On the effects of obesity treatment

Gudrún Höskuldsdóttir

Department of molecular and clinical medicine
Institute of medicine
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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gudrun.hoskuldsdottir@gu.se

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ABSTRACT

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Sahlgrenska Academy, University of Gothenburg
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Aim: In this thesis the effects of bariatric surgery in individuals with type 1 diabetes will be assessed as well as the effects of surgery on risk for heart failure and atrial fibrillation in individuals with type 2 diabetes. Intensive medical treatment of obesity will be compared with the most common surgical methods and factors predicting obesity and treatment outcomes evaluated.

Methods: Study I and II included individuals with diabetes registered in the National Diabetes Register (NDR) and Roux-en-Y gastric bypass (RYGB) surgery registered in the Scandinavian Obesity Surgery Registry that were matched with individuals that had not received surgical treatment for obesity. Study I included effects of RYGB on cardiovascular outcomes, mortality, serious hypo- and hyperglycemia, substance abuse, psychiatric health, kidney function and amputation in individuals with type 1 diabetes and obesity. In study II the effects of RYGB on the incidence of heart failure and / or atrial fibrillation in individuals with type 2 diabetes and obesity was evaluated as well as effects on mortality in individuals with preexisting heart failure. COX proportional hazards regressions were applied. Studies III-V included individuals from the BAriatric surgery SUbstitution and Nutrition (BASUN) study that received non-surgical treatment, including a period of very low energy diet, or surgical treatment with RYGB or sleeve gastrectomy. Study III includes a description of the BASUN population at baseline. In study IV, machine learning algorithms (conditional random forest) were used to rank the individual variables included in BASUN as well as domains of these variables with regard to their predictive value on BMI. Study V describes the results from the three treatments at two-year follow-up. The outcomes included were changes in anthropometric measures and metabolic parameters which were analyzed using linear regression

models as well as composite variables for successful and unsuccessful treatment that were analyzed using a logistic regression model. Clinical variables were divided into domains and their impact in predicting treatment success was computed using conditional random forest with conditional permutation.

Results: We found that RYGB reduced risk for cardiovascular disease and mortality in individuals with type 1 diabetes and obesity but increased risk for serious hyperglycemic events, including diabetic ketoacidosis, and substance abuse significantly. Individuals with type 2 diabetes and obesity that underwent RYGB had significantly lower risk for hospitalization for atrial fibrillation and heart failure in comparison with those that did not undergo surgery. Significantly lower mortality was observed in individuals with known heart failure that had undergone surgery in comparison with those that did not. Domains including socioeconomic status, age, sex, lifestyle and habits as well as potential anxiety and depression were shown to have strong predictive value on BMI levels. Bariatric surgery is more effective than medical treatment in the treatment of obesity, although medical treatment was also shown to be effective. There was no difference in safety measures between the treatment groups. Domains including anthropometry at baseline, metabolic disease, lifestyle and habits and socioeconomic status had predictive value on treatment success and domains including mental well-being and psychiatric disorders were also important in success of the different treatment options.

Conclusion: Bariatric surgery may be considered in individuals with type 1 diabetes after careful consideration of risk for serious hypo- and hyperglycemia. This treatment option is also important for individuals with type 2 diabetes and obesity to reduce risk for heart failure and atrial fibrillation and may even be considered in a selected population of individuals with known heart failure. Mental well-being and not only diagnosed psychiatric disorders could be an important factor in the treatment and follow- up with individuals with obesity. Although surgical treatment of obesity is more effective with regard to weight loss than medical treatment, medical treatment can also lead to meaningful weight loss. Deficiencies of vitamins and minerals, anemia or complications of treatment are not necessarily more common after bariatric surgery given good compliance to supplementary treatment and careful choice of treatment option.

Keywords: Obesity, diabetes, bariatric surgery

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SAMMANFATTNING PÅ SVENSKA

Tretton procent av världens vuxna befolkning lider av fetma. Det är fortfarande oklart vilka faktorer som ökar möjligheten till lyckad viktnedgång. Behandling av fetma kan delas upp i kirurgiska och icke-kirurgiska metoder. De vanligaste operationsmetoderna i Sverige är Roux-en-Y gastric bypass (RYGB) och sleeve gastrectomy (SG), men det är i nuläget inte säkerställt vilken av de två metoderna som långsiktigt har mest fördelaktig inverkan på vikt och följdsjukdomar och ger minst komplikationer. Icke-kirurgisk behandling av fetma som inkluderar strikt kalorirestriktion med *very low energy diet* (VLED) har också visat sig kunna vara effektiv. Fetma och typ 2-diabetes är kända riskfaktorer för utveckling av förmaksflimmer och hjärtsvikt men effekten av fetmakirurgi på risken för dessa komplikationer är oklar. Personer med typ 1-diabetes lider idag också av fetma i högre utsträckning än tidigare. Behandling av fetma hos dessa individer kan vara komplicerad eftersom begränsat energiintag kan leda till nedbrytning av fett, syraförgiftning (acidos), liksom svårigheter att rätt dosera insulin. Det saknas forskning kring behandling av fetma hos patienter med typ 1-diabetes och därför är bedömningen angående deras lämplighet att genomgå fetmakirurgi svår.

Det övergripande syftet med projektet var att utforska effekter och säkerhet av fetmabehandling i olika patientgrupper, och inte minst vid typ 1- och typ 2-diabetes. Effekten av de vanligaste kirurgiska metoderna, RYGB och SG, jämförs med medicinsk behandling med VLED, och faktorer som kan förutsäga effekt av fetmabehandling utforskas. Projektet utgår från två större forskningsprojekt; BASUN-studien och samverkan mellan Nationella Diabetesregistret (NDR) och Scandinavian Obesity Surgery Registry (SOReg).

I avhandlingen presenteras fem studier. Studie I och II inkluderar individer med diabetes som är registrerade i NDR, som har genomgått kirurgisk behandling av fetma i form av RYGB och som jämförs med andra med diabetes men inte har genomgått fetmakirurgi. Studie I omfattar individer med typ 1-diabetes, och effekten av RYGB på hjärtkärlsjukdom, överlevnad, extremt höga- och låga blodsockernivåer, psykisk hälsa och missbruk studerades. Studie II fokuserade på effekten av RYGB på utveckling av hjärtsvikt och förmaksflimmer hos individer med typ 2-diabetes och fetma, men även effekten på dödlighet hos patienter med känd hjärtsvikt. I studier III-V beskrevs BASUN-populationen innan behandlingsstart och effekten av den medicinska respektive kirurgiska behandlingen på vikt och markörer för

nutrition, blodfetter och blodsocker. Faktorer som kunde förutsäga fetma och sannolikheten att lyckas med behandling beskrevs med så kallad *machine learning* (artificiell intelligens).

Fetmakirurgi kan ha positiv effekt på risk för kardiovaskulär sjukdom och överlevnad hos individer med typ 1-diabetes men ökar också risk för syraförgiftning (acidos) och missbruk av alkohol och droger. Kirurgisk behandling av fetma minskar också risk för utveckling av hjärtsvikt och förmaksflimmer hos personer med typ 2-diabetes och fetma, men kan även vara ett alternativ för att minska dödlighet hos vissa individer med känd hjärtsvikt. Det är viktigt att ta hänsyn till psykiskt mående, inte bara kända psykiska sjukdomar, i behandling och uppföljning hos individer med fetma. Kirurgisk behandling av fetma är vanligtvis effektiv och leder inte till mer komplikationer än medicinsk behandling i minst två år. Medicinsk behandling som inkluderar strikt kalorirestriktion kan för vissa vara ett bra och effektivt alternativ till viktnedgång.

LIST OF PAPERS

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

I. Höskuldsdóttir G, Ekelund J, Miftaraj M, Wallenius V, Ottosson J, Näslund I, Gudbjörnsdottir S, Sattar N, Svensson AM, Eliasson B. Potential Benefits and Harms of Gastric Bypass Surgery in Obese Individuals with Type 1 Diabetes: A Nationwide, Matched, Observational Cohort Study. Diabetes Care 2020;43(12):3079-85.

II. Höskuldsdóttir G, Sattar N, Miftaraj M, Näslund I, Ottosson J, Franzén S, Svensson AM, Eliasson B. Potential Effects of Bariatric Surgery on the Incidence of Heart Failure and Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus and Obesity and on Mortality in Patients with Preexisting Heart Failure: A Nationwide, Matched, Observational Cohort Study. J Am Heart Assoc. 2021;10(7):e019323.

III. Höskuldsdóttir G, Mossberg K, Wallenius V, Al Nimer A, Björkvall W, Lundberg S, Behre CJ, Werling M, Eliasson B, Fändriks L. Design and baseline data in the BAriatic surgery SUbstitution and Nutrition study (BASUN): a 10-year prospective cohort study. BMC Endocr Disord 2020 Feb 14;20(1):23.

IV. Höskuldsdóttir G, Engström M, Rawshani A, Wallenius V, Lenér F, Fändriks L, Mossberg K, Eliasson B. The BAriatric surgery SUbstitution and Nutrition (BASUN) population: a data-driven exploration of predictors for obesity. Manuscript.

V. Höskuldsdóttir G, Engström M, Rawshani A, Lenér F, Wallenius V, Fändriks L, Mossberg K, Eliasson B. Effects two years after medical and surgical treatments of obesity: prospective cohort study. Manuscript.

CONTENT

ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AF	Atrial fibrillation
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
AUDIT	Alcohol use disorders identification test
BAI	Beck anxiety inventory
BASUN	BAriatric surgery SUbstitution and Nutrition study
BMI	Body mass index
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
DALY	Disability adjusted life years
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
EBMI	Excess body mass index
EDIC	Epidemiology of Diabetes Interventions and Complications study
EQ5D	EuroQol five-dimensional questionnaire
E%	Percentage of energy intake
GBD	Global Burden of Disease study
GLP1	Glucagon-like peptide 1
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HF	Heart failure
HR	Hazard ratio

IHD	Ischemic heart disease
LDL	Low-density lipoprotein
MICE	Multivariate Imputation by Chained Equation
MT	Medical treatment
NDR	National Diabetes Register
OR	Odds ratio
PHQ9	Patient health questionnaire-9
POMC/CART	Pro-opiomelanocortin / cocaine and amphetamine related transcript
PPI	Proton-pump inhibitor
QEWP-R	Questionnaire on eating and weight patterns-revised
RMR	Resting metabolic rate
RYGB	Roux-en-Y gastric bypass
SD	Standard deviation
SG	Sleeve gastrectomy
SGLT2	Sodium-glucose co-transporter-2
SGQ	Saltin Grimby questionnaire
SMD	Standardized mean differences
SOReg	Scandinavian Obesity Surgery Registry
TFEQ	Three factor eating questionnaire
TG	Triglycerides
TSH	Thyroid stimulating hormone
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
T4	Thyroxine
VLED	Very low-energy diet
WHO	World Health Organization
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 OBESITY

Thirteen percent of the world's adult population are obese and according to the World Health Organization (WHO), obesity causes more deaths than underweight. The prevalence of obesity has steadily increased since the late 1980´s and it nearly tripled between 1975 and 2016. (1, 2) In 2020, more than half of the Swedish adult population reported being overweight or obese. (3) Obesity is a chronic disease but opposed to individuals with hypertension, hyperglycemia and hyperlipidemia, those with obesity do not always receive structured clinical follow-up to assist with weight loss or maintenance of lost weight to the same degree.

In the 2020 report from the Global Burden of Disease study (GBD) (4), there were only three risk factors of the 87 analyzed that were increasing in exposure values of more than 1% per year. These three risk factors were high fasting blood glucose (1.37%), body mass index (BMI) > 25 kg/m^2 (1.94%) and ambient particulate matter pollution (1.78%). Exposures increasing more than 0,5% per year were classified as causing health concerns worldwide, currently and in the future. According to the GBD, no country reported a decline in the proportion of individuals with high BMI between 1990 and 2019. (4) In the report concerns were raised that the increase in high fasting blood glucose and BMI might overwhelm the decrease in global cardiovascular disease mortality that has been reported since 1990. Cardiovascular disease mortality has not only plateaued but actually started to increase again between 2017 and 2019. Concerning other common risk factors, high systolic blood pressure exposure increased by 0.08% between 1990 and 1999 and 0.51% between 2010 and 2019 which is concerning as well, although not to the same degree as blood glucose and BMI levels. High LDL cholesterol exposure has remained fairly constant during the last two decades (-0.33%) and smoking exposure decreased by 0.99%. (4) Although pride can be taken in the strides that have been taken in the treatment of hyperlipidemia and reduction in smoking the question remains, why is the treatment of obesity and hyperglycemia lagging behind?

1.2 PHYSIOLOGY AND ETIOLOGY OF OBESITY

The etiology of obesity is multifactorial. Fundamentally it is caused by an imbalance of caloric intake and expenditure but this is complicated by environment, medical conditions and genetics. A common misconception is that individuals with obesity have lower levels of energy metabolism compared to individuals with normal weight when in fact, energy expenditure is related to weight directly and individuals that weigh more expend more energy. (5) Along with weight, other factors that determine energy expenditure are sex, age and fat-free mass with lower levels being observed in females and with older age. The total energy expenditure of the individual is determined mainly by the resting (or basal) metabolic rate (RMR) and energy expenditure through exercise and non-exercise activity.(6) In the treatment of obesity, the resting metabolic rate can be approximated using the Harris-Benedict equation. (7) Non-Exercise Activity Thermogenesis was first described by Levine and includes the energy expended by smaller movements, talking, postural changes etc. throughout the day. (8) The thermogenesis induced by food intake also has a minor effect on energy expenditure. Although it is clear that individuals that weigh more expend more energy, it is still controversial whether or not a lower metabolic rate is responsible for the development of obesity. (6)

Hormones involved in appetite regulation, caloric intake and secretion of insulin

The main organs involved in lipid metabolism are adipose tissue, the gastrointestinal (GI) canal, liver, hypothalamus and pancreas (figure 1). A number of hormones and peptides are involved in the maintenance of body weight (9) and lipid metabolism and a few of these, that have been associated with obesity and the treatment of obesity, will be discussed in this section. Neurons within the arcuate nucleus of the hypothalamus are involved in control of appetite and energy metabolism. Pro-opiomelanocortin (POMC) and cocaine and amphetamine related transcript (CART) neurons produce anorectic peptides such as α-melanocyte stimulating hormone (α-MSH). Other neurons produce neuropeptide Y which is orexigenic. The main hormone produced by adipose tissue is leptin and leptin receptors in the hypothalamus regulate hunger and satiety. The gastrointestinal tract and its hormones play a major role in the intake of food, appetite and secretion of

insulin. Hormones secreted in the GI canal in response to hunger and satiety communicate with centers in the hypothalamus of the brain to mediate start and stop of food intake. Two pancreatic polypeptide (PP)-fold peptides are secreted in the gastrointestinal canal, peptide YY (PYY) and pancreatic polypeptide (PP). Levels of PYY increase postprandially and are

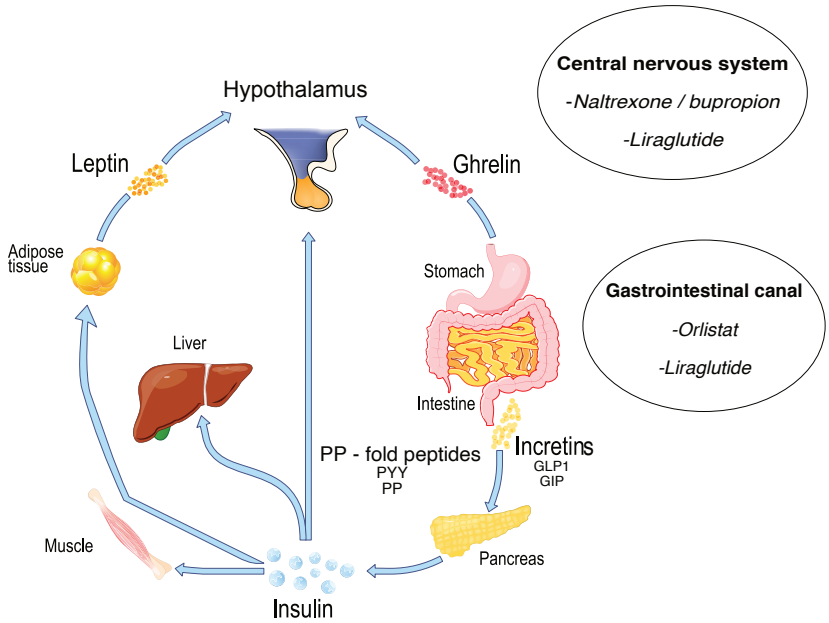


Figure 1. Hormones and organs involved in the control of hunger and satiety as well as effect sites of pharmaceutical options for the treatment of obesity. GLP-1: glucagon-like peptide-1, GIP: glucose-dependent insulinotropic polypeptide, PP: pancreatic polypeptide, PYY: peptide YY, PP: pancreatic polypeptide. Adapted and used with permission from ttsz 2019 (10)

dependent on the caloric content of the meal. These increasing levels have anorexigenic effects through satiety signals in the hypothalamus. PP is also released from the gastrointestinal canal in response to food and slows the passage of food through the gut. As with PYY, the levels of PP are also dependent on the energy content of the food. Although there does not seem to be any measurable resistance to PYY in individuals with obesity, the levels of PP secreted postprandially has been shown to be reduced in this group and, conversely, increased in individuals with anorexia.(11) Other GI hormones that are released in response to caloric intake are the incretins. These include glucagon-like peptide (GLP-1) secreted from the distal gut and glucose-dependent insulinotropic polypeptide (GIP) from K-cells in the intestinal

canal. These incretins are responsible for the *incretin effect*, the increased release of insulin in response to intake of glucose. Aside from increasing secretion of insulin and suppressing glucagon release, GLP-1 also slows gastric emptying and suppresses appetite. The circulating levels of GLP-1 postprandially have been shown to be reduced in individuals with obesity. GIP has direct effects on adipose tissue: stimulates import of glucose, synthesis of fatty acids as well as lipogenesis. GIP inhibits lipolysis. (11) Ghrelin is a peptide hormone that is secreted from the stomach and is known to increase appetite and is thus orexigenic. Levels of ghrelin increase in response to fasting, and through effects in the hypothalamus, encourage intake of food.(12) These levels decrease postprandially. The levels of decrease in ghrelin has been shown to be blunted or absent in individuals with obesity. (7, 11)

Etiology of obesity

Environmental factors, such as urbanization, can cause a shift in the balance of energy expenditure and intake that is unfavorable by leading to decreased levels of physical activity and easy access to energy dense food products. (5) Hormonal disorders such as untreated hypothyroidism and polycystic ovarian disease also increase risk for overweight. Medical conditions can damage the satiety centers in the hypothalamus and cause uncontrolled eating (hyperphagia), although this is rare. Pharmaceutical treatments such as cortisone, certain antidepressant, antipsychotic and antiepileptic medicines can increase appetite and therefore cause weight gain. The anabolic effects of large doses of insulin can also lead to weight gain. (13, 14) Monogenic obesity is due to single-gene disorders that cause disruption in central pathways of feeding and energy homeostasis. (15) These include mutations in the genes coding for leptin or leptin receptors and cause severe obesity in early childhood. Treatment with leptin can, in these individuals, have positive effects on weight. Prader Willi syndrome and Laurence-Moon-Biedls syndromes are also rare genetic diseases that lead to obesity, among other symptoms. (5)

1.3 OBESITY AND COMORBIDITY

According to the WHO, optimal BMI levels are between 18.5-24.9 kg/mg^2. Individuals with BMI levels between 25 and 29.9 kg/m^2 are classified as overweight and those with BMI over 30 kg/m^2 as obese. BMI levels between 30 and 34.9 kg/m^2 are defined as class 1 obesity, 35 and 39.9 kg/m^2 class 2 and a BMI over 40 kg/m^2 as class 3. The risk for comorbidities increases from BMI levels over 25 kg/m^2 with the risk for comorbidities becoming severe when BMI exceeds 40 kg/m^2. (1)

Obesity leads to a broad array of non-communicable comorbidities such as type 2 diabetes, hypertension, hyperlipidemia, sleep apnea, cardiovascular disease and musculoskeletal disease. It also increases risk for certain types of cancer and complicates intensive care treatment and anesthesia. (16-18) To quantify the effect that obesity has on health in general, measurements of disability adjusted life years (DALYs) or loss of disease-free years can be applied. Results presented by the GBD study showed that BMI > 25 kg/m^2 was a contributing factor in 4.0 million deaths of any cause in 2015 and 120 million DALYs. Of these BMI related DALYs and deaths, cardiovascular disease was the primary cause and diabetes the second leading cause. (18) A study of over 120,000 Europeans reported that obesity significantly reduces disease free years in individuals between 40 and 75 years old. The difference between individuals with obesity and individuals that were normal weight, was observed in all groups studied and was not dependent on sex, nicotine use, levels of physical activity or socioeconomic status. Severe obesity was associated with a loss of 7-8 disease free years and mild obesity with 3-4 years. (19)

Some studies have implied that being overweight but not obese is associated with lower risk for death after cardiovascular events or surgery and better survival in individuals with heart failure, as compared to being normal weight (BMI 18.5-24.99 kg/m^2), often referred to as the *obesity paradox*. (20) The obesity paradox has been proposed to be due to factors that introduce bias and is eliminated when effects of reverse causality are removed. The inverse relationship between obesity and smoking has been suggested as a major confounder and the obesity paradox does not seem to exist in non-smokers. (21, 22) Larger multinational prospective studies have presented evidence to support the recommended BMI level of 18.5-24.9 kg/m^2. (22, 23) The concept of *healthy obesity* has also been discussed

throughout the years but studies have shown that even individuals that are overweight and metabolically healthy have a strong tendency to progress to an unhealthy metabolic state and that being overweight is generally associated with a loss of disease-free years. (19, 24, 25)

Concomitant obesity and diabetes

Obesity and excess visceral- and subcutaneous adipose tissue in combination with insulin resistance are associated with higher levels of circulating free fatty acids and triglycerides as well as pro-inflammatory cytokines such as leptin, tumor necrosis factor-α, and interleukin-6 to name a few, which increases predisposition for comorbid disease. (26) Sensitivity to insulin is based on the effect of the hormone in skeletal muscles, liver and adipose tissue. Insulin resistance mainly presents as reduction in glucose clearance in the muscles, impaired suppression of glucose production in the liver as well as a decrease in lipolysis. This leads to an increase in insulin secretion by the beta cells of the pancreas in obese individuals, hyperinsulinemia. Insulin resistance is a prerequisite to the development of pre-diabetes and finally type 2 diabetes. (27) Thus, type 2 diabetes is a result of insulin resistance and inadequate insulin secretion to maintain normoglycemia.

Risk for heart failure and atrial fibrillation in obesity and type 2 diabetes

The cardiovascular risk in individuals with obesity and type 2 diabetes is well established. (23, 28-31) The increased risk for atrial fibrillation and heart-failure is also well known in this population. The results of a mendelian randomization study including data on over 360 000 individuals from the UK Biobank showed that increasing BMI was associated with increased risk for heart failure and atrial fibrillation, among other cardiovascular outcomes. (32)

Heart failure is often the first manifestation of heart disease in individuals with type 2 diabetes. The European Society of Cardiology (ESC) defines heart failure as a clinical syndrome characterized by typical symptoms (such as breathlessness, swelling of the ankles and fatigue) caused by a structural and/or cardiac abnormality that results in reduction of cardiac output and/or elevated intracardiac pressures at rest or during stress. This is often accompanied by common signs of heart failure, such as elevated jugular

venous pressure, pulmonary crackles and peripheral oedema. (33) The prevalence of heart failure in individuals with type 2 diabetes is four times higher compared to individuals without diabetes and it has been proposed that this prevalence is underestimated. (34) Earlier data from the National Diabetes Registry have illustrated that individuals with type 2 diabetes that have optimal glycemic control still have a risk for hospitalization for heart failure that is doubled in comparison with individuals without diabetes. (35) It has also been shown that obesity is a particularly strong risk factor for the development of heart failure in younger individuals with BMI levels over 35 kg/m^2 presenting risk that is nine times higher than risk in individuals with BMI between 18.5 and 20 kg/m^2. (36) The ESC has divided the etiology of heart failure into three groups: diseased myocardium, abnormal loading conditions and arrythmias. In this classification, type 2 diabetes and obesity are identified as metabolic diseases that cause disease of the myocardium. (33) However, diabetes and obesity are also involved in increased risk for cardiovascular disease through hypertension, kidney failure and volume overload leading to abnormal loading conditions. Hence, the roll of obesity and diabetes in the development of heart failure is therefore multifactorial. Atrial fibrillation is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. (37) Obesity and diabetes and related risk factors and comorbidities such as ischemic heart disease are strongly associated with the development of atrial fibrillation. (38, 39) This has been proposed to be secondary to oxidative stress, inflammation and fibrosis. (40, 41) Diabetes has been shown to be an independent risk factor for atrial fibrillation, particularly in younger individuals. Obesity increases risk for death in individuals with atrial fibrillation. Intensive reduction of weight and optimal glycemic control have been shown to cause fewer recurrences of atrial fibrillation.(37)

Type 1 diabetes and obesity

Type 1 diabetes is caused by autoimmune or, less commonly, idiopathic destruction of beta cells that cause loss of insulin production and need for lifelong treatment with insulin. The loss of insulin production leads to hyperglycemia, lipolysis and ketoacidosis. In 2020, there were 420 153 individuals registered in the National Diabetes Registry with a diabetes

diagnosis, of which 45 296 (10,8%) had type 1 diabetes. (42) More than 58% of the Swedish type 1 diabetes population was reported being overweight or obese and 19.5% obese in the beginning of 2021 and these percentages have increased annually since 1996. (43, 44) The treatment of obesity in individuals with type 1 diabetes can be complicated as the necessary reduction in caloric intake may lead to lipolysis and development of ketoacidosis as well as difficulty in insulin dosing. The risk for cardiovascular disease and mortality in individuals with type 1 diabetes has been described. (45-47) Insulin resistance, and other factors associated with the metabolic syndrome may also be present in obese individuals with type 1 diabetes and contribute to cardiovascular risk. (27, 48, 49) Better glycemic control achieved through higher insulin doses is often coupled to weight gain. In the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study, weight gain to BMI levels over 30 kg/m^2 was observed in approximately 25% of the intensive treatment group. This observed weight gain was also accompanied by insulin resistance and negative changes in cardiovascular risk factors. Despite intensive treatment during DCCT, the incidence of cardiovascular disease in those with excessive weight gain started to rise after 14 years and was similar to that observed in the conservatively treated group at 20 years indicating late effects of obesity and insulin resistance on cardiovascular risk even in individuals with good glycemic control and treatment of risk factors. (50) Previous data from the Swedish National Diabetes Registry have shown that obesity in individuals with type 1 diabetes may increase risk for major cardiovascular events and heart failure as well as mortality. (51) The risk for hospitalization for heart failure in individuals with type 1 diabetes and obesity, especially severe obesity, has been shown to be markedly higher than in normal weight individuals. This increased risk was not observed in those with type 1 diabetes that were overweight. (52)

1.4 TREATMENT OF OBESITY.

Clinical guidelines on the treatment of overweight and obesity are generally based on the individual's motivation to make lifestyle changes. According to the guidelines from the American College of Cardiology, American Heart Association and American Heart Association Task Force (53), follow-up of weight and risk factors is recommended at least annually for individuals that

are overweight or obese that are not ready to make lifestyle changes to reassess motivation and follow-up metabolic risk parameters. For individuals ready to make changes, the recommendations are based on the individual´s goals and adjustments should be made continuously based on the effectivity of the treatment. For BMI levels of 27-29.9 kg/m^2 with comorbidity or levels over 30 kg/m^2, high-intensity comprehensive lifestyle interventions with a trained professional or nutritionist should be offered with an option of adjunctive pharmacotherapy.

Although a weight loss of 3-5% may lead to meaningful risk reduction, generally a weight loss of 5-10% is recommended during the first 6 months. (54) Weight loss should be assessed regularly and if less than 5%, intensive behavioral treatment, pharmacotherapy or referral to bariatric surgeon should be considered. For individuals with class 2 obesity with comorbidity or class 3 obesity, referral to a bariatric surgeon is recommended. (53) Treatment of obesity in individuals with or without type 2 diabetes should be monitored often (at least 14-16 appointments during the first 6 months) to counsel in dietary choices, physical activity and behavioral changes. (53, 55) To increase the probability of sustained weight-loss the treatment program should continue for at least one year with a minimum of monthly contact. Follow-up for all individuals with overweight or obesity is recommended at least yearly outside of the active treatment period. The treatment options for obesity can be divided into three main areas: lifestyle or dietary changes, pharmaceutical treatment and surgical treatment.

Lifestyle and dietary changes

Lifestyle or dietary changes include all types of interventions that focus on reducing the intake of energy, increasing levels of physical activity as well as cognitive and behavioral treatment that aims to increase the individual's adherence to these changes. To achieve weight loss, a caloric deficit of at least 500 kcal/day is needed. For most individuals, this can be achieved by a dietary intake of 1200-1500 kcal/day for females and 1500-1800 kcal/day for men but more accurate estimates can be made after calculating the RMR for each individual. (53) In general, treatment based on mainly lifestyle interventions leads to a maximal weight loss of 5-10% during the first year. The most effective lifestyle or dietary treatment available is a very low-energy diet (VLED). This treatment restricts intake to 400-800 kcal/day in

the form of specific dietary products high in protein and supplemented with vitamins and minerals to minimize risk for loss of lean body mass and nutritional deficiency and is recommended for 12-20 weeks depending on the starting BMI. Individuals following a strict VLED should have follow-up with medical professionals during the treatment period. An expected weight loss of 1-2 kg/week can be seen during VLED treatment.

Pharmaceutical treatment of obesity

In Europe there are three pharmaceutical options available for the primary treatment of obesity; liraglutide (a GLP1 receptor agonists), a combination of bupropion and naltrexone and orlistat (figure 1). GLP1 receptor agonists have effects on weight by delaying gastric emptying, reducing appetite and promoting satiety through stimulation of the POMC/CART pathway in the hypothalamus and thereby decreasing intake of food. (13) Naltrexone/bupropion also has an effect on the hypothalamic melanocortin system that regulates food intake by simultaneously stimulating hypothalamic POMC neurons (bupropion) and blocking opioid mediated POMC autoinhibition (naltrexone). (56) Orlistat inhibits pancreatic lipase and reduces absorption of fat in the intestines by approximately 30%. (13) For individuals with concomitant type 2 diabetes, other GLP1 analogues are available as well as sodium-glucose co-transporter-2 (SGLT-2) inhibitors that have positive effects on weight. Pharmaceutical treatment alone can lead to weight loss of up to 5-10% during the first year but often reaches a plateau after 6-8 months of treatment. (14, 57) Recent data published on semaglutide (GLP1 receptor agonists) in the primary treatment of obesity confirm the positive effects on weight but usage in clinical practice is still off-label. (58) The addition of orlistat after a period of VLED has been reported to assist in further weight-loss and weight maintenance. (59, 60) A study including 25 individuals in each treatment group reported effects of the combination of VLED, intensive physical activity and 3.0 mg liraglutide daily that was comparable to effects of surgical treatment with sleeve gastrectomy with regards to weight loss and metabolic parameters. (61) Further studies on the effect of liraglutide after a period of VLED are ongoing (62) as well as studies on the effects of semaglutide on cardiovascular outcomes in individuals with obesity. (63) Combined treatment with glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists have shown

promising results with regard to glycemic control and weight loss and might also have a place in the treatment of obesity. (64)

Surgical treatment of obesity

In 2016, more than 630 000 bariatric surgical operations were performed worldwide. (65) In Sweden, 5400 operations were performed in 2017 and 4700 in 2019, the most common surgical methods being Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) (figure 2). (66) The first gastric bypass operation was performed by Dr. Mason in 1966 (67) and was later developed to include the Roux-en-Y loop to reduce bile reflux. (68) The procedure was described by Lönnroth in 1996. (69) The sleeve gastrectomy was first performed in 1988 in combination with a duodenal switch and laparoscopically in 1999. The method was first introduced as a primary treatment option for obesity in 2003, then in individuals with BMI over 60 to induce sufficient weight loss to make the performance of later RYGB possible. (70) The method has since become common as a stand-alone treatment option for obesity and in 2019 it was reported to be the surgical treatment of choice as often as RYGB in Sweden. (71)

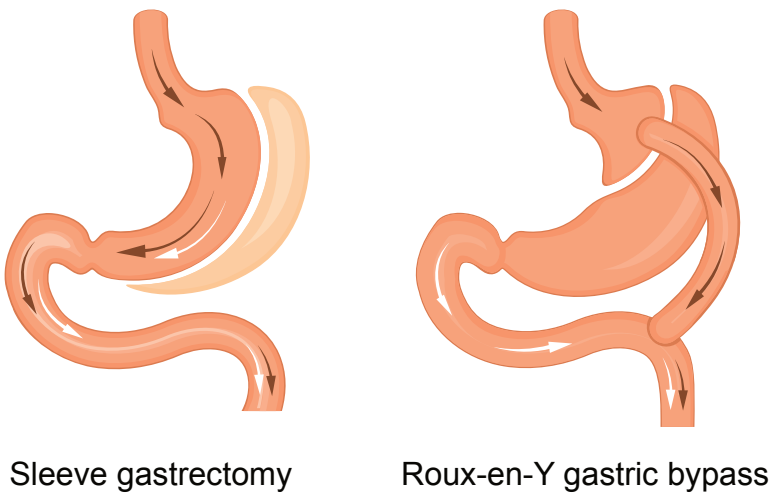


Figure 2. Anatomical changes after sleeve gastrectomy and Roux-en-Y gastric bypass surgery. Passage of food after the surgical procedure is indicated with brown arrows and passage of digestive juices with white arrows. Adapted and used with permission from nmfotograf 2019. (72)

The Swedish Obese Subjects study (SOS) has reported a maintained weight loss of 27% fifteen years after RYGB (73) and this surgical method has been reported to lead to diabetes remission in 36-38% of individuals with type 2 diabetes. (74, 75) The 5-year STAMPEDE trial reported diabetes remission 29% of individuals after RYGB, 23% after SG and 5% after intensive medical treatment according to guidelines from the American Diabetes Association. (74) The percentage of total weight loss after SG has been reported to be 27% one year postoperatively, 16% after seven years and excess weight loss between 50-55% after ≥ 7 years. (76, 77) Bariatric surgery can be considered to individuals with type 2 diabetes and BMI over 35 kg/m^2 or over 30 kg/m^2 when weight loss and improvements in comorbid conditions such as hyperglycemia are not achieved with non-surgical treatment. (55) There are no large studies on the effects of bariatric surgery in individuals with type 1 diabetes and obesity. Case reports and smaller studies have indicated positive effects weight and comorbid conditions such as hypertension and hyperlipidemia but there have been inconsistencies in reports on glycemic control. (78-83) Concerns on risk for diabetic ketoacidosis and hypoglycemia post-operatively have been raised. (80, 84)

Individuals with obesity are a large, but heterogenous group of individuals and the factors most related to successful treatment are still unclear. In this thesis the effects of bariatric surgery in individuals with type 1 diabetes will be assessed as well as the effects of surgery on risk for heart failure and atrial fibrillation in individuals with type 2 diabetes. Intensive medical treatment of obesity will be compared with the most common surgical methods (RYGB and SG) and factors predicting obesity and treatment outcomes evaluated.

2 AIM

The overall aim of the project reported in this thesis was to study which groups benefit the most from the treatment of obesity and which treatment option is the most effective. This was done in five separate studies as described below.

The specific aims of the included studies were:

I. To study the effects of gastric bypass surgery on cardiovascular disease, mortality, hypoglycemia, serious hyperglycemia, psychiatric disorders and substance abuse in individuals with type 1 diabetes and obesity.
II. To study the effects of gastric bypass surgery on the incidence of heart failure and atrial fibrillation in individuals with type 2 diabetes and obesity as well as the effect of surgery on mortality in individuals with type 2 diabetes, obesity and known heart failure.
III. To describe the BASUN population and the methods included in the planned prospective study.
IV. To study the predictive value of the clinical variables included in the BASUN study at baseline on BMI levels.
V. To describe the BASUN population two years after treatment, compare the effects of gastric bypass surgery and gastric sleeve as well as to study the predictive value of the clinical variables included on success and complications of obesity treatment.

	Study I	Study II	Study III	Study IV	Study V
Aim	Effects of RYGB in DM1 and obesity	Effects of RYGB on HF and AF in DM2 and obesity and mortality in HF	Description of BASUN population	Predictive value of clinical variables on BMI	Effects of surgical vs medical treatment of obesity
Design	Observational cohort study		Non-randomized prospective cohort study		
Main data sources	NDR & SOREG		BASUN		
Inclusion period	2007-2013		2015-2017		
Follow-up	9 years		NA	NA	2 years
Participants	774	10 642	971	1120	969
Subgroups	RYGB: 387 Controls: 387	RYGB: 5321 Controls: 5321	MT: 382 RYGB: 388 SG: 201	MT: 380 RYGB: 385 SG: 201 NT: 154	MT: 382 RYGB: 387 SG: 200
Primary outcomes	Mortality CVD Hospitalization for hypo- or hyperglycemia	Hospitalization for HF or AF Mortality in preexisting HF	NA	Importance of clinical variables in predicting BMI	Changes in anthropometric and metabolic variables
Statistical analysis	Time dependent propensity scores Cox proportional hazards regression Kaplan-Meier	Time dependent propensity scores Cox proportional hazards regression Kaplan-Meier	Descriptive statistics	Conditional random forest Conditional permutation	Linear regression Logistic regression Conditional random forest Conditional permutation

Table 1. Summary of studies. RYGB: Roux-en-Y gastric bypass, MT: medical treatment, SG: sleeve gastrectomy, NT: no treatment

3 PATIENTS AND METHODS

3.1 SUBJECTS AND DEFINITIONS

As described above, this thesis is based on five studies (summary of studies can be seen in table 1). Studies I-II include individuals with diagnosed type 1 or type 2 diabetes. According to the WHO, the diagnostic criteria for diabetes includes fasting plasma glucose of at least 7.0 mmol/L, two-hour plasma glucose of at least 11.1 mmol/L or HbA1c levels over 48 mmol/mol. In study I, the epidemiological and clinical definitions of type 1 diabetes were included: treatment with insulin only and diagnosis at an age of 30 years or younger (85), or as clinically determined by physicians. The epidemiological diagnosis has previously been validated as accurate in 97% of cases. (86) In study II, we included the epidemiological definition of type 2 diabetes: treatment with diet or oral antihyperglycemic agents only or onset of diabetes at 40 years or older with treatment with insulin with or without the combination with oral antihyperglycemic agents.

All of the individuals included in the five studies had diagnosed obesity according to the classification of the WHO, which includes a BMI of 30 kg/m^2 or more.

3.2 DATA SOURCES

Studies I and II

The patient populations included in these studies originated from the merging of two large nationwide Swedish registries, The National Diabetes Register (NDR) (87) and the Scandinavian Obesity Surgery Registry (SOReg) using personal identification numbers. (88) The NDR includes clinical information on 90-95% of individuals with a registered diabetes diagnosis in Sweden that is registered by the health care providers that provide follow-up for these individuals. Information on treatment, clinical measurements and comorbidities has been registered in the NDR database continuously since 1996. The SOReg contains information on 98% of all bariatric surgeries performed in Sweden and was started in 2007. Clinicians report information

on date and type of surgery as well as complications up to ten years postoperatively.

Patients with registered diabetes diagnosis in the NDR (type 1 diabetes in study I and type 2 diabetes in study II) who had undergone RYGB between January 2007 and December 2013 were identified in SOReg and matched with patients with the right diabetes diagnosis from NDR that had not undergone bariatric surgery. Information on the individuals included was also gathered from Statistics Sweden (socioeconomic variables), the Swedish Inpatient Registry (hospital admissions, coexisting conditions), Prescribed Drug Register (pharmaceutical treatment) and the Cause of Death Registry (cause and date of death) all of which have been previously validated (figure 3). (89) Codes from the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis registered after in-hospital treatment were used to define incident outcome events (cardiovascular events, serious hypo- or hyperglycemia, kidney failure, psychiatric disorders, substance abuse, heart failure, atrial fibrillation).

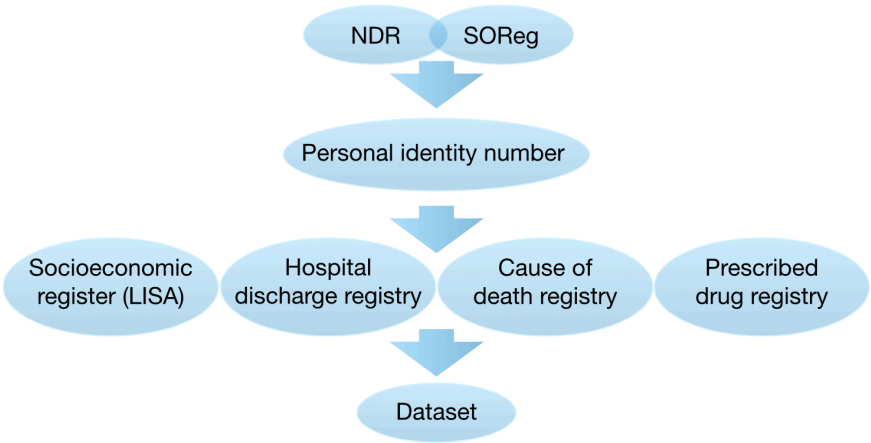


Figure 3. Swedish registries included to gather patient information for studies I-II. Höskuldsdóttir. Unpublished.

Studies III-V

These studies include participants from the BAriatric surgery SUbstitution and Nutrition (BASUN) study. The BASUN study is a non-randomized prospective cohort study that recruited patients that were referred to the Regional Obesity Center (ROC) at the Sahlgrenska University Hospital in Gothenburg for the treatment of obesity. It is conducted in clinical practice. The participants were consecutively included between May 2015 and November 2017. Follow-up is planned at 2, 5 and 10 years after treatment. The participants received medical or surgical treatment of obesity. Criteria for bariatric surgery in Sweden is based on international guidelines. These include a BMI of at least 40 kg/m^2 or 35 kg/m^2 with comorbidities such as type 2 diabetes or sleep-apnea. Contraindications for surgical treatment include active substance abuse, unstable psychiatric disorders, age under 18 years, malignant disease during the previous five years or poor general health. Age over 60 years old is a relative contraindication. The surgical methods included in the study were Roux-en-Y gastric bypass and sleeve gastrectomy (SG). Adults (at least 18 years old) with BMI over 30 kg/m^2 that were not interested in or did not qualify for surgical treatment were offered a one-year medical treatment program. The medical intervention included a VLED diet of 450-800 kcal for 12-20 weeks depending on the BMI at baseline. Of the individuals that start medical treatment at the obesity center, 85% begin with strict VLED. Contraindications for treatment with very low-calorie diets are mainly eating disorders, renal failure or severe psychological or medical disorders. The VLED period was followed by a 12-week period of food re-introduction. The Harris Benedict sex-specific equations were used to estimate individual energy needs and a 30% continued energy deficit recommended to achieve weight reduction until the end of the treatment year. During the treatment year the participants first had regular visits with a nurse during the VLED period, then during and after food re-introduction with a dietician and with a physician at 6 and 12 months for discussion of additive pharmaceutical treatment. General advice on physical activity was given at all visits. Demographic data, blood- and urine samples as well as measurements of height and weight were gathered at baseline and two-year follow-up. The participants also completed a booklet of questionnaires to cover gastrointestinal symptoms and eating habits, physical activity and quality of life, and psychological health (further information on the tests and questionnaires included can be found in the appendix, study III).

3.3 STATISTICAL ANALYSIS

In all of the studies, results from descriptive statistical analysis were presented as mean with standard deviation (SD) for continuous variables and numbers and proportions for categorical variables. Standardized mean differences (SMD) were used to indicate the size of the distance between the group means, using the difference in means divided by the SD. Statistical analysis in studies I-II were performed in R.4.0.2 and IV-V in R 4.0.3. In Study III, IBM SPSS 25.0 was used.

Propensity scores

The access to patient registries in Sweden is exceptional and makes studying and comparing large nationwide groups of patients possible. Studies based on register data are by nature observational cohort studies and do therefore not include randomization to treatment. When comparing groups that have and have not received treatment the problem of selection bias may arise. This refers to the possibility that individuals that received treatment have characteristics that made them choose or be chosen for treatment, that differ from the untreated group.

To adjust for this type of possible confounding in studies I and II, time dependent propensity scores were used. Propensity scores can be used to compare groups of individuals that have been exposed to treatment with individuals that have not (thus are still at risk for exposure). The propensity score estimates the probability that an individual would have been exposed to the outcome based on relevant covariates (i.e., chosen for treatment based on certain characteristics). Using a propensity score addresses the problem of high dimensionality, where there are many covariates that can affect the choice of treatment and thus making finding a match difficult. The propensity score can only take on values between 0 and 1 and is estimated using logistic models (in this case Cox proportional hazards regression) or generalized boosting models (decision trees). The individuals can then be matched on this score instead of for each individual variable. The individuals included in studies I and II were divided into two groups, those that received surgical treatment for obesity (the exposure) and those that did not. The individuals were matched using greedy 1:1 matching (matched on an individual basis based on the propensity score) to estimate the treatment effect in the treated

group. The propensity score was estimated at the time of the exposure (surgery) or the index date, and this became the date of selection for the matched control individual.

Regression and survival analyses

The relationship between two or more continuous variables can be explored using correlation or regression analysis. In correlation, the association between the two variables of interest in linear and the strength of this association is represented by the correlation coefficient. If one of the variables of interest is dependent on the other, regression is used. The dependent variable can be continuous or categorical. If the dependent variable is continuous, linear regression is used as opposed to logistic regression where the dependent variable is binary. In multiple logistic regression the relationship between the dependent variable and many independent variables is of interest. When the time to the event or outcome (the dependent variable) also needs to be taken into consideration, a Cox regressions model (or Cox proportional hazards model) can be used. Analyses that include time to an event are called survival analyses. Survival analyses can be divided into those that take different covariates into consideration, multivariate, (such as the Cox regressions model) and those that do not, univariate (such as the Kaplan-Meier method). The Kaplan-Meier method is often used to visualize survival by plotting the proportion of patients that "survive" (or have not experienced the outcome) past a particular point in time. The time is included in the x axis and for each event that occurs, a step down in proportion of individuals surviving past that point is observed.

Random forest and variable importance

Machine learning algorithms such as random forest have become common in medical research for predictive purposes. In using random forest, as opposed to linear regression, no assumptions to the model need to be made and predictor effects can be non-linear and interactive. Random forest uses a large number of decision trees which reduces variance and has the possibility to rank each variable with regard to relevance in predicting the outcome. This can be of particular interest in clinical studies. When considering predictive

value, the problem of correlation arises. Variables can have an independent impact in predicting outcome (marginal importance) and/or impact when interacting with other variables. Conditional permutation schemes can be used to minimize the effect of correlation between the variables and to reflect the impact of each independent variable. The accuracy of the random forest model is analyzed first with the variable included and then after it is permuted. The accuracy of the model and the importance of the variable have an inverse relationship with the accuracy decreasing more when important variables are permutated.

Missing data

According to Rubin, data can be missing completely at random (MCAR), at random (MAR) or not at random (MNAR). (90) If data is missing completely at random it cannot be predicted and thus not imputed. If data is missing at random it can be explained by data that is included, for example values of other variables that are not missing. This data can thus be imputed. If data is missing not at random there is a reason that this particular value is missing and needs to be inspected, not imputed. Data can be imputed using univariate imputation, using other values for that specific variable (within the same column). Multivariate mutation can also be used, taking into consideration values of other variables included (from other columns) to make predictions for the value of missing variable. The missing data in the included studies was assumed to be MAR and imputed using multivariate imputation using the Multivariate Imputation by Chained Equation (MICE) algorithms. MICE algorithms use regression models to estimate the value of the missing variable by creating many data sets with possible values of the variable. In the included studies ten sets of data were created and the results were then weighed together using Rubin´s rules.

3.4 METHODS

Study I

The aim of the study was to estimate the causal effect of bariatric surgery on outcomes related to obesity and type 1 diabetes. The main outcomes were all cause mortality, cardiovascular events and mortality, serious hyperglycemia (including diabetes ketoacidosis) and hypoglycemia requiring hospitalization. Secondary outcomes included were kidney disease, substance abuse (alcohol and narcotics) and psychiatric disorders. Time dependent propensity scores were applied to find controls for the surgical group (matched 1:1 on sex, age, BMI and calendar time). The surgical group included individuals with a type 1 diabetes diagnosis registered in NDR that had undergone RYGB (as registered in SOReg) and the controls were individuals with registered type 1 diabetes that had not undergone surgery. Descriptive statistics were used to compare the groups with regard to baseline characteristics with SMD levels of less than 0.2 being considered non-significant. Surgery was the only independent variable (exposure) and as the time to event was of interest, Cox proportional hazards regressions were applied. The models included were non-adjusted. The effect of the exposure on outcomes (cumulative incidence) was visualized using the Kaplan-Meier method and presented as Kaplan-Meier curves.

Study II

The aim of the second study was to explore the effects of bariatric surgery on incidence of heart failure and atrial fibrillation in individuals with type 2 diabetes and obesity. The primary outcomes included were hospitalization for heart failure and/or atrial fibrillation. Mortality in a subgroup of individuals with type 2 diabetes, obesity and known heart failure was included as a secondary outcome. Individuals with obesity that had a type 2 diabetes diagnosis registered in NDR and that had undergone RYGB that was registered in SOReg were matched with controls that also had a registered type 2 diabetes diagnosis but had not undergone surgery. As in study I, a propensity score was used to match the groups, 1:1, so that the individuals were comparable with regards to risk for exposure at the index date. As the outcome of interest was incidence of heart failure and atrial fibrillation, the analyses of the outcomes were based on individuals without preexisting

disease. However, a preexisting diagnosis for heart failure was not a censoring event for atrial fibrillation and vice versa. The subgroups with known heart failure were not matched. A SMD less than 0.1 was considered non-significant. Cox-proportional hazards regression were applied, first adjusted for age, education, country of birth, duration of diabetes, BMI, sex, HbA1c levels, blood pressure, smoking, levels of physical activity, presence of albuminuria, kidney function, levels of blood lipids and pharmaceutical treatment for hypertension. A less adjusted model, that included only age and exposure as independent variables, was also applied in comparison. This was partly due to the size of the subgroup with known heart failure that was analyzed separately. The Kaplan-Meier estimator was used to visualize the effect of surgery on the outcomes.

Study III

The aim of study III was to describe the study population and the methodology of the prospective BASUN study. The treatment options included in BASUN were medical treatment at the ROC at the Sahlgrenska University Hospital or bariatric surgery performed at one of the bariatric surgery centers in the region. This study included only descriptive statistical analysis. Distribution of the variables was assessed using Shapiro Wilks test and visual inspection of boxplots. As the distribution was not normal, non-parametric tests were applied (Kruskal Wallis for continuous variables and Fishers exact test for categorical variables). The significance level was set at $p < 0.05$.

Study IV

The aim of the fourth study was to explore the importance of the clinical variables included in BASUN in predicting BMI. All demographic and anthropometric data as well as results from lab tests and questionnaires investigating gastrointestinal symptoms, eating habits, levels of physical activity, quality of life and psychologic health gathered at baseline were included in the analysis. In total over 100 variables. The importance of the variables was examined using conditional random forest (machine learning algorithm). The variables were ranked individually and after being divided into 15 clinically relevant variable domains (Socioeconomic status, Age/sex,

Lifestyle and habits, Metabolic disease, Cardiovascular disease, Potential anxiety/depression, Biomarkers for cardiovascular disease and diabetes, Other biomarkers, Medication for cardiovascular disease or diabetes, Psychiatric disease, Gastrointestinal disease, Endocrine conditions, Musculoskeletal disease, Previous surgery and Other conditions). Three thousand trees were used for each binary classification model and a conditional permutation scheme was used to compute the importance of the variables. The ten strongest predictors were then studied separately and their relationship with BMI visualized after analysis with random forest that included 1500 trees.

Study V

The aim of the last study was to describe the results of the three treatments included in BASUN at two-year follow up. The primary outcomes included were changes in anthropometric measures (BMI, excess BMI (EBMI) and weight) as well as changes in metabolic variables such as blood glucose, blood lipids, vitamins, minerals and hemoglobin. As secondary outcomes, treatment success and failure and percentage of weight loss (at least 5%, 10% and at least 20%) were studied. The composite variable for treatment success included a reduction in EBMI of at least 50% or a BMI of less than 30 kg/m^2 at two-year follow-up without the individual having a history of surgery or in-hospital treatment during the follow-up period. Treatment failure was defined as a reduction of EBMI of less than 25% or surgery or in-hospital treatment during the follow-up period. Surgical treatment included were re-operations due to complications of the bariatric surgery or other procedures involving the gastrointestinal tract. In-hospital treatment for cardiovascular disease, infections, gastrointestinal disorders, complications of surgery, malignant disease or psychiatric disorders were also included. These surgical procedures and in-hospital periods were seen as complications and therefore included in the composite variables.

Time to event was not included in this study and thus linear regressions models were applied to analyze the changes in clinical variables from baseline to follow-up. The dependent variable was the clinical variable of interest and age, sex and baseline value of the variable were included as predictive variables. These predictors were used to create a reference grid

(for numeric predictors the mean value was used, for factor predictors the levels were used) and the mean value at each point in the reference grid is predicted. These are then weighed and reported as estimated marginal means with 95% confidence intervals.

A logistic regression model was applied to assess the likelihood of treatment success, presented as OR with 95% CI with the medical treatment group used a reference. In this study, the clinical variables available at baseline and follow-up were divided into 15 clinical variable domains (Anthropometry, Mental well-being, Lifestyle/habits, Metabolic disease, Biomarkers: vitamins/minerals, Biomarkers: CV/DM, Socioeconomic status, Biomarkers: other, Age/sex, Psychiatric disorders, Cardiovascular disease, Gastrointestinal disease, Musculoskeletal disease, Endocrine conditions and Other conditions). Here conditional random forest with conditional permutation was also used to compute the impact of each domain in predicting treatment success.

3.5 METHODOLOGICAL CONSIDERATIONS

On the journey from the hypothesis to generalization of the results for the target population, a number of systematic and non-systematic errors can arise. The systematic errors can be divided into *confounding*, *selection bias* and *information bias*. *Confounders* are factors that have an influence on both the independent and dependent variable. Confounders can be known or unknown. Known and unknown cofounders can be addressed by randomizing individuals to different treatment groups, and thus minimize the risk for unequal distribution of confounders between the groups. When this is not possible, as in the studies presented in this thesis, one can attempt to balance the groups equally with regard to known confounders, for example by matching. This was done using a propensity score, in studies I and II. In conducting cohort studies that do not include randomization or matching, stratification or adjustments can be used in the analysis phase to minimize effects of known confounders. In stratification, the data sample is stratified (divided) into groups of individuals by the confounding variable. For example, if age is thought to be a confounder, the data sample can be stratified into different age groups and each stratum analyzed separately. The results from the strata are subsequently weighed together depending on the target estimate. When adjusting for known confounders, these can be included in multivariable analysis, such as the regression analysis described in the statistical analysis section. In study II, possible confounders were included in the cox regression analysis and the models used in study V were adjusted for age and sex.

Selection bias arises when the study population is defined and leads to differences between the study population (sample) and the intended population of interest. This might cause problems with generalization of the results to a larger population – *external validity.* In the studies included in this thesis, the main problem of selection bias could have been *sampling bias*. This means that the certain individuals in the intended population were more likely to be chosen than others. The risk of this is minimized in studies I and II, by including data from nationwide registries that include almost all individuals with diabetes and those that have undergone bariatric surgery in Sweden. The individuals that were exposed to treatment were then matched with individuals that were comparable with regards to risk for the exposure. Participants to BASUN were gathered in a regional center for obesity

treatment that receives all referrals for obesity treatment for the whole region. All individuals referred for obesity treatment between 2015 and 2017 were considered for inclusion in BASUN. The Regional Obesity Center at the Sahlgrenska University Hospital is a regional center and thus the study population is representative for Region Västra Götalands with 1,7 million inhabitants. However, exclusion of individuals that do not understand Swedish make generalizations on this part of the population limited and thus decreases external validity.

Problems with the data collected for the study can also present problems – *information bias*. The measurement or registration of data might be erroneous and the problem of bias arises when the errors are not distributed evenly between the groups being compared (*differential misclassification*). The errors might cause over- or underestimation of the dependent variable or treatment effect between the groups. If the errors are, however, distributed evenly in all of the groups, this will not create a problem (*non-differential misclassification*). In studies I and II, errors could have occurred when the data was reported into the registries but it is unlikely that these errors will be greater in a specific group.

In prospective studies, like BASUN, loss to follow-up can also create a problem. This might also be the case for register data when time to event is included. In the analysis of BASUN, imputation was included to replace missing data but the analyses were also performed without imputation for comparison. Handling of missing data has been described. If the percentage of individuals lost to follow-up is larger in one of the study groups, this makes comparing the groups difficult as there could be a reason that these individuals are missing. In BASUN, this might, for example be individuals that achieved less weight loss and therefore chose not to report back to the study. In BASUN, the proportion of missing participants was the largest in the medical treatment group (41%) compared to 26% in RYGB group and 20% in SG group which could introduce differential misclassification. With regard to the studies from NDR and SOReg, the participants could be lost to follow-up if they emigrated, did not show up for planned health care visits or decided to withdraw their data from the registries. Participants might also be exposed to treatment during the follow-up which could influence the outcome. The participants in study I and II did not receive surgical treatment of obesity during the follow-up period and only two participants in the

medical treatment group in BASUN reported bariatric surgery during the follow-up period.

Finally, errors may be made during the analysis of the data with erroneous selection of statistical models or inappropriate adjustment of variables. Variables that are included in the causal pathway between the independent variable and the dependent variable (exposure and effect) should not be adjusted for. Adjusting for variables that do not influence the independent or dependent variable (thus by definition not confounders) is not necessary and might affect the precision of the statistical model.

In our studies, the presented differences in outcomes between treatment groups can be the result of *random error*, true causality or because of faulty data. To quantify the random error, probability (p) values and/or confidence intervals (CI) are presented. In clinical studies, the differences between groups are often of interest (for example treated vs untreated). The null hypothesis states that there is no difference between the groups. P-values are defined as the probability of obtaining the observed difference between the groups, or one more extreme, if the null hypothesis is in fact true. Most commonly a threshold value of <0,05 (5%) is used to reject the null hypothesis meaning that the probability of finding a difference when there is none is less than 5%. The p-value can be affected by the size of the study population and is hard to relate to clinical importance. Confidence intervals are used to describe the precision of the value reported and reports the range of plausible values for the real parameter of interest. A reported 95% CI means that we are 95% confident that the real value lies within the reported range.

3.6 ETHICAL CONSIDERATIONS

Study I and II are based on data from the merging of two national patient databases, NDR and SOReg as well as data from a number of national registries. The data from the various registries was linked by the National Board of Health and Welfare. Before being delivered to the researchers, the data is coded and anonymized. Data is continuously reported from caregivers around the country to NDR and SOReg and these registries include almost all individuals with diabetes and those treated with bariatric surgery in Sweden. All of the data are presented on a group level and thus are not traceable to a particular individual. The ethical aspects of register studies mainly concern data security and maintaining privacy of the individuals included. Risk for individual patients is minimized by coding and data de-identification. The individuals included in the registries have been informed that data from the registry is included in research and can at any time ask that their personal information be withdrawn. Informed consent for each particular study, however, is not collected.

Studies III-V are based on data from an ongoing prospective study. For this study, informed consent was obtained from each participant in the study before enrollment. Written and verbal information was given to each participant. To ensure that consent was given after the participant received and understood the information given, only individuals that understood Swedish were included. The participants may at any time, without explanation, choose to leave the study and are ensured that this will not influence their follow-up care in any way. The participants may wish that their information is withdrawn from the study. Each individual receives an ID number that is non-identifiable at enrollment. Identification codes are stored in a locked facility that is inaccessible to others than the principal investigator and research nurses. Blood- and urine samples will be saved up to 12 years and the participants have been informed of this.

The Ethical Regional Board of Gothenburg approved the studies included in this thesis (studies I and II: Dnr 563-12, studies III-V: Dnr 673-14).

4 RESULTS

4.1 STUDY I

Effects of bariatric surgery in individuals with type 1 diabetes

A total of 387 individuals with type 1 diabetes that had undergone RYGB were identified and matched with 387 individuals that had not undergone bariatric surgery. The groups were matched with regard to age (41-42 years), diabetes duration (18-19 years), levels of HbA1c (67.5 mmol/mol control, 70.1 mmol/mol RYGB), blood lipids and blood pressure (< 130/80 mmHg) as well as previous comorbidities and pharmaceutical treatment. There were minor differences with regard to sex (females 89% control, 77% RYGB) and levels of physical activity. The mean BMI in the control group was 39.5 vs 40.8 in the RYGB group (SMD 0.21). Around 14% in both groups were registered as smokers. The follow-up period was up to 9 years (mean of 4.8 years) for hospital admissions and up to 10 years for mortality (mean 5.7 years). A more detailed description of the groups at baseline can be seen in the appendix. A comparison of the outcomes is presented in figure 4.

Cardiovascular disease and mortality were significantly lower in the surgical group, specifically stroke and heart failure. The group that had undergone surgery had significantly more serious hyperglycemic events requiring hospitalization but the differences with regard to serious hypoglycemia did not reach significance. There was a trend towards reduced all-cause mortality in the surgical group and four individuals in this group died because of diabetes coma compared to one individual in the control group. The most common cause of death in the control group was cardiovascular disease or heart failure. The only secondary outcome that differed significantly between the groups was substance abuse which was more common in the surgical group. The mean HbA1c levels were slightly lower for the surgical group at 1 and 2 years after treatment (59.6 mmol/mol and 62.1 mmol/mol vs 67.2 mmol/mol and 67.4 mmol/mol at 1 and 2 years after index date). The BMI in the surgical group was 30.6 kg/m^2 and 28.8 kg/m^2 at 1 and 2 years compared to 37.5 kg/m^2 at both 1 and 2 years for the control group.

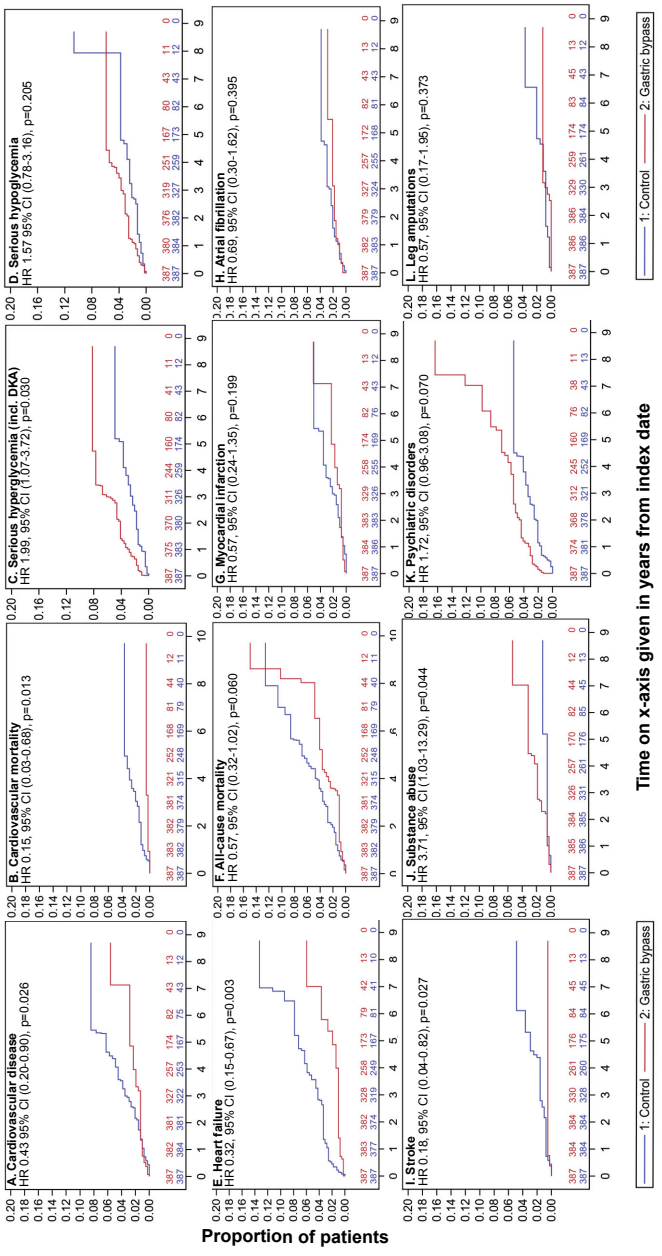


Figure 4. Cumulative incidence of outcomes with number of subjects at risk. American Diabetes Association, Benefits and Harms of Gastric Bypass Surgery in Obese Individuals with Type 1 Diabetes: A Nationwide, Matched, Observational Cohort Study, 2020. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.(91)

4.2 STUDY II

Effects of bariatrics surgery on incidence of heart failure and atrial fibrillation in individuals with type 2 diabetes

After the merging of NDR and SOReg, 5321 individuals with registered type 2 diabetes diagnosis and RYGB operations were identified and matched with 5321 individuals with type 2 diabetes that had not undergone surgery. The mean BMI of the surgical groups was slightly higher (42 vs 41 kg/m^2) but the mean diabetes duration for both groups was between 6 and 7 years with mean HbA1c levels below 60 mmol/mol. The groups were well matched with regard to cardiovascular risk factors and pharmaceutical treatment for heart disease and diabetes. Preexisting heart failure and atrial fibrillation was comparable between the groups (3% and 2.8% respectively) as was previous history of diseases that might affect acceptance for bariatric surgery (mainly psychiatric disease and substance abuse). Individuals in both groups with preexisting heart failure were analyzed separately and as these were not matched specifically, they differed with regards to most baseline characteristics. However, the surgical group had longer diabetes duration and worse metabolic parameters (HbA1c, blood pressure and blood lipids). This group also had more known cardiovascular disease and atrial fibrillation. Valvular disease was more common on the control group. The follow-up period for hospitalization was up to 9 years (mean 4.5 years) and for mortality 10 years.

An overview of cumulative incidence of outcomes can be seen in figure 5. An over 40% lower risk for hospitalization for atrial fibrillation was observed in the surgical group as well as 73% lower risk for hospitalization for heart failure (77% lower risk for hospital admission that included both diagnoses). The subgroup with known heart failure showed a significant reduction of mortality in the surgical group compared with the control group (HR 0.23, 95% CI 0.12, 0.46). Comparable results were shown for fully adjusted and less adjusted Cox regression models. Five individuals (3.5%) in the surgical group died of causes related to the circulatory system compared to 31 individuals (18.7%) in the control group. Heart failure was the registered cause of death for four patients in the control group but only one in the group that received surgical treatment.

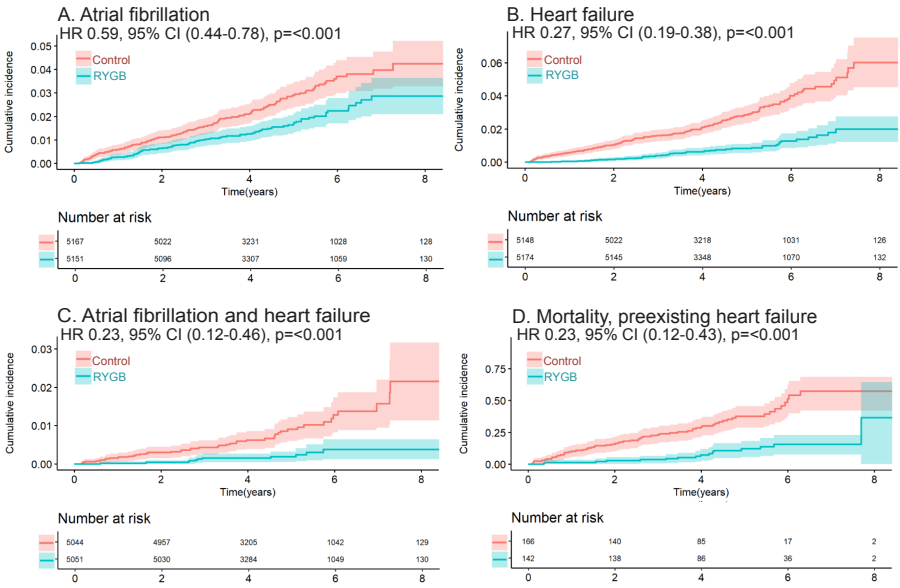


Figure 5. Cumulative incidence of atrial fibrillation and/or heart failure and mortality in individuals with preexisting heart failure. Höskuldsdottir et al, Potential effects of bariatric surgery on the incidence of heart failure and atrial fibrillation in patients with type 2 diabetes and obesity, and on mortality in patients with pre-existing heart failure: a nationwide, matched, observational cohort study. J Am Heart Assoc. 2021. Copyright and all rights reserved. Material from this publication has been used with the permission of Wiley. (92)

4.3 STUDY III

The BASUN population.

After being referred to the Regional Obesity Centre for treatment of obesity, 1127 individuals were invited to participate in the study. Of these, 589 individuals were accepted for surgical treatment (388 RYGB and 201 SG) and 382 for medical treatment, in total 971 individuals (figure 6). Table 3 summarizes baseline characteristics of the population. There were slight differences at baseline with regard to age and BMI but distribution of sex, education, smoking, marital status, treatment for metabolic disease, pain, anxiety or depression, other psychiatric disease and deficiencies of vitamins and minerals did not differ between the groups. There were differences in

levels of high-density lipoproteins and baseline but not low-density lipoproteins.

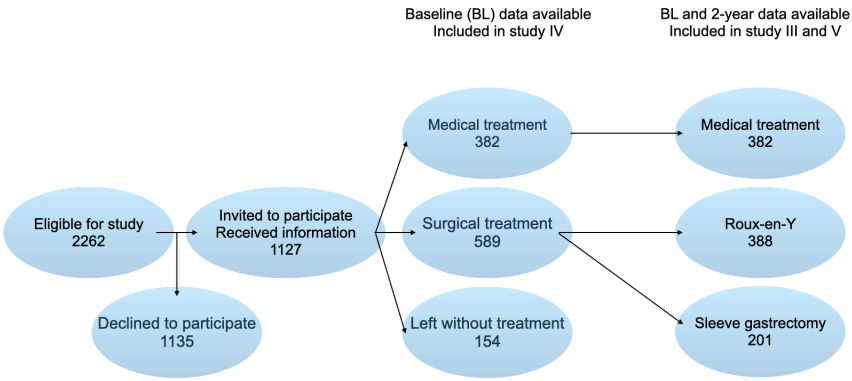


Figure 6. Recruitment of participants to BASUN. Höskuldsdottir. Unpublished.

Characteristics of participants in BASUN at baseline				
	MT	RYGB	SG	p
n	382	388	201	
Female	276 (72.3)	301 (77.6)	152 (75.6)	0.206
Age (years)	49 (18-78)	44 (18-62)	41 (18-63)	<0.001
BMI (kg/m^2)	40.1 (31.6-90.4)	41.8 (34.8-65.3)	41.6 (35-63.7)	<0.001
Married/cohabitation	206 (53.9)	242 (62.4)	121 (60.2)	0.955
HbA1c (mmol/mol)	36 (25-95)	37 (26-118)	36 (27-73)	0.173
HDL (mmol/l)	1.3 (0.6-2.6)	1.2 (0.4-2.3)	1.2 (0.7-2.0)	0.003
LDL (mmol/l)	3.1 (1.2-6.7)	3.2 (0.8-6.2)	3.3 (0.9-5.7)	0.627
Glucose-lowering drugs	55 (14.4)	55 (14.2)	28 (13.9)	0.990
BP-lowering drugs	135 (35.3)	112 (28.9)	58 (28.9)	0.109
Lipid-lowering drugs	52 (13.6)	51 (13.1)	23 (11.4)	0.768
Smoking	23 (6.0)	24 (6.2)	13 (6.5)	0.884

Table 3. Summary of baseline characteristics of participants in BASUN. Legend: Data are n (%) or median (range). MT: medical treatment, GBP: Roux-en-Y gastric bypass, SG: Sleeve gastrectomy. BMI: Body mass index. HDL: High-density lipoprotein. LDL: Low-density lipoprotein

4.4 STUDY IV

Predictors of BMI

Data from 1120 individuals included in the original BASUN population (MT n= 380, RYGB n=385, SG n=201 and 154 individuals that discontinued the study before treatment) were included in the analysis in study IV. A summary of baseline characteristics can be seen in table 4 and a more detailed version in appendix. All groups included more women, mostly individuals born in Sweden and the BMI levels were similar and within normal range. There were minor differences with regards to socioeconomic status and smoking but previous metabolic disease, including diabetes, hyperlipidemia, hypertension and sleep apnea as well as clinical parameters of these disorders, was similar. There were minor differences in answers from questionnaires focusing on anxiety and depression but not in reported diagnosis or treatment for these conditions. The groups were comparable with regards to factors that might influence choice of bariatric surgery (anemia, vitamin- or mineral deficiencies, alcohol use, eating habits, previous cancer, treatment with proton pump inhibitors or previous comorbidities).

Nine of the fifteen clinical domains had predictive value on BMI levels: Socioeconomic status, Age/sex, Other biomarkers, Lifestyle and habits, Biomarkers for cardiovascular disease and diabetes, Potential anxiety and depression, Metabolic disease, Medication for cardiovascular disease or diabetes and Other conditions (figure 7). With regard to individual variables; country of birth, marital status, sex, calcium levels, age, levels of TSH and HbA1c, AUDIT scores, binge eating reflected by the QEWP-R questionnaire and levels of TG were the ten strongest predictive variables. The relationship between these variables and BMI levels is presented in figure 8. Being born in Sweden, male sex and younger age were observed as predicting higher BMI levels. Binge eating, as reported by QEWP-R was also predictive for higher BMI. Higher levels of triglycerides and thyroid stimulating hormones as opposed to lower levels of HbA1c and calcium were predictive for higher BMI. Lower AUDIT scores predicted higher BMI. With regards to marital status, being married was predictive for lower BMI levels compared to living in cohabitation, being in a relationship without cohabitation, being single or living with parents that were predictive for higher BMI levels.

Characteristics of participants in study IV at baseline					
	MT	RYGB	SG	Discontinued	SMD
n	380	385	201	154	
Sex = Male	105 (27.8)	103 (26.8)	53 (26.5)	29 (18.8)	0.107
Age, years	44.20 (12.89)	45.01 (12.90)	44.51 (12.69)	39.82 (12.21)	0.211
BMI, kg/m^2	41.96 (4.80)	41.65 (5.47)	42.08 (4.32)	42.21 (4.59)	0.061
Nicotine:					0.181
Ex-smoker	86 (22.6)	126 (32.7)	53 (26.4)	42 (27.3)	
Non-smoker	268 (70.5)	227 (59.0)	141 (70.1)	104 (67.5)	
Smoker	26 (6.8)	32 (8.3)	7 (3.5)	8 (5.2)	
Born in Sweden	223 (84.8)	230 (83.0)	123 (82.0)	84 (85.7)	0.059
HbA1c, mmol/L	39.12 (11.11)	40.78 (12.64)	39.16 (10.39)	40.21 (11.21)	0.088
Triglycerides, mmol/L	1.54 (0.76)	1.63 (0.92)	1.74 (0.86)	1.41 (0.70)	0.225
HDL, mmol/L	1.26 (0.33)	1.32 (0.35)	1.35 (0.35)	1.22 (0.21)	0.242
LDL, mmol/L	3.20 (0.89)	3.35 (0.93)	3.32 (1.09)	3.28 (0.80)	0.093
Antihyperglycemic drugs	49 (12.9)	52 (13.5)	24 (11.9)	14 (9.1)	0.075
Antihypertensive drugs	111 (29.2)	114 (29.6)	55 (27.4)	35 (22.7)	0.085
Lipid-lowering drugs	43 (11.3)	46 (11.9)	27 (13.4)	11 (7.1)	0.108
Drugs for anxiety/depression	74 (19.5)	77 (20.0)	36 (17.9)	29 (18.8)	0.029

Table 4. Summary of baseline characteristics of BASUN participants included in study IV. Data are n (%) or mean (SD). MT: medical treatment, GBP: Roux-en-Y gastric bypass, SG: Sleeve gastrectomy. BMI: Body mass index. HDL: High-density lipoprotein. LDL: Low-density lipoprotein

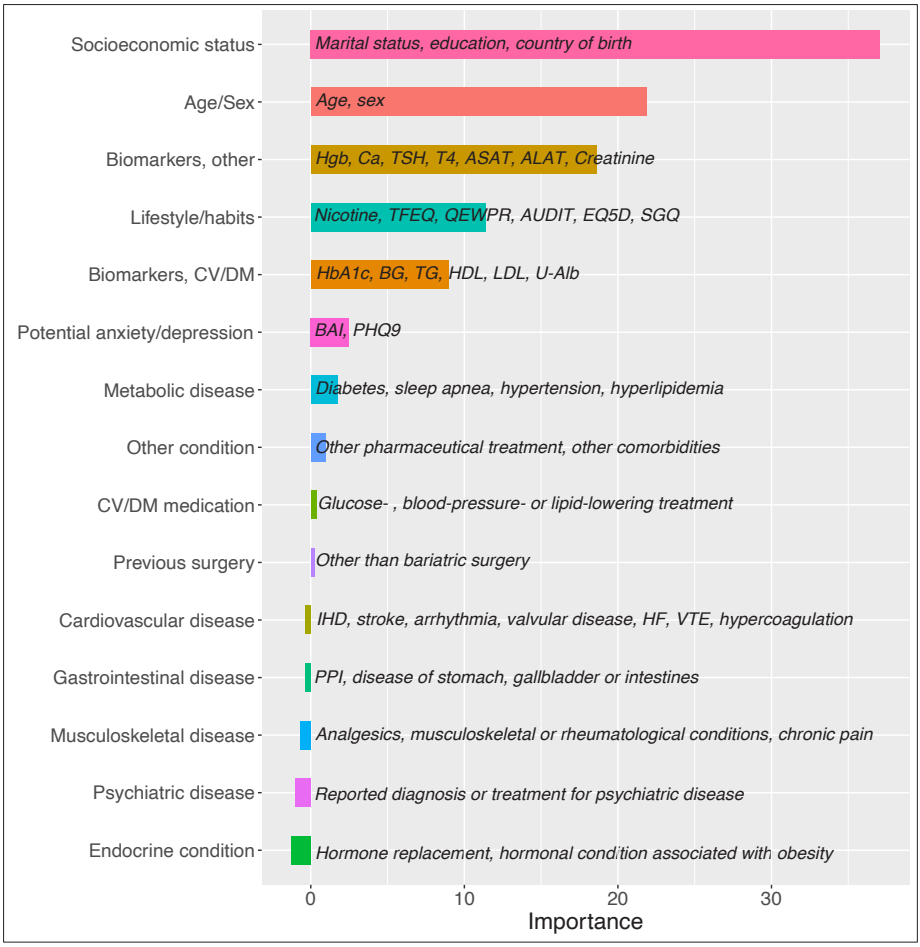


Figure 7. Predictive value of 15 clinical domains and the variables included within each domain. Höskuldsdottir. Unpublished. CV: cardiovascular, DM: diabetes mellitus, Hgb: hemoglobin, Ca: calcium, TSH: thyroid stimulating hormone, T4: thyroxine, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, TFEQ: three factor eating questionnaire, QEWP: Questionnaire on eating and weight patterns, AUDIT: Alcohol use disorders identification test, EQ5D: EuroQol five-dimensional questionnaire, SGQ: Saltin Grimby questionnaire, HbA1c: glycated hemoglobin, BG: blood glucose, TG: triglycerides HDL: high density lipoprotein, LDL: low-density lipoprotein, U-Alb: urinary albumin, BAI: Becks anxiety inventory, PHQ-9: Patient health questionnaire-9, IHD: ischemic heart disease, HF: heart failure, VTE: venous thromboembolism, PPI: proton-pump inhibitors

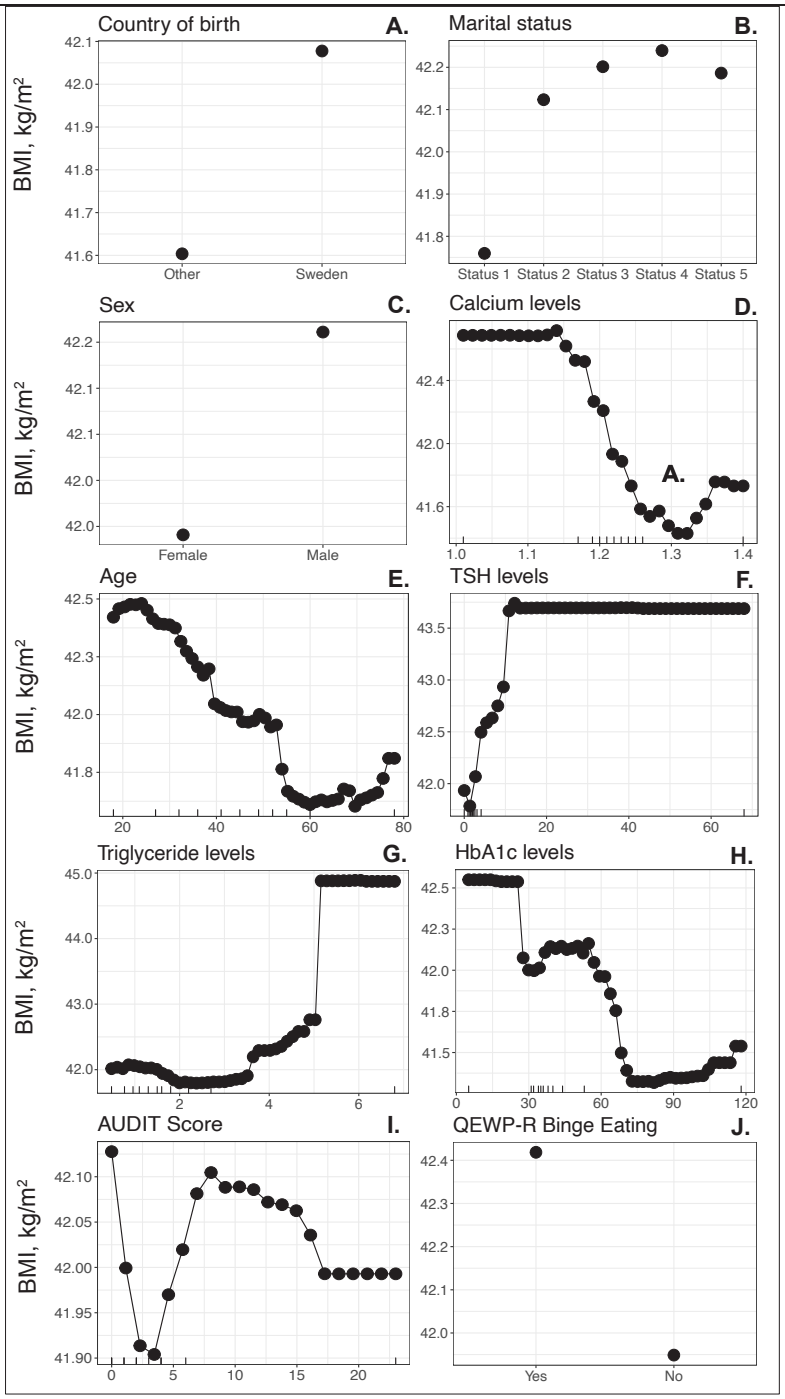


Figure 8. The relationship between the ten variables with strongest predictive value for BMI. Höskuldsdottir. Unpublished. Levels of BMI presented on the y-axis

4.5 STUDY V

Effects of medical and surgical methods of obesity

Of the 969 individuals that received treatment at the start of the BASUN study, data was available for 667 at two-year follow-up (MT n=225, RYGB n=284, SG n=158). A summary of the population at baseline can be seen in table 5.

Characteristics of participants in study V at baseline				
	MT	RYGB	SG	SMD*
n	382	387	200	
Sex = Male	103 (27.2)	85 (22.0)	50 (25.0)	0.08
Age, years	47.6 (14.2)	42.0 (11.3)	40.8 (11.0)	0.36
Weight at baseline, kg	118.1 (20.8)	122.4 (17.2)	123.9 (20.7)	0.19
BMI at baseline, kg/m^2	41.0 (5.39)	42.5 (4.1)	42.8 (4.9)	0.24
Nicotine				0.18
Smoker	24 (6.3)	24 (6.2)	14 (7.0)	
Ex-smoker	85 (22.3)	131 (33.9)	60 (30.0)	
Country of birth = Sweden	226 (80.7)	248 (87.6)	137 (86.7)	0.13
Diabetes	49 (12.8)	56 (14.5)	25 (12.5)	0.04
Hypertension	90 (23.6)	77 (19.9)	41 (20.5)	0.06
Hyperlipidemia	14 (3.7)	19 (4.9)	11 (5.5)	0.06
Sleep apnea	18 (4.7)	14 (3.6)	12 (6.0)	0.08
Cardiovascular disease	6 (1.6)	3 (0.8)	1 (0.5)	0.07
Depression/anxiety	42 (11.0)	19 (4.9)	20 (10.0)	0.15
Antihyperglycemic drugs	55 (14.4)	57 (14.7)	27 (13.5)	0.024
Antihypertensive drugs	141 (36.9)	116 (30.0)	58 (29.0)	0.113
Lipid lowering drugs	51 (13.4)	51 (13.2)	25 (12.5)	0.017
Drugs for anxiety/depression	92 (24.1)	72 (18.6)	51 (25.5)	0.111

Table 5. Summary of baseline characteristics of participants I study V. BMI: body mass index. Data are n (%) or mean (SD)

Primary outcomes

The changes in anthropometric and laboratory variables after two years are presented in figure 9. The mean BMI was 36.8 kg/m^2 in the MT group, 28.5 kg/m^2 after RYGB and 30.8 kg/m^2 after SG. The largest percentual weight loss was seen in the surgical groups (33% after RYGB and 27.5% after SG) compared to 8.9% after MT. There was a significant difference in weight loss in females between the treatment groups, with the greatest observed weight loss in the RYGB group. The difference between the surgical methods in reported weight loss in males did not reach significance. With regard to changes in excess BMI, the reported decrease was 27.5%, 70.1% and 82.6% for MT, SG and RYGB respectively (p-values < 0.001). The decrease in HbA1c in all of the treatment groups was comparable. Decrease in TG and increase in HDL was greatest in the surgical groups compared to MT but there was not a significant difference between RYGB and SG. The reduction of LDL was greatest after RYGB but did not differ significantly between MT and SG. Levels of vitamin D and folate increased in all groups without significant difference between the groups. There were slight reductions in hemoglobin levels and increases in B12 and iron in the surgical groups but there were no differences between RYGB and SG.

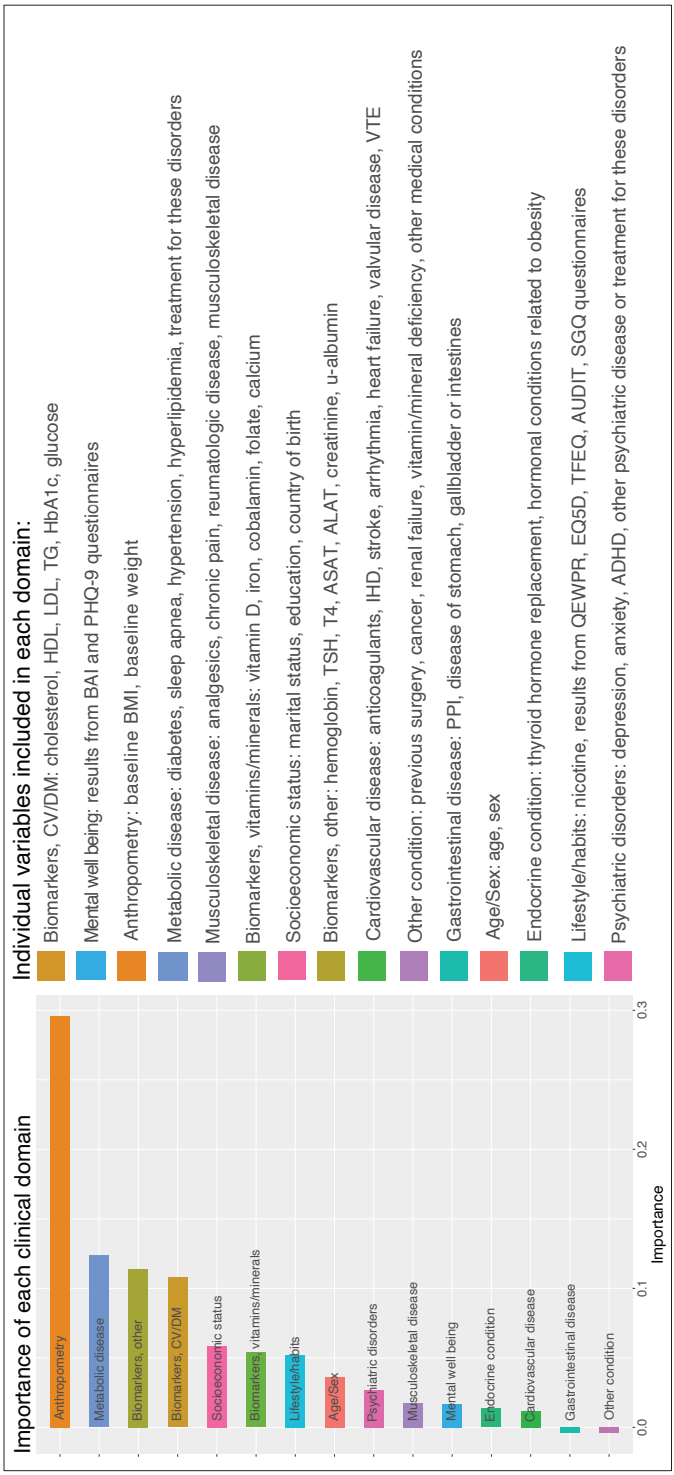
Secondary outcomes

The need for surgery and in-hospital treatment was similar between the groups (MT 7.4%, RYGB 8.2%, SG 6.5%; MT 19.5%, RYGB 18.6%, SG 20.3%, respectively, p-values n.s.). The likelihood for successful treatment was higher after surgery (odds ratio (OR) 5.89 for RYGB and 4.20 for SG), but not significantly different between the two surgical methods in reference to MT. The likelihood for treatment failure was lower in the surgical groups but did not differ significantly between the two surgical groups (OR RYGB 0.30, SG 0.38). The proportions of patients achieving a weight loss of at least 10 % were 45.3%, 99.6% and 95.6%, respectively, and the proportions of patients achieving a weight loss of 20% or more were 16.0%, 94.0%, and 74.7%, in MT, RYGB and SG, respectively (p-values < 0.001). Additionally, 61.3% of the MT group maintained at least 5% weight loss, compared to 99.6% after RYGB and 98.7% after SG. Ten individuals reported using liraglutide (MT: 9, SG: 1), 2 individuals in the MT group used orlistat and 8 individuals used an SGLT2 inhibitor (MT: 6, RYGB: 1, SG: 1). Two patients

died in both the MT and the RYGB groups but there were no fatalities in the SG group (p-value n.s.). In two cases, the cause of death was known (cancer) but unknown in two cases.

The proportion of individuals qualifying for binge eating according to the QEWP-R questionnaire was higher in the MT group compared to the surgical groups as well as emotional- and uncontrolled eating according to TFEQ. Scores for potential anxiety according to BAI and depression according to PHQ9 declined in all groups after treatment but scores for potential depression remained higher in the MT group at two-years. Quality of life scores according to EQ5D were comparable at baseline but higher in the surgical groups at follow-up. The proportion of individuals that reported physical inactivity declined in all groups after treatment and light and regular physical activity increased in both surgical groups. Risk for alcohol abuse according to AUDIT was comparable between the groups at baseline and two-year follow-up.

Figure 9. Changes in clinical variables presented as estimated means with 95% confidence intervals. Höskuldsdottir. Unpublished. RYGB: Roux-en-Y gastric bypass, SG: Sleeve gastrectomy


Importance of each clinical domain
Anthropometry
Metabolic disease
Biomarkers, other
Biomarkers, CV/DM
Socioeconomic status
Biomarkers, vitamins/minerals
Lifestyle/habits
Age/Sex
Psychiatric disorders
Musculoskeletal disease
Mental well being
Endocrine condition
Cardiovascular disease
Gastrointestinal disease
Other condition
0.0
0.1
0.2
0.3
Importance
Individual variables included in each domain:
Biomarkers, CV/DM: cholesterol, HDL, LDL, TG, HbA1c, glucose
Mental well being: results from BAI and PHQ-9 questionnaires
Anthropometry: baseline BMI, baseline weight
Metabolic disease: diabetes, sleep apnea, hypertension, hyperlipidemia, treatment for these disorders
Musculoskeletal disease: analgesics, chronic pain, reumatologic disease, musculoskeletal disease
Biomarkers, vitamins/minerals: vitamin D, iron, cobalamin, folate, calcium
Socioeconomic status: marital status, education, country of birth
Biomarkers, other: hemoglobin, TSH, T4, ASAT, ALAT, creatinine, u-albumin
Cardiovascular disease: anticoagulants, IHD, stroke, arrhythmia, heart failure, valvular disease, VTE
Other condition: previous surgery, cancer, renal failure, vitamin/mineral deficiency, other medical conditions
Gastrointestinal disease: PPI, disease of stomach, gallbladder or intestines
Age/Sex: age, sex
Endocrine condition: thyroid hormone replacement, hormonal conditions related to obesity
Lifestyle/habits: nicotine, results from QEWPR, EQ5D, TFEQ, AUDIT, SGQ questionnaires
Psychiatric disorders: depression, anxiety, ADHD, other psychiatric disease or treatment for these disorders

Predictive value of clinical domains

The predictive value for the 15 clinical domains analyzed with regard to successful treatment is presented in figure 10. For the overall cohort, variables related to anthropometry at baseline, metabolic disease, lifestyle and habits and socioeconomic status had predictive value, as well as different biomarkers. Results from the analysis for predictive value of the domains divided by the treatment groups can be seen in the appendix. When the MT group was analyzed separately, domains including metabolic disease, musculoskeletal disease, anthropometry at baseline, psychiatric disorders, socioeconomic status, lifestyle and habits and a number of biomarkers had strong predictive value. In the RYGB group mental well-being and a number of biomarkers, anthropometry, metabolic disease and lifestyle and habits had predictive value while psychiatric disorders, anthropometry and biomarkers were the strongest in the SG group.

Figure 10. (page 46) Predictive value of 15 clinical domains on the success of obesity treatment. Höskuldsdottir. Unpublished.

CV: cardiovascular, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low-density lipoprotein, TG: triglycerides, HbA1c: glycated hemoglobin, BMI: body mass index, TSH: thyroid stimulating hormone, T4: thyroxine, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, IHD: ischemic heart disease, VTE: venous thromboembolism, PPI: proton-pump inhibitors, BAI: Becks anxiety inventory, PHQ-9: Patient health questionnaire-9, QEWP: Questionnaire on eating and weight patterns, EQ5D: EuroQol five-dimensional questionnaire, TFEQ: three factor eating questionnaire, AUDIT: Alcohol use disorders identification test, SGQ: Saltin Grimby questionnaire, ADHD: attention-deficit/hyperactivity disorder

5 DISCUSSION

The main aim of this project was to improve the treatment of individuals with obesity. We have shown that individuals with type 1 diabetes might benefit from bariatric surgery with regard to cardiovascular risk and mortality but the risk for serious hyper- and hypoglycemia in this group requires careful consideration. We have also shown that bariatric surgery may reduce risk for heart failure and atrial fibrillation in individuals with type two diabetes and that bariatric surgery may even be considered in a selected group of individuals with type 2 diabetes and obesity with known heart failure. Surgical treatment of obesity is more effective than medical treatment including VLED with regard to weight loss but does not necessarily lead to more complications needing surgery or in-hospital treatment up to two years postoperatively. With good adherence to supplementary treatment, deficiencies of vitamins and minerals or anemia are not more common after surgical treatment in comparison with medical treatment. Medical treatment of obesity with VLED can also be an effective method for weight loss.

How much weight loss is meaningful?

In study V we defined successful treatment effect, in part, as being a reduction of excess BMI by at least 50% or reaching a BMI under 30 kg/m^2. But this is not to imply that weight reduction of smaller caliber is not meaningful. Generally, a minimum weight loss of 5% is recommended for metabolic effects such as insulin sensitivity and intra-hepatic fat but greater loss of weight is needed to observe effects on cardiovascular risk and mortality. (53, 93) The changes in insulin sensitivity derived from weight loss might also be organ specific. (93) In the Standards of Medical Care for the treatment of individuals with type 2 diabetes, a maintained weight loss of 5% is recommended as a first goal but then further weight loss should be encouraged to improve glycemic control.(55) Results from Look ahead study indicated that weight loss over 10% is needed to reduce risk for cardiovascular events in individuals with type 2 diabetes. (54) In study V we observed at least 10% maintained weight loss in 45.3% in the MT group compared to 99.6% after RYGB and 95.6% after SG. Over 60% of the MT group maintained a weight loss of at least 5% at follow-up.

Are the changes in metabolic parameters after bariatric surgery due to alterations of anatomy and hormonal effects or secondary to weight loss?

As previously mentioned, a number of hormones and inflammatory markers are involved in the pathophysiology of obesity and development of comorbidities. Food intake causes decreased levels of ghrelin and increased release of certain peptides, such as incretins and peptide YY. (11) Increased levels of these peptides and reduced levels of ghrelin have been reported after bariatric surgery. (94) This is likely to contribute to weight loss and changes in eating patterns after surgery.

It has been proposed that bariatric surgery and the anatomical and hormonal changes resulting from surgery, are responsible for positive effects on metabolic parameters such as insulin sensitivity, glycemic control and diabetes remission in individuals with type 2 diabetes that are independent of weight loss. These positive effects on glycemic control are observed directly after surgery, before major weight loss has occurred. (95-97) Surgery causing lipid malabsorption has been shown to cause even greater increases in insulin sensitivity than that observed after RYGB with comparable weight loss. (98) A comparison of RYGB and SG showed similar effects on glycemic control in individuals with type 2 diabetes after one year even though the decrease in BMI and observed GLP-1 levels were lower in the SG group, supporting the theory of other contributing mechanisms. (99) However, medical treatment leading to similar weight loss as bariatric surgery has been shown to have effects on metabolic variables that are comparable to those observed after surgery, implying that it is primarily the weight loss that drives these changes. (100, 101) The difficulty in reaching weight loss comparable with bariatric surgery after medical treatment makes the comparison of the effects of these methods on metabolic parameters difficult.

We observed positive effects on HbA1c in all treatment groups in study V and the difference between the groups was not significant. However, the mean HbA1c levels in all groups at the start of our study were not within diabetic range. We also observed positive effects on TG and HDL in all treatment groups but the effects were greater, but comparable, in the surgical groups. The effect on LDL was significantly greater in the RYGB group than in the other two groups with no significant difference between the medical treatment group and SG. The greater effect on LDL levels after RYGB

compared to SG has been observed in other studies and further studies are ongoing. (102-104)

In study II, we observed significant improvements in weight, glycemic control and cardiovascular variables in the surgical group which is likely to have contributed to the risk reduction in this group with regard to heart failure and atrial fibrillation. However, a causal mediation analysis on individuals with type 2 diabetes and obesity indicated that the reduction of mortality risk after bariatric surgery was mainly due to weight reduction rather than improvements of glycemic control, blood pressure and blood lipids which might also indicate that similar results could be seen with other methods leading to comparable weight gain. (75) Obesity in individuals with both type 1 and 2 diabetes has been shown to greatly increase risk for heart failure.(32, 51, 52) The substantial risk reduction observed for heart failure hospitalization after bariatric surgery in study I and II further supports the effect of excess weight as a risk factor and of weight loss in preventing development of heart failure.

Is Roux-en-Y gastric bypass more effective than sleeve gastrectomy?

In study V we observed comparable weight loss in the two surgical groups, 33% after RYGB and 27.5% after SG. The mean BMI at two-year follow-up was 28.5 kg/m^2 and 30.8 kg/m^2 after RYGB and SG respectively. There was a significant difference in weight loss in females between the treatment groups, with the greatest observed weight loss in the RYGB group. There was not a significant difference between the surgical methods in reported weight loss in males. With regard to changes in excess BMI, the reported decrease was 70.1% and 82.6% for SG and RYGB respectively. This confirms previous reports that have not shown significant differences between weight effects of RYGB and SG. (105-107) The results from the STAMPEDE trial were in favor of RYGB with regard to weight loss and diabetes remission at 5 year follow-up. (74) The results with regard to changes in TG and HDL were similar to the ones we observed but the differences between the surgical groups with regard to changes in LDL levels were not observed in the STAMPEDE study. A recent randomized study from Norway reported that diabetes remission one year after surgery was more often achieved after RYGB than SG. (103) This difference at one year

has been seen in further studies but results regarding longer follow-up have been inconclusive. (108) Separate analysis of individuals with known diabetes was not included in our studies.

Can treatment with very low energy diet lead to long-term weight loss?

Of the participants in BASUN that received medical treatment, 45% maintained weight loss of at least 10% at two year follow up and over 60% weight loss over 5% as presented in study V. Medical treatment including VLED has been shown to be effective in treatment of obesity and lead to positive effects on cardiovascular risk factors such as blood pressure, blood lipids and plasma glucose. (109) These effects have been directly related to amount of weight lost. VLED in primary care setting has also been reported to lead to diabetes remission (defined as glycated hemoglobin (HbA1c) levels ≤ 6% or 42 mmol/mol) in close to 50% of individuals with type 2 diabetes and BMI over 27 kg/m^2 that did not require treatment of insulin and with a maximal diabetes duration of six years. (101) The effects of VLED are most extensive with structured follow up, increased levels of exercise and the role of cognitive behavioral treatment has also been explored but needs further research. Pharmaceutical treatment to assist in weight maintenance was uncommon in the BASUN population which is likely to have affected the outcome. Weight loss causes changes in levels of hormones and peptides involved body weight regulation which makes maintaining the weight difficult. Changes in levels of PYY, GIP and leptin cause changes in appetite and have been shown to be persistent for one year after treatment with VLED.(9) This makes maintaining weight loss in an environment with easy access to energy dense food difficult and follow up pharmaceutical treatment with Orlistat or GLP-1 analogues should be considered to support further weight loss after VLED. (59-61, 109) A major strength of the BASUN study is the structured follow-up of the individuals in the medical treatment group with monthly visits with nurses and/or dieticians throughout the treatment year. The cost of pharmaceutical treatment options for individuals with obesity without concomitant type 2 diabetes might have influenced the proportion of individuals treated with these agents in the study.

Which factors are important in maintaining weight loss?

In their review from 2005, Elfhag and Rössner described factors that are associated with maintained weight loss. Some of the factors associated with successful maintenance of weight were achieving weight loss goals, larger initial weight loss, increased physical activity, regular meals including breakfast, less intake of dietary fat, self- monitoring, stability and motivation to name a few. (110) Similarly, ten-year follow-up of the National Weight Control Registry reported that decreased every-day physical activity, dietary restraint and self-monitoring of weight, as well as increased disinhibition and intake of energy from fat were related to weight regain. (111) Regular follow-up visits should address these factors and assist in self-monitoring, provide dietary consultations and motivate the individual. Setting goals that are reachable is an important factor, which is also implied in guidelines where an initial weight loss of 5% is recommended as the first step. (53) Bariatric surgery and treatment including VLED cause substantial weight loss during the treatment phase which is one of the factors for success. Self-monitoring is an influential factor with regard to reducing energy intake and increasing energy expenditure. Demographic factors such as age, sex or socioeconomic variables or baseline levels of weight or physical activity have not been shown to be associated with maintaining lost weight. (112)

The participants in the medical treatment group in BASUN (studies III-V) received dietary recommendations based on the Nordic Nutrition Recommendation (113) after their individual energy requirement had been estimated using the Harris Benedict sex-specific equation. (114) An energy deficit of 30% was calculated to maintain weight loss and the recommended intake of macronutrients included 15-20% of energy intake (E%) from protein, 30 E% fat and 50-55 E% carbohydrates. Several trends in diets have been observed during the last few years and the composition of diets is a popular source of debate. Generally, hypocaloric diets with recommended levels of protein that are based on the individual's preferences and culture can be applied in the treatment of obesity. (6) Diets containing different levels of protein, fat or carbohydrates have not been shown to be more effective in long-term weight loss or maintenance than isocaloric diets containing the recommended levels. (13, 53) However, diets with strict restrictions of certain food products can result in problems with adherence. (6) Intermittent fasting has not been proven to lead to long-term weight loss. (115, 116) Although periods with VLED have been shown to be effective in

inducing substantial weight loss, continuous replacement of meals after the strict VLED period has not been shown to be more effective than a general restriction of calories with regard to maintained weight loss. (116, 117) As previously mentioned, addition of pharmaceutical alternatives to assist in weight maintenance should be considered. (13, 59, 61, 118)

Is there risk for harm with obesity treatment?

The possible risks with bariatric surgery have been described. (119) Increased risk for alcohol abuse and self-harm is well established and this was also observed in study I. (120) The risk for substance abuse, anemia and malnutrition warrant careful selection of individuals for surgical treatment of obesity. We did not observe an increased incidence of hospitalization, surgical treatment or deficiencies of vitamins or minerals in the surgical population included in BASUN in comparison with the medical treatment group at two-year follow-up in study V. This indicates good adherence to supplements and that the choice of treatment was appropriate.

Serious hypoglycemic events are known complications of bariatric surgery and are thought to be, in part, due to the increased release of GLP-1 postoperatively that has been mentioned earlier. (121) This increased risk for hypoglycemia was also observed numerically in the population of individuals with type 1 diabetes included in study I. The study only included serious hypoglycemia that required hospital admission and not events that were treated outside of the hospital. The difference between the groups with regard to hypoglycemia might be larger. An increased risk for diabetes ketoacidosis was also observed in this group after bariatrics surgery as has been reported earlier. This is already apparent on day 2-3 postoperatively and indicates miscalculations in insulin needs after surgery. (80, 84) Early involvement of a diabetes team is warranted to assist in adjustments of insulin treatment. Post-operative hypoglycemia has also been reported directly after bariatric surgery in individuals with type 1 diabetes. In our study we did not include information on usage of insulin pumps or continuous glucose monitoring systems which could have given more information on glycemic variability postoperatively. Reports of glycemic control after bariatric surgery in individuals with type 1 diabetes have been inconclusive. (80, 122, 123)

Side effects of VLED have also been reported, most commonly hair loss, constipation, dizziness, cold intolerance and fatigue that can be generalized to large weight loss. Biliary colic has also been reported but is uncommon. (101, 124) These side effects are generally temporary and directly related to ongoing treatment. We only included hospital admissions in the BASUN study and not common side effects. Pharmaceutical treatment for hypertension and diabetes may need adjusting to avoid hypotension and hypoglycemia. Reports on increased risk for eating disorders during or after VLED have been inconclusive. (109)

Although obesity is an independent risk factor for heart failure there is no clear consensus on recommendations for weight loss in individuals with known heart failure. Heart failure is a catabolic condition and worsening disease often leads to cachexia. Inducing extreme weight loss might have negative effects on survival and the ideal body composition with regard to survival in heart failure is still unclear. (20) Generally losing large amounts of weight is not recommended in individuals with BMI > 35 kg/m^2 with known heart failure. (33) The results presented in study II still indicate that there might be a subgroup of individuals with known heart failure that could benefit from bariatric surgery.

Can we define factors that predict obesity and effects of obesity treatment?

Machine learning algorithms have been used to accurately predict childhood obesity. (125) However, the development of obesity in adults is more complex and models for predicting obesity in adults have to include large amounts of data. In study IV we took advantage of the diverse data available for the BASUN population at baseline to apply machine learning algorithms for exploration. The analysis included were mainly hypothesis generating. BMI, age, nicotine use, blood pressure, blood glucose, blood lipid profiles, adiposity, levels of physical activity and family history have previously been identified as risk factors associated with obesity after analysis with various machine learning models. (126) In comparison, we found that domains including socioeconomic status, age, sex, lifestyle and habits had the strongest predictive value on BMI. Interestingly, results from questionnaires focusing on the patients´ mental well-being had stronger predictive value in comparison with known psychiatric disorders or pharmaceutical treatment for

these disorders. Untreated psychiatric disease, known eating disorders and substance abuse are contraindications for bariatric surgery.

The results with regard to different biomarkers such as triglycerides, liver transaminases and HbA1c should be interpreted with caution as it is more likely that the levels of these biomarkers are the result of obesity and not vice versa. The largest part of the population included has BMI levels within a relatively small range. The differences in BMI levels observed when individual variables were analyzed are hard to incorporate into clinical practice (figure 8) and the combination of different variables in domains might be of more value.

In further analysis of data from the BASUN population in study V, we applied machine learning algorithms, random forest, to explore which clinical domains had predictive value with regard to success of obesity treatment. Here, the participants´ mental well-being or known psychiatric disorder strongly predicted treatment success in the different treatment groups. When considering bariatric surgery, previous psychiatric illness is taken into consideration as risk for depression and self-harm may increase after surgery. The strength of the questionnaires used to assess well-being implies that they might be of value in evaluating and treating individuals with obesity and not only known psychiatric disorders.

6 CONCLUSIONS

In the studies included in this thesis we have shown that bariatric surgery may be considered in individuals with type 1 diabetes after careful consideration of risk for serious hypo- and hyperglycemia and with early involvement of a diabetes team.

Bariatric surgery is an important option for individuals with type 2 diabetes and obesity to reduce risk for heart failure and atrial fibrillation and may even be considered in a selected population of individuals with known heart failure.

Mental well-being, as assessed by questionnaires, and not only diagnosis of psychiatric disorders could be an important factor in the treatment and follow-up with individuals with obesity.

Although surgical treatment of obesity is more effective with regard to weight loss than medical treatment with VLED, medical treatment can also lead to meaningful weight loss.

The positive effect of bariatric surgery on triglycerides and levels of HDL-cholesterol is greater than after medical treatment. RYGB might have greater effect in decreasing LDL-levels.

Deficiencies of vitamins and minerals, anemia or complications of treatment are not necessarily more common after bariatric surgery in comparison with medical treatment given good compliance to supplementary treatment and careful choice of treatment option.

7 FUTURE PERSPECTIVES

Although the treatment of obesity has been improved greatly during the last decades the prevalence continues to increase.

We have shown in study I that bariatric surgery could be considered in individuals with type 1 diabetes and obesity, however, further studies are needed. Comparing effects of bariatric surgery and medical treatment with VLED in this population might be of value. The effects of pharmaceutical treatment of obesity in individuals with type 1 diabetes are also needed.

The results of study II implied that bariatric surgery could be an option for a selected population of individuals with type 2 diabetes, obesity and known heart failure to reduce mortality in this group. Our study included a relatively small population of individuals with known heart failure and the groups compared were not matched. The role of bariatric surgery and weight loss treatment in general in individuals with heart failure needs further exploring, especially in younger individuals where obesity is likely to be a strong contributor to cardiac disfunction.

In studies I and II we only included RYGB as the surgical method but SG has become more common during the last years. Including SG in further studies based on the merging of data from NDR and SOReg could be valuable in comparing these methods.

In study IV we presented individual variables and domains of variables that might have value in predicting BMI. Further analyses of this are needed before this can be considered in clinical practice. Dividing the population into class 1-3 obesity and looking at the predictive strength of the variables in different levels of obesity could be of interest.

We have shown that medical treatment of obesity that includes VLED is effective. However, pharmaceutical treatment to assist in further weight loss and weight maintenance was uncommon in the population included. Further studies on additive treatment of obesity drugs after VLED are needed.

Further evaluation of newer pharmaceutical treatment such as GLP-1 receptor agonists and combinations of these and GIP are needed. Treatment including

mechanisms involving other gastrointestinal peptides, such as PYY, PP or ghrelin, on appetite and satiety as well as passage of food through the gut, might also be future possibilities.

The BASUN study is an ongoing prospective study with planned follow-up at 5 and 10 years. Sub-studies on the participants with diabetes, studies focusing on psychiatric health and further analysis of eating habits, to name a few, are already planned. Further studies in the group that received medical treatment could also be of value, specifically focusing on the group that maintained weight loss over 10% and defining characteristics of this group.

Further analysis on the predictive value of different variables, or combinations of variables, for successful or unsuccessful treatment will be of interest. Comparing results from regression models, random forest models and models using gradient boosting, for example, could be of value in trying to find variables that are of greatest importance. Ultimately, the results from further analysis could be combined to create a risk calculator that could assist in making treatment choices, taking into consideration likelihood for successful treatment results as well as risk for complications.

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