

Identifying predictors of long-term effects of bariatric surgery

Analysis of samples and data from the Swedish Obese Subjects (SOS) study

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“The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge”

- Daniel J. Boorstin

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ABSTRACT

Aim of the thesis: To identify predictors of long-term treatment outcomes after bariatric surgery.

Material and methods: The Swedish Obese Subjects (SOS) study is a prospective controlled intervention study comparing bariatric surgery (n=2010) and conventional obesity treatment (n=2037). Data on anthropometry, biochemical variables, and questionnaires are available from over 20-years of follow-up. Data on mortality and morbidity were obtained from national registers. DNA for genetic analysis was extracted from samples of whole blood.

Results: In *Paper I*, carriers of the chromosome 16p11.2 microdeletion, which is strongly associated with obesity, had significantly higher BMI, insulin levels, and systolic blood pressure at baseline compared to non-carriers. However, long-term weight loss and changes in risk factors were similar in both groups. *Paper II* showed that individuals with obesity at the age of 20 had greater initial weight reduction following bariatric surgery compared to those who developed obesity later in life. However, the effects of surgery on cardiometabolic health were similar across subgroups defined by obesity onset. In *Paper III*, we found that bariatric surgery was associated with a reduced risk of breast cancer in women with obesity, with the greatest treatment benefit observed in women with hyperinsulinemia at baseline. *Paper IV* found an association between the A-allele in rs9939609 in the fat mass and obesity-associated protein (*FTO*) gene, and breast cancer risk in women with obesity after bariatric surgery.

Conclusion: In conclusion, the presence of a microdeletion on chromosome 16p11.2 or the age of obesity onset did not affect treatment outcomes following bariatric surgery. In contrast, baseline insulin levels and a risk allele in the *FTO* gene were associated with treatment benefits on cancer risk after bariatric surgery in women with obesity.

Keywords: Bariatric surgery, obesity, predictor, cancer, cardiovascular disease, *FTO*, insulin

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SAMMANFATTNING PÅ SVENSKA

Fetmakirurgi är idag den mest effektiva metoden för att gå ned i vikt och bibehålla viktnedgång under lång tid. Utöver viktnedgång ger fetmakirurgi även skydd mot fetmarelaterade sjukdomar som kardiovaskulära sjukdomar, metabola sjukdomar och cancer. Trots kirurgins positiva effekter finns ändå undergrupper som inte svarar lika väl vad gäller viktnedgång eller prevention av fetmarelaterade sjukdomar. Syftet med den här avhandlingen är att identifiera biologiska markörer som kan hjälpa till att förutsäga behandlingsutfall efter fetmakirurgi och på så sätt möjliggöra individualiserad fetmabehandling.

Till grund för detta används data från Swedish Obese Subjects (SOS) studien. SOS är en prospektiv, matchad interventionsstudie där över 4000 deltagare med fetma rekryterats under åren 1987 – 2001. Hälften av deltagarna behandlades med fetmakirurgi och andra hälften utgör en kontrollgrupp. Studiedeltagarna har därefter följts upp regelbundet under en 20-års period, med antropometriska mätningar så som vikt, blodtryck och midjemått. Blodprover har även tagits och deltagarna har svarat på enkätundersökningar om livskvalité och livsstil. Information om sjukdomar och död har inhämtats från nationella kvalitetsregister såsom cancerregistret, dödsorsaksregistret och patientregistret. För vissa studier har vi genomfört DNA-analyser för att kartlägga genetisk variation hos deltagarna.

I delarbete 1 undersökte vi om bärare av en deletion på kromosom 16, som är starkt associerad med fetma, har lika god effekt av fetmakirurgi när det gäller viktnedgång och fetmarelaterade sjukdomar. Vi genomförde DNA-analyser på 1843 prover från deltagare som genomgått fetmakirurgi och identifierade 9st bärare av deletionen. Efter fetmakirurgi fann vi inga signifikanta skillnader mellan bärare och icke-bärare av deletionen, varken när det gäller viktnedgång eller riskfaktorer för kardiovaskulär sjukdom.

I delarbete 2 undersökte vi om studiedeltagare med fetma i ung ålder, definierat som 20 år, har lika god effekt av fetmakirurgi när det gäller viktnedgång och fetmarelaterade sjukdomar. Vi fann att de med fetma vid 20 års ålder initialt hade signifikant större viktnedgång än de som var normalviktiga vid 20 års ålder, men att denna skillnad försvann över tid. För övrigt hade alla grupper, inklusive de med övervikt vid 20 års ålder, inga signifikanta skillnader i effekten av fetmakirurgi vad gäller viktnedgång, skydd mot metabola- och kardiovaskulära sjukdomar, eller cancer.

I delarbete 3 undersökte vi om fetmakirurgi minskar risken att utveckla bröstcancer hos kvinnor med fetma. Vi fann att fetmakirurgi var associerad med en minskad risk för bröstcancer. Vi fann även att riskminskningen var mest uttalad hos de kvinnor som hade höga insulinnivåer före operationen.

I delarbete 4 analyserade vi en genetisk variant i *FTO*-genen, kallad rs9939609, som är associerad med fetma. Vi undersökte om denna variant påverkar risken att utveckla bröstcancer hos kvinnor med fetma och om den påverkar bröstcancerriks hos kvinnor som genomgår fetmakirurgi. Vi fann ingen association mellan varianten och bröstcancerriks. Däremot fann vi att hos kvinnor med fetma som genomgick fetmakirurgi var bärarskap av A-allelen associerat med minskad risk för bröstcancer.

Sammanfattningsvis har vi identifierat flera biologiska markörer för behandlingsutfall efter fetmakirurgi. Dessa markörer kan potentiellt ingå i prediktionsmodeller utformade för att förutsäga behandlingseffekt efter fetmakirurgi hos enskilda patienter. På detta sätt kan man identifiera patienter som är bäst lämpade för fetmakirurgi, men också patienter där andra behandlingsalternativ är att föredra. Min förhoppning är att denna avhandling kommer att utgöra en liten, men viktig, del i utvecklingen av precisionsmedicin inom fetmabehandling.

LIST OF PAPERS

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

- I. **Long-term effects of bariatric surgery in patients with obesity and chromosome 16p11.2 microdeletion.**
Kristensson FM, Andersson-Assarsson JC, Kanerva N, Peltonen M, Carlsson B, Carlsson LMS. *Surgery for Obesity and Related Diseases*, 2017. 13(8): p.1321-1326.
- II. **Effects of Bariatric Surgery in Early- and Adult-Onset Obesity in the Prospective Controlled Swedish Obese Subjects Study.** Kristensson FM, Andersson-Assarsson JC, Svensson PA, Carlsson B, Peltonen M, Carlsson LMS. *Diabetes Care*, 2020. 43(4): p. 860-866.
- III. **Breast Cancer Risk After Bariatric Surgery and Influence of Insulin Levels – A Nonrandomized Controlled Trial.** Kristensson FM, Andersson-Assarsson JC, Peltonen M, Jacobson P, Ahlin S, Svensson PA, Sjöholm K, Carlsson LMS, Taube M. *JAMA Surgery*, 2024. 159(8): p. 856-863.
- IV. **FTO rs9939609 genotype and breast cancer risk after bariatric surgery in the Swedish Obese Subjects study.** Langegård E*, Kristensson FM*, Andersson-Assarsson JC, Peltonen M, Svensson PA, Jacobson P, Ahlin S, Sjöholm K, Carlsson LMS, Taube M. *Equal contribution. Manuscript submitted 2024-08-23, currently under review.

CONTENTS

Abbreviations	xii
Definitions in short.....	xiii
1 Introduction.....	1
1.1 Obesity	1
1.2 Obesity associated diseases.....	2
1.3 Obesity treatment	3
1.4 Bariatric surgery.....	3
1.4.1 Surgical Methods.....	4
1.4.2 Effects of bariatric surgery	8
2 Aim.....	11
2.1 Specific aims	11
3 Participants and Methods	12
3.1 Study design.....	12
3.2 Outcome measures	14
3.2.1 Clinical data.....	14
3.2.2 Questionnaires.....	15
3.2.3 National registers.....	15
3.2.4 Genotyping	15
3.3 Main statistical analyses.....	16
3.3.1 Paper I	17
3.3.2 Paper II.....	17
3.3.3 Paper III.....	17
3.3.4 Paper IV.....	17
3.4 Methodological considerations	18
3.4.1 Study design	18
3.4.2 Internal and external validity.....	19
3.4.3 Genotyping	19
3.5 Statistical considerations.....	20

3.5.1	Confounding.....	20
3.5.2	Longitudinal data.....	20
3.6	Ethical approvals.....	21
4	Results and Discussion.....	22
4.1	Paper I.....	22
4.2	Paper II.....	26
4.3	Paper III.....	31
4.4	Paper IV.....	35
5	Conclusion.....	38
6	Future perspectives.....	39
	Acknowledgement.....	40
	References.....	42

ABBREVIATIONS

BMI	Body mass index (kg/m ²)
CI	Confidence interval
DNA	Deoxyribonucleic acid
FTO	Fat mass and obesity-associated protein
GB	Gastric banding
GBP	Gastric bypass
GLP-1	Glucagon-like peptide 1
GS or SG	Gastric sleeve / sleeve gastrectomy
HDL	High-density lipoprotein
HR	Hazard ratio
LDL	Low-density lipoprotein
PCR	Polymerase chain reaction
PYY	Peptide YY
SNP	Single nucleotide polymorphism
SOS	Swedish Obese Subjects
VBG	Vertical banded gastroplasty
WHO	World Health Organization

DEFINITIONS IN SHORT

Monogenic obesity	When a single mutation on a gene leads to obesity. Usually involves mutations within the leptin-melanocortin pathway. (Huvenne et al. 2016, Faccioli et al. 2023)
Oligogenic obesity	When mutations affect a subset of genes leading to obesity. Usually involves genetic deletions. (Huvenne,et al. 2016)
Polygenic obesity	When several genetic variants exert a small effect on weight, but the cumulative effect leads to obesity. (Huvenne et al. 2016)

1 INTRODUCTION

1.1 OBESITY

Obesity, defined as having a BMI $> 30\text{kg/m}^2$, is one of the most common diseases globally¹. The prevalence is approximately 15%¹, and is projected to continue to increase worldwide². The rapid rise in prevalence over the last few decades is attributed to an increasingly obesogenic environment, characterized by easy access to and increased consumption of energy dense foods^{3,4}, combined with decreased physical activity⁵. However, despite the obesogenic environment, there is a significant heterogeneity in the population, with some individuals being much more susceptible to developing obesity than others. This heterogeneity can in part (40-70%) be explained by genetic variation between individuals^{6,7}. The majority (90-95%) of people with obesity are thought to have polygenic obesity, meaning that they carry several genetic variations that, on their own, only slightly affect body weight, but accumulated lead to an obese phenotype^{8,9}. Among the first genetic variants that were associated with polygenic obesity were single nucleotide polymorphisms (SNPs), in the fat mass and obesity-associated protein (*FTO*) gene. Genetic variation in rs9939609 in *FTO* is associated with not only body weight and BMI, but also food intake, insulin resistance, type 2 diabetes risk, and breast cancer risk¹⁰⁻¹⁵. The remaining 5-10% of people with obesity have mono- or oligogenic forms of obesity, meaning that the affected individual carry one or a few genetic mutations with a large effect on body weight^{8,16,17}. These mutations primarily act on pathways in the central nervous system, affecting eating behavior, inducing hyperphagia, and decreasing satiety^{16,18}. In addition to obesity, many individuals with mono- or oligogenic mutations also exhibit syndromes and concomitant neurodevelopmental disorders⁸.

Regardless of the type of mutation, a strong genetic predisposition to obesity often manifests early in life, as overweight or obesity. As such, children with severe obesity are often subject to genetic investigations¹⁷. If left untreated, childhood overweight and obesity usually persists and deteriorates into adulthood, leading to increasing adverse health effects¹⁹⁻²¹.

1.2 OBESITY ASSOCIATED DISEASES

Obesity has a direct mechanical impact on health, including decreased mobility, impaired lung function, and weight-related joint pain. It is also associated with several major diseases such as cardiovascular disease, metabolic disorders, and cancer²². As a result, people with obesity have an increased mortality rate and reduced life expectancy²³.

The biological mechanisms behind obesity-related diseases differ and are partially unknown. What we do know, is that adipose tissue is metabolically active and exerts metabolic control through regulation of fatty acids, cytokines, and hormones. In the obese state, the production of several of these molecules increases, which in turn affects the development of metabolic diseases²⁴. For example, the increased levels of cytokines and hormones impairs glucose uptake in skeletal muscles and inhibits glucose production in the liver, mediating insulin resistance²⁵. In response to the insulin resistance, pancreatic beta-cells increase insulin production, leading to a compensatory hyperinsulinemia to maintain euglycemia. Genetic predisposition then determines the continued response of the beta-cells, where some individuals maintain beta-cell function, while others develop dysfunction and impaired glucose tolerance, which may progress into type 2 diabetes²⁴. Another example of metabolic disease is dyslipidemia, which affects up to 70% of people with obesity²⁶. As obesity increases fatty acid levels, triglyceride synthesis increases, leading to elevated levels of LDL-cholesterol, apolipoprotein B, and decreased levels of HDL-cholesterol²⁷. Apart from metabolic disease, people with obesity also have a 3.5 fold increased risk of developing hypertension²⁸. The pathophysiology of obesity-induced hypertension is complex and involves increased blood volume, activation of the sympathetic nervous system, insulin resistance, impaired sodium regulation, and activation of the renin-angiotensin-aldosterone system^{28,29}. Moreover, all of the diseases above constitute important risk factors for cardiovascular disease. As such, obesity is a strong risk factor also for cardiovascular diseases such as angina pectoris, myocardial infarction, stroke, and heart failure^{22,30,31}. Additionally, obesity causes pathological changes in heart structure, such as ventricular hypertrophy and atrial enlargement, which promote heart failure and atrial fibrillation^{31,32}.

Obesity is also associated with at least 13 different types of cancer³³ and is thought to account for up to 40% of cancer incidence worldwide³⁴. Various mechanisms have been suggested underlying the association between obesity and cancer. Obesity induces secretion of pro-inflammatory cytokines from

adipocytes leading to systemic inflammation, which in turn may promote cancer development³⁵. As stated above, obesity also leads to insulin resistance and increased insulin levels, where insulin itself may act as a growth factor promoting cancer development³⁶. Lastly, obesity can affect steroid hormone production, such as estrogen, which in turn may promote cancer development for hormone sensitive cancers^{37,38}.

1.3 OBESITY TREATMENT

Currently, there are several different treatment strategies for obesity, which can be roughly divided into three main categories: lifestyle interventions, pharmacotherapy, and bariatric surgery. The first category involves changes in diet and physical activity and is essential for overall health improvement³⁹. However, adopting a healthy lifestyle seems to exert its greatest effect in preventing the development of overweight and obesity³⁹. For individuals who have already developed obesity, lifestyle changes may help improve obesity-related comorbidities, but are rarely sufficient for achieving large and sustained weight loss⁴⁰.

Pharmacotherapy for obesity is a rapidly advancing area, with several new drugs recently introduced. Among these are GLP-1 agonists, such as semaglutide, and GLP-1 + GIP dual agonists, such as tirzepatide and retatrutide, which have shown weight loss effects up to 14.9%⁴¹, 20.9%⁴², and 24.2%⁴³, respectively. However, data is still lacking on their long-term effects on weight and comorbidities. The last category, bariatric surgery, constitute the base of this thesis and will be described in the paragraphs below.

1.4 BARIATRIC SURGERY

Bariatric surgery involves a variety of surgical procedures on the gastrointestinal tract, designed to promote weight loss. Initially, it was roughly divided into two main categories: restrictive and malabsorptive procedures. The former focuses on restricting stomach volume to limit food intake, while the latter aims to induce malabsorption of nutrients⁴⁴. However, further studies have shown that much of the effects of bariatric surgery seem to result from changes in neural and endocrine pathways⁴⁴.

Both the stomach and intestines are innervated by vagal nerves, which connect to the hypothalamus in the brain. The hypothalamus is an important regulator

of hunger, appetite and satiety. Most bariatric procedures have been shown to affect vagal nerve function and therefore, it has been suggested that part of the weight loss from surgery is due to its influence on vagal nerve function⁴⁵.

Additionally, bariatric surgery induces changes in several gastrointestinal hormones that are important regulators of eating behavior, affecting hunger and satiety⁴⁵. Among the most important of these hormones are leptin, ghrelin, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY)⁴⁵. Leptin suppresses appetite and increases energy expenditure⁴⁵. Contradictory to leptin's effect, bariatric surgery has been associated with reduced leptin levels⁴⁶. However, it has been suggested that the surgery also improves leptin sensitivity, thereby promoting weight loss⁴⁷. Studies are more inconsistent regarding ghrelin, a hormone that promotes hunger⁴⁵, some studies show reduced levels after bariatric surgery, and other studies show increased levels or no difference⁴⁸. Of the two latter, both GLP-1 and PYY have been shown to increase after bariatric surgery. Increased levels of GLP-1 and PYY have been associated with decreased hunger, increased satiety, and slower gastric emptying⁴⁶. GLP-1 also increases insulin secretion and inhibits glucagon secretion, improving blood glucose levels in patients with type 2 diabetes⁴⁹. Research on the mechanisms of bariatric surgery contributed to the development of current GLP-1 agonists, which are now used clinically for weight loss and diabetes treatment⁵⁰.

Today, the two main bariatric procedures are sleeve gastrectomy and gastric bypass⁵¹. This dissertation is based on data from the Swedish Obese Subjects (SOS) study, an intervention study investigating the effects of the bariatric procedures: gastric bypass, gastric banding and vertical banded gastroplasty. The latter two are older methods seldom used today.

1.4.1 SURGICAL METHODS

1.4.1.1 GASTRIC BANDING

In gastric banding (GB), an adjustable- or non-adjustable band of synthetic material is placed proximally on the stomach. This creates a small pouch in the upper part of the stomach and restricts the passage of food to the rest of the stomach and intestines. The procedure slows and limits food intake, leading to weight loss⁴⁴. GB was most popular in the 1990s and early 2000s as it is relatively simple compared to the other methods⁴⁵. However, later studies showed poor long-term weight loss outcomes⁵². Weight regain, combined with

complications such as band slippage and perforation, has made it much less used today⁴⁵.

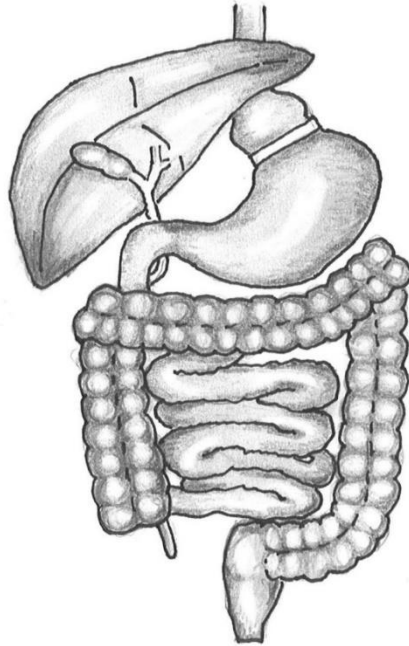


Figure 1 Gastric Banding. Illustration by Per-Arne Svensson.

1.4.1.2 VERTICAL BANDED GASTROPLASTY

Vertical banded gastroplasty (VBG) is similar to GB. It also involves a band placed proximally on the stomach, however instead of going around the stomach, a hole is created through which the band is anchored. To complete the pouch, the remaining upper part of the stomach is then separated from the rest of the stomach by stapling. The procedure restricts the passage of food to the rest of the stomach and intestines. Similarly to GB, VBG slows and limits food consumption inducing weight loss. An advantage of VBG compared to GB is that it avoids the risk of band slippage. However, VBG involves a greater tissue insult than GB, as it requires modifications in the stomach anatomy. VBG was most popular during the 1980s and 1990s but was gradually replaced by GB over time⁴⁵. As with GB, studies showed poor long-term weight loss

outcomes^{45,53}. VBG patients also suffered from complications such as band erosion, dysphagia and stenosis^{53,54}.

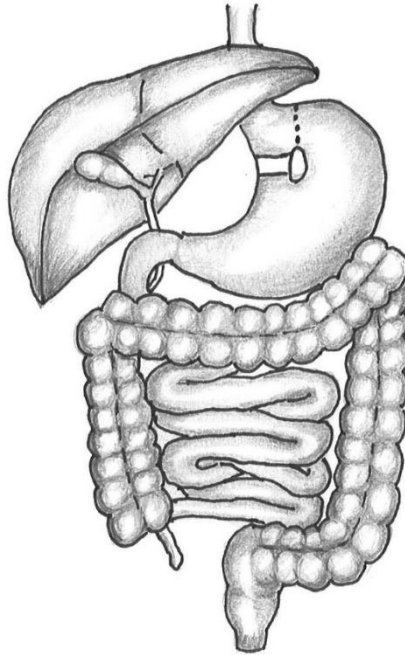


Figure 2 Vertical Banded Gastroplasty. Illustration by Per-Arne Svensson.

1.4.1.3 GASTRIC BYPASS

Gastric bypass (GBP), is one of the most used methods for bariatric surgery today⁵¹. In GBP, the stomach is divided into two parts. The upper part is connected to the esophagus and constitutes a small pouch. The remaining lower part of the stomach is disconnected or “bypassed” from the esophagus but remains in the abdomen. The jejunum is then divided distally to the ligament of Treitz and its distal part is connected to the gastric pouch through a gastro-entero anastomosis. An alimentary limb is then constructed and connected back to the part of the jejunum proximal to the jejunal division. This lower anastomosis is called the jejuno-jejunostomy or entero-entero anastomosis. The GBP procedure leads to a separation of food from gastric, pancreatic, and biliary secretions along the alimentary limb down to the lower

anastomosis. Initially, it was believed that GBP induced weight loss primarily by reducing stomach size and decreasing nutrient absorption. However, as discussed above, more recent research suggests that the procedure induces weight loss by affecting neuro-hormonal pathways^{44,45}. GBP has been popular since the 1990s and several studies have shown a positive effect on both short- and long-term weight loss^{44,55}. Although the method is generally safe, a rare but important complication is intestinal hernia, which requires emergency surgery. Other less severe complications include gallstone disease, marginal ulcers and vitamin deficiencies⁵⁴.

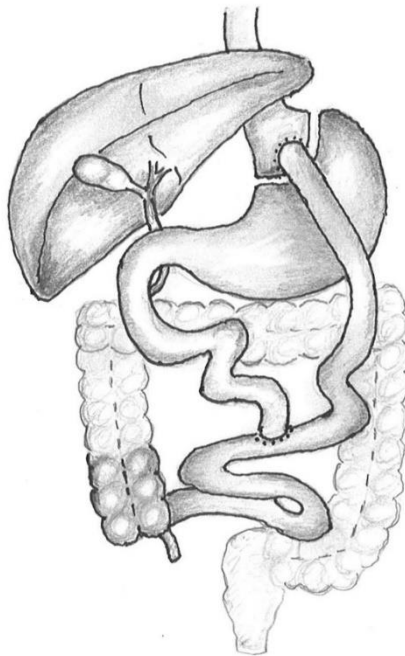


Figure 3 Gastric Bypass. Illustration by Per-Arne Svensson.

1.4.1.4 SLEEVE GASTRECTOMY

Sleeve gastrectomy, also called gastric sleeve (GS), is the newest technique that together with GBP constitutes the most common bariatric procedures today⁵¹. In GS 75-85% of the stomach is removed along the greater curvature using staples, leaving a cylindrical or “sleeve”-shaped ventricle. The procedure

leads to a decreased capacity of the stomach to retain food, and subsequently a more rapid delivery of nutrients to the small intestine. As with GBP, the procedure is thought to induce weight loss by affecting neuro-hormonal pathways⁴⁴. The procedure has gained popularity since its introduction 2005⁵⁶, however data on long-term outcomes is still lacking. Complications involve staple line leaks and vomiting from over-eating⁵⁴.

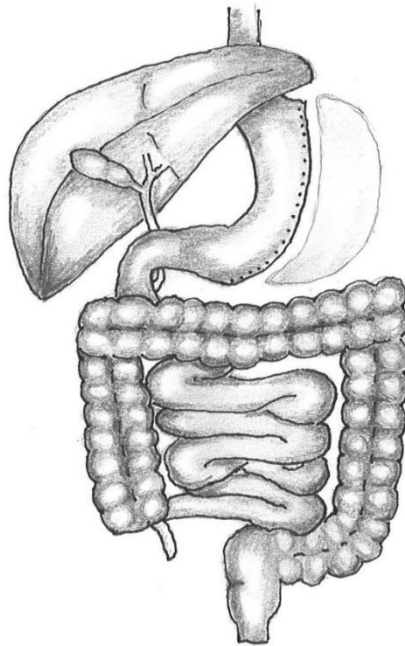


Figure 4 Sleeve Gastrectomy. Illustration by Per-Arne Svensson.

1.4.2 EFFECTS OF BARIATRIC SURGERY

To date, bariatric surgery is the most effective treatment for large and long-term weight loss in people with obesity, with an average weight loss of 25-30% after 10 years^{55,57}. Besides reducing body weight, bariatric surgery also has a positive impact on several of the earlier mentioned comorbidities of obesity, such as cardiovascular disease, metabolic disease and cancer^{55,57}. In accordance, bariatric surgery has also been shown to reduce mortality in people with obesity and it increases longevity^{58,59}. However, although generally

associated with improved health, the effects on weight loss and prevention of comorbidities are highly variable, with some patient subgroups displaying reduced treatment benefits⁶⁰. Studies have suggested several different biological markers as predictors of weight loss after bariatric surgery, including sex^{61,62}, age^{61,62}, presence of metabolic disease^{61,63}, eating behaviors⁶⁴, and genetics⁶⁵. However, many of these studies are limited by small sample sizes, short follow-up periods, or retrospective designs, leading to inconsistent findings. To address these limitations, large-scale prospective studies with detailed patient information are better suited to identify reliable predictors of bariatric surgery outcomes, including both weight loss and resolution of obesity comorbidities.

Studies have shown a strong genetic influence on weight loss with non-surgical interventions⁶⁶. However, the effect of genetics on bariatric surgery outcomes has only been partially explored, and results are difficult to interpret⁶⁵. In monogenic obesity disorders, mutations within the leptin-melanocortin pathway are most common¹⁶. Some studies show poorer treatment outcomes from bariatric surgery in patients with genetic variants in this pathway⁶⁷, while others show no differences¹⁶. The effects of oligogenic forms of obesity, such as the chromosome 16p11.2 593kb microdeletion, Prader-Willi and Bardet-Biedl syndromes, on bariatric surgery outcomes are unclear¹⁶. In polygenic obesity, several genetic variants in the *FTO* gene have been associated with higher BMI¹⁰, earlier onset of obesity^{10,68}, and comorbidities like insulin resistance¹³, type 2 diabetes¹², and breast cancer¹⁴. Some studies suggest that genetic variation in *FTO* may reduce weight loss after bariatric surgery, but results have been inconsistent^{65,69-71}. To our knowledge, no studies have explored the effects of genetic variation in *FTO* on outcomes other than weight loss after bariatric surgery.

As mentioned earlier, a strong genetic drive often manifests as early-onset obesity¹⁷. Early-onset obesity typically persists into adulthood and is associated with higher rates of comorbidities and increased mortality compared to normal-weight peers^{20,21}. Interestingly, a study on 3-year weight loss after bariatric surgery showed that patients with early-onset obesity experienced smaller weight loss compared to other obesity subtypes⁷². It is unclear if early-onset obesity affects other obesity-related comorbidities after bariatric surgery.

In addition to genetics, metabolic diseases such as type 2 diabetes also influence bariatric surgery outcomes, with lower weight loss reported in patients with diabetes^{61,63}. This is interesting, as bariatric surgery greatly

improves, and in some cases completely resolves, type 2 diabetes by enhancing insulin sensitivity^{55,73}. The underlying mechanisms behind these improvements in insulin levels are unknown, but insulin itself may constitute a predictor of surgical outcomes. As mentioned earlier, insulin can act as a growth factor and is considered a risk factor for cancer development⁷⁴. In line with this, the SOS-study have previously shown that bariatric surgery is associated with a reduced risk of female specific cancers, especially in women with hyperinsulinemia⁷⁵. However, the role of insulin in disease development remains largely unknown.

Although bariatric surgery is generally considered a safe procedure, it is not without risks. As with all surgical procedures, there is a perioperative risk of complications, including death. Bariatric surgery has a reported 30-day mortality rate of 0.2%⁷⁶, similar to other common surgical procedures⁴⁴. In addition and as mentioned earlier, there are several long-term complications to bariatric surgery such as intestinal hernia, dumping, stricture formation, marginal ulcer, hypoglycemia, anemia, vitamin deficiencies, and more⁵⁴. Accounted together, the overall risk of long-term complications has been reported to be around 6% over a 5-year period, according to the Scandinavian obesity surgery registry⁷⁷. As such, even though mortality and risk of complications are relatively low, it must be considered before undergoing surgery⁵⁷. The risks also highlight the need to identify predictors to help determine which patients are most likely to benefit from bariatric surgery while protecting those unlikely to benefit from being exposed to unnecessary risks.

2 AIM

The overall aim of this thesis is to identify predictors of long-term outcomes after bariatric surgery in the Swedish Obese Subjects study, including predictors of weight loss, cardiovascular disease, metabolic disease, and cancer risk.

2.1 SPECIFIC AIMS

Paper 1. To determine the frequency of the chromosome 16p11.2 593kb microdeletion in the surgery group of the Swedish Obese Subjects study and compare the outcomes of bariatric surgery in carriers and non-carriers of the microdeletion.

Paper 2. To compare outcomes after bariatric surgery in individuals with obesity at age 20, to those that developed obesity later in life.

Paper 3. To investigate the association between bariatric surgery and breast cancer in women with obesity and explore whether treatment benefit is modified by baseline insulin levels.

Paper 4. To investigate the association between the single nucleotide polymorphism rs9939609 in the *FTO* gene and breast cancer incidence in women with obesity. In addition, explore whether rs9939609 modifies the association between bariatric surgery and breast cancer risk, and if this may be mediated by insulin.

3 PARTICIPANTS AND METHODS

3.1 STUDY DESIGN

This thesis is based on data and sample analyses from the Swedish Obese Subjects (SOS) study, a prospective, matched intervention study primarily designed to investigate whether bariatric surgery and the resulting weight loss are associated with reduced mortality. Predefined secondary aims included the effects of bariatric surgery and weight loss on cardiovascular disease, biliary disease, diabetes, cost effectiveness, and health-related quality of life^{55,78}.

Study recruitment took place between 1st September 1987 and 31st January 2001, through campaigns in mass media and at 480 primary care centers in Sweden. During that period, 11.453 standardized application forms were sent to the SOS-secretariat. Of these, 8966 applicants fulfilled self-reported age and BMI criteria and were provided written information about the surgical and nonsurgical treatment methods offered by the SOS-study. In addition, applicants also completed questionnaires and were asked if they wanted to participate as surgically or non-surgically treated participants. Of these, 7593 applicants returned their questionnaires and were offered participation in a registry examination at their primary health care center or at a specialist clinic for people with obesity. Of the 6905 individuals who underwent the registry examination, 5335 fulfilled inclusion and exclusion criteria and were deemed eligible for study participation (Figure 5). Inclusion criteria were BMI of ≥ 34 kg/m² for men and ≥ 38 kg/m² for women, as well as age ranging from 37 to 60 years. Exclusion criteria included previous bariatric surgery, gastric or duodenal ulcer within the past 6 months, prior surgery for gastric or duodenal ulcer, myocardial infarction within the past 6 months, ongoing malignancy or active malignancy within the past 5 years, substance abuse (drugs or alcohol), bulimic eating pattern, psychiatric or cooperative issues contraindicating bariatric surgery, and other contraindications such as chronic glucocorticoid or anti-inflammatory treatment^{78,79}.

Participants interested in surgery were invited for a visit at their registered surgical department, where they received further information about the bariatric procedure and were evaluated for eligibility by a surgeon. Participants who elected surgery and were deemed eligible, were scheduled for operation. On average, the surgical visit took place 8 months after the registry examination and 5 months prior to the operation. Approximately 8 weeks

before a participant were operated, a matched control was selected from the pool of eligible participants who had not elected surgery. Matching was conducted using the sequential treatment assignment method, which aims to balance confounding factors⁸⁰. The following 18 matching variables were included; age, sex, height, weight, hip and waist circumference, triglyceride concentrations and serum cholesterol, diabetes, systolic blood pressure, smoking, pre- or post-menopausal state in women, four psychosocial variables associated with mortality, and two personality traits related to treatment preferences⁷⁸. The entire matching process was computerized with no involvement of the investigators.

An inclusion examination was performed for participants scheduled for surgery, as well as for their matched controls, 4 weeks before surgery, on average 13 months after the registry examination. The inclusion examination included anthropometric measurements, questionnaires, and blood samples. Data from the inclusion examination constitutes the baseline data of the SOS-study⁷⁸.

In total, 2010 participants were recruited to the surgery group and 2037 to the control group. The surgically treated participants underwent adjustable or nonadjustable gastric banding (GB; n=376), vertical banded gastroplasty (VBG; n=1369) or gastric bypass (GBP; n=265) (Figure 5). Participants in the control group received the non-surgical obesity treatment that was customary at the health care center where they were registered. Such obesity treatment ranged from major lifestyle interventions to no treatment at all. No pharmacotherapy for obesity were available in Sweden until 1998, and therefore the majority of study participants did not have this as an option for obesity treatment at study inclusion^{78,79}.

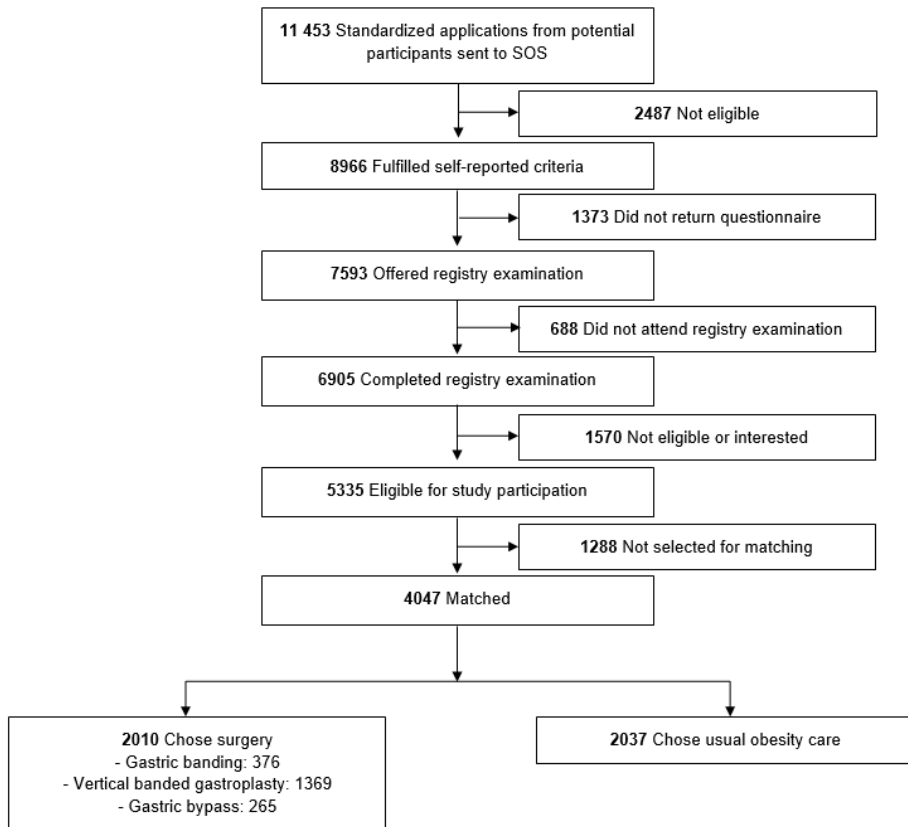


Figure 5 SOS-study Flowchart. Illustration by Felipe M Kristensson.

3.2 OUTCOME MEASURES

3.2.1 CLINICAL DATA

Follow-up examinations were performed at the participants' registered health care provider at 6 months and at 1, 2, 3, 4, 6, 8, 10, 15, and 20 years after study inclusion. At each examination, several anthropometric measurements were taken, including height, weight, hip and waist circumference, as well as blood pressure. Samples of whole blood, serum, plasma, and urine were collected at inclusion and at the 2-, 10-, 15-, and 20-year examinations. Blood biochemistry were analyzed at inclusion and after 2, 10, 15, and 20 years at the Central Laboratory, Sahlgrenska University Hospital (Gothenburg, Sweden; accredited according to ISO/IEC 15 189).

3.2.2 QUESTIONNAIRES

During the inclusion- and follow-up examinations after 6 months and 1, 2, 3, 4, 6, 8, 10, 15, and 20 years from study inclusion, participants received questionnaires with inquiries of current and previous weight, diseases, medications, socioeconomics, sleeping habits and lifestyle.

3.2.2.1 ENERGY INTAKE AND PHYSICAL ACTIVITY

Energy intake was estimated from dietary data collected using a validated semi-quantitative diet questionnaire⁸¹ completed 4 weeks prior to inclusion and at all follow-up visits. Work-related physical activity and leisure-time was estimated from questionnaires completed 4 weeks prior to inclusion and at all follow-up visits.

3.2.3 NATIONAL REGISTERS

The following national registers are used for the studies included in this dissertation: The Swedish Person and Address Register (SPAR) is a public register containing information on all current addresses of living SOS-participants and information if they are deceased and/or migrated in or out of Sweden. The Swedish Cancer Registry contains information on diagnosis of malignant tumors in Sweden with a 95% coverage of which 99% are morphologically verified⁸². The Swedish Cause of Death Register contains information on the official cause of death for an individual and has a coverage of 100% of deaths in Sweden, of these 96% have an underlying cause recorded⁸³. The National Patient Register contains information about somatic diseases and treatment within specialist care in Sweden, with approximately 80% coverage of outpatient care, and 99% coverage of inpatient care⁸⁴. Registry of the Total Population is a register over all legal residents in Sweden.

3.2.4 GENOTYPING

DNA was extracted from whole blood samples in the SOS-cohort using the AGOWA mag kit (LGC Group, Teddington, Middlesex, UK).

A two-step process was used to identify carriers of the 16p11.2 593kb microdeletion. First, participant DNA was genotyped for 21 single nucleotide polymorphisms (SNPs): 14 within the deleted region, 4 downstream and 3 upstream. Genotyping was done at the Mutation Analysis Core Facility (MAF), Karolinska Institute, Stockholm, Sweden, using the Sequenom MassARRAY platform (Sequenom Inc., San Diego, California). The assay was designed using the MassARRAY Assay Design 3.1 software (Sequenom).

In the second step, the presence of the deletion was confirmed using the multiple ligation dependent probe amplification (MLPA) Autism kit (cat no: P343, MRC Holland, Amsterdam, Netherlands), which included 11 probes for the 16p11.2 region (9 within and 2 flanking the deletion). Labeled MLPA products were detected with an ABI Prism 3730 Genetic Analyzer (Life Technologies Ltd, Paisley, UK) with GeneScan500 LIZ size standard (Life Technologies) at the KIGene Core Facility, Karolinska Institute, Stockholm, Sweden.

The *FTO* SNP rs9939609 was genotyped using the TaqMan allelic discrimination PCR assay (Applied Biosystems, Thermo Fischer Scientific, Waltham, Massachusetts, USA). Genotyping was performed using the Viiia7 Real-Time PCR system (Applied Biosystems). Data analysis was performed in the Viiia7 Real-Time PCR system software v1.3.

3.3 MAIN STATISTICAL ANALYSES

All statistical analyses were performed per-protocol, meaning that all participants were included in their original study group until surgery to restore normal anatomy was performed in the surgery group or any bariatric surgery was performed in the control group, after which participants were censored from the analysis. Descriptive statistics are given as means with standard deviation or counts and percent when applicable. Differences between groups are analyzed using the Students T-test or Fischer's exact test.

For the majority of obesity comorbidities, cumulative incidence rates, calculated as 1 minus the Kaplan-Meier estimate, were used to analyze time from baseline to first event. Observations were censored if the study participant emigrated from Sweden, withdrew their consent, altered their intervention, died before the end of follow-up for reasons other than the event, or were alive at the end of follow-up, at the corresponding date. Differences in cumulative incidence between groups were analyzed using log-rank tests for unadjusted analyses, and Cox proportional hazard regression models for adjusted analyses. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Interaction effects was evaluated using Cox proportional hazards models with an interaction term.

Multilevel mixed-effect regression models were used to analyze group differences in changes of continuous variables over time. Observations were

considered nested within the individuals and the statistical tests and CIs were calculated controlling for repeated measurements.

All p-values are two-tailed and an alpha below 0.05 was considered statistically significant unless otherwise stated.

3.3.1 PAPER I

Before statistical testing, a logarithmic transformation was applied for systolic blood pressure and serum insulin due to some extreme values. No statistical testing was performed for obesity comorbidities during follow-up due to the low number of deletion carriers.

3.3.2 PAPER II

To identify study participants with early onset obesity, BMI at 20 years of age was estimated using self-reported weight at 20 years of age, combined with height measured at baseline. Self-reported weight at 20 years of age was collected from the questionnaire at the registry examination. Participants were then stratified into subgroups defined as having normal BMI (BMI <25 kg/m²), overweight (BMI 25–29.9kg/m²), or obesity (BMI ≥30kg/m²) at 20 years of age.

The incidence and remission of type 2 diabetes were analyzed using logistic regression models for the 2- and 10-year follow-up. Results are presented as odds ratios (ORs) with 95% CIs.

3.3.3 PAPER III

To analyze the effect of insulin and related metabolic variables on breast cancer risk, incidence rates were calculated in subgroups based on median levels of insulin, blood glucose, HOMA-IR, BMI, and alcohol use, as well as by smoking status.

3.3.4 PAPER IV

Hardy-Weinberg equilibrium was calculated on allele frequencies for rs9939609 in the *FTO* gene. Genotype data was analyzed using a dominant model and divided into two groups based on the A-allele, creating one group of homozygous carriers of the T-allele (TT-group) and one group of A-allele carriers (heterozygous or homozygous carriers of the A-allele, TA/AA- group).

3.4 METHODOLOGICAL CONSIDERATIONS

3.4.1 STUDY DESIGN

Randomized controlled trials (RCTs) are usually considered the gold standard in clinical research as they provide the strongest evidence for causality. In RCTs, the intervention is randomly assigned to participants, and those who do not receive the intervention serve as controls. Randomization helps prevent or reduce bias from both known and unknown confounders, ensuring that the intervention remains as the primary factor behind a treatment effect. When randomizing, it is assumed that confounders are evenly distributed across treatment groups. Randomization can be further improved by blinding, where participants are unaware whether they are receiving the intervention or not. In double blinding, both the participants and investigators are unaware of who receives the intervention. Blinding, simple or double, helps minimise the placebo effect, which otherwise can affect treatment outcome⁸⁵.

The SOS study is a matched prospective intervention study, meaning it is non-randomized, as participants took part in electing their intervention after consulting a physician. Before study start, six out of seven ethic review boards involved in the SOS study rejected a randomized design due to concerns of high postoperative death rates after bariatric surgery, ranging from 1-5% during the 1970s and 1980s⁸⁶. The matching in the SOS study is supposed to reduce the effects of non-randomization by equalizing treatment groups⁸⁰. Importantly, both treatment groups underwent the same inclusion and exclusion criteria, meaning that all participants were eligible for surgery.

Although a non-randomized design is not optimal, it is questionable whether a randomized study could have ever been performed. Apart from the challenge of recruiting 4,000 participants willing to accept randomization of bariatric surgery, there is also difficulty with crossover, as many participants in the control group may opt for surgery over time. Randomized designs are also susceptible to higher dropout rates compared to prospective cohort studies, further complicating long-term follow-up. Furthermore, while there were concerns about the risks of surgery at the SOS study's start, today the benefits of surgery usually outweighs surgical risks, making it unethical not to offer surgery to patients with obesity. The difficulty of conducting prospective intervention studies on bariatric surgery is evident by the fact that the SOS study is among the only studies of its kind. Most other studies on long-term effects of bariatric surgery are instead of retrospective design. In addition to its

prospective design, the SOS study also contains highly detailed participant data, which offers a unique opportunity for research.

3.4.2 INTERNAL AND EXTERNAL VALIDITY

Internal validity refers to how well a study measures the variables it intends to examine and establishes their relationship without interference from confounding factors. Since participants took part in electing their intervention, there is a risk of selection bias in the SOS study. Selection bias may occur when factors that affect the outcome, such as mortality, may also affect the participant's choice of intervention. For example, a person prone to risk-taking may choose surgery but also engage in other risky activities that could affect mortality⁸⁷. To reduce selection bias, participants in the SOS study were matched, and later analyses has been adjusted for known risk factors of mortality.

External validity refers to how well study results can be generalized to a larger population⁸⁷. The aim of the SOS study was primarily to investigate whether bariatric surgery, and the resulting weight loss, are associated with reduced mortality. One important note is that two of the three surgery methods used in the SOS study, gastric banding and vertical banded gastroplasty, are rarely used today. This is a common problem in long-term studies, as methods and procedures evolve over time. However, as the main effects of bariatric surgery seemingly are due to weight loss rather than the specific procedure, it can be argued that the SOS study's results remain valid also today. In support of this, separate studies on outcomes from vertical banded gastroplasty and sleeve gastrectomy shows similar magnitudes of weight loss^{55,88}. Another important factor supporting the external validity of the SOS study is that participants were able to take part in electing their intervention, which closely reflects current clinical practice.

3.4.3 GENOTYPING

The Sequenom MassARRAY platform is a commercially available technique that allows for genotyping of several thousands of samples and up to 40 single nucleotide polymorphisms (SNPs) per run making it a good candidate for the initial screening for the chromosome 16p11.2 microdeletion. However, multi-ligand dependent probe amplification or MLPA is considered the gold standard for detection of genetic deletions and copy number variations⁸⁹. As MLPA is more expensive and time consuming than Sequenom, we chose to start with

the SNP assay and then confirm our findings using MLPA for optimal use of our resources.

The TaqMan allelic discrimination PCR assay is useful for genotyping a smaller number of SNPs in thousands of samples. It comprises a robust, cheap and fast method.

3.5 STATISTICAL CONSIDERATIONS

3.5.1 CONFOUNDING

A confounder is a variable that is associated with both the outcome- and exposure variable in a study. The association interferes with the interpretation of a study as it can falsely imply causality between an outcome- and exposure variable, but it can also hide a true causality. Therefore, it is important to identify potential confounders and manage them accordingly. As mentioned above, randomization is one method to deal with confounding as it aims to distribute confounders, both measured and unmeasured, evenly between the groups being compared. Another method is stratification, meaning a subdivision of the comparison groups based on a variable whose effect you want to omit from the analysis⁸⁵.

Linear regression models are another way to manage confounding variables. It is a mathematical model that assumes a linear relationship between the outcome or dependent variable and the exposure or independent variable. A major advantage with such models is that they can fit several independent variables and estimate the separate effect of each independent variable on the dependent variable. This means that you can estimate the effect of the exposure variable as well as potential confounding variables on the outcome variable in the same analysis. Apart from study design, statistical methods therefore play an important role in managing confounders and improving study validity. In the SOS study, as well as many other studies, regression models and stratification are used extensively.

3.5.2 LONGITUDINAL DATA

The SOS study is a prospective study, meaning that it follows its participants over time, continuously collecting data from multiple time points. To compare differences between participants and groups over time, we have primarily used multilevel mixed-effect regression models. Multilevel mixed-effect regression

models are similar to linear regression models, but they also include fixed and random effects in the analysis. A major advantage with a multilevel mixed-effect regression model is that it can utilize data from multiple time points also when data is missing at some time points, which becomes increasingly common as a study progresses. Another advantage is that it can adjust for within-person correlations.

3.6 ETHICAL APPROVALS

When the SOS study was started, the study protocol was approved by seven regional ethics review boards (Göteborg, Malmö/Lund, Linköping, Örebro, Stockholm, Uppsala, and Umeå, ethical permit number: 152-86). Ethical approvals have been updated, and additional approvals have been obtained, for the use of data from the national registers used in this thesis. The ethical approvals relevant to this thesis, in addition to 152-86, are S604-01, T508-17 and 2022-03879-01. Written or oral informed consent was obtained from all participants. The SOS study is registered at ClinicalTrials.gov (NCT01479452).

4 RESULTS AND DISCUSSION

4.1 PAPER I

The 593kb microdeletion in chromosome 16p11.2 BP4 and BP5 region, is one of the most common types of syndromic obesity, affecting 1 out of 2000 people in the general population^{90,91}, and up to 1% in a population of people with obesity⁹². The microdeletion is associated with an altered satiety response, leading to early onset obesity, developmental delay, and neurodevelopmental disorders⁹⁰. To our knowledge there are no previous reports of the effects of this microdeletion on the outcomes after bariatric surgery. The aim of paper I was therefore to determine the frequency of the 16p11.2 593kb microdeletion in the surgery group of the SOS-study and to compare the outcomes of bariatric surgery in carriers and non-carriers of the microdeletion.

DNA was available for 1843 participants in the SOS surgery group. Among these, 4 men and 5 women were carriers of the 16p11.2 microdeletion, constituting 0.49% of the cohort (Table 1). Of these 9 participants, none had a previous diagnose of syndromic obesity. The frequency of 0.49% is lower than previously reported from other cohorts of people with obesity^{92,93}, which may be due to selection effects in the SOS study's recruitment process. The 16p11.2 microdeletion is associated with cognitive deficits⁹¹, which may have led to fewer carriers applying for the study. Additionally, one of the exclusion criterion in the SOS-study was psychological problems leading to poor cooperation⁷⁸, which may also have disfavored inclusion of deletion carriers.

At baseline, carriers of the 16p11.2 microdeletion had higher BMI, fasting insulin, and systolic blood pressure, compared to non-carriers. Two carriers of the 16p11.2 microdeletion had type 2 diabetes. No other significant differences in cardiovascular risk factors were observed (Table 1).

Table 1. Paper I - Baseline data stratified by detection of the chromosome 16p11.2 593kb microdeletion. From Kristensson et al., *SOARD* 2017;13:1321-1326. ©2017 by American Society for Metabolic and Bariatric Surgery. Reprinted with permission.

Variable	Carriers	Non-carriers	p-value
N	9	1834	
Age, years	46.9 (4.4)	47.2 (6.0)	0.887
Male gender, %	44.4	29.7	0.464
Body mass index, kg/m²	46.8 (6.0)	42.3 (4.5)	0.003
Weight, kg	124.3 (23.2)	120.8 (16.6)	0.530
Fasting blood glucose, mmol/L	5.6 (2.6)	5.2 (2.0)	0.557
Fasting serum insulin, mU/L	32.4 (21.1)	21.4 (13.7)	0.029
Systolic blood pressure, mmHg	159.8 (16.2)	144.9 (18.8)	0.018
Diastolic blood pressure, mmHg	94.0 (10.9)	89.8 (11.2)	0.261
Triglycerides, mmol/L	1.8 (0.3)	2.3 (1.6)	0.359
Total cholesterol, mmol/L	5.6 (1.2)	5.9 (1.1)	0.553
HDL cholesterol, mmol/L	1.4 (0.3)	1.4 (0.3)	0.896
Diabetes type 2, %	22.2	17.5	0.662
Hypertension, %	88.9	78.2	0.693
Current daily smokers, %	22.2	26.3	1.000
Caloric intake/day, kcal	3017 (989)	2948 (1266)	0.871
Perceived health status, score	3.6 (1.1)	3.7 (1.3)	0.751

Among the deletion carriers, 3 underwent gastric banding, 4 vertical banded gastroplasty, and 2 gastric bypass. Large weight loss was observed in both carriers and non-carriers of the 16p11.2 microdeletion following surgery (Figure 6). At the 1-year follow-up, the percent excess BMI lost (%EBMIL) was 71.9% for carriers and 62.2% for non-carriers (37.9 kg and 30.6 kg, respectively; $p=0.031$). Both groups experienced partial weight regain, and at 10 years, %EBMIL was 25.5% and 41.5% (15.7 kg and 21.3 kg respectively; $p=0.377$). Energy intake and perceived health status remained similar between carriers and non-carriers throughout follow-up ($p=0.173$ and $p=0.198$, respectively), with improvements during the first year, compared to baseline.

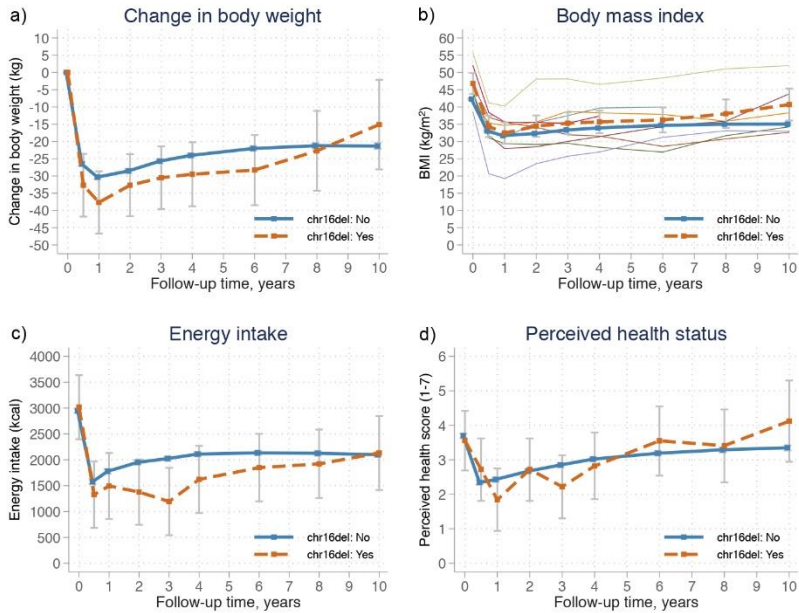


Figure 6. Mean changes in weight (A), BMI (B), energy intake (C), and perceived health status (D). Changes in BMI for individual carriers of the 16p11.2 microdeletion are presented with narrow lines (B). Error bars represent 95% CIs. From Kristensson et al., *SOARD* 2017;13:1321-1326. ©2017 by American Society for Metabolic and Bariatric Surgery. Reprinted with permission.

Cardiovascular risk factors improved similarly in both carriers and non-carriers during follow-up, with no significant changes between the groups (Figure 7). Both carriers who had type 2 diabetes at baseline were in remission at the 2-year follow-up but experienced relapse at the 10-year follow-up.

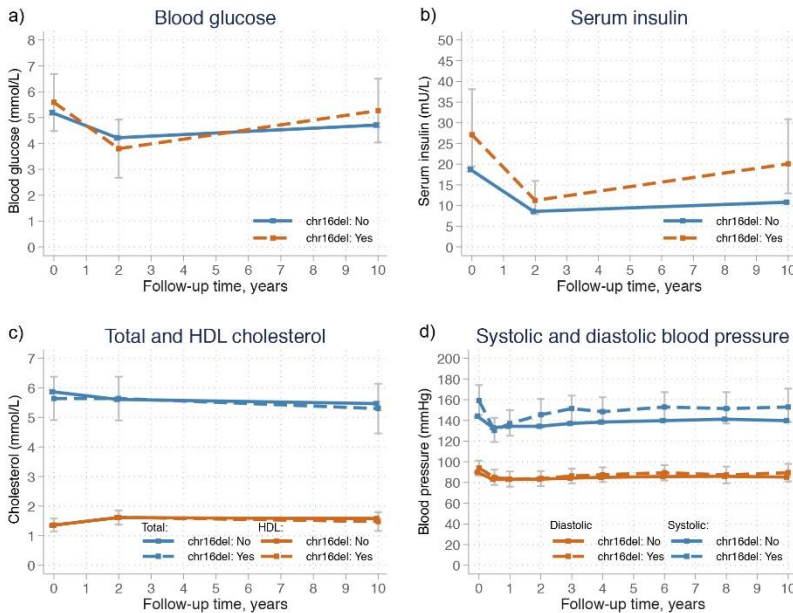


Figure 7. Mean changes in blood glucose (A), serum insulin (B), total and HDL cholesterol (C), and systolic and diastolic blood pressure (D). Error bars represent 95% CIs. From Kristensson et al., *SOARD* 2017;13:1321-1326. ©2017 by American Society for Metabolic and Bariatric Surgery. Reprinted with permission.

It is still unclear how the chromosome 16p11.2 microdeletion induces obesity. Studies have found associations between the deletion and changes in brain structures affecting the reward system, as well as changes in eating behavior and satiety^{90,94}. Eating disorders have previously been associated with less favorable outcome after bariatric surgery and patients with such disorders are therefore often denied surgery^{95,96}. As the chromosome 16p11.2 microdeletion affects eating behavior¹⁸, individuals with this genetic alteration may be expected to experience poorer treatment outcomes after bariatric surgery. However, our study showed a similar treatment response in both carriers and non-carriers of the microdeletion, indicating that bariatric surgery is a valid treatment option for obesity in affected individuals.

We concluded that the response to bariatric surgery is similar in people with obesity, regardless of the presence of the chromosome 16p11.2 microdeletion. Bariatric surgery was associated with substantial long-term weight loss and had the same positive effect on risk factors in carriers and non-carriers of the microdeletion.

4.2 PAPER II

Previous research suggest that early onset obesity reduces weight loss after bariatric surgery⁷². Similarly, in individuals with type 2 diabetes, short diabetes duration has been associated with better treatment effect after bariatric surgery⁹⁷. However, to our knowledge, no studies have examined if early onset obesity affects outcomes of bariatric surgery other than weight loss. The aim of paper II was therefore to compare outcomes after bariatric surgery in individuals with obesity at age 20, to those that developed obesity later in life.

Baseline characteristics of surgery and control participants, stratified into subgroups by BMI at 20 years of age, are shown in Table 2. In both the surgery and control groups, those who had obesity at 20 years of age had higher weight and were younger at baseline, compared to those who had normal weight at the age of 20 years.

Table 2. Paper II - Baseline data for subgroups stratified by treatment and BMI at 20-years of age. From Kristensson et al., *Diabetes Care* 2020;43:860-866. ©2020 by the American Diabetes Association. Reprinted with permission.

Variable	Surgery group			Control group		
	BMI<25 (n=725)	BMI 25-29.9 (n=744)	BMI>30 (n=528)	BMI<25 (n=869)	BMI 25-29.9 (n=721)	BMI>30 (n=439)
Estimated BMI at 20 years						
Men, %	190 (26.2)	227 (30.5)	166 (31.4)	233 (26.8)	224 (31.1)	131 (29.8)
Age, years	49.0 (5.7)	47.0 (5.9)	44.9 (5.4)	50.0 (6.0)	48.7 (6.3)	46.1 (5.9)
Weight, kg	117.5 (14.9)	120.3 (15.9)	126.7 (18.4)	112.3 (14.8)	115.0 (16.6)	118.9 (18.5)
Body mass index, kg/m²	41.5 (4.1)	42.1 (4.1)	44.0 (5.0)	39.4 (4.2)	40.1 (4.7)	41.7 (5.3)
Waist/hip ratio	0.99 (0.07)	0.99 (0.08)	1.00 (0.08)	0.98 (0.07)	0.98 (0.07)	0.98 (0.08)
Fasting blood glucose, mmol/L	5.21 (2.02)	5.07 (1.88)	5.26 (2.12)	4.90 (1.66)	4.93 (1.88)	5.02 (2.04)
Fasting serum insulin, mU/L	21.55 (11.90)	21.02 (12.96)	22.28 (16.83)	18.23 (10.56)	17.84 (12.18)	17.85 (11.64)
Systolic BP, mm Hg	145.7 (18.9)	144.8 (18.7)	144.5 (18.8)	138.5 (17.7)	138.3 (18.4)	136.2 (17.8)
Diastolic BP, mm Hg	89.8 (11.0)	90.2 (11.1)	89.6 (11.3)	85.3 (10.2)	85.1 (11.0)	84.7 (11.0)
Total cholesterol, mmol/L	5.95 (1.12)	5.84 (1.12)	5.77 (1.14)	5.74 (1.07)	5.59 (1.05)	5.42 (1.02)
HDL cholesterol, mmol/L	1.38 (0.31)	1.33 (0.32)	1.33 (0.32)	1.36 (0.34)	1.34 (0.32)	1.34 (0.32)
Triglycerides, mmol/L	2.25 (1.20)	2.23 (1.63)	2.28 (1.73)	2.09 (1.60)	1.99 (1.32)	1.94 (1.32)
Diabetes type 2, %	134 (18.5)	109 (14.7)	98 (18.6)	106 (12.2)	93 (12.9)	63 (14.4)
Hypertension, %	216 (29.8)	208 (28.0)	138 (26.1)	245 (28.2)	206 (28.6)	99 (22.6)
Current daily smokers, %	150 (20.7)	176 (23.7)	188 (35.6)	183 (21.1)	126 (17.5)	111 (25.3)
Eversmokers, %	486 (67.0)	502 (67.5)	379 (71.8)	496 (57.1)	414 (57.4)	281 (64.0)
Caloric intake/d, kcal	2927 (1276)	2905 (1182)	2972 (1302)	2616 (1059)	2606 (1007)	2527 (1089)

All surgery subgroups experienced long-term weight loss in the range of 15-20% after 8-10 years (Figure 8). There were small, but significant, differences in weight loss between surgery subgroups (interaction $p=0.032$), with the largest weight loss among individuals with obesity at the age of 20 years. Within the control subgroups, weight changes were less than 3%, and there were no significant differences between subgroups.

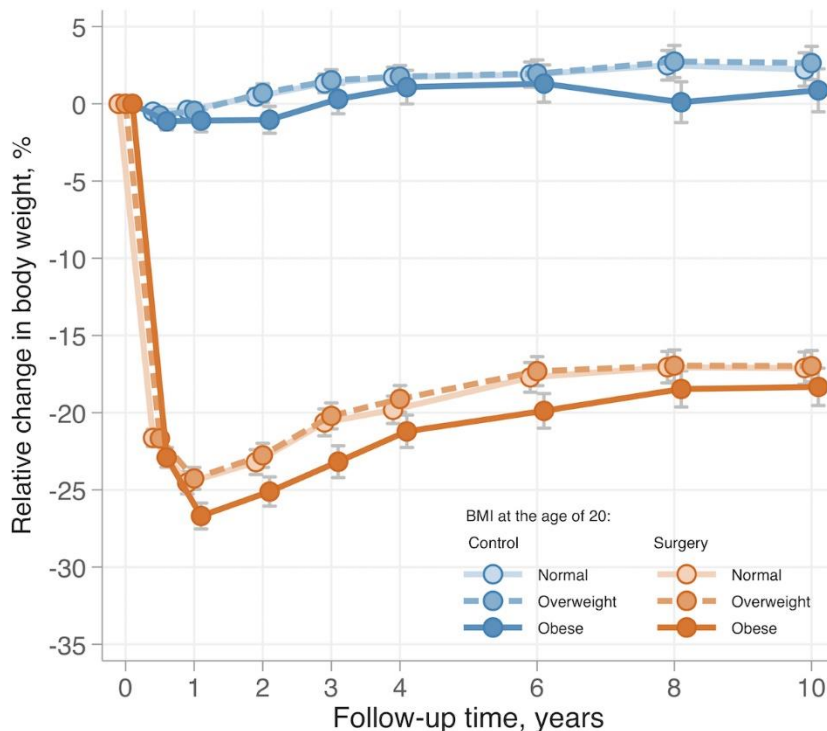


Figure 8. Body weight change in percent between subgroups stratified by treatment and BMI at 20 years of age. Error bars represent 95% CIs. From Kristensson et al., *Diabetes Care* 2020;43:860-866. ©2020 by the American Diabetes Association. Reprinted with permission.

Among participants without type 2 diabetes at baseline, the incidence of type 2 diabetes was lower in all surgery subgroups compared to their respective control groups at both the 2- and 10-year follow-up (Figure 9A). No significant differences in type 2 diabetes incidence were observed between the surgery subgroups at 2 and 10 years (interaction $p=0.905$ and 0.972 , respectively). At baseline, there were 339 participants in the surgery group and 229 participants in the control group with type 2 diabetes. Bariatric surgery increased remission of type 2 diabetes at both 2- and 10-year follow-up in all surgery subgroups,

compared to the control subgroups, (Figure 9B). There was no significant difference in remission of type 2 diabetes between the surgery subgroups at 2 and 10 years (interaction $p=0.201$ and $p=0.951$, respectively). Regardless of type 2 diabetes status at baseline, the incidence of microvascular complications was lower in all surgery subgroups compared to their respective control groups. However, no significant differences were observed between the surgery subgroups in participants without, and with type 2 diabetes at baseline (interaction $p=0.682$, and $p=0.698$, respectively). Likewise, there were no significant differences in treatment benefit between the surgery subgroups regarding cardiovascular disease, myocardial infarction, stroke or cancer (interaction $p=0.674$, $p=0.781$, $p=0.927$, and $p=0.810$, respectively). Surgical complications were also similar across the subgroups (interaction $p=0.568$).

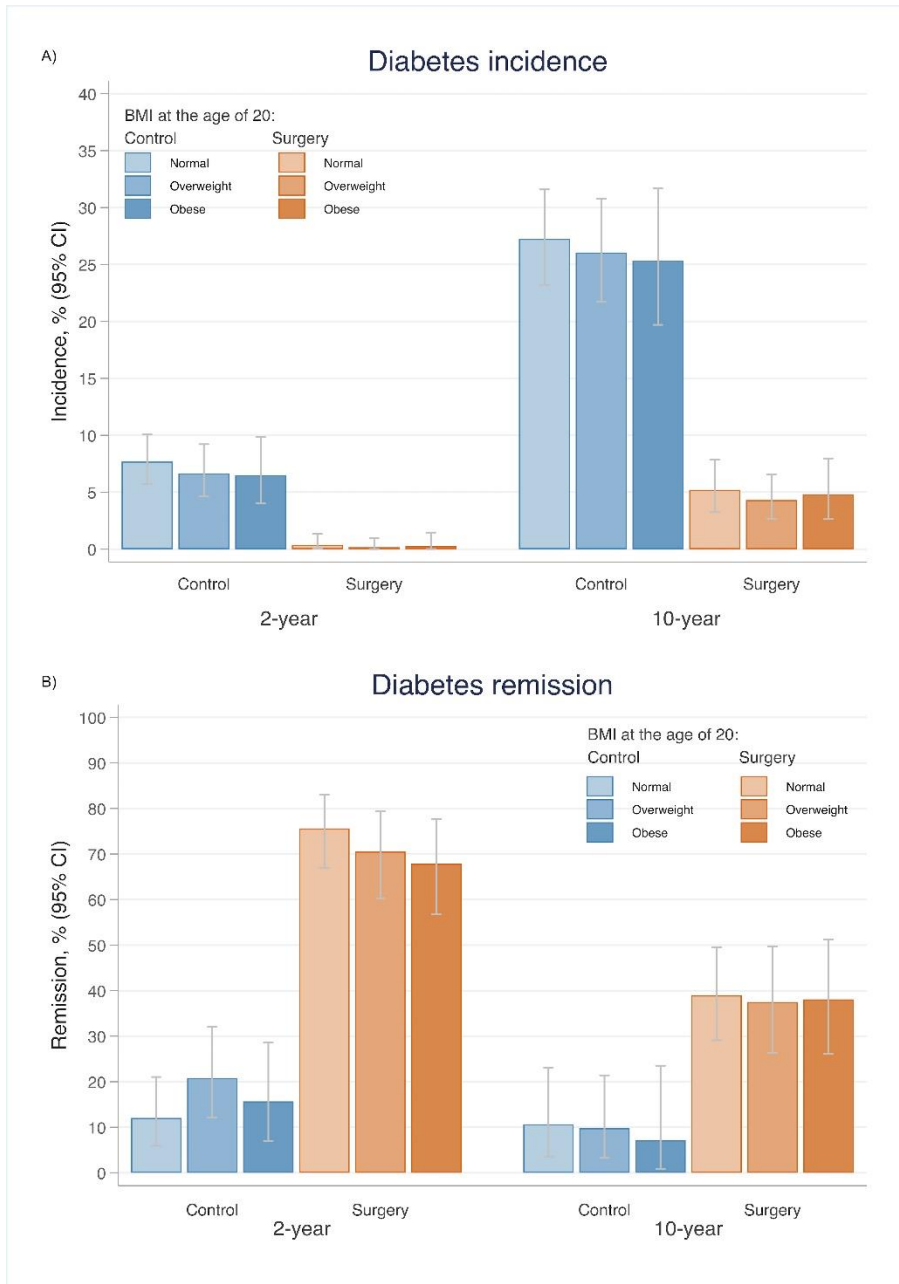


Figure 9. Type 2 diabetes incidence (A) and remission (B), at 2 and 10 year follow-up. Subgrouping is based on treatment and BMI at 20 years of age. Error bars represent 95% CIs. From Kristensson et al., *Diabetes Care* 2020;43:860-866. ©2020 by the American Diabetes Association. Reprinted with permission.

Early onset obesity is an interesting factor to explore since it may affect both weight loss after bariatric surgery⁷², and in extension obesity comorbidities. Early onset obesity is commonly seen in people with a strong genetic predisposition to obesity¹⁷. As mentioned above, genetic variants associated with obesity often affects eating behavior by reducing satiety and increasing hunger^{11,16}, which in turn may affect weight loss after bariatric surgery negatively^{95,96}. By studying people with early onset obesity in a general context rather than focusing on specific genetic variants, we may not only uncover the effects of different genetic variants on bariatric surgery, but also other factors such as poor eating patterns established at an early age. Regardless of the underlying cause of obesity, our results are positive, showing that weight loss following bariatric surgery is as substantial, and possibly even slightly greater, in participants with obesity at 20 years of age compared to those who developed obesity later in life. Apart from weight loss, another concern with early onset obesity is that these individuals often have a longer exposure to the disease, and it is unknown if this affects treatment outcome after bariatric surgery. However, our findings indicate that bariatric surgery had comparable long-term effects on several obesity-related comorbidities, including type 2 diabetes, microvascular complications, cardiovascular disease, and cancer, regardless of BMI status at the age of 20 years. Importantly, the risk of surgical complications was also similar across all surgery subgroups.

We concluded that the treatment benefits of bariatric surgery in adults are comparable regardless of obesity status at 20 years of age.

4.3 PAPER III

Obesity constitutes a major risk factor for breast cancer^{33,98}, one of the most common cancers in women, as well as a leading cause of cancer-associated death⁹⁹. Retrospective studies have indicated that bariatric surgery reduces breast cancer risk in women with obesity^{100,101}. In the SOS-study, we have previously shown that bariatric surgery reduces the risk for female specific cancer, especially in women with hyperinsulinemia⁷⁵. In paper III, the aim was therefore to investigate the association between bariatric surgery and breast cancer in women with obesity and explore whether treatment benefit is modified by baseline insulin levels.

In this paper, we only analyzed women in the SOS study. The study population comprised 2867 women of which 1420 had undergone surgery and 1447 received usual care. The two groups differed significantly in 12 of 17 baseline

characteristics, but differences were small and without a clear distribution of risk factors in favor of any group (Table 3).

Tabell 3. Paper III - Baseline data on women stratified by treatment. From Kristensson et al., JAMA Surgery 2024;159:856-863. ©2024 by American Medical Association. Reprinted with permission.

Characteristic	Surgery group (n=1420)	Usual care group (n=1447)	P value
Age, years	47.2 (6.0)	48.8 (6.3)	<0.001
BMI, kg/m²	42.8 (4.3)	40.7 (4.6)	<0.001
Blood glucose, mg/dL	92 (34)	86 (31)	0.001
S-Insulin, µIU/L	19.9 (12.9)	16.4 (9.6)	<0.001
HOMA-IR, µIU/L*mmol/L	5.3 (5.2)	4.2 (3.5)	<0.001
S-Cholesterol, mg/dL	224 (42)	216 (39)	<0.001
S-HDL-C, mg/dL	54 (12)	54 (12)	0.534
S-Triglycerides, mg/dL	186 (106)	159 (80)	<0.001
Alcohol consumption, g/d	3.2 (4.5)	3.3 (5.1)	0.484
Daily smoking, No. (%)	366 (25.8)	284 (19.7)	<0.001
Diabetes at baseline, No. (%)	203 (14.4)	158 (10.9)	0.006
Nr. Children	2.3 (1.3)	2.1 (1.4)	0.011
Previous breast cancer, No. (%)	1 (0.1)	2 (0.1)	0.574
Postmenopausal, No. (%)	433 (30.5)	529 (36.6)	0.001
Hysterectomy, No. (%)	84 (5.9)	56 (3.9)	0.011
Oophorectomy, No. (%)	11 (0.8)	9 (0.6)	0.624
Hormone/anticonception, No. (%)	214 (15.1)	202 (14.0)	0.399

Over a median follow-up of 23.9 years, 154 breast cancer events were registered, 66 in the surgery group and 88 in the usual care group (Figure 10). In unadjusted analysis, bariatric surgery was associated with a reduced risk of breast cancer compared to usual care, hazard ratio (HR) 0.68 (95% CI: 0.49–0.94; p=0.019). However, after adjusting for age, BMI, alcohol consumption, and smoking status, the association was no longer significant, adjusted (adj) HR 0.72 (95% CI: 0.52-1.01; p=0.06). While there are some retrospective studies that have shown an association between bariatric surgery and reduced breast cancer risk in women with obesity^{100,102}. To our knowledge, this is the

first prospective intervention study indicating an association between bariatric surgery and reduced risk of breast cancer in women with obesity.

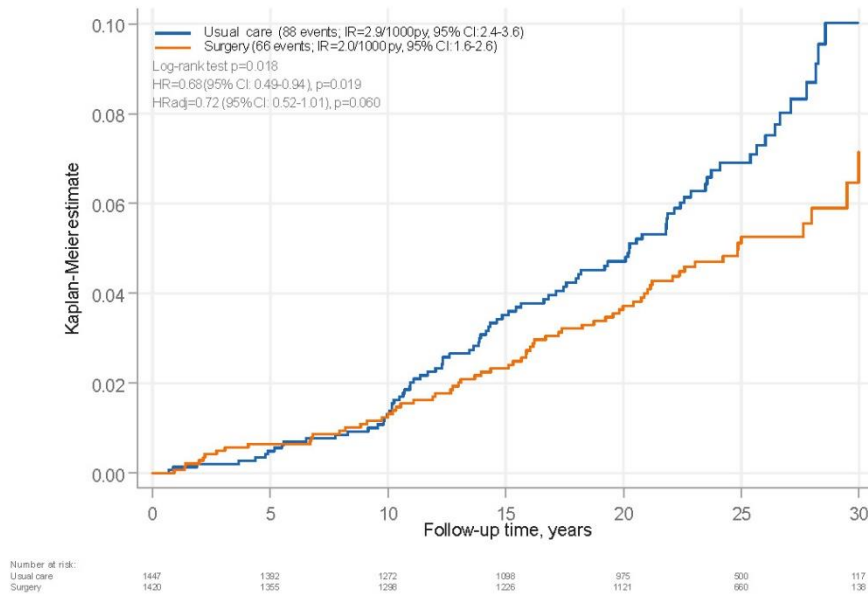


Figure 10. Cumulative incidence of breast cancer in women stratified by treatment. From Kristensson et al., *JAMA Surgery* 2024;159:856-863. ©2024 by American Medical Association. Reprinted with permission.

Next, we explored whether treatment benefit could be modified by baseline insulin levels. We found that women with baseline insulin levels above the median (15.8 $\mu\text{IU/L}$) experienced a greater reduction in breast cancer risk after bariatric surgery, HR 0.48 (95% CI: 0.31-0.74; $p=0.001$), compared to those with insulin levels below the median, HR 0.95 (95% CI: 0.59-1.53; $p=0.84$). This association remained significant after adjusting for age, BMI, alcohol consumption, and smoking status, adjHR 0.55 (95% CI: 0.35-0.86; $p=0.008$), and adjHR 1.01 (95% CI: 0.61-1.66; $p=0.97$), respectively, test of interaction $p=0.02$ (Figure 11). These results are similar to our previous study on female-specific cancer where hyperinsulinemia was associated with a greater risk reduction⁷⁵.

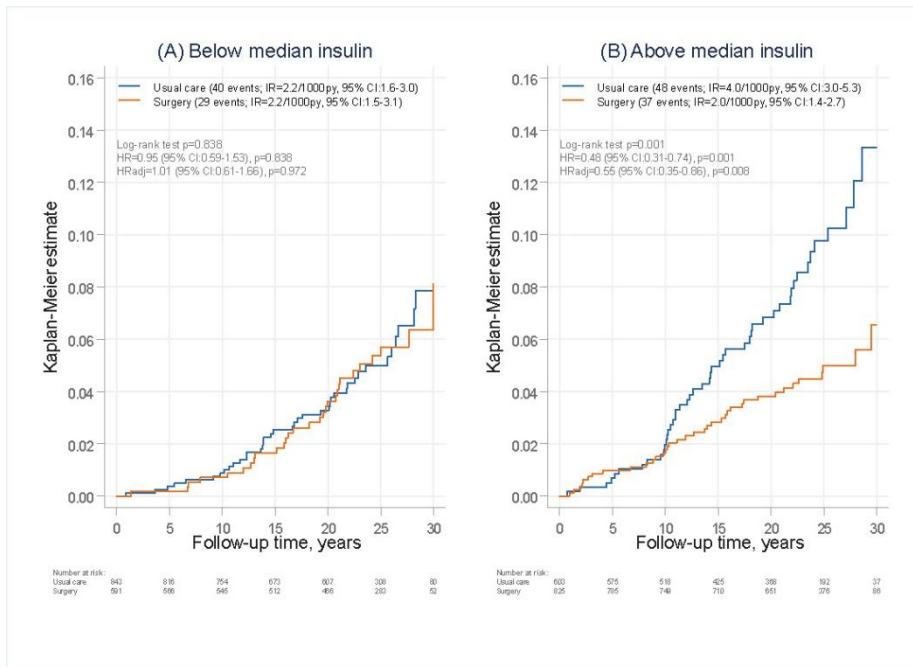


Figure 11. Cumulative incidence of breast cancer in women stratified by treatment and median baseline insulin levels. From Kristensson et al., *JAMA Surgery* 2024;159:856-863. ©2024 by American Medical Association. Reprinted with permission.

Although several studies suggest that bariatric surgery protects against cancer development in people with obesity^{103,104}, the exact mechanisms behind this protection remain unknown. However, it is primarily thought that the weight loss induced by surgery counteracts several different pathways through which obesity induces cancer^{105,106}. As mentioned before, obesity may affect cancer development through many different paths such as inducing inflammation³⁵, affecting levels of steroid hormones^{37,38} and other hormones such as insulin³⁶. Insulin constitutes an especially interesting candidate as it acts as a growth hormone and has been shown to induce cell mitosis as well as inhibit apoptosis¹⁰⁷. It is also common that breast cancer cells over-express insulin receptors¹⁰⁸, and in line with this hyperinsulinemia has been linked to poorer treatment outcomes in women with breast cancer¹⁰⁹. Despite our current knowledge, further studies are needed to deepen our understanding of the biological mechanisms behind bariatric surgery and cancer development¹¹⁰.

We concluded that bariatric surgery was associated with a reduced risk of breast cancer in women with obesity, and that the surgical treatment benefit was seen primarily in women with hyperinsulinemia at baseline.

4.4 PAPER IV

The *FTO* gene is an especially interesting gene as variations in it have been associated with both increased BMI¹⁰ and obesity comorbidities such as diabetes^{12,13} and breast cancer^{14,15}. The effects of variations in *FTO* and the outcomes of bariatric surgery is only partially explored⁷⁰. Further studies on genetic variation in *FTO* may not only reveal predictors of treatment outcome, but also elucidate mechanisms by which obesity mediate disease¹¹¹. In paper IV we therefore aimed to examine the association between rs9939609 in *FTO* and breast cancer incidence in women with obesity. As well as explore whether rs9939609 modifies the association between bariatric surgery and breast cancer risk, and if this may be mediated by insulin.

For this paper, we analyzed only the women in the SOS study. Rs9939609 was successfully genotyped in 2584 of 2596 (99.5%) women where DNA was available. Of these, 1881 were hetero- or homozygous carriers of the A risk-allele (TA/AA), and 703 were non-carriers (TT). The allele frequencies for rs9939609 were 0.483 for the A-allele and 0.517 for the T-allele, and these were in Hardy-Weinberg equilibrium ($p=0.33$). Our reported frequency is slightly higher than previously reported frequencies of 0.410 in a general population. We speculate this may be due to the higher prevalence of obesity within the SOS-cohort since the A-allele is associated with a higher BMI¹⁰. In both carriers and non-carriers of the A-allele, women undergoing surgery were younger but other cancer risk factors were less favorable (Table 1, Paper IV reprint).

For the first aim, we analyzed the SOS control group and compared breast cancer incidence between carriers (TA/AA) and non-carriers (TT) of the rs9939609 risk A-allele. During a median follow-up period of 22.7 years, 77 breast cancer events occurred in the control group; 57 in the risk A-allele carrier (TA/AA) group, and 20 in the non-carrier (TT) group. There was no significant difference in breast cancer incidence between the risk A-allele carriers (TA/AA) and non-carriers (TT) (Figure 3, Paper IV reprint). As such, we could not find the previous described association between rs9939609 and breast cancer risk^{14,15}. The lack of association may be due to the higher BMI in the SOS-cohort discussed above as BMI constitutes an independent risk factor

for breast cancer³³. This paper also constitutes a secondary analysis on the SOS-cohort, and other possible explanations are therefore the limited number of breast cancer events and insufficient statistical power.

For the first part of the second aim, we analyzed the entire female SOS-cohort and compared breast cancer incidence between participants in the surgery and control groups, stratified by genotype. During a median follow-up of 23.9 years, there were 135 breast cancer events, 77 in the control group and 58 in the surgery group. Of the 58 participants with breast cancer diagnosis in the surgery group, 34 were carriers of the A-allele (TA/AA) and 24 were non-carriers (TT). Among the risk A-allele carriers (TA/AA), bariatric surgery was associated with a reduced incidence of breast cancer adjHR 0.53 (95% CI: 0.34-0.83; p=0.005), while there was no association in the non-carrier group (TT), interaction p=0.031, (adjusted for age, BMI, smoking and alcohol intake) (Figure 4, Paper IV reprint).

The exact biological mechanisms by which *FTO* influences breast cancer risk is poorly understood, but it is thought that multiple factors are involved¹¹². The rs9939609 polymorphism lies in intron 1 of the *FTO* gene and does not directly affect the *FTO* protein structure. Instead, this polymorphism is believed to influence *FTO* gene expression¹¹³. A potential mechanism by which variation in the *FTO* gene may increase breast cancer risk is through the upregulation of the Iroquois homeobox 3 gene (*IRX3*)¹¹⁴. The function of *IRX3* is vital for the maturation of adipocytes, supporting the link between *FTO* and obesity¹¹⁴. In addition, the *IRX3* gene has been suggested to be involved in the development of breast cancer¹¹⁵. *FTO* may also influence cancer development by modifying RNA, as it acts as an N6-methyladenosine (m6A) demethylase in humans^{116,117}. Since m6A affects RNA processing, stability, and translation^{116,117}, changes in m6A demethylase function could explain *FTO*'s role in cancer development¹¹³. Another hypothesis is that genetic variation in *FTO* indirectly affect breast cancer risk by altering body weight and subsequent metabolic processes¹¹¹. As described above, obesity promotes inflammation³⁵, steroid hormone production^{37,38} and insulin resistance³⁶. However, as genetic variation in *FTO* is associated with an increased risk of not only obesity, but also insulin resistance, type 2 diabetes and breast cancer, it may play a more complex role as a mediator of these diseases¹¹¹.

To further explore the effect of genotype and insulin on breast cancer risk, we stratified treatment groups by both genotype TA/AA vs TT and median levels of insulin at baseline (15.7 mU/L), (Supplement Figure 1, Paper IV reprint). In

women with baseline insulin levels above median, bariatric surgery was associated with a reduced incidence of breast cancer in carriers of the A risk-allele (TA/AA) adjHR=0.36 (95% CI: 0.20-0.66; p=0.001), while there was no association in the non-carrier group (TT), interaction test p=0.036. Among women with baseline insulin levels below the median, there was no significant association between bariatric surgery and breast cancer incidence, regardless of genotype, in both unadjusted and adjusted analyses.

Lastly, we speculated that genetic variation in *FTO* might affect insulin levels and as such act as a mediator of both breast cancer risk and metabolic disease. To test this, we analyzed the changes in insulin levels over time between different genotype groups. During the follow-up period, insulin levels decreased in both risk-allele (TA/AA) carriers and non-carriers (TT) in the surgical group, remaining lower than baseline levels, with a nadir at two years. In contrast, insulin levels in the control group remained largely unchanged compared to baseline throughout the follow-up period in risk-allele (TA/AA) carriers as well as non-carriers (TT) (Supplement Figure 2, Paper IV reprint). A mixed model analysis was conducted to investigate the association between rs9939609 and insulin levels during follow-up. There were no significant differences in insulin levels between risk-allele (TA/AA) carriers and non-carriers (TT). This suggests that the modifying effect of the rs9939609 genotype on treatment response is not mediated by changes in insulin levels. Alternatively, it could also indicate that insulin and rs9939609 influence breast cancer risk through separate pathways. Further studies are warranted to explore the relationship between the rs9939609 genotype and insulin more comprehensively.

We concluded that in women with obesity, the *FTO* rs9939609 genotype modifies the association between bariatric surgery and reduced breast cancer risk.

5 CONCLUSION

In conclusion, the presence of a microdeletion on chromosome 16p11.2 or the age of obesity onset did not affect treatment outcomes following bariatric surgery. In contrast, baseline insulin levels and a risk allele in the FTO gene were associated with treatment benefits of bariatric surgery in women with obesity. These biological factors may help predict outcomes after bariatric surgery and provide insights into the underlying mechanisms of disease development. Further studies on these mechanisms could reveal novel therapeutic targets and aid the development of new drugs.

6 FUTURE PERSPECTIVES

The idea to identify predictors of treatment outcomes after bariatric surgery is not new, nor is the concept to predict treatment effects after an intervention unique to the field of surgery¹¹⁸. Previous attempts to develop predictive models for bariatric surgery have primarily relied on multilinear regression models¹¹⁸. However, since these models assume linear relationship, their predictive ability is limited, and there are currently no widely adopted model used in clinical practice¹¹⁸.

With rapid improvements in technology, such as cheaper and faster whole genome sequencing and the development of AI, new opportunities for more accurate predictive models are emerging. Whole genome sequencing in particular enables us to generate highly detailed data on individual patients relatively cheap and easy. This genomic data, combined with other patient information, can be merged into large datasets, which can be analyzed using AI-models such as machine learning¹¹⁹. These AI tools have the potential to create predictive models with a significantly higher accuracy than multilinear models^{119,120}. There are already some clinical uses of AI-models, primarily in radiology, but the development is fast and predicted to soon involve more medical fields¹¹⁹.

In the field of bariatric surgery, the research team working with the Swedish Obese Subjects study is currently collaborating with several European research groups within the Stratification of Obesity Phenotypes to Optimize Future Therapy (SOPHIA) EU IMI-project, to develop a predictive model for weight loss¹²⁰. A prototype model has already been tested on the SOS-cohort, but further work is needed to improve this model and to develop new ones that also predict effects on obesity-related comorbidities.

The long-term goal of these models, is to improve patient care by enabling clinicians to give the right treatment to the right patient, and thereby avoiding unnecessary harm to those unlikely to benefit from surgery.

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