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To cut or not to cut – The association between weight loss and cardiometabolic health in adolescents and adults after Roux-en-Y Gastric Bypass

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By

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POPULÄRVETESKAPLIG SAMMANFATTNING

Energi kan inte förstöras, bara omvandlas och hos människan lagras energiöverskott som fett. Ansamling av fett sker vid en positiv energibalans. Fetma är därför definierat som en abnorm ansamling fettväv i kroppen. Fetma leder till ett långvarigt sjukdomsförlopp som kan skada individen, någon som kan börja redan i barndomen. Målet med all fetmabehandling är att skapa en negativ energibalans. I denna avhandling undersöks ett sätt att göra det, nämligen viktminskningskirurgi och mer specifikt Roux-en-Y Gastric Bypass (RYGB).

Studie I undersökte förekomsten av viktminskningskirurgi efter avslutad barnfetma behandling. Vid 30 års ålder uppskattas mer än var femte att ha genomgått viktminskningskirurgi. Vid tiden för kirurgi var medianåldern 20.9 år och fetmarelaterad sjuklighet identifieras hos 31.7% före viktminskningskirurgi.

Studie II som byggde på preliminära resultat i studie IV, utforskade effekten av ”otillfredsställande viktkirurgisk behandling” hos vuxna. Förekomsten av ”otillfredsställande viktkirurgisk behandling” uppgick till 23.1% vilket var associerat till åter- och nyinsjuknande i diabetes typ 2, höga blodfetter och högt blodtryck. Genom att använda mätningar från innan, ett och två år efter kirurgi kunde en modell för att förutse risken för ”misslyckad kirurgisk behandling” tas fram. Modellen testades på delar av studiedeltagarna och även på ungdomarna i Studie IV. Modellen tycks vara precis och vara värdefull i klinik.

I studie III undersöks effekten av viktminskning genom RYGB på kondition, funktionell kapacitet och kroppssammansättning hos tonåringar två år efter kirurgi. Resultaten visar att tonåringar ökar sin syreupptagningsförmåga och funktionella kapacitet och att viktminskningen bestod av både fett- och fettfri massa. Förbättringarna i syreupptagningsförmåga hos tonåringar tycks vara bättre än de som rapporterats hos vuxna.

I studie IV utforskades heterogeniteten av viktförändring upp till fem år efter RYGB hos tonåringar. Under första året skedde den största viktminskningen men det fanns skillnader mellan individerna. Mellan år ett och två förekom en varierande viktökning hos 40% av deltagarna. Vid år fem, uppnådde en tredjedel minst en av definitionerna för ”otillfredsställande viktkirurgisk behandling” (definierat som ett BMI över 35 eller 40 beroende på start BMI, eller mindre än 20% total viktnedgång, eller som mindre än 50% nedgång av viktöverskottet) detta var i sin tur associerat till markörer för fetmarelaterad sjuklighet.

Som sammanfattning, om viktminskningskirurgi fördröjs till vuxen ålder tycks risken för fetmarelaterad sjuklighet öka. RYGB är en effektiv behandlingsmetod för viktminskning hos tonåringar. Resultaten på gruppnivå tycks vara lika bra som eller bättre än hos vuxna. Tonåringar tycks dock ha en större variation av viktminskning och ”otillfredsställande viktkirurgisk behandling” kan motverka de positiva effekterna av RYGB. Att uppskatta risken för ”otillfredsställande viktkirurgisk behandling” kan vara av betydelse vid uppföljning för rikta sig till dem som troligen behöver mer omfattande hjälp för att bibehålla viktminskningen.

ABSTRACT

Energy cannot be destroyed, and in humans excess energy is stored as fat in adipose tissue. Accumulation of fat is thus the result of a positive energy balance, and obesity is defined as an excess amount of adipose tissue. Obesity can be harmful to the individual because it leads to a protracted disease course that can start as early as in childhood. The goal of all obesity treatments is to reverse the positive energy balance. This thesis investigates one of the means of achieving such a reversal, namely the bariatric Roux-en-Y gastric bypass (RYGB) surgery procedure.

Study I investigated the prevalence of bariatric surgery after childhood obesity treatment. By the age of 30, more than one fifth of children treated for childhood obesity were estimated to have underwent bariatric surgery. At the time of surgery, the median age was 20.9 years, and an obesity-related comorbidity was identified in 31.7% of patients before surgery.

Study II, building on preliminary results from Study IV, investigated the effect of surgical treatment failure five years after RYGB. The prevalence of surgical treatment failure was 23.1% and in turn associated with and increased likelihood of relapse and incidence of type 2 diabetes, dyslipidemia and hypertension. A model for predicting the risk of surgical treatment failure was developed using measurements from before surgery and one and two years after surgery. The model was tested on parts of this study population and on the population in Study IV. The model was found to be accurate and could prove clinically useful.

Study III investigated the effect of RYGB-induced weight loss on cardiorespiratory fitness, functional capacity and body composition in a group of adolescents two years after surgery. The results show that adolescents improve their oxygen uptake and functional capacity and that the weight loss consisted of both fat and non-fat mass. The improvements in oxygen uptake among adolescents may be greater than those reported in adults.

Study IV explored the heterogeneity of weight loss up to five years after RYGB in adolescents. Most of the total weight loss was observed during the first year, but it was not equal among participants. Between year one and two, weight regain occurred to varying extents in 40% of participants. By year five, a third of participants met at least one definition of surgical treatment failure (defined as a body mass index of above 35 or 40, losing less than 20% of initial weight, or losing less than 50% of excess weight), which was in turn negatively associated with obesity-related risk markers.

In summary, if surgical treatment is delayed into adulthood, it is likely that obesity-related comorbidities will manifest. Roux-en-Y gastric bypass surgery is an effective treatment in inducing weight loss in adolescents. Overall, results are on par with or better than those in adults. However, adolescents were observed to exhibit greater variation in weight loss, and surgical treatment failure can hamper the positive effects of RYGB. The model for predicting surgical treatment failure can be used as a risk assessment tool when monitoring subjects following RYGB and to target those likely in need of additional follow-up and support in order to maintain long-term weight loss.

LIST OF SCIENTIFIC PAPERS

I. **Brissman M**, Lindberg L, Beamish AJ, Marcus C, Hagman E. High estimated prevalence of bariatric surgery in young adults treated for pediatric obesity. Surgery for Obesity and Related Diseases. 2021;17(2):398-405.

II. **Brissman M**, Beamish AJ, Olbers T, Marcus C. Prevalence of insufficient weight loss 5 years after Roux-en-Y gastric bypass: metabolic consequences and prediction estimates: a prospective registry study. BMJ Open. 2021;11(3):e046407.

III. **Brissman M**, Ekbom K, Hagman E, Mårild S, Gronowitz E, Flodmark C-E, Olbers T, Marcus C. Physical Fitness and Body Composition Two Years after Roux-En-Y Gastric Bypass in Adolescents. Obes Surg. 2017;27(2):330-337.

IV. **Brissman M**, Hagman E, Flodmark C-E, Dahlgren J, Ekbom K, Olbers T, Marcus C. Poor initial weight loss, weight regain and long-tern surgical treatment failure after Roux-en-Y gastric bypass surgery in adolescents; effects on metabolic risk markers. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

%EBMIL	Percentage excess body mass index loss
%TWL	Percentage total weight loss
6MWT	Six minute walk test
AMOS	Adolescent Morbid Obesity Surgery study
ASMBS	The American Society for Metabolic and Bariatric Surgery
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body mass index
BMI SDS	Body mass index standard deviation score
BORIS	the Swedish Childhood Obesity Treatment Register
BPD/DS	Biliopancreatic diversion / duodenal switch
CVD	Cardiovascular disease
CRF	Cardio Respiratory Fitness
DXA	Dual-Energy X-ray Absorptiometry
FABS-5+	Follow-up of Adolescent Bariatric Surgery at 5 Plus Years
FFM	Fat free mass
FM	Fat mass
HR	Hazard Ratio
ICD	International Classification of Diseases
IOTF	International Obesity Task Force
IQ	Intelligence quota
OR	Odds Ratio
RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
SOReg	The Scandinavian Obesity Surgery Registry
T2D	Type 2 diabetes
Teen-LABS	Teen-Longitudinal Assessment of Bariatric Surgery
VO_2max	Volume of maximal oxygen consumption

1 INTRODUCTION

Obesity is defined as an excess amount of adipose tissue that threatens to harm the health of an individual (1). It is caused by a long-term positive energy balance wherein caloric intake exceeds caloric expenditure, resulting in excess calories being stored as fat. Obesity in adulthood is associated with several negative health consequences, such as type 2 diabetes (T2D), cardiovascular disease (CVD), certain forms of cancer, reduced quality of life and all-cause mortality (2-4).

Obesity is seemingly simple and straightforward as it is clear what to look for, causes, and consequences if left untreated.
In this simplistic view of obesity, the treatment is obvious: the energy balance must be reversed, which boils down to the common advice to eat less (reduce caloric intake) and exercise more (increase energy expenditure).

Unfortunately, reversing the energy balance has proven difficult to achieve, and global trends in obesity prevalence and incidence remain positive, with obesity increasing over the last five decades (5).

Thus, the question is not *what* causes obesity, but rather *why* people consume too many calories or exercise too little. As with any why question, there is almost an infinite number of answers. Genetic and environmental factors likely contribute in fairly equal proportion at the group level (5). However, the answer to why a given individual consumes too many calories is likely to differ widely.

The fact that there is also great heterogeneity in how well and for how long individuals tolerate obesity before comorbidities emerge has sparked an often confusing debate regarding the possibility of a sub-population of metabolically healthy obese individuals (6) and the existence of an ‘obesity paradox’ (7, 8). The obesity paradox implies that obesity is associated with better survival prognosis in a number of diseases e.g. heart failure, stroke, T2D (9). Such examples indicate that obesity is a heterogeneous and complicated disease.

Research on obesity is broad and spans from genetical studies and in vitro and in vivo cell studies of adipose tissue functions to epidemiological studies comprised of millions of individuals. This thesis aims to elucidate some of the complexity regarding reversing energy balance through surgically induced weight loss, focusing on adolescents who undergo the Roux-en-Y gastric bypass (RYGB) surgical procedure.

2 BACKGROUND

2.1 OBESITY

2.1.1 Epidemiology

Worldwide, the prevalence of obesity has been estimated to be 12% in adults (10) and 5–7% in children (5.6% in girls, 7.8% in boys) (10, 11). Childhood obesity shows extreme regional differences, with small Pacific islands such as the Cook Islands having a prevalence of up to 30% and mainland USA 20% (11). The prevalence of childhood obesity in Sweden is not known exactly but is estimated to be 4–5% in children 6 to 9 years old and 7–8% in adolescents (12). Obesity in childhood is very likely to persist into adulthood (13).

2.1.1.1 Nature, nurture or both?

Humans live in an obesogenic environment. Over the last 50 years, the average food supply expressed as daily kcal per capita has increased from ~ 2,900 kcal/day to ~ 3,750 kcal/day in North America and from ~ 3,000 kcal/day to ~ 3,500 kcal/day in Western Europe (14). Although many people live in this environment, not everyone develops obesity. The influence of genetic predisposition is evident, and more than 500 genetic loci have been associated with adiposity traits (15, 16). The most substantial evidence of hereditary factors in obesity comes from twin and adoption studies (17). Moreover, socioeconomic status (SES) is associated with obesity, though the directions differ depending on the country or society. High SES is associated with low prevalence of obesity in high-income countries and high prevalence of obesity in low-income countries (18).

2.1.1.2 Individual traits

Individual traits may also be important, and a lack of self-control and willpower have been described as characteristics associated with obesity. In a meta-analysis of personality traits and obesity risk in adults, ‘high conscientiousness’ (e.g. high self-control and orderliness) was associated with a lower risk, whereas results from other personality traits were inconclusive (19). In children and adolescents, intellectual disability has been associated with obesity (20, 21). Although there is debate over the direction of causality, there are indications of a potential link between intelligence quotient (IQ) and obesity. An inverse association between IQ and obesity has been demonstrated even when adjusting for potential confounders such as mental disorders (22). A longitudinal study of Swedish male conscription data suggested that IQ at the age of 18 is inversely associated with body mass index (BMI) at age 40 (23).

Although the influence of individual factors may be present, no factors provides a clear explanation given that BMI has increased in all age groups in the USA since the 1980s (24).

2.2 BODY MASS INDEX

The most commonly used technique to diagnose obesity today is BMI. First developed by Belgian mathematician and statistician Quetelet in 1832 (25) and later supported by Keyes in 1972 (26), BMI is calculated by using weight in kilograms divided by stature in meters squared; the product provides a relatively reliable proxy measure of adiposity in adult humans.

The World Health Organisation (WHO) classification of weight status for adult BMI is based on generally increased risk of mortality starting from a BMI of 25 kg/m^2 and the differences in obesity management and treatment for those below or above a BMI of 35 kg/m^2 (27).

The following list provides the WHO categories for adult BMI in kg/m^2:
<18.5 = underweight
18.5–24.99 = normal weight
25–29.99 = overweight
30–34.99 = Obese class 1
35–39.99 = Obese class 2
>40 = Obese class 3

2.2.1 Body mass index in children and adolescents

In healthy children, increased height and weight follow a growth pattern, which makes BMI unsuitable for determining weight status. Instead, statistical models have developed using the common definition that when a child's BMI exceeds a specific age- and sex-adjusted threshold, an obesity diagnosis can be confirmed. The deviations from the median or mean are expressed as percentiles or as standard deviation scores (SDS).

Several models have been developed (28-30) to track and compare BMI in children. These models are typically based on a national reference population measured before the onset of the obesity epidemic. International models based on populations from specific countries are also available (31, 32). In such models, BMI is often expressed as percentiles with ~ 95^{th} corresponding to obesity or a specific SDS/z-scores from the mean or median in regard to the child's age and sex. In Sweden, the use of the International Obesity Task Force (IOTF) reference is largely agreed upon when diagnosing childhood obesity (31). However, in adolescents it may be justified to use the ranges of adult BMI, especially if target height is reached and the subjects have a BMI above 35 kg/m^2 and are to be followed over time (33).

2.3 ADIPOSE TISSUE

Adipose tissue is at the heart of obesity. The amount, location and phenotype of adipose tissue is of importance for understanding obesity-related comorbidities (34).
Adipose tissue is generally and roughly divided into white adipose tissue (WAT) and brown adipose tissue (BAT). Despite increased interest in BAT for its thermogenic and energy expenditure characteristics in obesity research, this thesis does not cover anything related to BAT.

The best known function of WAT is the ability to store energy, and it does so in the form of lipids, namely triglycerides. When the supply of energy is greater than the demand, adipocytes expand in size (35). When the demand for energy increases, the stored energy within WAT can be released as free fatty acids and glycerol in a process called lipolysis.

The ability to store and release energy is crucial for humans, and the survival of newborn babies is dependent on this ability during the first 72 hours of life (before lactation properly starts). Adipose tissue is recognised as an endocrine organ with important functions which were unravelled during the intensified research period accompanying the obesity epidemic (36, 37). Humans share biological traits with other species, and although adipose tissue displays intraspecies variations in location and role, the ability to store and release energy has been tremendously important for the survival and prosperity of most—if not all—living species (38).

2.3.1 The depots of adipose tissue

In humans, WAT is located in different depots of the body, predominantly in subcutaneous sites. Subcutaneous depots are roughly divided into android, which is characterised by central storage in the abdomen region, and gynoid, which is characterised by storage in the gluteofemoral region (39). The difference between storage depots has been found to be associated with metabolic disease, with android depots more likely to exhibit diseases such as type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease (40-42). Gynoid depots are viewed as less harmful (43).
Adipose tissue can also be found around or inside organs. Visceral adipose tissue is located around digestive organs and is independently associated with metabolic risks (42). Ectopic fat is stored around or inside organs, such as in liver and muscle tissue, and can impair the functioning of the organ (44).

2.3.1.1 Adipose dysfunction in obesity

Humans display individual variability in why and when subcutaneous depots fail to effectively store excess energy as those depots are designed to be ‘energy sinks’. A proposed sequence of events starts with a long-term, positive energy balance that pressures the adipose tissue to expand, which does so up to a point by increasing the size of the adipocyte (rather than recruiting or proliferating new adipocytes) and thus rendering it hypertrophic. Beyond this point, excess energy is stored in less well designed depots. Thus, visceral and ectopic fat accumulation is believed to be the result of impairment in the storage function of subcutaneous WAT depots (45).

Furthermore, there is evidence of individual variation regarding the number and size of adipocytes. For a given percentage of body fat, adipose tissue may show either hypertrophy (few and big adipocytes) or hyperplasia (more and small adipocytes) (46). Hypertrophic adipose tissue has been associated with metabolic disease, which is, proposed by some scholars, to originate from insulin resistance in the hypertrophic adipocyte (47). The suppressive effect of insulin on lipolysis would in turn be reduced and consequently circulating free fatty acids are increased. Others have suggested that the total amount of adipose tissue may be of similar importance for the increase of circulation free fatty acids (48). What most agree upon are that free fatty acids act on other tissues, such as muscles, causing peripheral insulin resistance that leads to an increased demand for insulin produced by pancreatic beta cells (which are also affected by free fatty acids (49). Over time, this system overload threatens the longevity of the pancreatic beta cells, and T2D emerges as a consequence. Adipose tissue may also be subject to hypoxia due to its rapid growth, which give rise to a pro-inflammatory profile and further fuels negative effects on other organs (50).

2.3.2 Body composition

The content and composition of the human body can be assessed and described in five models based on different compartments that are referred to as levels: the atomic level, molecular level, cellular level, tissue-system level and whole body level (51, 52). The last two levels are most frequently utilised in in vivo research on humans to estimate body composition.

2.3.2.1 Whole body level: Mass and shape

Anthropometrical measures such as weight, height, waist circumference and skinfold thickness have been collected and studied in humans since the 1830s. Further calculations and the use of algorithms allow simple measures of mass, form and frame to transform into estimates of body composition (53).
The major benefit of anthropometrics is that they are cheap and easily obtained, and the amount of data available allows the possibility of reducing bias related to various disease risks (53). Waist circumference has been shown to be a fair predictor of abdominal adiposity (54). However, there are also shortcomings to anthropometrics; for example, weight does not discriminate between fat or lean tissue, nor does the fixed relationship between weight and height expressed as BMI.

2.3.2.2 Tissue-system level

For the tissue-system level, non-invasive methods to estimate body composition have been developed, and densitometry, bioelectric impedance analysis and dual-energy X-ray absorptiometry (DXA) are frequently utilised in both clinical and research settings (55).

Over recent decades, densitometry has shifted from hydrostatic (underwater) weighing (56) to air displacement plethysmography (57) and provides estimates of fat mass (FM) and fat-free mass (FFM) through equations and assumptions of tissue-specific density in relation to body weight and volume.

Bioelectric impedance analysis measures the resistance in human tissue. Based on measurements of conductivity in specific tissues, total body water is estimated (58). The method relies on assumption of a constant share of water in specific tissues as well as assumptions of proportions of the human body that allow calculation of both FM and FFM in relation to body weight and height.

Dual-energy X-ray absorptiometry is a full-body X-ray technique. The intensity of the beam reflects differently depending on the thickness, density and chemical composition of the scanned object. Dual-energy X-ray absorptiometry is therefore suitable for distinguishing between bone content, FM and FFM (59).

2.4 CONSEQUENCES OF OBESITY

Obesity results in disease and ultimately a shorter lifespan. How hazardous obesity is has been the focus of multiple studies and meta-analyses over the years, with results demonstrating J- or U-shaped associations between BMI and all-cause mortality (3, 4, 60).

2.4.1 The medical consequences of obesity

Obesity-related comorbidities such as CVD (61-63), T2D (64), non-alcoholic fatty liver disease (65), various forms of cancer, musculoskeletal disorders and mental illnesses such as depression (2) are frequently observed in adults. Although obesity-related comorbidities can also be present in childhood (66) their prevalence is lower than in adults. Nonetheless, childhood obesity leads to a protracted disease course (67, 68), and pre-stages and elevated risk markers are often observed in children with obesity (69, 70). In a study of 2.3 million adolescents, being overweight and obesity were associated with cardiovascular death in adulthood (71). Furthermore, estimates of life expectancy are dramatically reduced; for example, 18-year-old males and females with a BMI $\geq$ 40 are estimated to have a shorter lifespan of about 10 years and five to seven years, respectively (72). Premature death before the age of 30 is higher in children treated for obesity than in matched controls from the general population (73). Moreover, there has been a reported association between obesity status in young adulthood and disability pension before the age of 40 in Sweden (74).

2.4.1.1 Cardiovascular disease

Both functional and structural changes in the cardiovascular system can be observed in patients with obesity. Hypertension is common and may lead to increased stress on the cardiac chambers, resulting in hypertrophy of the left ventricular wall that can already be observed in obese adolescents (75). Early signs of vascular impairment are also evident in young children with obesity. Increased intima media thickness (76) and endothelial dysfunction (77) are more common compared to normal-weight peers and are associated with atherosclerosis later on in life. Hypertension and the absence of nocturnal dipping has been reported to be more common in children with obesity (70).

2.4.1.2 Type 2 Diabetes

Obesity in childhood and adolescence is associated with the pre-stages of T2D, particularly increased insulin resistance and increased levels of fasting glucose (69). In early adulthood, obesity is associated with young onset T2D (78, 79), which is particularly hazardous since the young onset T2D progresses faster, and mortality before the age of 30 is higher in individuals with T2D compared to type 1 Diabetes (80).

2.4.1.3 Orthopaedics

Childhood obesity is associated with orthopaedic problems (81). Increased risk of bone fractures and musculoskeletal pain and discomfort is more common in children with obesity (82). The association between musculoskeletal pain and obesity may also explain the association between lower physical activity and adolescents with obesity (83).

2.4.2 Psychological consequences of obesity

2.4.2.1 Stigmatisation and bullying

Obesity is associated with reduced health-related quality of life in adolescents (84) and adults (85). Weight stigmatisation and bullying are more prevalent in children and adolescents with obesity (86), and children with obesity are more often portrayed with negative attributes such as being lazy or unintelligent (87). Furthermore, childhood obesity has been associated with lower SES in adulthood, independent of IQ (88). However, a review on the topic suggests that although existent, the impact of obesity on psychological wellbeing may be overestimated (89).

2.4.2.2 Cognitive function

Obesity in adolescence is associated with impairments in cognitive functioning as well as alterations of the brain structure (90). Compared to normal-weight peers, adolescents with obesity and severe obesity have shown impairment in memory, attention and executive functions (91). However, the association between obesity and cognitive functions may be revisable either through exercise in children (92) or by weight loss in adults (93).

2.5 OBESITY TREATMENT

The goal of any obesity treatment is essentially to reverse the positive energy balance; the most common approach to achieving this is to try to reduce caloric intake through methods including dieting, medical drugs and bariatric surgery, each of which is further divided into sub-methods or techniques.

The only other way to reverse energy balance is to increase energy expenditure, which is most commonly done by engaging in physical activity (exercise or training).

2.5.1 Behavioural treatment

The cornerstones of obesity treatment is behavioural treatment, which is often comprised of lifestyle advice regarding diet and exercise; such treatment has been tested and delivered with varying degrees of success (94). A concern regarding this approach is that weight loss results are hard to maintain over an extended period of time following the end of the intervention. Early initiation of obesity treatment is more likely to be effective as age has been shown to be an important factor (95). A reduction in the degree of obesity, expressed as > 0.25 BMI SDS, has shown to be effective in reducing cardiovascular risk markers (96). Results of weight loss in adolescents can be described as modest at best (97, 98). In intervention studies, often despite the best efforts of mostly multidisciplinary teams, the summarised effect is a 1.2 kg/m^2 lower BMI in adolescents in intervention compared to controls (98), and calls for more effective treatment for adolescents have been made (67). Similarly, in adults, short-term outcomes are generally promising, but weight regain over time is often observed (99).

2.5.2 Physical activity

The definition of physical activity is 'any voluntary movement in skeletal muscle that increases energy expenditure' (100). By definition, physical activity involves a behaviour that increases energy expenditure, hence its place in obesity treatment. However, it is not by any means necessary when it comes to weight loss, gain or maintenance.

2.5.2.1 Other purposes of physical activity

Physical activity is strongly associated to health and longevity. The understanding that physical activity is beneficial for humans has existed since Hippocrates' time, but it was not until Jeremy N. Morris' pioneering studies of workplace physical activity in the 1950s that the research field emerged. Morris found that bus conductors were less likely to develop coronary heart disease than their immediate co-workers, the drivers, and the observation was repeated in postmen compared to other government workers (101), although the original study may have been confounded by pre-existing differences in weight (102). Since then, physical activity has been associated with improvements in several cardiometabolic risk factors. In both the short and long terms, physical activity improves insulin sensitivity (103) and reduces risk of T2D (104). Physical activity may even suppress a genetic predisposition for obesity (105).

Although the accumulated evidence clearly shows health benefits for physical activity in individuals with obesity, obesity in itself has been suggested to be a barrier to becoming more physically active in adolescents and adults (106, 107).

2.5.2.2 Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is an important marker for health. CRF is often measured during strenuous physical activity and expressed as the maximal volume of oxygen consumption (VO_2max), and it has been associated with lower all-cause mortality independently of BMI (108). Unlike physical activity, CRF is not a behaviour and can be considered a surrogate endpoint of increased physical activity, although it is at least 50% genetically determined (109). In children and adolescents, CRF and physical activity have been shown to independently reduce cardiometabolic risk (110, 111).

2.5.3 Pharmacological treatment

A number of anti-obesity drugs have been tested over the last century (112). The history of anti-obesity drugs is unfortunately filled with market withdrawals due to cardiovascular and psychological side effects as well as drug abuse (113).

Anti-obesity drugs for adolescents in Sweden and the European Union are limited to Orlistat, which works by inhibiting fat uptake. Despite positive results (114), discontinuing treatment is common in adolescents (115). Glucagon like peptide 1 (GLP-1) analogue (Liraglutide), has been tested in adolescents for its anti-obesity effects and has shown positive results with an average weight loss of -2.7% compared to the weight gain of 2.4% with placebo after 56 weeks (116). In adults, another GLP-1 analogue (Semaglutide) has shown impressive weight loss results of -14.9% compared to -2.4% with placebo after 68 weeks (117).

Currently available anti-obesity drugs for adults in Sweden include Mysimba (Bupropion, Naltrexon) and GLP-1 analogues under various brand names (Liraglutide, Semaglutide), but only Orlistat is reimbursed in Swedish.

2.5.4 Bariatric surgery

The umbrella term of 'bariatric surgery' includes various surgical procedures with the common aim of inducing weight loss. Weight loss after surgery was first thought to rely on two mechanisms: restricting food intake by limiting the size of the stomach and malabsorption of nutrients due to shortening/re-routing of the intestines. Today, the endocrine response following surgery has been recognised as a more impactful mechanism in the durability of weight loss (118).

2.5.4.1 History of bariatric surgery

Beginning in the 1950s, surgeons at the University of Minnesota started performing surgery to induce weight loss. The first procedure intentionally designed for weight loss was the jejunoileal bypass (JIB) (119). Mild side effects were deficiencies of vitamins A and D, which can lead to night blindness and osteoporosis. Severe side effects such as liver and kidney failure could also occur due to toxic bacteria growth in the bypassed intestine (120). The JIB is no longer performed.

Roughly a decade later, the procedure now known as RYGB emerged (121). Mason et al. found that patients who had surgical sub-total gastrectomy for other medical reasons lost substantial weight as a side effect. The RYGB has since the 1960s been modified (122) to reduce initial problems with bile reflux. In 1994, the first RYGB surgery was performed laparoscopically (123), which led to an increase in operations. Operations in Sweden peaked at 7,000–8,000 annually between 2010–2013 (124).

During the 1970s, Scopinaro et al. developed the biliopancreatic diversion (BPD) (125), which exhibited a malabsorption similar to the JIB. The technique evolved during the 1990s to the sleeve gastrectomy (SG) with duodenal switch (BPD/DS) (126), wherein the small intestines are divided distally at approximately 75% of their length and the distal portion is connected with the stomach pouch. The remining intestine is rerouted to carry bile and enzymes from the liver and pancreas before joining the distal portion carrying food. The joint common channel is post-surgery approximately one meter, thus limiting absorption of nutrients.

Due to the complexity associated with the BPD/DS technique and, generally, surgery in patients with an extremely high BMI, surgeons began performing BPD/DS surgery in two steps, starting with the SG (127). Results were surprisingly favourable from the SG alone, leading to the SG becoming a viable standalone procedure. In an SG, the stomach is surgically shaped into a tube-like structure without alteration of the intestines (128).

Gastric banding is a purely restrictive method where an elastic band is surgically placed around the stomach to limit the amount of solid food that can pass through. Gastric banding has virtually stopped in Sweden (124).

2.5.4.2 Modern procedures

There are currently two common bariatric procedures in Sweden, the RYGB and the SG. The RYGB was previously the dominant procedure, but the SG has risen in popularity over the last decade and is now the most common procedure in Sweden. The BPD/DS is performed but at a much lower rate than the SG or RYGB. Both the RYGB and SG can result in substantial weight loss that can be maintained over time. Differences between the procedures were covered in a review by Pucci (129).

Eligibility criteria for bariatric surgery were set by the National Health Institute in 1991 (130) and require a BMI over 40 kg/m^2 or over 35 kg/m^2 in the presence of obesity-related complications, age 18–60 years old, and previously unsuccessful attempts to lose weight.

2.5.5 The RYGB

The RYGB has the ability to induce weight loss and facilitate weight maintenance over many years. It can resolve and ameliorate diseases related to obesity such as T2D, dyslipidemia and hypertension (131). The weight loss nadir is usually between 12–24 months after surgery and is followed by a maintenance phase with minor weight regain (132). In the Swedish Obese Subjects trial, an average total weight loss of 27% was maintained over 15 years following RYGB (133), and Adams et al. showed that 12 years after the RYGB, 70% of patients retained a weight loss of 20% or more of their total body weight (134). Compared to non-surgical intervention, the RYGB produces far superior results, and bariatric surgery is considered the most effective treatment for severe obesity (135).

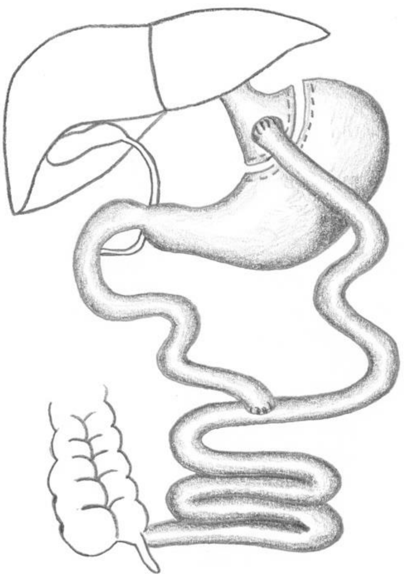

Figure 2.1. *Illustration of the Roux-en-Y Gastric Bypass. Credit Lena Lundgren.*

2.5.5.1 Surgical technique (Figure 2.1.)

The RYGB is almost exclusively performed laparoscopically (124). The surgeon creates a small pouch from the proximal part of the stomach, and the remaining part of the stomach is connected by a limb of 100–150cm to the jejunum. The pouch of 15–30 mL is reconnected with the jejunum and effectively bypasses the duodenum to form a Y between the two stomach pouches and their connection to a common intestine (136). The RYGB is performed across the globe with various variations (137) to the length of limbs, and longer or more distal variations have a slightly more pronounced malabsorption element (138). Moreover, though it is possible to reverse the RYGB, it is technically challenging and poses higher risks of complications than primary surgery (139).

2.5.5.2 Safety and complications of the RYGB

The RYGB is a safe method and has a 0.06% mortality rate reported within 90 days in Sweden (140). Common complications associated with surgery are also reported after bariatric surgery, such as bleeding, infection and blood clots (141). There are also a number of complications that can occur long term (after 30 days) following the RYGB, including increased risk of gallstones, anaemia, vitamin deficiencies, dumping syndrome and postprandial hyper-insulinemic hypoglycaemia (118, 141, 142). According to Swedish data, complications occur in 5–12% of patients, depending on follow-up time (143).

Alcohol and substance abuse after bariatric surgery have been reviewed (144, 145), and although there are studies reporting an increase in such abuse post-surgery, a connection is not conclusive and may be linked to pre-surgical habits (145).

Although the absolute numbers are low, self-harm, suicide attempts and suicide have been seen to increase after bariatric surgery in a systematic review (146). Studies from Sweden also show increased risks of suicide and self-harm after bariatric surgery compared to both the general population (147) and to matched controls in lifestyle obesity treatment (148). However, the association may be confounded by selection bias as individuals seeking bariatric surgery have higher incidence of self-harm and suicide attempts overall.

2.5.5.3 Heterogeneity of outcomes

It is known that both weight loss outcomes and cardiometabolic outcomes vary between and within individuals over time (149-151). Initial weight loss is likely of importance and has been associated with overall weight loss (152). Weight regain in various amounts is normally observed to occur after the initial weight loss phase, but the difference between individuals is large and may be more significant in adolescents (153). Cardiometabolic outcomes also show variability and declining rates of remission over time has been reported from studies with long-term follow-up (134, 154) and in association with weight regain (151).

2.6 BARIATRIC SURGERY IN CHILDREN AND ADOLESCENTS

Bariatric surgery has been performed on adolescents since the 1970s, but until the early 2000s it was mostly studied and reported as cases and case series. Over the years a number of reviews on bariatric surgery in adolescent have been published mostly showing promising short- and medium-term results (155-159). Results from one of the latest reviews (159), which included six studies of RYGB with more than five years of follow-up, show an average BMI loss between 11.4 to 21.0 kg/m^2. Resolution of comorbidities were reported to be between 88% and 100% for T2D, 76% and 100% for hypertension or elevated blood pressure and 64% and 100% for dyslipidaemia. Comparison between adults and adolescents showed that adolescents may have greater weight loss and resolution of comorbidities (160, 161), indicating that performing surgery at a younger age may be favourable. Bariatric surgery in adolescents has been estimated to be cost-effective after the initial cost of the procedure has levelled off, which typically occurs after a few years (162).

The American Society for Metabolic and Bariatric Surgery (ASMBS) updated their guidelines in 2018 (163) and the American Academy for Pediatrics issued a policy statement in 2019 (164) that both concluded that bariatric surgery should be considered in adolescents with severe obesity. The recommendations are largely based on results from three trials conducted with adolescents: the Adolescent Morbid Obesity Surgery study (AMOS) (165), the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) (166) and the Follow-up of Adolescent Bariatric Surgery at 5 Plus Years (FABS-5+) (167). These studies all demonstrated the safety and effectiveness of bariatric surgery in adolescents.

However, there are notable differences between countries regarding views and utilisation of bariatric surgery in children and adolescents. These differences can be highlighted by a case report from Saudi Arabia in which the SG was performed on a 2.5 year-old child (168), which stands in sharp contrast to the ASMBS guidelines (163) that bariatric surgery should be considered for adolescents (ages 12–19 years old) with severe obesity.
There are also differences in the utilisation of bariatric surgery in adults between European countries. Compared to the neighbouring country of Denmark, which had < 250 operations per 1 million residents, Sweden had a significantly higher frequency of > 750 operations per 1 million residents (169).

2.6.1 Mechanisms of weight loss after the RYGB

Although the mechanisms of weight loss are not fully understood, several reviews have tried to summarise current knowledge of the multifactorial mechanisms leading to weight loss after the RYGB (118, 129, 170, 171).

2.6.1.1 Mechanical constraint

A small gastric pouch limits the ability to ingest food, thereby reducing meal size portions and caloric intake in the first year after an RYGB (172). Over time the gastric pouch may dilatate and the capacity to ingest larger volumes of food increases, and while pouch dilatation is not conclusively associated with weight loss outcomes (173), it has been the target of revisional surgery (174).

2.6.1.2 Gut hormones

Endocrine signalling is affected by the RYGB. Ingested nutrients pass through the created pouch more rapidly and trigger an alternate endocrine response from the intestines. The gut hormones of GLP-1 and peptide tyrosine-tyrosine 3-36 (PYY) have a suppressive effect on appetite. Increased circulation of GLP-1 and PYY postprandially are evident after the RYGB, and GLP-1 has been shown to be increased in response to a meal 10 years after the RYGB (175).

The hormone ghrelin, which stimulates hunger, has been seen to decrease following the RYGB, in sharp contrast to its observed increase in diet-induced weight loss (176).

2.6.1.3 Gut microbiota

Changes in gut microbiota have been reviewed after the RYGB (177), and the promotion of certain bacteria over others may be due to both alterations of the anatomy leading to increased bile acid (178) and to different preferences in food pre- and post-surgery (179).

2.6.1.4 Behavioural changes

Food preferences are reported to change following the RYGB, with intake of fruit and vegetables increasing and of energy-dense foods decreasing (179, 180).

Physical activity in the form of exercise enhances weight loss and improves lipid profile after bariatric surgery in adolescents and adults (181, 182). Although self-reported physical activity is often observed to increase after bariatric surgery, there is little support for the increase of physical activity in either the short (183, 184) or long term (185) when compared to objectively measured physical activity.

2.6.2 Not all weight loss is equal

Weight loss can be achieved in various ways, but the result beyond weight per se is not equal. The following paragraphs provide examples of different modes of weight loss.

Reduction of weight through amputation of a limb does not improve but rather harms metabolic health (186). Liposuction removes weight primarily constituted of fat from subcutaneous sites. Given the definition of obesity, it would be intuitive to think that liposuction would be associated with medical improvements, but liposuction does not improve metabolic health (187), indicating that it is not purely the amount of adipose tissue but rather a combination of amount and function of adipose tissue that is associated with metabolic health. Both examples illustrate that it is not mass per se, nor even FM per se, that cause obesity-related comorbidities.

Thus, in order for weight loss to be beneficial, it has to be voluntary and result from a negative energy balance. Weight loss resulting from lifestyle or pharmacological interventions has shown positive effects on metabolic health after a weight loss of 5–15%, where greater weight loss often equals better metabolic effect (188). There are clear differences in both short-term and long-term results between surgically and non-surgically induced weight loss (135). The biological response to diet-induced weight loss is much different than the response to surgically induced weight loss. Non-surgically induced weight loss is harder to maintain, and there is evidence of a biological response to defend the earlier ‘set point’ of weight, even if that point was in the range of obesity (189, 190). Differences between the two types of weight loss may be due to the effect of gut hormones. Diet-induced weight loss is associated with increases in ghrelin and decreases in GLP-1 and PYY. Post-prandial GLP-1 levels are known to remain exaggerated 10 years after an RYGB (175) and likely contribute to both maintained weight loss and resolution of T2D.

3 RESEARCH AIMS

3.1 GENERAL AIM

The general aim of this thesis was to describe and investigate the prerequisites and effects of bariatric surgery in adolescents and young adults. Questions addressed include, what can be expected if surgery is delayed until young adulthood? What are the outcomes of weight loss heterogeneity? What can be expected when adolescents undergo bariatric surgery? The underlying question is whether it is ethically and medically justified to treat a disease originating from overnutrition in adolescents with an irreversible major surgical procedure with lifelong consequences.

3.1.1 Study specific aims

3.1.1.1 Study I

The aim of Study I was to determine the proportion of patients previously treated in Swedish childhood obesity treatment programs who proceed to bariatric surgery in early adulthood and relevant factors influencing this.

3.1.1.2 Study II

The aim of Study II was to investigate the prevalence of weight regain, surgical failure and the impact of the RYGB on metabolic health in adults after five years and to investigate if the risk of surgical treatment failure could be predicted by developing a prediction model.

3.1.1.3 Study III

The aim of Study III was to describe cardiorespiratory fitness, functional capacity, body composition outcomes and self-reported physical activity after two years in adolescents undergoing RYGB.

3.1.1.4 Study IV

The aim of study IV was to investigate if poor initial weight loss and early weight regain in adolescents after RYGB affects metabolic risk markers for obesity-related comorbidities during the first two years after surgery as well as long-term weight outcomes.

4 MATERIALS AND METHODS

This thesis consists of four studies. Studies I and II are observational cohort studies. Study I is based on data from the Swedish Childhood Obesity Treatment Register (BORIS), and Study II is based on data from the Scandinavian Obesity Surgery Registry (SOReg). Studies III and IV are clinical trials and are part of the AMOS study. Detailed information about the methods used are presented in the included papers I-IV. This chapter briefly describes the study design and methods and elaborates on methodological and statistical considerations.

4.1 STUDY I

4.1.1 The Swedish Childhood Obesity Treatment Register

The BORIS is a quality register for childhood obesity treatment in Sweden (191) based on local healthcare providers' treatment data. The BORIS has covered childhood obesity treatment from 1994 and has come to include more than 100 treatment facilities, ranging from primary healthcare units to specialised clinics in a university hospital setting. For study III, we requested data from 1994 to 2016.

4.1.2 Registry linkage

In Study I, the BORIS was linked to several national registers using Swedish personal identification numbers. Detailed information on the registry methodology can be found elsewhere (192).

4.1.2.1 The Swedish Childhood Obesity Treatment Register

Measurements of anthropometrics and blood chemistry are entered into the registry by local healthcare providers. Analyses of blood samples are performed in different parts of Sweden by accredited laboratories.

4.1.2.2 The National Board of Health and Welfare

The National Board of Health and Welfare performed the registry linkages between the BORIS and the Swedish Cause of Death Register, the Swedish National Patient Register and the Swedish Prescribed Drug Register.

Data on death for this study was retrieved from the Swedish Cause of Death Register (193) and used for censoring in statistical analysis.

Medical diagnoses were retrieved from the Swedish National Patient Register (194). Surgical procedures according to the Nordic Medico-Statistical Committee (195) classification (code JDF) in conjunction with a diagnosis of obesity by the International Classification of Diseases (ICD-10 - code E66) were obtained to verify that cases in fact underwent bariatric surgery.

Data on prescribed and dispensed drugs from the Swedish Prescribed Drug Register (196). Anatomical Therapeutic Chemical Classification (ATC) codes was used to identify the presence of cardiometabolic disease through the use of anti-diabetic drugs (ATC A10 B), lipid-lowering drugs (ATC C10), blood-pressure-lowering drugs (ATC C02-03, C09, C07 -AB, -AG, -F) and weight loss drugs (ATC A08 AB01 [Orlistat]).

4.1.2.3 Statistics Sweden

Statistics Sweden performed the registry linkages between the BORIS and the Swedish Total Population Register and the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Studies.

Information on ethnic decent was obtained from the Swedish Total Population Register (197) to classify individuals as having Nordic descent (individuals born in Nordic countries or born with at least one parent from a Nordic country) or non-Nordic descent.

Socioeconomic status was calculated using data from the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Studies (198). The SES variable was calculated as a mean score of both parents regarding weighted scores for education (compulsory, upper secondary, university [0,1,2]), occupation (unemployed last six months [yes = 0, no = 1]) and income quartiles (0,1,2,3) by the year the child was 15 years old. Income was adjusted to the consumer price index of 2015 as provided by Statistics Sweden. The summarised score (0–6) was categorised as low SES (0–1.5), medium-low SES (2–3), medium-high SES (3.5–4.5) and high SES (5–6).

4.1.3 Participants from the Swedish Childhood Obesity Treatment Register

Children aged 5–18 were entered into the study from the BORIS and followed into adulthood. Information on participants' parents was similarly retrieved through registry linkage.

Inclusion criteria were set as follows:
Aged 5 to 18 years old at treatment initiation
Diagnosed with obesity according to the International Obesity Task Force (31)
Aged 18 or older and alive and living in Sweden at time of registry linkage (Dec 31, 2017)

Exclusion criteria were set as follows:
Diagnose of brain tumour
Presence of genetic syndromes (Prader Willi, Laurence-Moon-Bardet-Biedl, Morbus Down, Russel-Silver, Noonan, Klinefelter, Fragile X and Turner)
Bariatric surgery before age of 18

4.1.4 Study design

Study I was a cohort study.

4.2 STUDY II

4.2.1 The Scandinavian Obesity Surgery Registry

In Study II, the data source was the SOReg. The SOReg was formed in 2007 and collects data from surgical units performing bariatric surgery. Since 2011, the registry covers 95–99% of all bariatric surgeries performed in Sweden (199).

4.2.2 Participants from the Scandinavian Obesity Surgery Registry

In accordance with the study protocol, data was requested from the SOReg on all surgical units that had yearly cohorts with a retention rate above 60% five years after surgery; this was to limit possible bias introduced by loss in follow-up data.

We included subjects that had undergone the RYGB because other types of surgical procedures were very uncommon between 2007 and 2011. Within this period, 96–97% of all bariatric surgery was the RYGB thus greatly limiting any bias that may be introduced by surgeons choosing which type of surgery a patient receives.

Inclusion criteria were set as follows:
Yearly cohort with at least 60% retention rate five years post-surgery
Alive at time of follow-up
Primary RYGB

Exclusion criteria were set as follows:
SG
BPD
Under 18 years or over 55 years at time of surgery
Open or converted surgical access
Pre-surgical BMI of less than 35kg/m^2

4.2.3 Study design

Study II was a prospective registry study.

4.3 STUDIES III AND IV

4.3.1 The Adolescent Morbid Obesity Surgery study

Studies III and IV are part of the AMOS. The AMOS is a nationwide Swedish 10-year prospective study investigating the safety and feasibility of performing the RYGB on adolescents. It is registered on clinicaltrials.gov with the number NCT00289705. The general aim of the AMOS was to study if the positive effect of RYGB in adults could also be seen in adolescents. Results from the AMOS study show long-term weight loss, improvements in metabolic risk markers and quality of life and complications (165, 200). The evaluation of psychological outcomes, including binge eating, indicate that improvements can be seen in the short and medium terms, but a sub-group did not improve their mental health (201-204), and mental health problems persisted five years after the RYGB and may also be associated with long-term weight loss (205, 206). Desires for body contouring due to excess skin post-surgery were reported (207). Dietary intake was reduced by 10% (208), and 50% of participants adhered to supplements recommendations (209) five years after surgery. A mixed method identified that when asked about adherence, truthful answers were given (210). Bone mineral density decreased from high values pre-surgery towards normal values at two years after surgery (211). Desire for more frequent follow-ups after the first year were reported from a qualitative interview sub-study (212).

4.3.2 Participants from the Adolescent Morbid Obesity Surgery study

Eighty-one adolescents enrolled and underwent RYGB between April 2006 and May 2009. Participants were referred to surgery from three centres in Sweden in Stockholm, Gothenburg and Malmö. All surgical procedures were performed in Gothenburg by the same surgical team (213). Study I comprised the participants from the Stockholm centre, which followed an extended study protocol including measures of physical fitness. Study II comprised the participants from the full AMOS with the addition of four individuals who were enrolled within the time of inclusion but had surgery outside the study timeframe; these individuals followed the same study protocol with follow-ups.

Inclusion was opened 2006 and closed in 2009.

Inclusion criteria were set as follows:
BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with comorbidity
13–18 years
Passed peak height growth velocity
Passed psychological assessment
Minimum of one year conventional obesity treatment
Puberty maturity equal or above Tanner stage 3

Exclusion criteria were set as follows:
Mental retardation
Inadequate or insufficient treatment for ongoing psychological disorder
Ongoing drug abuse
Monogenetic obesity or secondary obesity with syndromes or brain injury

4.3.3 Study design

The AMOS is a non-randomised controlled trial. Measurements were collected from before surgery and one, two and five years after surgery. The AMOS had two control groups: an adults group matched to BMI and sex that underwent RYGB and a conventionally treated group of adolescents from the BORIS. None of the papers in this thesis include results in comparison to the control groups

4.4 ASSESSMENT AND COMMENTS ON METHODOLOGICAL ASPECTS

4.4.1 Anthropometrics

In Studies I and II, data were retrieved from high-validity quality registers, namely the BORIS (191) and SOReg (214). In Study III, assessment of weight and height was performed as described in Paper III. In Study IV, which includes the full AMOS cohort, measurements from two additional centres were included as described in the two- and five-year publications (165, 200).

4.4.2 Biochemical markers

In Studies I and II, blood samples were collected and analysed in various parts of Sweden by accredited labs. Data on biochemical markers were registered in either the BORIS or SOReg, from which the information was extracted. In Studies III and IV, blood samples were collected and analysed according to study protocol. All analyses were performed by accredited laboratories. Data was checked for implausible values and, if found, excluded from further analysis.

4.4.3 Register data

In Studies I and II, data was requested and retrieved from national registers. Methodologically, registers have both advantages and disadvantages compared to other types of studies. Major benefits are that large samples of data can be obtained at a low cost and researchers does not have to wait for the outcome of interest. Thus, register studies can generate hypotheses more quickly than traditional cohort designs. At the same time, the researcher is limited to the data already collected when using register data. Furthermore, causality can only be suggested and requires an experimental design to be confirmed.

4.4.4 Metrics of weight

Weight and weight loss can be expressed through a large range of metrics. In this thesis, weight in kilograms and BMI as kg/m^2 are used to express absolute values. Change in weight over time is expressed in kilograms, BMI and relative terms. Percentage total weight loss (%TWL) refers to the difference in weight relative to the original weight between two measurement timepoints. Similarly, excess weight loss or excess BMI loss (%EBMIL) refers to the amount of excess weight (weight above a BMI of 25 was considered as excess) lost between two timepoints. The calculations for %TWL and %EBMIL used in this thesis are presented below:

%TWL was calculated as ((baseline BMI - year five BMI)/baseline BMI)*100

%EBMIL was calculated as ((baseline BMI - year five BMI)/(baseline BMI - 25))*100

4.4.5 Metrics of body composition

Body composition measured by DXA in Studies III and IV is expressed in two components, FM and FFM (which includes bone mineral content). Absolute units of kilogram or FFM index can be calculated similarly to weight.

Relative proportions are also used within this thesis. A methodological and scientific concern lies in which of these metrics best describe change over time, and the scientific community has not yet reached a consensus. In addition, in Study IV there is a variable which expresses change in FM in relation to change in body mass, in relative terms. An example to facilitate the understanding of that variable is provided below.
For example, at timepoint 1, individual A weighs 100 kg and has a FM of 40 kg. At timepoint 2, weight is 70 kg and FM is 10 kg, resulting in a loss of weight that is 100% FM loss (-30/-30 = 1).

Given the construct of the variable based on two relative variables, it is possible to exceed 100%. This phenomenon occurs if an individual reduces their FM and simultaneously increases their FFM.

As a second example, at timepoint 1, individual B weighs 100 kg and has an FM of 30 kg, and at timepoint 2, weight is 85 kg and FM is 10 kg, resulting in lost weight that is ~133.3% FM (-20/-15 = ~1.33), which is only possible if the individual simultaneously gained FFM.

4.4.6 Definition of surgical treatment failure, weight regain and poor initial weight loss

4.4.6.1 Surgical treatment failure

In Studies II and IV, surgical treatment failure five years after the RYGB was defined as meeting at least one of three previously published definitions (215, 216): (A) < 50% EBMIL, (B) < 20% TWL, or (C) BMI > 35 kg/m^2 if baseline BMI was < 50 kg/m^2 or > 40 kg/m^2 if baseline BMI was > 50 kg/m^2. Given the lack of an all-encompassing, unambiguous definition (151, 215, 217, 218), these definitions were chosen because they have been used in other studies and represent three of the most common ways to assess weight loss.

4.4.6.2 Weight regain

Weight regain was defined as early or late weight regain. Early weight regain was defined as any change in weight (kg) between year one and two. Late weight regain was defined in accordance with Odom et al. (219) as a change in weight from the weight loss nadir expressed in relative terms and classified in three categories: > 15% regain of BMI nadir, 0.1–14.9% regain of BMI nadir and no weight regain.

4.4.6.3 Poor initial weight loss

Poor initial weight loss was defined as < 25% TWL during the first year, which was similar to a previous study investigating predicting long-term weight loss by Manning et al. (152).

4.4.7 Body composition

Body composition in Studies III and IV was assessed by DXA (Lunar DPX-L, version 1.5E; Lunar Corp, Madison, WI USA or Lunar Prodigy X-R. model 6830, Madison, WI, USA). Dual energy X-ray absorptiometry provides detailed estimates on FM and FFM in addition to bone density. The method is non-invasive and has been validated in populations with obesity (220).

4.4.8 Physical fitness

In Study III, cardiorespiratory fitness was assessed by the Astrand ergometer bicycle test (221), which is a sub-maximal test. A maximal test was not chosen although they are considered the gold standard (222). Maximal tests require motivation and experience to continue until exhaustion and are therefore often not suitable for individuals with obesity. Functional capacity was assessed by the six-minute walk test (6MWT), which has previously been tested for reliability and validity in children and adolescents with obesity (223).

Physical activity is important for CRF and overall health. In Study III, physical activity was summarised in a semi-structured interview on participants' exercise and physical activity habits and thus self-reported. It is known that self-reported physical activity post-bariatric surgery is prone to error and bias in adults (183-185). Objective measurements such as accelerometery or the use of standardised questionnaires such as the International Physical Activity Questionnaire (224) would have been preferable.

4.5 STATISTICS

Data was analysed using SPSS (versions 22–25, IBM Corp., Armonk, NY, USA), SAS Statistical Software (version 9.4, Cary, NC, USA) or STATA (version 15.1, StataCorp., TX, USA). Descriptive data is presented as mean ± standard deviation (mean ± sd), median with interquartile range (IQR) or proportions (%). Mean comparisons are presented with mean ± sd or with mean and 95% confidence intervals (95% CI). Hazard ratios (HR) and odds ratios (OR) are presented with 95% CI.

4.5.1.1 Statistics considerations

Statistical calculations are used to summarise, aggregate and reduce large sets of data or data points in an effort to make data more understandable. Most statistical tools are made to predict and estimate beyond the sample, which is difficult to do accurately; as per the quotation by George Box, 'all models are wrong but some are useful'.

In Study I, the main statistical method was proportional cox regression. Cox regression stems from survival analysis and is therefore suitable for investigating events that may occur over time.

In Study II, the main statistical method used was logistic regression, which is a form of linear regression that handles binary outcomes. In addition to using logistic regression to develop the prediction model, measurements of biochemical markers, blood pressure and use of medication were all are coded (0 = below threshold/no drug use or 1 = above threshold/drug use). These binary variables were then used to classify individuals with T2D, dyslipidaemia and hypertension. Because the dataset extracted from the SOReg had missing data on these underlying measurements for various reasons, we accepted and treated missing data as a 0 in the process of classification. This conservative approach to handling missing data may result in underestimations as reported 0s may actually be a mixture of real 0s and missing 1s.

In Study III, the main statistical method used was the linear mixed model, (LMM). The LMM is a flexible statistical method that builds on the simpler linear regression model by allowing for both fixed and random effects and specification of the correlation matrix (e.g. timepoint A may be more correlated to timepoint B than to timepoint C). The LMM was used in Study I to assess repeated measurements, and the method can handle missing data under the assumption of missing at random. The results from the LMM were chosen over the more classical measure of ANOVA because the LMM maximises the use of observations and the results between the two methods were very similar.

In Study IV, the main statistical method used was the univariate general linear model. The general linear model is essentially a form of linear regression but is designed to output mean comparisons rather than to calculate them post-test. Mean comparison was adjusted according to Bonferroni. A validation of the developed model for predicting surgical treatment failure was also done. Sensitivity, specificity, positive and negative predictive value as well as total accuracy were reported with a 95% CI.

4.6 ETHICAL APPROVAL

Studies I and II were approved by the regional ethics committee in Stockholm, Sweden (No. 2016/922-31/1 and 2017/1793-31). Studies III and IV were approved by the regional ethics committee in Gothenburg, Sweden (No. 523-04 and 584-07).

4.6.1 Ethical considerations

Ultimately, the choice of undergoing bariatric surgery lies with the patient based on the principle of autonomy. Autonomy is regarded as one of the most sacred rights in modern society. The right to choose for one's own body is fundamental and something most adults see as a basic right. When it comes to children, that right is divided between the legal guardians of the child (most often the parents) and the child themselves after a certain age. For bariatric surgery, an elective major irreversible surgical procedure with lifelong consequences, an adolescent's consent is an absolute requirement. However, in order to give informed consent, knowledge is required for both short- and long-term risks and benefits.

The balance between risks and benefits is especially delicate with elective procedures. As noted, RYGB has the possibility to induce substantial weight loss and prevent, resolve and ameliorate many of the diseases related to obesity. Nonetheless, the response is not uniform, and complications are relatively common. Expectations must be managed accordingly, and in addition to information regarding surgical complications, the risks of poor weight loss, weight regain and surgical treatment failure should be presented as well as the fact that bariatric surgery is unlikely to ameliorate mental health problems. It is also important that patients are informed of potential consequences of not undergoing bariatric surgery and the availability of other non-surgical obesity treatments. All of these factors should be delivered in a language suited for adolescents and addressed before informed consent can be considered valid.

At the same time, it is worth questioning what acceptable knowledge is and understanding if the long-term consequences of RYGB are unknown. Five years is a common definition for long term in medicine, but it is arguably too short when it comes to adolescents with a long life expectancy.
The fact that obesity is reversible without surgical procedures (albeit anecdotal) emphasises the complexity and highlights the need for an extremely cautious selection of patients.

Hence, bariatric surgery is not for everyone. Still, although an understanding of very long-term consequences is lacking, the benefits of surgery likely outweigh the risks for adolescents with severe obesity who manifest or are in the pre-stages of obesity-related comorbidities.

5 RESULTS

Detailed results are presented in Papers I–IV. The following sections summarise the studies, present descriptive data and highlight novel results and main findings.

5.1 STUDY PARTICIPANTS

5.1.1.1 Study I

In Study I, 6,502 individuals were included from the BORIS childhood obesity cohort. Participants (45% female) had a median IQR age of 13.5 (4.0) years at obesity treatment initiation, were in treatment for 2.8 (2.7) years and were 21.7 (5.2) years old at the time of follow-up.

5.1.1.2 Study II (Table 5.1)

In Study II, 5,963 individuals followed for five years after RYGB surgery were included from the SOReg. Participants (79.1% female) had a mean ± sd age of 39.4 ± 9.0 years and a BMI of 42.9 ± 5.1 at baseline.

5.1.1.3 Studies III and IV (Table 5.1)

In Study III, a sub-study of the AMOS, 41 participants were followed for two years post-RYGB surgery at the Stockholm centre. Participants (75.6% female) were between 14–18 years old and had a mean ± SD BMI of 46.0 ± 6.6 kg/m^2 at time of inclusion.

Study IV included participants from the AMOS study (n = 81) as well as four additional participants who fulfilled the inclusion criteria for the AMOS and accepted enrolment but were operated on outside the study timeframe. The total study population was n = 85. Participants (67.1% female) were between 13–18 years old and had a BMI of 45.5 ± 6.0 kg/m^2 at time of inclusion.

Table 5.1 Baseline characteristics of the surgical samples from the Adolescents Morbid Obesity Surgery study and from the Scandinavian Obesity Surgery Register

	AMOS		SOReg	
	n	Mean (sd)	n	Mean (sd)
Age, years	85	16.5 (1.2)	5936	39.4 (9.0)
Sex, % female	85	75.6%	5936	79.1%
Body weight, kg,	85	133.0 (22.1)	5936	122.8 (20.0)
Height, m	85	170.7 (9.3)	5936	168.8 (8.9)
Body mass index, kg/m^2	85	45.5 (6.0)	5936	42.9 (5.1)
Fat, %	76	52.1 (4.0)		
Fat mass, kg	76	67.9 (11.6)		
Low density lipoprotein, mmol/L	84	2.6 (0.7)	4110	3.1 (0.9)
High density lipoprotein, mmol/L	85	1.1 (0.3)	4188	1.2 (0.4)
Triglycerides, mmol/L	84	1.3 (0.6)	4314	1.7 (1.4)
Fasting glucose, mmol/L	79	5.6 (0.5)	2861	5.9 (1.9)
Hba1c, mmol/mol	83	35.1 (3.9)	4168	40.6 (11.4)
Fasting insulin, mu/L	79	31.2 (17.6)		
Systolic blood pressure, mmHg	78	125 (12)	2960	133 (16)
Diastolic blood pressure, mmHg	78	77 (10)	2960	83 (10)
High-sensitive CRP, mg/L	79	7.6 (6.2)		

AMOS – The Adolescent Morbid Obesity Surgery study
SOReg – The Scandinavian Obesity Surgery Register

5.2 BARIATRIC SURGERY IN YOUNG ADULTS AFTER CHILDHOOD OBESITY TREATMENT

In Study I, the prevalence of bariatric surgery in young adulthood was investigated in a cohort originating from the BORIS. The crude prevalence of bariatric surgery was 8.2%, median age at surgery was 20.9 (IQR 4.2) years and 52.3% underwent surgery before the age of 21 years old. The cumulative incidence of bariatric surgery at 30 years old was estimated to be 21.5% (95% CI 19.3–24.2), Figure 5.1. Childhood obesity treatment was insufficient in reducing obesity, and 85.7% had obesity that persisted until the last clinical visit. Treatment did not prevent obesity-related comorbidities in adulthood, and pharmacological treatments were found in 17.4% distributed as follows; antidiabetic (7.8%), lipid-lowering drugs (1.4%), blood-pressure-lowering drugs (6.3%) or weight-loss drugs (4.0%; Orlistat). Of those who proceeded with bariatric surgery in young adulthood, pharmacological treatment for obesity-related comorbidities was found in 31.7% before surgery.

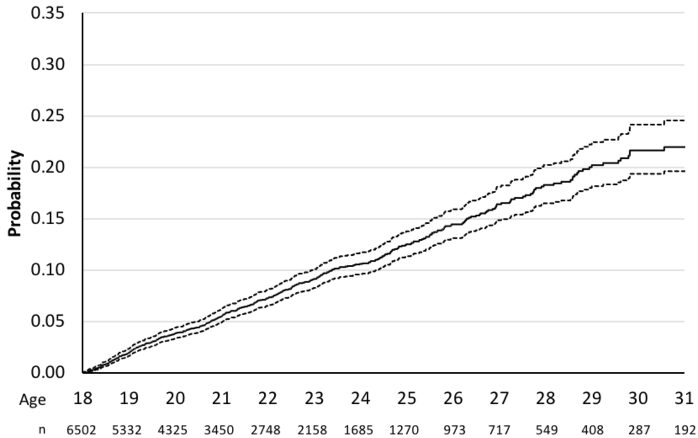

Figure 5.1 *Kaplan-Meier illustration of bariatric surgery in the childhood obesity cohort (mean estimated cumulative incidence with 95% confidence intervals).*

5.2.1 Factors associated with RYGB

Female sex was associated with the RYGB in all included studies. Although Study I included more males then females, 70% of surgery recipients were female. In Study II, 79.1% of included participants were female. In the AMOS study, 75.6% of participants were female. Furthermore, in Study I, a high degree of obesity (expressed per unit of BMI SDS) at treatment initiation HR = 3.59 (95% CI 2.99–4.31) and at end of treatment HR = 3.75 (95%CI 2.84–4.95), and consequently a poor response (increase above 0.25 BMI SDS) to treatment HR = 1.94 (95% CI 1.50–2.50), was associated with RYGB in young adulthood. Moreover, individual HR = 1.27 (95% CI 1.05–1.53) and paternal HR = 1.25 (95% CI 1.04–1.49) cardiometabolic disease was associated with RYGB.

5.3 WEIGHT LOSS AFTER RYGB

In the SOReg sample (Study II), participants at year five had a mean BMI of 30.4 ± 5.2 kg/m^2, mean weight loss of 35.8 ± 13.8 kg, mean BMI reduction of 12.6 ± 4.7 kg/m^2, mean %TWL of 29.1 ± 9.8% and mean %EBMIL of 72.2 ± 25.2%.
In the AMOS sample (Study IV) at year five, mean BMI was 32.3 ± 6.3 kg/m^2 and mean weight loss was 36.9 ± 19.8 kg, mean BMI reduction was 13.3 ± 6.8 kg/m^2, mean %TWL was 27.5 ± 12.7% and mean %EBMIL was 65.8 ± 29.2%.

5.3.1 Heterogeneity of weight loss

In both Studies II and IV, weight loss after RYGB was heterogenous (for complete definitions please see Methods 4.4.6).
In the SOReg sample (Study II), poor initial weight loss, was observed in 17.1% of the participants. Early weight regain, between year one and two, was observed in 38.7% of the participants (4.5 ± 3.9 kg, range 1–38 kg). Late weight regain, >15% regain was observed in 19.9% of the participants (17.7 ± 7.2 kg, range 7–101 kg) and defined as 0.1%–15% regain was observed in 59.3% of the participants (5.7 ± 3.5 kg, range >0-19 kg). Five years after RYGB, surgical treatment failure was observed in 23.1% of the participants.

In the AMOS sample (Study IV), poor initial weight loss was observed in 20.0% of the participants. Early weight regain was observed in 41.0% of the participants (4.4 ± 2.9 kg, range >0-13 kg). Between year two and five weight regain was observed in 69.4% of the participants (11.4 ± 9.1 kg, range >0-37 kg). Five years after RYGB, surgical treatment failure was observed in 34.0% the participants.

5.4 IMPROVEMENT IN CARDIOMETABOLIC HEALTH

The effect of the RYGB on cardiometabolic health was substantial. In Study II, the prevalence of T2D was reduced from 15.1% at baseline to 6.4% at year five, while dyslipidaemia was reduced from 60.7% to 16.4% and hypertension from 28.4% to 18.9% (all $p < 0.001$).

5.4.1 Weight loss and cardiometabolic health

In Studies II and IV, the effect of weight loss on cardiometabolic health was investigated. In Study II, participants who met at least one definition of surgical treatment failure had increased odds of T2D (OR = 2.1; 95% CI 1.6–2.7), dyslipidaemia (OR = 1.8; 95% CI 1.6–2.1) and hypertension (OR = 1.9; 95% CI 1.6–2.2). Surgical treatment failure was also associated with a higher incidence and relapse for T2D, dyslipidaemia and hypertension as well as lower rates of remission ($p < 0.05$).

In Study II, surgical treatment failure was associated with higher mean HbA1c (mmol/mol) 34.4 ± 3.8 vs. 32.7 ± 3.8 ($p = 0.044$), f-insulin (mU/L) 12.9 ± 6.6 vs. 7.6 ± 2.7 ($p < 0.001$), triglycerides (mmol/L) 1.0 ± 0.4 vs. 0.8 ± 0.3 ($p = 0.008$), high sensitive C-reactive protein (mg/L) 2.6 ± 3.3 vs. 1.5 ± 1.5 ($p = 0.040$) and a trend for lower high density lipoprotein (mmol/L) 1.5 ± 0.6 vs. 1.7 ± 0.5 ($p = 0.087$), all adjusted for sex, pre-surgery BMI and corresponding marker at baseline.

5.5 PREDICTING SURGICAL TREATMENT FAILURE

In Study II, surgical treatment failure was assessed according to three definitions (see Methods 4.4.6). A model for predicting the outcome was developed based on age, sex, baseline BMI, %TWL (expressed negatively between baseline and year one) and change in weight (between year one and year two). The calculation was done based on the coefficient presented from the model (see Table 5.2). The model provided a reliable prediction with area under the curve = 0.8743. The model was applied to adolescents from AMOS in Study IV, and sensitivity was 100% (95% CI 88.1–100), specificity 94.64% (95% CI 85.13–98.88), positive predictive value was 90.6% (95% CI 76.27–96.67) and negative predictive value was 100%. Overall accuracy was 96.5% (95% CI 90.03–99.27). The threshold for prediction estimates of surgical treatment failure was set at 0.5, and a total of three individuals were misclassified with increased risk of surgical treatment failure.

Table 5.2 Final multivariable model for predicting surgical treatment failure five years after surgery.

	BETA (B)	S.E.	WALD	P	EXP(B)	95% CI
Sex (0 = male)	-0.00545	0.099	0.003	0.956	0.995	0.818-1.209
Age at surgery, years	0.00299	0.005	0.361	0.548	1.003	0.993-1.013
BMI at surgery, kg/m²	0.14949	0.009	283.640	<0.001	1.161	1.141-1.182
Percentage BMI loss	0.22310	0.008	794.848	<0.001	1.250	1.231-1.269
Change in weight between	0.15982	0.008	382.606	<0.001	1.173	1.155-1.192
Intercept	-1.09588	0.513	4.569	0.033	0.334	

BMI – Body mass index
S.E. – Standard error
95% CI – 95% Confidence interval

5.6 BODY COMPOSITION

Change in body composition after RYGB in adolescents was evident. Study III demonstrated that weight loss after RYGB in adolescents consisted of both FM and FFM. Mean FM loss 33.9 ± 13.3 kg and mean FFM loss was 9.6 ± 5.2 kg from baseline to year two. In Study IV, marked differences in changes to body compositions were found between the sexes. Expressed as the proportion of FM loss of total weight loss, males' mean weight loss over the five year study period consisted more of fat mass loss 87.0±21.2 compared to females 75.6±15.6 (p=0.014). No differences were found in %TWL between the sexes (see Figure 5.2). Surgical treatment failure was associated with a higher percentage body fat at year five in Study IV, 48.0 ± 6.3 vs. 36.2 ± 9.3 (p<0.001).

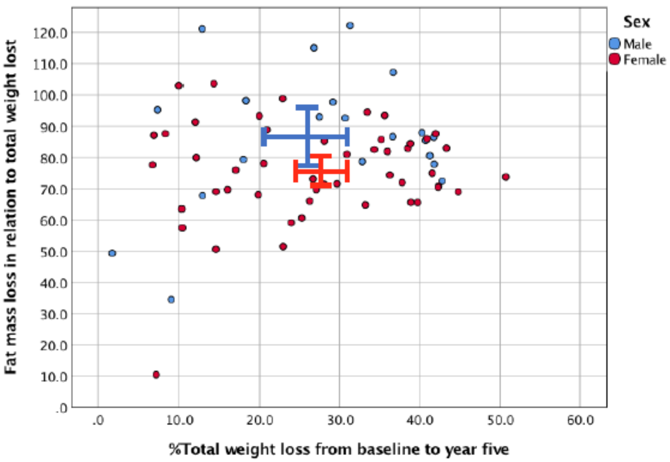

Figure 5.2, *Proportion of fat mass of weight lost expressed in % over total weight lost. Males' weight loss consisted more of fat mass loss compared to females from baseline to year five (p = 0.014). No difference between sex in % total weight lost.*

5.7 PHYSICAL FITNESS

In adolescents from the Stockholm centre (Study III), CRF increased after the RYGB. Relative to body mass, VO_2max increased from 21.1 mL/kg/min at baseline to 34.9 mL/kg/min ($p < 0.001$) at year one and was maintained until year two (ns). VO_2max relative to FFM increased from 45.4 mL/FFM/min at baseline to 56.8 mL/FFM/min at year one ($p = 0.001$) and was maintained until year two. Absolute VO_2max (L/min) was maintained from 2.8 L/min at baseline for the whole group to 3.0 L/min (ns) at year two. In non-smokers, absolute VO_2max increased from baseline to year two ($p = 0.005$).

Walking distance during the six-minute walk test (6MWT) increased from 536 m at baseline to 619 m ($p < 0.001$) at year one and was maintained until year two at 608 m (ns).

6 DISCUSSION

6.1 MAIN FINDINGS

The main findings of this thesis are that conventional lifestyle-based obesity treatment was insufficient in counteracting the need for bariatric surgery and preventing obesity-related comorbidities in young adulthood.

Roux-en-Y gastric bypass surgery in adulthood resulted in heterogenous weight loss, and 23% of adult participants met the definition of surgical treatment failure five years after surgery. Adolescents were seen to have better results than anticipated for improvements in cardiorespiratory fitness two years after surgery, indicating that there could be additional benefits of surgery at a younger age.

However, after five years, the results of weight loss heterogeneity were more pronounced in adolescents, and 34% met the definition of surgical treatment failure. In both adults and adolescents, surgical treatment failure had an inverse association with cardiometabolic health. By using easily obtainable information from before surgery to two years after surgery, surgical treatment failure at year five could be predicted with high accuracy.

6.2 DELAYING EFFECTIVE TREATMENT

One simple factor to consider regarding the timing of bariatric surgery is what happens between adolescence and young adulthood in individuals with severe obesity. Among a group of young adults from the BORIS, 8.2% were found to have proceeded with bariatric surgery in young adulthood, and more than a fifth were estimated to have undergone bariatric surgery before the age of 30 years old. Thus, despite conventional lifestyle-based childhood obesity treatment, the need for effective obesity treatment remains into young adulthood, confirming previous findings that childhood obesity is very likely to persist into adulthood (13) and that childhood obesity leads to a protracted disease course (68). We found no association between cardiometabolic risk markers in childhood and bariatric surgery in adulthood, but at time of surgery, 31.7% of participants had received pharmacological treatments for an obesity-related comorbidity; this suggests a rapid deterioration of cardiometabolic health from childhood to young adulthood given that the median age at surgery was less than 21 years old. The apparently higher prevalence of obesity-related comorbidities found in those proceeding with bariatric surgery may also explain why they chose to undergo surgery. However, the overall prevalence of pharmacological treatment pre-surgery in the SOReg sample was 25.4%, but this study only included treatment for T2D, dyslipidaemia and hypertension, whereas Orlistat was included in the BORIS. Nonetheless, delaying bariatric surgery from adolescence to young adulthood is likely to increase the risk of developing obesity-related comorbidities.

6.3 DURABILITY OF SURGICALLY INDUCED WEIGHT LOSS

The effect of the RYGB on weight loss was substantial and sustained, with a mean five-year weight loss of -29.1% TWL in adults and -27.5% TWL in adolescents. Hence, for the majority of participants included in this thesis, RYGB was very effective in inducing weight loss. The mean weight loss results align with previous literature on both adolescents and adults (133, 134, 166, 167).

However, there was a large spread around the mean, and weight regain and surgical treatment failure were investigated in both adults and adolescents. Results show that adolescents may have a greater risk of meting at least one of the definitions of surgical treatment failure (adolescents 34% vs. adults 23.1%), confirming previous observations that younger age may be associated with weight regain (225) and heterogeneity of weight loss (226). Early onset of obesity has been shown to negatively affect weight loss after RYGB (227), a factor present in all participants of the AMOS sample but not present in the population of adults in the SOReg.

However, the difference may be overestimated. As can be noted from Table 5.1, adolescents were on average 11.2 kg heavier despite being less than half the age of the adult sample. This as well as the fact the adolescents in the AMOS were the first in Sweden to be considered for bariatric surgery suggests a more obesogenic phenotype. Another possible explanation for the difference in prevalence of surgical treatment failure between the studies was differences in retention rate. In the AMOS, the retention rate was 100% at year five, compared to 70.1% in the SOReg. It is plausible that patients who experience poor weight loss outcomes are hesitant to attend follow-up visits. An indication supporting this hypothesis was found in the adult SOReg study, where participants who failed to reach the five year follow-up were more likely to meet the definitions of surgical treatment failure at year one or two.
Notably, this finding may reflect something about the high expectations bariatric surgery candidates often have prior to surgery (228-230). It is plausible that when expectations are not met, a sense of disappointment emerges that may in turn lead to a reluctance to attend follow-up visits. Most of these patients have struggled to lose weight for a large part of their lives, and bariatric surgery is often seen as a last resort when everything else has failed.

However, the question remains whether it is fair to assume that any one-time treatment for a chronic disease can provide results that last for the rest of one’s lifespan. Advances in other medical fields suggest that a combination of treatments is necessary to maintain results; for example, the transplant of a solid organ can be expected to last longer with the help of an adjuvant treatment (231).
Current guidelines suggest an active treatment in individuals with poor weight loss (142). Although more studies are warranted, it has been shown that weight loss can be modified post-surgery (232, 233). A systematic review and meta-analysis showed mixed results in terms of significance but favoured intervention (234). A meta-analysis associated exercise training with an increased weight loss of 2 kg in addition to a better cardiometabolic profile (235), similar to what increased physical activity showed (236). Pharmacological treatment with GLP-1 (Liraglutide) showed a mean weight reduction of 7.1 kg in RYGB patients in post-surgery weight management (237). Similarly, 24 months of treatment with Liraglutide resulted in a mean BMI loss of 4.8 kg/m^2 six years after the RYGB procedure (238).

6.3.1 Prediction of poor long-term outcomes

An attempt to predict surgical treatment failure was made by including information from pre-surgery and up to two years after surgery to develop a model. The model performed well both with the sample from the SOReg and with the small adolescent sample from the AMOS. The model could accurate predict individual risk of surgical treatment failure and thus be a useful tool for clinicians when evaluating post-surgery weight loss.
The model developed for this study is not the first of its kind, and there has been a surge in

interest in predicting weight loss after bariatric surgery in the past few years (239-241), with at least one more study currently in progress (242). However, by comparison with other models, the model developed using the SOReg included easily obtainable information from a larger sample, increasing robustness and generalisability alongside easy application of the model.

Arguably, predicting the five year outcome becomes progressively easier if chronologically adjacent variables, e.g. post-surgery information is included. Only using pre-surgical information would be superior as that could pre-emptively target individuals at high risk of poor initial weight loss, which was a factor of major importance. We tried to make a model based on only pre-surgical information and, like others, failed (243) to achieve a good enough model for that. However, by including other factors, it may be achievable. One potentially valuable factor is that adolescents with self-reported poor mental health were more likely to meet the definition of surgical treatment failure. This finding is not new, and heterogeneity of long-term outcomes based on pre-existing or developed poor mental health has been shown both in the AMOS (206) and elsewhere (219, 244). Although self-reported mental health may introduce bias, this information is easily obtainable pre-surgery and likely a factor worth including. Moreover, advances in the field of genetics analysis that primarily make such analysis more affordable render genetic factors interesting to include as they are associated with weight loss outcomes after bariatric surgery (245, 246). However, including data in a model beyond what is routinely measured in clinical settings limits the usability of the model in large parts of the world and would require enormous effort for standardisation of pre- as well as post-surgical management. Adding to a model almost always increase its complexity, and there is arguably a trade-off between precision and usefulness.

Moreover, based on estimates that around 70% of bariatric surgery recipients are likely to experience substantial and sustained weight loss, the presented model can also predict those who are at low risk of surgical treatment failure and are likely to manage without extensive follow-up; this could potentially be a cost-saving approach when allocating resources for follow-up.

6.4 CARDIOMETABOLIC EFFECTS OF BARIATRIC SURGERY

Overall, the results of this thesis confirm the positive effect of bariatric surgery on cardiometabolic disease. In adolescents, biochemical markers were almost entirely normalised, while in adults, the prevalence of T2D, dyslipidaemia and hypertension were dramatically reduced five years after surgery.

6.4.1 The association between weight loss and health improvements

Despite the overall positive effects of bariatric surgery, not all patients were found to benefit equally, though cardiometabolic improvements were found to be associated with weight loss. This finding confirms previously published associations between weight loss and cardiometabolic outcomes (151, 247-250). However, a complete understanding of this association remains elusive.

6.4.1.1 Several possible factors contributing to metabolic health

Similar to the variability between individuals regarding factors that predispose obesity and obesity-related diseases, response to bariatric surgery likely depends on multiple factors, including genetics, gut hormones, adipose tissue phenotype, behaviour, physical activity, eating patterns and food choices. All of these factors are likely to contribute to improvements in cardiometabolic health after bariatric surgery, and there are likely also links between them. In terms of weight regain and surgical treatment failure, these factors could potentially counteract each other and explain why some individuals can preserve metabolic improvements despite weight regain.

As noted, there are several altered endocrine responses after the RYGB procedure, many of which are known to vary between individuals (251), and GLP-1 levels are also found to be lower in individuals with weight regain (252). Another piece of evidence for the importance of GLP-1 comes from studies on post-surgery pharmacological treatment with GLP-1 analogues, which induce weight loss similar to revisional surgery (238) and improve glycaemia in individuals with persistent T2D post-surgery (253).

Weight loss induced by bariatric surgery has also been shown to affect muscle and adipose tissue morphology (254, 255). The reduction in hypertrophic adipocytes has been suggested as a contributor to metabolic improvement beyond weight loss. In a five-year follow-up, the benefits of bariatric surgery on adipose phenotype and function were reported to persist despite moderate weight regain (256). Nevertheless, it remains to be seen if more pronounced weight regain negatively influences adipocyte morphology. In the AMOS, both fat % and high sensitive CRP were higher in those with surgical treatment failure at year five, possibly indicating dysfunction and hypertrophy of the adipose tissue. Judging by the known plasticity of the adipose tissue, it is plausible that hypertrophy of adipocytes re-emerges with pronounced weight regain and may cause relapse of obesity-related comorbidities.

Behavioural factors, including eating patterns and food choices (257, 258), are also shown to be associated with post-surgery weight loss in adults. Regarding adolescents, the picture is less clear as no association was found between lifestyle factors such as dietary habits and weight loss outcomes in the FABS-5+ study (153) .

The results from the studies in this thesis show the marked effect of surgical treatment failure on cardiometabolic disease, indicating a strong association between weight dynamics and health even after the RYGB. However, although surgical treatment failure was associated with higher levels of cardiometabolic risk markers in adolescents and with relapse and incidence of obesity-related comorbidities in adults, most cardiometabolic markers remained normalised in adolescents, and adults without presurgical cardiometabolic disease were very unlikely to develop cardiometabolic disease regardless of weight loss outcome at year five. Hence, there may be protective mechanisms following RYGB surgery that are of importance for the timing of surgery.

6.5 BENEFITS OF BARIATRIC SURGERY PERFORMED AT A YOUNGER AGE

Benefits of bariatric surgery in adolescents have previously been proposed (160, 165, 166) in relation to the resolution and amelioration of obesity-related diseases.

Adolescents improved their VO_2max in relation to body mass and FFM, and the absolute values were maintained for the whole group over two years. The latter finding, of maintained absolute VO_2max, is partly in contrast to studies on adults who often (259, 260) but not always (261) demonstrate a reduction in absolute VO_2max after bariatric surgery. Notably, the increase of VO_2max relative to FFM may be greater in adolescents (261-263). These results add to the literature suggesting that results of bariatric surgery in adolescents may be superior to those in adults (160, 166). In the Teen-LABS study, physical activity after bariatric surgery was associated with improved lipid profile and weight loss three years after surgery (182); this is an interesting finding that could be investigated in the sub-group of adolescents from the Stockholm centre. Furthermore, the increase in CRF could potentially be a mediating factor contributing to the superiority of bariatric surgery in adolescents regarding resolution and amelioration of obesity-related diseases since CRF is an important marker of health independent of weight status.

6.5.1.1 Possible reasons for increased CRF

The reason for the discrepancy in CRF response to bariatric surgery between adults and adolescents is unknown and likely depends on several factors.
Speculatively, obesity in children and adolescents is associated with an increase in FFM (264, 265). Cardiac structures may also be effected, most likely as a response to increased strain from excess mass when performing everyday activities. This adaptation could be seen as a continuous ‘training’ of the skeletal muscle and heart, and obesity is associated with increased cardiac output (266). Twelve months after the RYGB in adults, cardiac output decreased but stroke volume relative to body surface area increased (267). This lingering cardiac effect may partially explain the improvements in CRF for adolescents. Another potential factor could be a greater ability to partake in more intensive physical activity. Although reports on adults show that physical activity does not increase, a meta-analysis shows that exercise training post-surgery increases CRF (268).
Furthermore, the accumulation of ectopic fat in skeletal muscle and the reversal of this as a consequence of bariatric surgery may also promote improved functioning of the muscle tissue. There is great variability in CRF in genetical predisposition (109), and gene expression related to CRF may be influenced by bariatric surgery; while this idea is hypothetical, it has been shown that bariatric-surgery-induced weight loss affects gene expression in adipose and muscle tissue (254, 255).

6.6 TO CUT OR NOT TO CUT?

The short answer is yes, adolescents with severe obesity should be offered bariatric surgery. This conclusion is based on the included studies, personal experience, the literature studied and years of reflection on the question.

Questions of both a medical and ethical nature remain. From the medical perspective, everything is associated with risk: doing nothing may increase risk of disease, doing something may also increase risk, such as complications. Ideally, the best treatment is 100% curative, has 0% complications and works for 100% of those who receive it, as schematically illustrated in Figure 6.1. However, such outcomes are impossible. As such, which risks should be accepted given the complications associated with elective major surgery?

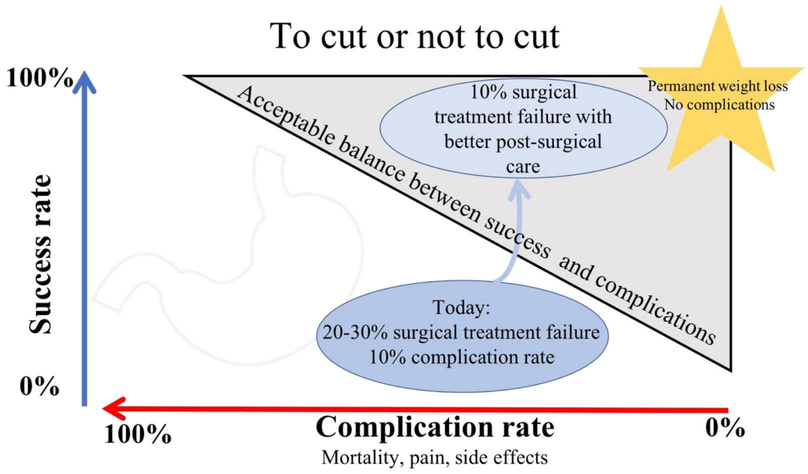

Figure 6.1. *Schematic illustration of the delicate decision at hand.*

The benefits of RYGB include, substantial weight loss, but as shown, this varies between individuals, and more than 30% of adolescents met at least one definition of surgical treatment failure stemming from either poor initial weight loss or weight regain (often in combination). Comparably, almost one in four adults met the same definition.

For adult patients, it has been reported that pre-operatively, 74% of bariatric surgery candidates would be disappointed with a weight loss of 20%, and only 57% would be willing to undergo a surgical procedure resulting in 20% weight loss (229). While patients' desire to lose weight is a strong factor for seeking bariatric surgery, it is not the only factor.
The other major benefit of bariatric surgery is the expected positive effect on obesity-related disease which was rated as more important than weight loss by adult patients (269). Although stemming from different studies, these two factors, identified by bariatric surgery candidates, were, as demonstrated in this thesis, related. One of the definitions used for surgical treatment failure was 20% TWL which was, as discussed, associated with cardiometabolic risk.

Given that 20–30% of RYGB recipients do not achieve or maintain that amount of weight loss, it is time to act.

Demonstrated in this thesis, it is possible to detect those at the greatest risk of surgical treatment failure, which can enable targeted intervention for those in need and thus better distribute resources.
Efforts should be made to integrate bariatric surgery into multimodal treatment pathways similar to those that exist in other medical fields such as cancer care or solid organ transplant. Bariatric surgery represents the best treatment available for adolescents and adults with severe obesity, but given the mixed results demonstrated in this thesis, it should not be seen as a standalone treatment. Rather, active treatment should be readily deployed in agreement with current guidelines (142), which should be simplified by a multidisciplinary and multimodal treatment approach.

Another question is where adolescents should be followed post-bariatric surgery. It is known through studies on other chronic diseases (270) that transfer from paediatric care to adult care often results in loss of information and loss of patients. Considering that the participants of the AMOS study have reported a desire and need for more follow-up (212), as in previous reports of adolescents desiring healthcare provider continuity in obesity treatment (271), it may be reasonable to keep adolescents in paediatric treatment even after age 18.

All things considered, adolescents with severe obesity should be offered bariatric surgery, but healthcare professionals must be and ready for the consequences by planning for the worst and hoping for the best.

6.7 LIMITATIONS

There are several additional limitations to this study not discussed elsewhere.

We evaluated long-term weight outcomes and the prevalence of surgical treatment failure as our main objective in two studies. Though the SOReg sample was sufficiently large for sub-group analysis, the AMOS sample was not, and caution is needed when interpreting the results because effects may be over- or underestimated due to study size. The apparent association between RYGB-induced weight loss and improvements in cardiometabolic health is dependent on several factors and mechanisms, many of which we had no possibility to include in our studies, such as gut hormones and microbiota, genetics and behavioural aspects. Many of these unmeasured factors could potentially provide a causal pathway for surgical treatment failure and obesity-related comorbidities. However, weight loss or weight regain are likely the predominant factors of cardiometabolic health given their association with all investigated comorbidities.
The study based on the SOReg was designed to study the risk of surgical treatment failure and effects on cardiometabolic health. Results should not be interpreted in the opposite direction e.g. as what x%TWL/EBMIL is required to prevent outcomes such as disease relapse. A more appropriate design for that would be a clinical trial where more measures of relevance can be obtained.

In the AMOS, the included adolescents were the first adolescents in Sweden to undergo bariatric surgery. As such, they may have represented the most severe cases of obesity, which may limit the generalisability of the findings to the broader population. Poor mental health was present and above the norm in AMOS before surgery (201); therefore, the association between adolescents and the outcome of surgical treatment failure may be overestimated. The lower number of males in the surgical samples mirrors the female predominance typically seen in studies of bariatric surgery but limits generalisability, especially in adolescents.

6.8 CLINICAL IMPLICATIONS

Bariatric surgery is now available for adolescents with severe obesity in Sweden. Adolescents may be particularly vulnerable to heterogeneity of weight loss and should be followed by specialists prepared to deploy the additional support required to optimise long-term weight outcomes.

Finally, inconsistent follow-up may be higher in adolescents outside the frame of a research study, and it may be reasonable to keep adolescents in paediatric care post-surgery even after reaching adulthood to maintain continuity.

6.9 PERSONAL REFLECTION

6.9.1.1 Bariatric surgery in children

I have often found myself explaining why bariatric surgery was performed or even considered in children, and the topic evokes emotion. My personal opinion is that it would be unethical not to offer patients the best available treatment based on a measure of chronological maturity. During my studies and work within the field of childhood obesity, sufficient evidence has been accumulated regarding the benefits of bariatric surgery in adolescents, and bariatric surgery is now available for adolescents with severe obesity in Sweden. For that I am glad and even though this thesis point at some, as I see it, unresolved problems I am optimistic that the outcomes of bariatric surgery can be modified by post-surgery intervention facilitated by early detection of those with high risk of surgical treatment failure.

However, there are a few points that remain problematic. How can it be ensured that the family of an adolescent is ready to manage the post-surgical demands, such as a completely different eating pattern, particularly since the adolescent will most likely remain in the same family that has been unable to limit prior weight gain. How can expectations be managed? In my experience, adolescents have wild expectations regarding almost everything and bariatric surgery is no exception.

7 CONCLUSIONS

Roux-en-Y gastric bypass has the ability to induce substantial and sustained weight loss over at least five years in both adolescents and adults, and adolescents may have added benefits over adults. However, the response to bariatric surgery is not homogenous. Poor initial weight loss, weight regain and ultimately surgical treatment failure are common, and the otherwise significant beneficial effects on cardiometabolic health can consequently be hampered. Concerningly, adolescents seem to demonstrate greater heterogeneity of weight loss, but this should not deter the use of bariatric surgery in adolescents. Delaying surgery from adolescence into young adulthood may allow time for the development of obesity-related comorbidities, which not only jeopardise immediate health and wellbeing but may also reduce the chances of success of surgical intervention performed when diseases are already manifested. Accurate prediction of long-term weight loss outcomes can and should be applied to target individuals in need of additional support in order to improve overall outcomes after Roux-en-Y gastric bypass both in adolescents and in adults.

8 FUTURE PERSPECTIVE

Much has changed since bariatric surgery emerged in the 1960s. Surgical techniques and methods have changed, evolved and been refined to meet today's standards, though the view of bariatric surgery as a standalone treatment for severe obesity has largely persisted. Two studies in this thesis investigated and found striking heterogeneity in weight loss after the RYGB procedure, which was in turn associated with cardiometabolic disease.

Further understanding of how individual traits influence the outcome of bariatric surgery is needed. There has been an explosion over the last decade in studies investigating the effects of behaviour, genetics, adipose tissue phenotype and gut hormones on weight loss and metabolic outcomes after bariatric surgery. While such studies can deepen understanding, information for many of these factors is not easily obtained in clinical settings, and meanwhile patients are likely to experience unwanted weight gain and relapse of comorbidities. Thus, a reasonable approach could be to more carefully monitor weight loss during the first two years. Using a model to predict individuals who are on the path to less optimal outcomes could inform targeted and personalised post-surgery intervention. Future studies should consider whether and how much post-surgery weight loss can be modified by additional support. A contemporary approach to follow-up could be a digital support system similar to what already been tested with promising results (272, 273).

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