journal of Preventive Cardiology 2018;25(2):173-180.

III. Björck L, Lundberg CE, Schaufelberger M, Lissner L, Adiels M, & Rosengren A. Body mass index in women aged 18 to 45 and subsequent risk of heart failure.
European Journal of Preventive Cardiology 2020;27(11):1165-1174.

IV. Persson CE, Björck L, Lagergren J, Lappas G, Giang KW, & Rosengren A. Risk of heart failure in obese patients with and without bariatric surgery in Sweden – a registry-based study.
Journal of Cardiac Failure 2017;23(7):530-537.

V. Lundberg CE, Björck L, Adiels M, Lagergren J, & Rosengren, A. Risk of myocardial infarction, ischemic stroke, and mortality in patients who undergo gastric bypass for obesity compared with non-operated obese patients and population controls.
Under review.

CONTENT

ABBREVIATIONS

AMI	Acute myocardial infarction
BMI	Body mass index
BSA	Body surface area
CHD	Coronary heart disease
CI	Confidence intervals
CVD	Cardiovascular disease
HR	Hazard ratio
ICD	International Classification of Diseases
IQR	Inter quartile range
kg	Kilo gram
LISA	Longitudinal Integration Database for Health Insurances and Labour Market Studies
m	Meter
Patient register	National Patient Register
NOMESCO	Swedish Classification of Operations and Major Procedures
PIN	Personal identification number
PRR	Prevalence risk ratio
RYGB	Roux-en-Y gastric bypass
SD	Standard deviation
SOS	Swedish Obese Subjects study
WHO	World health organization

INTRODUCTION

OVERWEIGHT AND OBESITY

PREVALENCE

The prevalence of overweight and obesity has nearly tripled in Sweden and worldwide during the past 50 years,[1] and is now a major global public health problem. The global prevalence of overweight in 2016 was at 39% and that of obesity at 13%.[2] A particular matter of concern is that 18% of all children and adolescents aged 5–19 were overweight or obese in 2016. This sharp increase in a matter of just a few decades has caused the World Health Organization (WHO) to declare a global obesity epidemic.[2] In Sweden, more than half of the adult population were overweight and almost 20% were obese in 2013.[3] In particular, the prevalence of severe obesity, defined as a body mass index (BMI) of ≥35 kg/m^2 has more than doubled in Sweden and worldwide during the last few decades. In young Swedish men (mean age 18 years), the prevalence of obesity (BMI≥30 kg/m^2), increased from around 1% during 1969–1974 to 3.4% during 1996–2005, where the highest prevalence difference between periods was found in severe and morbid obesity (BMI≥ 40kg/m^2). The increase was substantially higher for those young men whose parents had the lowest educational level.[4] Similarly, among young Swedish women (mean age 28 years) with weight recorded at their first antenatal visit, obesity increased from 4.5% to 10.2% between 1992 and 2010.[5] However, data on temporal trends in prevalence of moderate and severe obesity in young women are limited.

CLASSIFICATIONS AND DEFINITIONS

The WHO's definition of overweight and obesity is "abnormal and excessive fat accumulation that may impair health".[2] There are several anthropometrical measures which can be used to assess overweight and obesity, such as BMI, waist circumference, sagittal abdominal diameter and body surface area, which all have their advantages and disadvantages. BMI is the most commonly used proxy for assessing overweight and obesity across populations.[2] BMI is calculated as the weight in kg divided by the height in m^2.[6] The most recent classifications of weight status, defined by WHO, along with definitions used in this thesis can be found in Table 1. Because previous research has indicated that the risk of several CVD starts already at what WHO defines as normal weight,[7, 8] further subdivision of this category may be appropriate in order to capture potential differences in risk within comparatively broad category.

Table 1. *Classification of weight status according to the WHO with further subdivision of the normal weight category as used in this thesis.*

BMI	*WHO classification*	*Classifications used in thesis*
< 18.5	Underweight	Underweight
18.5 to <20.0	Normal weight	Low normal weight
20.0 to <22.5	Normal weight	Normal weight
22.5 to <25.0	Normal weight	High normal weight
25.0 to <30.0	Pre-obesity	Overweight
30.0 to <35.0	Obesity class I	Obesity
35.0 to <40.0	Obesity class II	Severe obesity
≥ 40.0	Obesity class III	Morbid obesity

Abbreviations: BMI= body mass index, WHO= World Health Organization

CAUSES AND CONSEQUENCES OF OVERWEIGHT AND OBESITY

CAUSES

The basic physiological cause of the accumulation of overweight is an imbalance between calory intake and expenditure. Therefore, both diet and physical activity are of importance for maintaining energy balance and a healthy weight.[9] There is a large body of evidence showing that a good dietary pattern is of great importance in order to maintain a good health and a healthy weight.[10] A healthy eating pattern, associated with lower prevalence of cardiovascular risk factors, is characterized by a high intake of high-fibre and low-fat foods, and a low intake of foods containing high levels of fat or sugar.[11] To the contrary, over the past decades, there has been a substantial increase in the intake of ultra-processed, energy-dense food, containing high levels of fat and sugar and with a low nutritional value, in Sweden and worldwide.[12, 13] Simultaneously, the overall physical activity level has decreased and been replaced by a more sedentary lifestyle,[2] where an estimated one third of the population in the Nordic countries was physically inactive in 2014.[14]

The causes of this shift towards more unhealthy behaviours, associated with increased levels of overweight and obesity worldwide, are multifactorial.[15] The relationship between factors and causes of obesity have been well illustrated in the Obesity System Influence Diagram.[16] The map shows how overweight and obesity are caused by genetic, behavioural, socioeconomic and environmental factors. In the diagram the causes of obesity are divided

into clusters of factors such as biology, early life growth patterns, living environment and infrastructure, economic drivers of food production and consumption, along with food intake and physical activity behaviours. All these factors together have created new "obesogenic" environments, promoting unhealthy lifestyles, and are making it harder for individuals to attain healthy lifestyles. This is especially true for younger people who are growing up in these environments. For example, these factors have promoted and caused overconsumption of unhealthy foods, poor dietary habits, low levels of physical activity, and with this, difficulties in maintaining a healthy weight.[17] What has especially affected dietary habits is the availability of low-cost ultra-processed foods along with major investments in marketing of such products.[17] Furthermore, increasing levels of physical inactivity are the result of more automated work, increasingly sedentary occupations, higher levels of screen time, and, with motorized transport, less engaging in physically active commuting.[14, 18]

THE ROLE OF SOCIOECONOMIC STATUS

There is a large body of evidence showing an association between socio-economic status and weight, where a lower socioeconomic status is associated with an increased risk of overweight and obesity. Contextual factors which cause an uneven distribution of overweight and obesity include factors such as cultural identity, gender, economy, physical and social environment, social networks, and socioeconomic status.[19] In addition, obesogenic environments are often related to poor socioeconomic conditions, hence, younger people with low socioeconomic status who are growing up in these environments are set on a path leading to increased risk of obesity already in young adulthood.[20] Widening social inequalities have been observed during the last decades in both men, women and youths worldwide.[20-22] In Sweden, individuals living in areas with low socio-economic status have shown to have lower levels of physical activity and higher prevalence of CVD risk factors.[23] This inequality of health in the population is a challenge for the health care system.

CONSEQUENCES

Overweight and obesity are major causes of premature disability, morbidity and mortality.[24, 25] Excess weight is the cause of multiple adverse health effects, such as CVD, diabetes, musculoskeletal disorders, system inflammation and some cancers.[25-27] Overweight and obesity are also associated with poor quality of life, learning disabilities and poor school performance among children.[28] The onset of overweight and obesity early in life is associated with an increased risk of remaining overweight and obese

during adulthood, inducing a lifelong weight struggle.[29] The tracking of obesity into adulthood causes more severe medical complications than if obesity develops during adulthood.[30] Because of this, obesity has a major impact on public health, imposing a significant financial burden on national health services. In particular, this is true for morbid obesity.[31]

OBESITY AND CARDIOVASCULAR DISEASE

CORONARY HEART DISEASE

In Sweden, the overall mortality from coronary heart disease (CHD) decreased by approximately two-thirds for men and women aged 35–84 years between 1987 and 2009.[32] Despite this overall downward trend in Sweden and worldwide,[24, 32] CVD, mainly CHD and stroke, are the leading cause of death worldwide.[24, 33] Approximately 70% of all deaths globally among individuals with obesity is attributed to CVD.[26] However, premature deaths from CVD are to a large extent preventable.

There are several pathways between obesity and excess weight on the risk of CHD. In short, the predominant underlying cause of CHD is atherosclerosis, a chronic inflammatory artery disease that leads to the appearance of plaque in the coronary vessel wall.[34] The prevalence of plaque increases with age, appearing earlier in men than in women, and is largely caused by metabolic risk factors which, in turn, to a major extent are related to lifestyle, leading to modifiable risk factors such as hypertension, dyslipidemia, and diabetes. INTERHEART, a large retrospective case-control study investigating causes of acute myocardial infarction (AMI) in 52 countries found that 90% of the cases could be attributed to 9 modifiable risk factors,[35] confirming that good dietary patterns, adequate physical activity and a healthy weight, in addition to abstaining from smoking, are the key factors in preventing AMI.[10, 36, 37]

The accumulation of excess weight in itself causes metabolic dysfunction, which increases blood pressure along with increased glucose and lipid levels, which are mediators in the pathway towards developing diabetes, atrial fibrillation, heart failure, ischemic stroke and CHD.[26, 38, 39] In addition, significant weight loss has several beneficial effects on cardiovascular morbidity and mortality caused by obesity.[40, 41] The increase in overweight and obesity is thought to partly explain a levelling-off, or even increase, of the prior decline in CVD in the young.[42-45]

HEART FAILURE

Heart failure is a serious clinical condition, with 5-year mortality rates similar to that of many cancers, despite improvements in treatment.[46] The prevalence of heart failure in the adult population in high-income countries is estimated at approximately 1–2%, and the lifetime risk among men and women aged 55 years at approximately 1 in 3.[47] Heart failure is a leading cause of mortality among men and women aged 65 years and older,[48] and the risk of heart failure increases steeply with age.[49] In recent years, heart failure has become increasingly common among younger persons, aged <45 years, in Sweden[42] and Denmark.[50] Obesity and an elevated BMI are strong well-known risk factors for heart failure.[7, 51, 52] Hence, the increasing levels of overweight and obesity in Sweden[5, 53] and worldwide[54] could potentially explain rising rates of heart failure among younger persons. A previous study of young men (aged 18–25 years old) found a steep increase in risk of early heart failure with increasing BMI, with an up to 10-fold increase in risk among those with BMI≥35 compared with BMI 18.5–20 kg/m^2.[7] In this thesis we sought to investigate whether a similar association between elevated BMI and heart failure existed also in young women.

Heart failure is a condition defined by typical symptoms of breathlessness, ankle swelling and fatigue, along with clinical signs caused by a structural and/or functional cardiac abnormality, which in turn causes reduced cardiac function.[47] Heart failure is an important component in CVD and represents an advanced stage of a variety of cardiovascular disorders without a clear single classification of causes.[47] The most prominent causes of heart failure in Sweden and other high-income countries are hypertension and CHD.[51] Heart failure can also be a result of acquired or congenital heart disease, arrhythmias or cardiomyopathies. In addition, there is a close link between atrial fibrillation and heart failure, where atrial fibrillation is both a risk factor and an adverse cardiovascular outcome associated with heart failure.[55, 56]

ATRIAL FIBRILLATION

Atrial fibrillation is the most common sustained cardiac arrhythmia, with around 43.6 million cases worldwide in 2016.[57] The lifetime risk of developing atrial fibrillation is 1 in 3 at an index age of 55 years[57] and the risk increases steeply with age and is higher for men.[58] Atrial fibrillation is one of the major causes of stroke, cardiovascular mortality and heart failure.[55, 56] Although atrial fibrillation is more common in men, it is associated with a greater risk for stroke and cardiovascular death among women, compared to men.[55]

There are numerus genetic and modifiable risk factors for incident atrial fibrillation, which in turn also is associated with aging and male sex, including hypertension,[59] valvular disease, diabetes, renal failure, chronic artery disease,[60, 61] physical activity, alcohol intake, smoking and obesity.[57] Obesity and elevated BMI have increasingly been recognised as major risk factors for atrial fibrillation.[62-64] The increased risk associated with obesity seems to be mediated trough left atrial dilation,[65] increased left ventricular mass and diastolic dysfunction.[56, 66] Together with BMI, both an elevated waist circumference and sagittal abdominal diameter, and weight gain over the life course, have independently been associated with atrial fibrillation in middle-aged populations.[62, 63, 67] Some studies have found a strong correlation between stature, measured by both height and body surface area (BSA), and the risk of atrial fibrillation, in a male population[67] and in a large patient population with impaired left ventricular function.[68] BSA has shown to be the best predictor of atrial fibrillation in healthy older populations,[69] while an increased BMI and BSA measured in young men (aged 18 years old) showed to be associated with an increased risk of atrial fibrillation later in life.[70] However, this relationship has not been investigated in women. As the height across the world's population on average has increased by 5 to 10 cm since 1900,[71] along with increasing mean BMI,[54] it is of interest to further explore the relationship between weight and height to that of incidence of atrial fibrillation.

TREATMENT OF OBESITY

Overweight and obesity are to a large extent preventable through a supportive environment that promotes healthy behaviors and makes it easier for individuals to choose healthy foods, and to attain adequate levels of physical activity in order to maintain a healthy body weight.[72] However, to date there are few successful treatments for obesity resulting in sustained weight loss. Currently, there are three main types of treatments available for obesity. These are life style interventions, pharmacotherapy, and bariatric surgery.[73] Although lifestyle interventions and pharmacotherapy are important and meaningful treatments, bariatric surgery has been shown to be the most effective treatment with regards to sustained weight loss for individuals with severe and morbid obesity.[73, 74]

BARIATRIC SURGERY

Bariatric surgery is a collective name for restrictive and/or malabsorptive surgeries with the purpose of physically restricting the size of the stomach, slowing down digestion, by removing or by-passing parts of the digestive

tract, reducing absorption of calories.[75] In Sweden, the treatment is usually initiated with a very low energy diet for a period of weeks, depending on the patient's starting weight. Post-surgery the patients are given nutritional recommendations and lifestyle guidance, and are followed up within the public healthcare at 6 weeks, and at 6-, 12-, and 24-months post-surgery.[76] Those eligible for surgery are patients with BMI $\geq$40, or BMI $\geq$35 with serious obesity related complications, such as diabetes, hypertension, and sleep apnea.[77] Contraindications to surgery are drug and alcohol abuse, psychiatric disorders, cancer within the last five years, and general poor mental or physical health.[78]

In Sweden and worldwide, the number of bariatric surgery procedures have increased along with the increase in prevalence of obesity and morbid obesity.[79] From 2000 and onwards, bariatric surgery became increasingly popular as a treatment for severe and morbid obesity in Sweden,[80] and between 2000 and 2014, the most commonly performed bariatric surgery was the Roux-en-Y gastric bypass (RYGB).[80] Bariatric surgery in general, and RYGB in particular, have shown to improve prognosis for patients with morbid obesity through a significant initial weight loss. Reports from the Scandinavian Obesity Surgery Registry have shown that patients who undergo bariatric surgery on average have BMI $\geq$45 at time of the surgery. During the year after surgery the BMI usually stabilizes around 32, after which the patients remain weight stable for about 5 years, after which there is usually some recurrent weight gain.[81] The Swedish Obese Subjects study (SOS) is the largest and most longstanding of the non-randomized trials, starting in 1987, comparing 2,010 patients undergoing obesity surgery with 2,037 matched usual care obese controls, demonstrating significant and largely persistent weight loss as well as remission of type 2 diabetes, lower rates of AMI, onset of new diabetes and mortality from all causes.[82] However, only about 30% of the participants underwent RYGB, and only patients aged 37 and older were included in the study.

RYGB is associated with improved cardiac function,[83, 84] and improvements in blood pressure, blood lipid levels, and dysglycemia.[84, 85] The surgery is also associated with improvement or complete resolution of obesity-related cardiovascular risk factors in morbidly obese patients.[82, 86] Still, some relapses of obesity related comorbidity have been observed along with accumulating weight gain during 5 years post-surgery.[85] Due to limited study sizes, there are few studies that have been able to study the risk of fatal and non-fatal AMI and ischemic stroke as separate events. The reported benefits of the RYGB on AMI and ischemic stroke have also varied to a great extent potentially depending on differences in sample sizes, follow-up times and

characteristics of patients.[87] In addition, to which extent bariatric surgery affects risk of heart failure is not well studied. Due to the strong association between BMI and heart failure,[51] the substantial weight loss following bariatric surgery should reduce the risk of heart failure among these patients.

AIMS

The overall aim of this thesis was to investigate trends in BMI and to estimate the impact of body size, body weight and obesity on the risk of early CVD and mortality in young women and in obese patients with and without surgical treatment for obesity. The aims of the individual studies were:

I. To investigate trends in social inequalities in BMI in young/mid-adulthood women aged 20 to 45 years in Sweden.

II. To investigate the relationship between early adult life body size and the risk of atrial fibrillation in women.

III. To investigate the relationship between BMI in young Swedish women (aged 18–45 years) and risk of early hospitalization for heart failure.

IV. To test the hypothesis that the risk of hospitalization for heart failure and overall mortality would decrease among patients who have undergone bariatric surgery, compared with patients with an obesity diagnosis who have not undergone such surgery.

V. To estimate the risk of AMI, ischemic stroke, and cardiovascular-related and all-cause mortality after RYGB surgery, compared with both non-operated obese patients and matched population controls.

METHODS

DATA SOURCES

All studies included in this thesis were based on data from Swedish national quality-, health data-, and population registers. These registries are a unique source of population-based personal data. The information from these registries can be linked through the ten-digit personal identity number (PIN) assigned to all Swedish residents at birth or at immigration (see Figure 1). All PINs are unique, with the exception of some dates of birth where there is a shortage of some PIN combinations, in which case the PIN of deceased residents can be reused and given to an immigrant if needed.[88] As the Swedish healthcare system offers tax-paid primary-, in- and outpatients care to all citizens, the quality- and health data registries include more or less complete data on all citizens relevant to the register, regardless of household income, social status or work status.

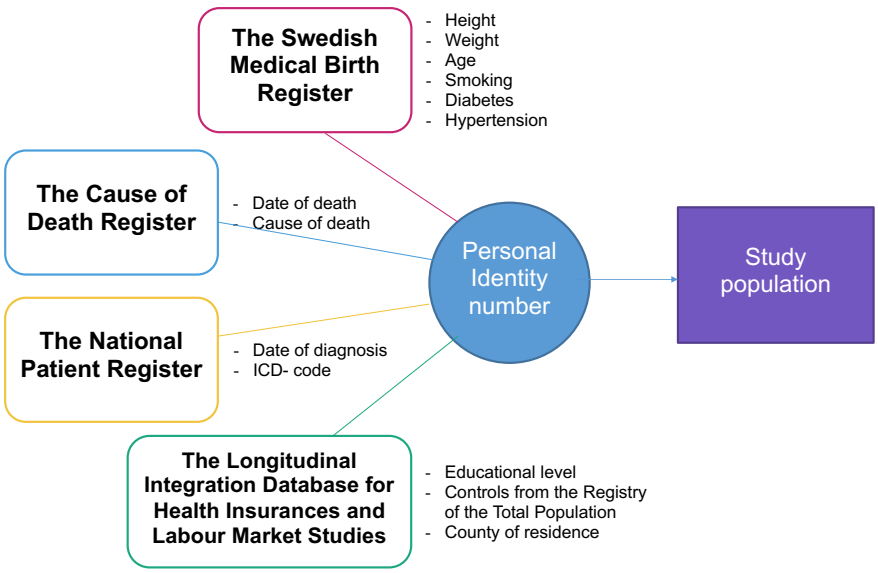


Figure 1. Overview of data sources and obtained variables.

THE MEDICAL BIRTH REGISTER (STUDY I–III)

The Swedish Medical Birth Register was established in 1973 and includes 99% of all births in Sweden since. It is compulsory for all healthcare providers to report information from medical records for prenatal, delivery and neonatal care to the registry.[89] During the first 10 years, the information sent to the register included national Medical Birth Reports, written by secretaries at obstetric clinics, with the purpose to communicate information between the delivery unit, antenatal centre, and paediatrics health care. From 1982 and onwards, the content and purpose of the register expanded, and came to include information on diseases prior to and during pregnancy, and from 1983 and onwards lifestyle factors, such as smoking, pre-pregnancy weight, and height. The register was used to collect information on weight, height, age, diabetes, hypertension and smoking status for Study I–III. Until 1990, pre-pregnancy weight was calculated by subtracting gestational weight gain from delivery weight. In addition, weight at delivery was reported using only two digits, hence, all weights above 99 kg were recorded as 99 kg. During 1990 and 1991 no data on pre-pregnancy BMI was collected. Finally, from 1993 and onwards weight was measured and height was self-reported during the first antenatal visit, which usually occurs between week 8 and week 12 of gestation (<12 weeks in 90% of women). Overall, from 1983 and onwards the register includes valid information on height and weight in approximately 80% and 70% of all women, respectively.

THE NATIONAL PATIENT REGISTER (STUDY II–V)

All main and contributory diagnoses from in- and outpatient care are registered according to the Swedish version of International Classification of Diseases (ICD) in the National Patient Register (Patient register).[90] A predecessor to the register was first founded in the 1960's when the National Board of Health and Welfare started to collect information on in-patients of public hospitals, at the time including only patients treated in psychiatric care and some patients in somatic care from 6 of 26 counties in Sweden. From 1987 and onwards, the register includes complete records on principal and contributory discharge diagnoses for all hospitalizations in Sweden, and on specialist's outpatient visits since 2001. The register has been validated overall and for specific diseases in several studies. The overall accuracy of patient records has been found to be between 85 and 95%, with the highest accuracy found among patients treated at internal medicine or cardiology departments, with 86% and 95% accuracy, respectively.[91] ICD version 8 was in use from 1968 to 1986, ICD-9 from 1987 to 1996, and ICD-10 from 1997 and onwards. All surgical procedures are coded according to the Swedish version of the Nordic Medico-Statistical Committees (NOMESCO)

Classification of Surgical Procedures Version 1.9. This version was in use from 1997 and onwards.

THE CAUSE OF DEATH REGISTER (STUDY II–V)

The Cause of Death Register contains data on causes of death from 1961 and onwards. There are also historic records from 1952 to 1960. The register contains the underlying cause of death coded according to current version of the international version of the ICD. The accuracy of the register is high. In general, 96% of all individuals in the register has a recorded specified underlying cause of death.[92] This register was used to collect information on dates and causes of deaths for Study II–V.

THE LONGITUDINAL INTEGRATION DATABASE FOR HEALTH INSURANCES AND LABOUR MARKET STUDIES (STUDY I–III, V)

The longitudinal integrated database for health insurance and labour market studies (LISA) is a database held by Statistics Sweden.[93] It incorporates data from several Swedish registers e.g., the register of the total population and the Swedish Social Insurance Agency. It contains individual information on demographics, education and training, employment/unemployment, and income and social insurance. It is also possible to link data for family members, and those who share households. Information is available from 1990 and onwards, and all Swedish citizens who are aged 16 years and older, with 80% national coverage. For the purpose of this thesis, we used LISA to obtain information on county of residence (Study I), and educational level (Study I–III, V). County of residence was collected from the date of the first antenatal visit. For Study II, the latest information of the participants' education was used. For Study I, III, and V, educational level was obtained at study baseline. Educational level was then categorized into three groups: low (≤9 years), intermediate (10–12 years), and high (>12 years) level of formal education. For Study V, LISA was also used to obtain matched population controls from Sweden's Registry of the Total Population.

STUDY POPULATIONS AND PROCEDURES

The cohorts included in the studies in this thesis were derived from The Swedish Medical Birth Register (Study I–III), and the NPR (Study IV–V). An overview of participants and study designs can be found in Table 2.

Table 2. *Overview of participants, data sources, study designs, cohorts in all studies.*

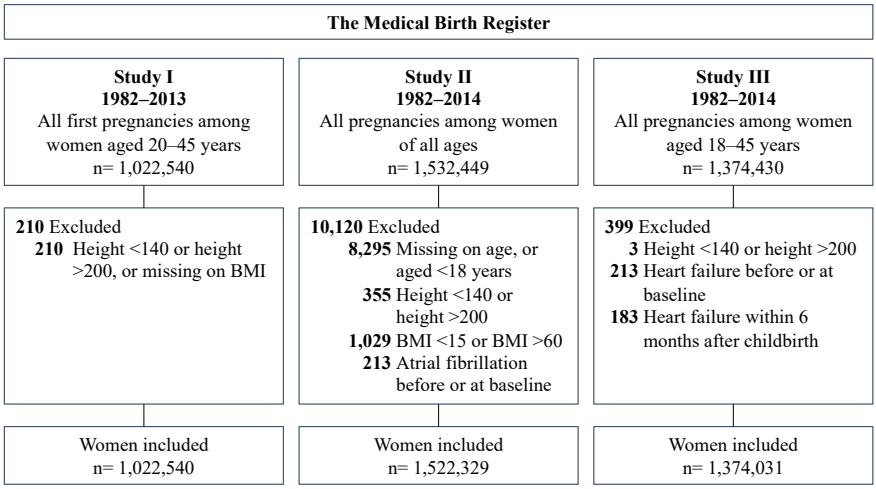
Study	*I*	*II*	*III*	*IV*	*V*
Data sources	Medical birth register, LISA	Medical birth register, LISA, Patient register, The Cause of Death Register	Medical birth register, LISA, Patient register, The Cause of Death Register	Patient register, The Cause of Death Register	Patient register, The Cause of Death Register, LISA
Study design	Cross-sectional/ Prevalence	Perspective cohort	Perspective cohort	Prospective cohort	Prospective cohort
Study period	1982–2013	1982–2014	1982–2014	2000–2012	2001–2016
Inclusion criteria	Women aged 20–45 years, at first pregnancy in the medical birth register	Women aged ≥18 years and registered in the medical birth register	Women aged 18–45 years registered in the medical birth register	Patients aged 18–74 years with a primary diagnosis of obesity in the patient register	Patients aged 20–65 years with a primary diagnosis of obesity in the patient registry between 2001–2013

Abbreviations: Patient register= National patient register, LISA= Longitudinal Integration Database for health insurances and Labour Market Studies

PROCEDURE STUDY I–III

In total, 1,532,449 pregnancies with information on weight and height were recorded from 1982 to 2014, of which 1,028,497 was first time pregnancies. Inclusion and exclusion criteria for Study I–III can be found in Figure 2. By this design, we included 99% of all births in Sweden during these years, and >85% of all Swedish women.[94]

Measured weight and self-reported height registered during the first antenatal visit in the Medical Birth Register was used as a proxy for pre-pregnancy weight to calculate BMI. This is generally before any significant pregnancy-related weight gain, and previous studies describe the weight gain associated to pregnancy during this time as negligible (0.5–2.0kg).[95, 96] As visual inspections of annual body weight deciles showed a larger than expected increase in body weight between 1989 and 1992, the weights for these years were adjusted by estimating the annual weight increase within deciles from 1992–2003, with a practically linear result. BMI was divided into eight clinically relevant groups: <18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30.0, 30.0 to <35.0 and 35.0 to <60 kg/m^2.



Abbreviations: BMI= body mass index

Figure 2. Inclusion and exclusion criteria for Study I–III

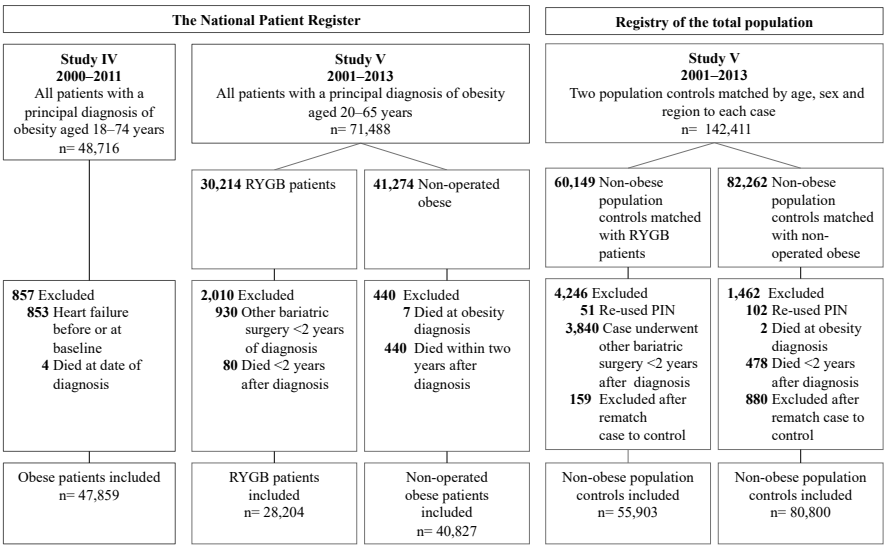
PROCEDURE STUDY IV–V

Study IV included all patients aged 18 to 74 years who had obtained a first recorded principal diagnosis of obesity in the Patient register between 1 January 2000 and 31 December 2011. Study V included all individuals 20 to 65 years of age who obtained a first recorded principal diagnosis of obesity in the Patient register between 1 January 2001 and 31 December 2013. For each patient with obesity, two population controls without any diagnostic code for obesity or surgical code for bariatric surgery matched by age, sex and county of residence were randomly selected from the Swedish Register of the Total Population. Inclusion and exclusion criteria can be found in Figure 3. Bariatric surgery codes used for assigning cohorts and censoring are presented in Table 3.

Table 3. *Codes from the Swedish version of the NOMESCO Classification of Surgical Procedures.*

Procedure	*NOMESCO code*[a]
Roux-en-Y gastric bypass	JDF10, JDF11
Vertical banded gastroplasty	JDF00, JDF01
Gastric banding	JDF20, JDF21
Gastric sleeve	JDF96, JDF97

Abbreviations: NOMESCO= Swedish Classification of Operations and Major Procedures



[a] Codes used for defining operation and for censoring bariatric surgery patients before and during study periods. Abbreviations: RYGB= Roux-en-Y gastric bypass

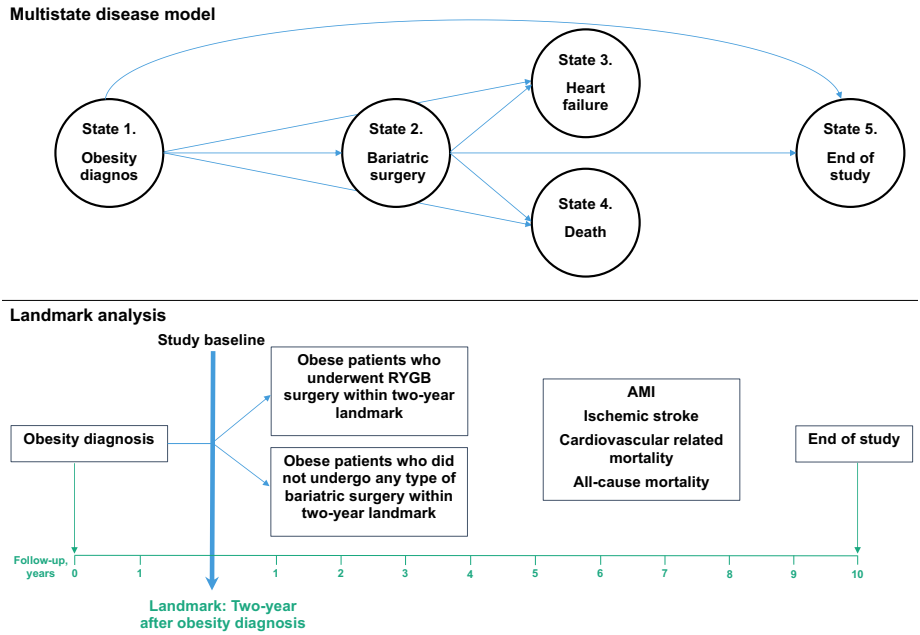
Figure 3. Inclusion and exclusion criteria for Study IV and V.

In Study IV and V there were two different start dates that had to be take into account when calculating person-time at risk. First, the date of obesity diagnosis and second the date of bariatric surgery, if they underwent such surgery, which potentially could cause an immortal time bias. Immortal time bias occurs in cohort studies when participants in the exposed group wrongfully is assigned follow-up time that should be accounted to the unexposed group.[97] There are different approaches to resolve the problem of immortal time bias. In this thesis, two approaches were used to investigate differences in risk of CVD between bariatric surgery patients and non-operated obese: multistate disease model (Study IV) and landmark analysis (Study V) (see Figure 4).

MULTISTATE DISEASE MODEL

In Study IV, we fitted a multistate disease model in order to assess the relative risk of heart failure and mortality comparing patients with an obesity diagnosis, with and without bariatric surgery. All patients started at the date of an obesity diagnosis being recorded (State 1) and transitioned trough the model throughout the study period; State 2) bariatric surgery, State 3) Heart failure, State 4) Death, State 5) End of study. The relative risks between bariatric surgery and non-operated obese patients were then assessed by comparing transition probabilities between the states. Hence, person-time in

the non-operated group was calculated from obesity diagnosis until first event of either bariatric surgery, heart failure, death, or end of study. Person-time among the operated group was calculated from date of bariatric surgery until a first event of heart failure, death, or end of study.



Abbreviations: RYGB= Roux-en-Y gastric bypass, AMI= acute myocardial infarction

Figure 4. Schematic figure over the multistate disease model and the landmark analysis.

LANDMARK ANALYSIS

In Study V, we used landmark analysis, and assigned a time-point (landmark), representing study baseline, two-years after the obesity diagnosis. All morbidity and mortality occurring before this landmark were considered as comorbidity, and all morbidity and mortality after the two-year landmark were considered as events. All participants with an obesity diagnosis were then divided into two groups: one group including all patients with obesity who underwent RYGB surgery within the two-year landmark, and one non-operated obese group, where patients did not undergo any type of bariatric surgery within these two years from obesity diagnosis. Through this procedure, we included 81% of all individuals who underwent RYGB surgery during the study period.

OUTCOMES, EXPOSURES AND COMORBIDITY

All outcomes and comorbidities were defined by ICD codes in the National Patient Register (Study II–V) and the Cause of Death Register (Study IV–V). ICD version 8 was in use from 1968 to 1986, ICD version 9 from 1987 to 1996, and ICD-10 from 1997 and onwards (see Table 4 for diagnostic codes). An overview of outcomes and exposures can be found in Table 5.

Table 4. *Codes from the Swedish version of the International Classification of Diseases 8th, 9th, and 10th revision.*

Diagnosis	*ICD-8*	*ICD-9*	*ICD-10*
Atrial fibrillation	427.92	427D	I48
Cardiomyopathy	425	425	I42, I43
Congenital heart disease	746, 747	745–747	Q20–Q28, Q87, Q89, Q90, Q96
CHD	410–414	410–414	I20–I25
Diabete[a]	250	250	E10–E14
Heart failure	427.00, 427.10	428	I50
Hypertension[a]	401–405	401–405	I10–I15
Ischemic stroke	433, 434, 436	434, 436	I63, I64
Malignancy	140–208	140–208	C00–C97
AMI	410	410	I21
Obesity	277	278A, 278B	E65, E66
Sleep apnoea	-	327.2, 780.5	G47.3
Stroke (ischemic and haemorrhagic)	431, 433, 434, 436	431, 433, 434, 436	I61–I64
Valvular disease	394–396, 398, 424	394–398, 424	I05–I09, I33–I39

Abbreviations: ICD= international classification of diseases, CHD= coronary heart disease, AMI= acute myocardial infarction. The codes were used to define exposure, outcomes and comorbidity. Comorbidity was defined as having one of the above stated ICD codes registered in the Nationeal Patient Register prior to or at study baseline. [a] In Study II and III, hypertension and diabetes were defined as diagnosed and/ or self-reported

Table 5. *Overview of outcomes, exposures, follow-up and statistical methods in the separate studies.*

Study	*I*	*II*	*III*	*IV*	*V*
Study baseline	First antenatal visit	First antenatal visit	First antenatal visit	Obesity diagnosis	Two-year landmark after obesity diagnosis
Assessed exposure	Social inequalities	BSA, BMI, Height	BMI	Bariatric surgery	Obesity diagnosis, RYGB
Outcome	BMI Overweight Moderate and severe obesity	First diagnosis of atrial fibrillation	First diagnosis of heart failure in first or any position	First diagnosis of heart failure in first or any position All-cause mortality	AMI Ischemic stroke Cardiovascular-related mortality All-cause mortality
Statistical methods	Logistic regression	t-test/chi-square test Incidence rates Cox proportional hazard regression models	Incidence rates (Poisson regression) Cox proportional hazard regression models	chi-square test Kaplan-Meier Incidence rates Cox proportional hazard regression models	Age- and sex-adjusted incidence rates Cox proportional hazard regression models
Covariates	-	Model 1: Age Model 2: Model 1 + year of pregnancy, parity, baseline disorders: diabetes, hypertension, heart failure, smoking, educational level, heart failure during follow-up (time-dependent)	Model 1: Age, year of pregnancy parity Model 2: Model 1 + baseline disorders: diabetes, stroke, hypertension, congenital heart disease, cardiomyopathy, atrial fibrillation, cancer, valvular disease, and CHD Model 3: Model 2 + smoking, education	Model 1: Age, sex Model 2: Model 1 + baseline disorders: CHD, hypertension, and diabetes	Model 1: Age, sex, educational level

Abbreviations: BSA= body surface area, BMI= body mass index, RYGB= Roux-en-Y gastric bypass , AMI= acute myocardial infarction, CHD= coronary heart disease

STUDY I–III

In Study I, the exposures were education and county of residence, which were used as markers for social inequalities. The outcome studied was trends in mean BMI and in the prevalence of BMI categories. In order to make the data from 1982 to 2013 comparable, the data was standardised. Because the mean age and educational level among first time mothers gradually increased over time, age was standardised to the age distribution in 2013 using 5-year age groups, and standardised within each educational level. Finally, maternal age also differed across counties, hence, all county data were standardised within each county, to the age distribution in 2013. For Study II, three different anthropometrical measures were assessed as exposure for the risk of atrial fibrillation. In addition to the eight BMI categories, we also used BSA in the quartiles: 1.12–1.62, 1.63–1.71, 1.72–1.82, and 1.83–3.02, height in cm in the quartiles: 150–162, 162–166, 167–170 and >170. For Study III, BMI was assessed as exposure for the risk of heart failure. As a large proportion of patients diagnosed with heart failure have other primary discharge diagnoses e.g., cardiomyopathy or congenital heart disease, a recorded heart failure diagnosis in any position was assessed. In addition, a hierarchical classification was used to distinguish between mutually exclusive causes of heart failure: i) congenital heart disease and valvulopathies, ii) CHD, and/or diabetes, and/or hypertension, iii) cardiomyopathy, and (iv) other causes.[42]

STUDY IV–V

In Study IV, any type of bariatric surgery was assessed as exposure for the risk of heart failure and mortality among patients with an obesity diagnosis from the National Patient Register. In Study V, both diagnosis of obesity and RYGB surgery was assessed as exposure for the risk of AMI, ischemic stroke, cardiovascular-related and all-cause mortality compared with matched population controls without a diagnosis of obesity.

STATISTICAL ANALYSES

Descriptive statistics were presented with means and standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and frequencies with percentages for categorical variables. Differences in baseline characteristics (Study II, IV) were determined by two-tailed t-test for continuous variables and chi-square tests for dichotomous variables.

Follow-up started at date of antenatal visit (Study II–III), obesity diagnosis (Study IV), or at two-year landmark after obesity diagnosis (Study V). In Study II–V, all individuals were followed until i) study outcome, ii) death, iii) reaching a maximum follow-up of 10 years, or iv) end of follow-up, 31 December 2014 (Study II–II), 31 December 2012 (Study IV), or 31 December 2016 (Study V). Incidence rates was calculated as the ratio of events and person-years of follow-up time (Study II, IV). In Study III, incidence rates with 95% CI were calculated using Poison regression. In Study V, age- and sex- adjusted incidence- and mortality rates were calculated with approximated 95% CIs. Univariate- and multivariate Cox proportional hazard regression models was used to calculate hazard ratios (HR) with confidence intervals (CI) in order to calculate relative risk of outcomes by exposures in Study II–V. Model adjustments can be found in Table 5. Methods based on weighted residuals were used to measure proportionality assumptions for the regression models.[98] Variables that did not fulfil the proportionality assumptions were stratified. All final models across studies fulfilled the assumptions of proportional hazard. All statistical data management and statistical analyses were performed using SAS version 9.4[99] (Study I–V), and R[100] versions 4.0.2 (Study I), 3.3.2 (Study II), 3.2.2 (Study III), and 3.6.2 (Study V).

STUDY SPECIFIC ANALYSES

Logistic regression was used to calculate prevalence risk ratios (PRR) with 95% CI,[101] in order to assess differences in proportions of overweight, moderate- and severe obesity. PRR was calculated by educational level within each period, and stratified by educational level across the six periods (Study I).

Cox regression models was also used to generate spline plots, with BSA, BMI and height as restricted cubic splines[102] in Study II and BMI in Study III, in order to illustrate continuous risk of atrial fibrillation and heart failure. The categories BSA: <1.63, and height: <162 was used as references in Study I, and BMI 20.0–<22.5 as a reference in Study I–II. In order to assess risk of atrial fibrillation by BSA independently from BMI in Study II, the multivariable model was stratified by low-normal (18.5–<20.0), normal (20.0–<22.5 and 22.5–<25.0), and high BMI (≥25.0). In Study III, cox regression models was also used to calculated the population-attributable risk,[103] hence, the excess risk of heart failure associated with BMI ≥22.5 vs. <22.5 kg/m^2.

In Study V, contrast matrices were used to compare HRs between all four groups for all outcomes. As the hazard was not proportional during the ten-year follow-up, the follow-up time was split in two time periods, and both short- (≤3years) and long-term (>3–10) risk was assessed. In this study, we refrained from including pre-existing comorbidities as covariates, because they should not be considered as confounders, as they have a mediating effect on the casual pathway between obesity and the outcomes studied.

ETHICAL CONSIDERATIONS

All data used in the studies were anonymized by the register holders before being handled by any researcher. The investigations are in accordance with the principles outlined in the Declaration of Helsinki. The studies were approved by the Regional Ethical Review Board in Gothenburg or Stockholm, Sweden. The record numbers can be found in Table 6.

Table 6. *Ethical approvals*

Study	*Ethical Review Board*	*Diary number*
Study I–III	Gothenburg	103–15
Study IV	Stockholm	2012/210–31/2
Study V	Gothenburg	579–15

RESULTS

An overview of number of participants, age, sex and follow-up time in all studies can be found in Table 7. As Study I and V are not yet published, the results are presented in condensed form.

Table 7. *Overview of cohorts in all studies.*

Study	*I*	*II*	*III*	*IV*	*V*
Participants, n	1,022,330	1,522,329	1,374,031	47,859	211,017
Mean age, years	28.8	28.3	27.9	42.5	42.0
Sex, % female	100	100	100	71.0	73.1
Follow-up time, years	-	Mean: 16.6	Mean: 15.3	Heart failure median: 3.7 Mortality median: 3.8	RYGB median: 4.1 Non-operated: median 4:8

Abbreviations: n= number, RYGB= Roux-en-Y gastric bypass

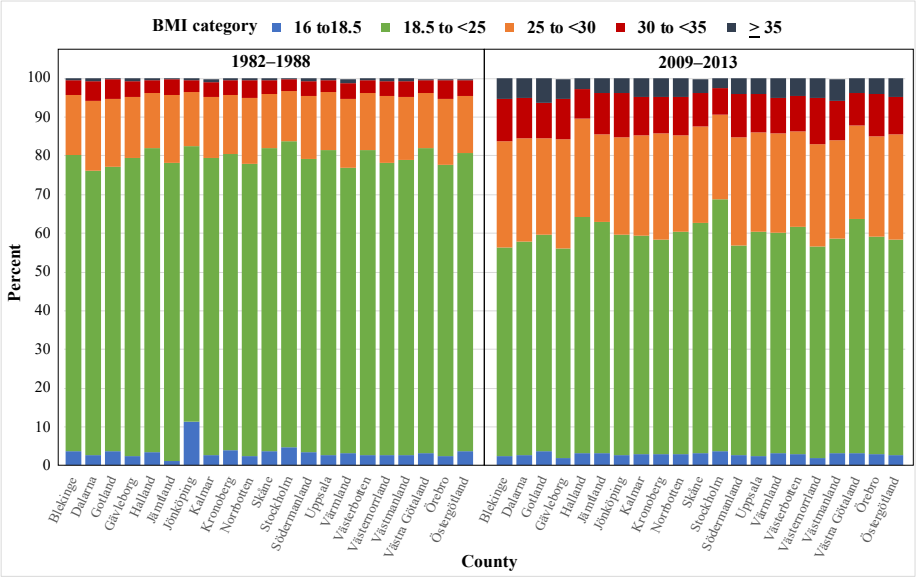
PREVALENCE OF OVERWEIGHT AND OBESITY

In Study I, the aim was to investigate trends in social inequalities in mean BMI and in the prevalence of BMI categories among Swedish women.

The study period ranged from 1982 to 2013 and incorporated a total of 1,022,330 women with a mean age of 28.8 years (range 20 to 45 years). During the study period, mean BMI increased gradually across all educational levels and all Swedish counties, with an overall mean BMI of 22.7 (SD 3.2) kg/m^2 in 1982, to a mean BMI of 24.3 (SD 4.6) kg/m^2 in 2013.

The age-standardised proportions of women with normal BMI (BMI 18.5–<25 kg/m^2) decreased by approximately 15% from the first period to the last. Instead, a higher proportion of women were overweight (BMI 25–<30 kg/m^2) or obese (BMI $\geq$30kg/m^2), with a prevalence of 22.9% and 10.5%, respectively. The proportion of women with moderate and severe obesity increased to fairly high levels during the last period. The prevalence of overweight and obesity increased substantially across the three educational levels over the study period. The age- and education standardised proportions of BMI categories by county of residence during the first period 1982–1988 and the last 2009–2013 can be found in Figure 5. The proportion of women

across counties with a normal BMI decreased by approximately 20%, in favour of increasing prevalence of overweight, moderate and severe obesity. Throughout the study period, the counties with the three largest Swedish cities had the lowest prevalence of overweight and obesity.



Abbreviations: BMI= body mass index

Figure 5. Trends in age-standardised prevalence of BMI categories

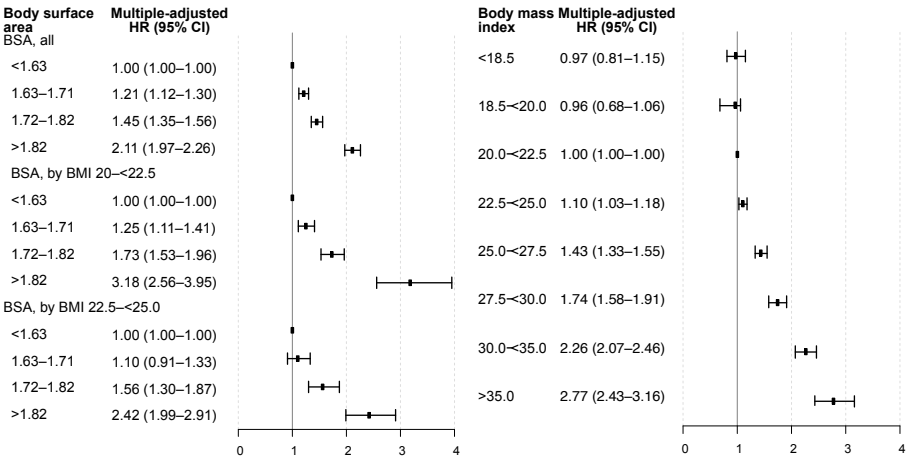
RISK OF ATRIAL FIBRILLATION BY BODY SIZE AND WEIGHT

In Study II, we investigated the relationship between body size and weight measured early in life, and the risk of atrial fibrillation later in life, among Swedish women.

The study cohort included 1,522,329 women with a mean age of 28.3 years. Characteristics at baseline showed that mean BMI increased by increasing BSA, and that 68.4% of the women in the highest BSA quartile were overweight or obese. Comorbidity was fairly rare regardless of baseline BSA and BMI. Over a period of slightly more than 33 years (mean 16.6 years), 6,993 women (0.5%) were diagnosed with atrial fibrillation. The risk of atrial fibrillation increased by all anthropometric measures. The incidence rate ranged from 0.18 and 0.19/ 1,000 person-years in the lowest BSA and BMI

groups, to 0.45 and 0.63/ 1,000 person-years in the highest (BSA >1.82 and BMI ≥35).

With the lowest BSA quartiles as a reference, there was a stepwise increase in relative risk of atrial fibrillation, with an up to two-fold risk in the highest BSA quartile (HR=2.11, CI=1.97–2.26) (see Figure 6). Similar relative risks were found for BMI categories, where the risk started to increase at BMI 22.5–25.0 with a HR of 1.10 (CI=1.03–1.18) up to a HR of 2.77 (CI=2.43–3.16) for women with BMI ≥35. The stepwise increased relative risk by BSA quartiles persisted after stratifying by BMI categories.



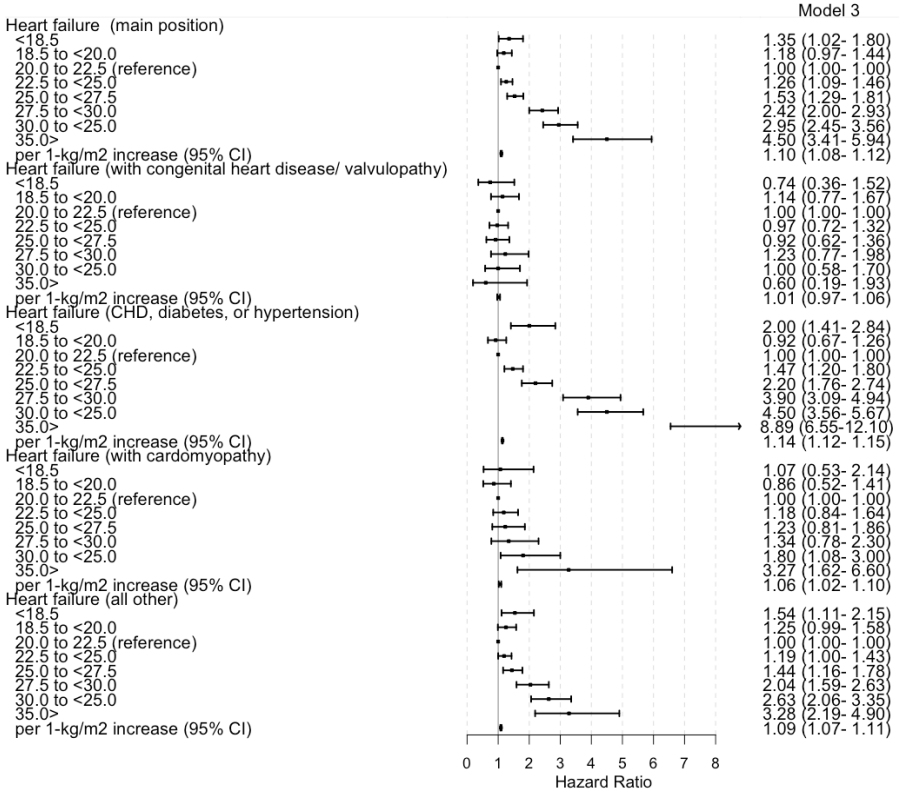
Abbreviations: HR= hazard ratio, CI= confidence intervals, BSA= body surface area, BMI=body mass index. The models were adjusted for age, baseline disorders, smoking, pregnancy year, parity, educational level, and heart failure during follow-up.

Figure 6. Risk of atrial fibrillation by BSA quartiles (overall, and in women with low normal and high normal weight) and by BMI categories.

RISK OF HEART FAILURE IN YOUNG WOMEN

In Study III, we investigated the relationship between early life BMI and the long-term risk of heart failure among Swedish women. The study population comprised 1,374,031 women with a mean age of 27.9 years. During the 33 years of follow-up (median 15.3), 2,513 women (0.2%) were hospitalized with heart failure recorded as a main or contributory diagnosis. The most common comorbidities associated with the heart failure were CHD, diabetes or hypertension (957 cases), followed by valvular disease (congenital or acquired) (311 cases), and cardiomyopathy (257 cases).

The incidence of heart failure in any diagnostic position was lowest for women with BMI 20.0–<22.5 with an incidence rate of 8.69 per 100,000 person-years, and increasing to 34.2/ 100,000 person-years in women with BMI ≥35. The relative risk of heart failure was elevated already at a high-normal BMI, and increased by each BMI category (see Figure 7). With BMI category 20.0–<22.5 as reference, the risk increased stepwise up to almost a five times increased risk for women with BMI ≥35 (HR=4.50, CI=3.41–5.94). This pattern was similar when assessing the relative risk for mutually exclusive related conditions, with the exception of heart failure with valvular disease, where no such relation was found.



Abbreviations: CI= confidence intervals, CHD= coronary heart disease. The model was adjusted for age, baseline disorders, smoking, pregnancy year, parity, and educational level.

Figure 7. Risk of heart failure and mutually exclusive related conditions

RISK OF HEART FAILURE IN PATIENTS WITH OBESITY

In Study IV, we assessed the risk of heart failure and overall mortality among patients with obesity who had undergone bariatric surgery compared with that of patients with obesity who did not undergo such surgery.

During the study period between 1 January 2000 and 31 December 2011, 47,859 individuals (mean age 42.6 years, 66.8% women) who were diagnosed with a principal diagnosis of obesity in the Patient Register were eligible for this study. Of those, 22,295 patients (mean age 40.7 years, 75.9% women) underwent bariatric surgery. There were 944 (3.7%) cases of heart failure among the non-operated obese and 89 (0.4%) cases among the operated obese during a mean follow-up time of 3.7 years. In addition, there were 938 (3.7%) deaths among the non-operated patients and 251 (1.1%) among the operated obese, during a median follow-up time of 3.8 years.

Incidence of heart failure was substantially higher among the non-operated obese compared to the operated obese, with incidence rates of 6.9 and 1.0/ 1,000 person-years respectively (see Table 8). The relative risk of heart failure was substantially lower among the operated obese compared to the non-operated obese, with a HR of 0.37 (CI=0.30–0.46). In addition, the relative risk of mortality was also lower among the operated obese, but not to the same extent as to that of heart failure (HR=0.78, CI=0.68–0.90).

Table 8. *Incidence rates and relative risks of heart failure and mortality.*

Outcome	*Event/ Population*	*Incidence/ mortality rates[a] (95% CI)*	*Multiple-adjusted HR (95% CI)*
Heart failure			
Operated obese	89/22,295	1.0 (0.8–1.3)	0.37 (0.30–0.46)
Non-operated obese	944/25,564	6.9 (6.4–7.3)	1 (reference)
Mortality			
Operated obese	258/22,295	2.9 (2.6–3.3)	0.78 (0.68–0.90)
Non-operated obese	931/25,564	6.7 (6.3–7.1)	1 (reference)

Abbreviations: CI= confidence intervals, HR= hazard ratio. The model was adjusted for sex, age, and baseline disorders. [a] per 1,000 person-years

RISK OF AMI, ISCHEMIC STROKE, CARDIOVASCULAR-RELATED AND ALL-CAUSE MORTALITY

In Study V, we estimated the risk of AMI, ischemic stroke, and cardiovascular-related and all-cause mortality in obese patients with obesity who had undergone RYGB surgery compared with non-operated obese, and matched population controls.

During the study inclusion period, between 1 January 2001 and 31 December 2013, there were 28,204 patients with obesity who underwent RYGB surgery within two years of obesity diagnosis (mean age 40.8 years, 75.5% women). In addition, there were 40,827 patients with obesity who did not undergo any type of bariatric surgery within two years of obesity diagnosis (mean age 43.1 years, 68.5% women). In addition, the study population comprised 55,903 non-obese population controls matched with the RYGB patients and 80,800 non-obese population controls matched with the non-operated obese.

The median follow-up times for all outcomes across groups ranged from 4.0–4.9, where non-operated obese and their population controls had just over 0.5 years longer follow-up time for most outcomes. RYGB patients had a markedly reduced risk of AMI compared with non-operated obese throughout the study period. There was no clear difference in relative risk of ischemic stroke between the RYGB patients and non-operated obese. However, the RYGB patients had a markedly decreased short-term risk of cardiovascular-related and all-cause mortality compared with non-operated obese, but not thereafter. The RYGB patients had similar risk of AMI, but a persistent excess risk of ischemic stroke, cardiovascular-related and all-cause mortality, compared with population controls. Non-operated obese had a marked excess risk of all outcomes compared with population controls.

DISCUSSION

FINDINGS AND IMPLICATIONS

PREVALENCE OF AND SOCIAL INEQUALITIES IN OVERWEIGHT AND OBESITY

In Study I, we found that mean BMI has increased markedly among young first-time mothers during the past decades. This is in line with previous studies that also indicates that mean BMI is increasing among young individuals in Sweden and worldwide.[1, 4, 5] Alongside this marked increase in mean BMI, we also found an alarmingly high prevalence rates of moderate and severe obesity in 2009–2013, that were more than twice that of the prevalence in 1982. In addition, we identified growing social inequalities in pre-pregnancy BMI, with a gradient in educational level favouring women with higher level of education and living in counties with major cities. These results are similar to those found in previous studies linking educational level to increased likelihood of overweight and obesity among both younger adults,[21, 104, 105] and middle-aged populations.[106, 107] A recent Swedish nationwide study illuminated a similar social gradient in BMI in young men, where the differences in prevalence of obesity increased continually from 1968 to 2005.[4] Hence, worryingly, the social inequalities among young Swedish men and women are growing and will, if these trends continue, cause an increasing divide in serious health problems later in life when CVD are more common, where those with lower socioeconomic status will be most affected.

BODY SIZE, OBESITY AND EARLY CARDIO-VASCULAR DISEASE

BODY SIZE AND EARLY ATRIAL FIBRILLATION

In Study II, we identified body size measured early in life as an independent risk factor for early onset of atrial fibrillation in young adult women, with a stepwise gradient with increasing risk for atrial fibrillation by increasing BMI, height, and BSA. This is in line with a previous study where self-reported body surface in adolescence has been shown to predict risk of atrial fibrillation among middle-aged men.[67] In addition, previous studies have also found a linear association, but between BMI measured later in life, and the risk of atrial fibrillation.[63, 65, 108] This association was independent of other metabolic risk factors.[63] Instead, a partial explanatory factor for this

relationship could be an enlarged left atrium, which has been associated with an increased risk of atrial fibrillation in women with obesity aged 60 years and older.[109, 110] As the increased risk, observed in our study persisted also in women with a larger body size, regardless of BMI, other aspects than obesity must also be considered. A hypothesis is that with a larger body size comes altered dimensions of the heart, which could play a role in the onset of atrial fibrillation. Even though the relationship between body size and atrial fibrillation have been well described, more precise investigations considering various components of body size with respect to the size of the left atrium, should perhaps be investigated further. Both body size and BMI should be considered when evaluation patients' risk of attaining atrial fibrillation. Considering the increase in height and weight in most populations world-wide during recent decades,[54, 71] along with the increase in overweight, obesity and its sequelae, the prevalence of atrial fibrillation is expected to increase, which will have major public health implications. A different pathology of future patients with atrial fibrillation might be expected.

BMI, OBESITY AND EARLY HEART FAILURE

In Study III, we found a J-shaped relation between BMI in young adulthood and risk of heart failure later in life where the lowest risk was found among women with BMI 21 kg/m^2. The risk started to increase already at high-normal weight BMI, and women with BMI 35 kg/m^2 and over had a fivefold increased risk of heart failure. This pattern was evident for mutually exclusive related conditions, with the exception of heart failure with valvular disease, but particularly for cases of heart failure with CHD, diabetes, or hypertension. Similar results have been found in a Swedish population-based study of young men (mean age 18 years), where men with BMI 35 kg/m^2 and over had a tenfold risk of heart failure compared to those with BMI 18–20 kg/m^2, who had the lowest risk.[7] The potential mechanisms for the relationship between an elevated BMI and the risk of heart failure are multiple but not yet entirely clarified. Some potential explanatory mechanisms are the impact of obesity on hemodynamic changes, neurohormonal activation, and increased oxidative stress.[111, 112] These factors are in turn associated with cardiac remodelling, left ventricular hypertrophy, left atrial enlargement, and ventricular hypertrophy,[113, 114] especially in individuals with long lasting obesity.[115]

In Study IV, we showed that patients with an obesity diagnosis who had undergone any type of bariatric surgery had up to a 63% reduced risk of heart failure and a slightly reduced risk of mortality, compared with non-operated patients with obesity. These results are in line with another study that found a 54% reduced risk of heart failure after RYGB compared with non-operated

obese patients who engaged in a behavioural targeted weight loss intervention.[116] The differences in risk between these studies were most likely due to the differences in achieved weight loss in the control groups during follow-up. In our study, we compared bariatric surgery with all patients with an obesity diagnosis in the Patient register, regardless of whether they underwent any type of treatment for their obesity, with a likely minimal weight loss, on average. In the other study,[116] the risk of the RYGB patients was compared with that of individuals who engaged in a lifestyle intervention, after which they obtained a moderate weight loss, while the RYGB patients had a marked weight loss post-surgery.[116] Thus, these results together represent a continuum of risks among patients with obesity, and strengthens the causal role between obesity in the development of heart failure. This was also confirmed by the stepwise increase in risk of heart failure by BMI identified in our study of young women (Study III), and previously in young men,[7] as well as by previous studies showing that an elevated BMI is associated with an increased risk of developing heart failure.[51, 52] In addition, a recent study found that individuals with the most significant weigh loss within one year of the bariatric surgery were also those found to have lowest risk of heart failure up to 20 years after baseline.[117] Simultaneously, weight loss after bariatric surgery has been shown to reverse the disturbances in the left ventricular function that were caused by obesity.[118] Hence, the weight loss induced by bariatric surgery is most likely the major factor influencing the risk of heart failure among patient who undergo bariatric surgery. Furthermore, surgical treatment for obesity is associated with lower incidence of known risk factors for heart failure,[51] such as diabetes, hypertension, and CHD,[40] which could be another plausible explanation for the lower risk of heart failure post-surgery, as observed in our study.

When assessing the incidence of heart failure, the criteria used to define heart failure will have a major impact on the rates. Heart failure is commonly diagnosed in primary care, hence, including cases diagnosed in primary care will mean a higher incidence of heart failure,[119] compared with studies which include hospitalizations only.[42] In a study including hospitalizations of heart failure among Swedish population aged 45–54 years, an incidence of heart of about 0.5/ 1,000 person-years was found. In our study of young women, the incidence was substantially lower for the women with BMI 20–22.5 with rates of 0.09/ 1,000 person-years, but more similar for those with BMI$\geq$35 0.3/ 1,000 person-years. Given that the mean age among these women was 28 years, and that the risk of heart failure increases substantially with age, lower rates were expected among these young women. However, the rates for both the operated and non-operated obese patients in those ages in Study IV were

2–3 times higher than that of the general population. Hence, even after bariatric surgery, there seems to be an excess risk of heart failure compared with the general population.

OBESITY AND EARLY AMI AND ISCHEMIC STROKE

In Study V, we found that patients with obesity who had undergone RYGB surgery had lower 10-year risk of AMI compared with non-operated obese patients, and a similar risk to that of controls from the general population. Some previous studies of risk of AMI after RYGB surgery shows similar results,[40, 120, 121] while another did not find any difference between groups up to eight years post-surgery.[122]

There was no clear association between the RYGB surgery and the risk of ischemic stroke. The results showed that RYGB patients and non-operated obese patients had similar risks of ischemic stroke during the initial part of the follow-up, and a borderline significant reduced risk up to 10 years of follow-up. This indicates that the surgery might not be as effective for prevention of ischemic stroke, as it seems to be for AMI and heart failure. Previous studies have shown somewhat conflicting results. Some studies found, in agreement with our study, that RYGB patients maintained an excess risk compared with population controls,[120] while there was no difference compared with non-operated obese patients.[121] In contrast, compared with non-operated obese patients, previous studies have found a 34% reduction in fatal and non-fatal ischemic stroke,[40] and a marginally significant 49% reduction of incidence of ischemic stroke.[121] The differences in outcome between studies could be due to differences in definition of stroke and follow-up times. It is also likely that RYGB has a varying effect on the risk of ischemic stroke. A reduced BMI has been demonstrated to improve risk factors for AMI and ischemic stroke, such as serum cholesterol, plasma glucose, and blood pressure.[38] RYGB surgery has also been associated with the improvement of these risk factors,[85, 122, 123] and should theoretically reduce the risk of AMI and ischemic stroke to the same extent. Unfortunately, we lack information on weight status and lifestyle factors that is associated with increased risk of AMI and ischemic stroke. RYGB patients who engage in healthier behaviours post-surgery have had a more significant and maintained weigh loss.[124, 125] Speculatively, because the RYGB patients in this study represents patients with widely heterogeneous adherence to health-related behaviours post-surgery, with widely varying differences in weight loss, associations may have been obscured. Furthermore, the RYGB patients in the present study were relatively young. As the risk of ischemic stroke increases with age, future studies on older populations with longer follow-up might find more clear associations.

OBESITY AND EXCESS RISK OF MORTALITY

In Study V, we also found that RYGB surgery seems to delay cardiovascular-related mortality a few years, with a marked risk reduction during the first year's post-surgery, and a risk that became more parallel to that of non-operated obese during the latter part of the study. The same magnitude of risk reduction was not fond for all-cause mortality, and there was no difference in risk between RYGB patients and non-operated obese patients during the latter part of the follow-up. An explanation could be that RYGB patients have an increased risk of deaths from other causes. Some studies have identified an increase in deaths from external causes, such as suicide, accidents, and alcoholism among RYGB patients.[126, 127] Furthermore, the RYGB patients had an excess risk of both cardiovascular-related, and all-cause mortality compared with population controls throughout the study period. Larger risk reductions were expected, given the negative impact of BMI on cardiovascular-related morbidity,[38] as well as the associations of RYGB surgery with reduction in risk factors and overall risk of CVD and heart failure.[85, 122, 123] However, some studies have indicated that certain subgroups of patients with obesity may benefit more from the surgery than others. Factors that have been associated with a large reduction in mortality post-surgery is male sex[128] and higher age.[127, 129] Therefore, the heterogeneity of the group studied might have attenuated the results. An explanation could also be that longer follow-up is needed in order to see greater differences in mortality between RYGB patients, non-operated obese and non-obese population controls.

IMPLICATIONS AND LIFETIME PERSPECTIVE

The alarming increase in mean BMI and in overweight and obesity worldwide, particularly in adolescents and young adults, can be described as a global obesity epidemic and is a major public and global health concern. As described in Study I, the mean BMI in first time mothers has increased by 1.6 BMI units between 1982 and 2013, with the highest relative increase in the prevalence of obesity and severe obesity, along with growing social inequalities. Overweight and obesity in youth have continuously been associated with an increased risk of being overweight and obesity also in adulthood.[29] Additionally, the odds of childhood overweight and obesity are substantially increased among children whose mothers had pre-pregnancy obesity.[130] Because long lasting significant weight loss is hard to achieve,[131] early onset of overweight and obesity are likely to lead to lifelong weight-management struggles and prevalent overweight and obesity. This tracking of obesity throughout the life course has been associated with atherosclerosis,[132] and detrimental to the heart structure where, in particular, long-lasting

obesity has been associated with left ventricular systolic and diastolic dysfunction, and cardiac remodeling.[115] Furthermore, several studies from our and other groups have documented an unexpected increase, in an otherwise overall downward trend, in onset of early heart failure,[42, 133] CHD,[43] and ischemic stroke[44, 45] among younger men and women (aged ≤45). In this thesis and in previous studies, we have been able to show that an elevated BMI measured early in life is associated with an increased risk of early onset of atrial fibrillation (Study II), heart failure,[7] (Study III), cardiomyopathy,[134,135] AMI, ischemic stroke, and cardiovascular-related mortality.[7,8] Also, alarmingly, this increased risk starts already at a low-normal of BMI of 20.0–22.5 for men and 22.5–25.0 for women. We have therefore strong reasons to believe that the increase in BMI, overweight and obesity identified among young Swedish men[4] and first-time mothers (Study I) during the past decades is associated with the contemporary increase in early CVD that we now see among young adults aged 55–70 years. Of particular concern is that the social inequalities among young Swedish men and women are growing and will, if these trends continue, contribute to a social divide in serious health problems later in life when CVD are more common, where those with lower socioeconomic status will be most affected.

STRENGTHS AND LIMITATIONS

A major strength of all studies was the nation-wide coverage, and the ability to include all women aged 18–45 years who gave birth in Sweden during the study periods (estimated coverage 99%) (Study I–III), and almost all patients in Sweden who underwent bariatric surgery during the study time periods (Study IV–V). Swedish registry data offers nationwide coverage, high accuracy and completeness of data. This, together with the affordable access to relatively homogenous health care nationwide, results in high quality research data with long-term follow-up, large number of cases, and almost complete follow-up of outcomes through the Patient Register and the Cause of Death Register.[91, 136, 137]

The greatest strengths of these studies are also the source of the greatest limitations. Because the population-registers utilized in the studies in this thesis were not originally created for research purposes, some of the obtained data are limited, and we lack detailed information on many variables of interest. The estimation of weight for the study period 1982–1989 in Study I–III and the self-reported height is a limitation. Although it is unlikely that this would have a major impact on the overall pattern described in these large-scale studies, it should be taken into account when interpreting the results. In

addition, we lack information on other anthropometry such as abdominal obesity. However, BMI is considered a good measure for investigating trends and prevalence in large populations.[2]

We unfortunately lack information on anthropometrical data in Study IV and V. However, reports from a Scandinavian obesity surgery registry show that that Swedish patients with obesity who underwent bariatric surgery during the same time period as that of our studies lost a substantial amount of excess weight post-surgery,[81] while limited weight reduction was found among non-operated obese persons.[82, 138] Likewise, there was no information on weight for the controls from the general population. However, the average BMI among Swedish adults is estimated at around BMI 26 kg/m^2.[1] Far from all individuals with obesity have an obesity diagnosis in the Patient register, hence, if we would compare the non-operated obese group with population controls that had a normal BMI, we might would have found greater risk differences between groups. Also, because the diagnosed patients with obesity have sought health care for their obesity, they might have worse health than those undiagnosed in the general population.

We lack information on echocardiographic data and severeness of the heart failure diagnoses which could be of interest for clinical implications. There could be a difference between operated and non-operated obese patients, where obese patients undergoing bariatric surgery might suffer from less severe heart failure not resulting in hospitalization during the study period. If so, we would have overestimated the relative risks between the groups. Furthermore, we only had access to data on hospital care. Including data also from primary care, especially when assessing morbidity related to overweight and obesity, would generate richer information on participants. Even so, given that heart failure is a serious condition, it is unlikely that persons within this comparably low age span should not have been managed in a hospital specialist setting at some point. We only included patients with a principal diagnosis of obesity, because those patients are more likely to be those actively seeking treatment for their obesity or obesity-related morbidity, in contrast to those who receive their obesity diagnosis in conjunction with hospitalization for other conditions. If those patients had been included, our comparison group would most likely have included individuals that were in generally poorer health, unable or unmotivated for treatment, or who might not be eligible for surgery.

Finally, there is a risk of residual confounding in Study II–IV because the adjustments of the Cox regression models did not alter the relative risks in a significant way. It would be of interest to further look into factors that might

account for the remaining risk difference, such as weight change over time and important behavioural factors such as smoking, physical activity, dietary patterns, and alcohol consumption.

SELECTION BIAS

As treatment for obesity is to a great extent placed on the patients' own considerations, knowledge, and responsibility, the effect of the treatment will also vary to a great extent. Bariatric surgery is not a standard treatment offered to all individuals with obesity. A multidisciplinary bord assesses the eligibility of all patients who wants to undergo bariatric surgery, and makes an overall assessment of the patients physical and mental health.[76] Hence, the decision to operate is to a great extent depending on the patients request for health care along with the board's assessment of the mental and physical state of the patient. In addition, because there are no randomised controlled trials investigating the benefits of bariatric surgery, in all previous studies on bariatric surgery the participants were free to choose bariatric surgery or conventional obesity treatment. Therefore, all studies on the benefits of bariatric surgery compared with non-operated obese patients, introduces a selection bias of unknown size, indicating that there will always be fundamental differences between the groups. Because not all patients with an obesity diagnosis are eligible for surgery, the non-operated obese group might have poorer mental and physical health status than the surgery group. In addition, there might be other dimensions of patients' characteristics that led to the decision to operate, including eligibility or contraindications to surgery and individual preference of the patient.[76] Social determinants, such as socioeconomic status and possibly other dimensions of patients' characteristics, affects both the prevalence of obesity and treatment seeking behavior. Although low socioeconomic status is associated with both obesity and risk of CVD,[107, 139] a Swedish and a Canadian study (two countries with universal health-care insurance systems) have found that individuals with the lowest socioeconomic status were less likely to undergo surgery.[140, 141] These factors all affect both the decision to operate and the patients' ability to stay motivated and to follow recommended post-operation diet plans and physical activity to stay healthy, and could therefore play an important role in observed risk reduction in the participants who underwent surgery. So far, these considerations seem to have received little attention in the context of eligibility for bariatric surgery and outcomes after surgery. All these facts should be considered when interpreting the results from Study IV and V.

CONCLUSION

The findings of the studies of young women in this thesis indicate that:

- mean BMI is increasing in young Swedish women. The proportions of young first-time mothers with moderate and severe obesity have increased significantly during the last decades while social inequalities are increasing.

- there is a clear association between increasing BSA, BMI and height measured early in life and early onset of atrial fibrillation.

- there is a clear association between an increased BMI measured early in life and early onset of heart failure.

The findings of the studies of patients with obesity indicates that:

- bariatric surgery for obesity could prevent early hospitalization for heart failure.

- RYGB surgery seems to reduce the risk of AMI and postpone cardiovascular-related and all-cause mortality in patients with obesity. There was, however, no clear association between RYGB surgery and relative risk of ischemic stroke in these patients.

FUTURE PERSPECTIVES

This thesis contributes with new knowledge by highlighting trends of increasing BMI in general, and for moderate and severe obesity in particular, among young Swedish first-time mothers. Obesity has a major impact on public health and causes great financial costs for societies. Especially morbid obesity is the cause of a great economic burden due to increased need for health care compared to those who have normal weight.[31] Approximately 50% deaths from CVD and cancer could be prevented by strategically focusing on preventive and promotive strategies for modifiable risk factors, such as obesity, physical activity and a healthy diet. Furthermore, there is a need for structural population-based strategies targeting vulnerable subgroups, e.g., those with low socioeconomic status, in order to achieve less overweight and obesity across all groups in society,[107] and lower rates of early-onset cardiovascular morbidity and mortality.

We also further explored the relationship between obesity and early onset of premature morbidity and mortality in CVD. Even though the relationship between body size and atrial fibrillation has been well described, more precise investigations considering various components of body size with respect to the size of the left atrium, should perhaps be investigated further. This of course also applies to the relationship between BMI measured early in life and later risk of heart failure. It would be of interest to further look into and identify factors that might account for risk differences over time, such as weight change and important behavioural factors such as smoking, physical activity, dietary patterns, and alcohol consumption.

Given the steep reduction in risk during the first year post-surgery, along with the somewhat similar risk during longer follow-up, it is possible that RYGB postpones cardiovascular related diseases by a couple of years. What impact this shift of risk forward in time has on the overall benefits of surgery is yet to be studied. Additional studies should also focus on identifying subgroups that gain the greatest benefits from RYGB surgery, as well as which patients that might fare better with medical and behavioural targeted treatments. Finally, the effect of the selection bias in operated and non-operated obese patients on cardiovascular outcomes needs to be further investigated. More data are needed on characteristics of patients with obesity selected for surgical, medical, or behavioural treatment for obesity before a firm conclusion on the effectiveness of bariatric surgery for prevention of cardiovascular morbidity and mortality can be made.

RELATED PUBLICATIONS NOT INCLUDED IN THIS THESIS

Dikaiou P, Björck L, **Lundberg CE**, Adiels M, Manhem K, & Rosengren A. Obesity, overweight and risk for cardiovascular disease and mortality in young women. *European Journal of Preventive cardiology*. 2020; 2047487320908983. Online ahead of print.

Robertson J, Lindgren M, Schaufelberger M, Adiels M, Björck L, **Lundberg, CE**, Sattarm N, Rosengren A, & Åberg M. Body mass index in young women and risk of cardiomyopathy: a long-term follow-up in Sweden. *Circulation*. 2020; 141(7):520-529

Persson CE, Rothenberg E, Hansson PO, Welin C, & Strandhagen E. Cardiovascular risk factors in relation to dietary patterns in 50-year old men and women: a feasibility study of a short FFQ. *Public Health Nutrition.* 2019;22(4):645-653.

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