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BARIATRIC SURGERY: PREDICTORS OF OUTCOME - RESULTS FROM A NATIONAL DATABASE (SOREG) WITH PARTICULAR EMPHASIS ON PATIENTS' AGE.

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Bariatric surgery: Predictors of outcome - results from a national database (SOReg) with particular emphasis on patients' age.

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Tidevarv komma, tidevarv försvinna, släkten följa släktens gång” – till dig mormor.

Abstract

A global pandemic of obesity and its health-related concerns, in form of comorbidities, increased risk of mortality, and reduced health-related quality of life, is ongoing. At the same time, conservative treatment for obesity, including life-style changes (mainly diet regimens and physical activity), is most often associated with unsatisfactory long-term results, and the most effective treatment for obesity itself as well as obesity-related health problems is surgery (1-3). Due to the increase in obesity, a simultaneously rise in bariatric procedures has occurred. Further, due to a worldwide increasing age, as well as rise in age-related obesity, bariatric procedures in patients over 60 years has also increased. Thus, between 1999 and 2005 older patients (≥60 years) accounted for 2,7% of the total number of procedures, compared to almost 10% during the period 2009-2013 (4). The safety and outcome of bariatric surgery for elderly has been debated, while benefits of preoperative weight loss before surgery is more consolidated (5-7). In conclusion, the aim of this thesis was to evaluate the effects of bariatric surgery in relation to preoperative weight loss and outcome in the elderly.

In the first (I) paper, the correlation between preoperative weight loss and preoperative body mass index (BMI) in relation to postoperative weight loss was analysed. We used a cohort of 9,570 patients in a complete data set. A preoperative weight loss in the 25th, 50th, and 75th percentile of 0%, 4.5%, and 8.6% was seen, respectively. Patients in the 50th percentile were compared for preoperative weight loss with reference (25th percentile), with a postoperative weight loss 5.0 and 5.3% higher at one and two years, respectively ($p<0.001$). Corresponding values for patients in the 75th percentile were 11.8% and 10.1 % ($p<0.001$). A more pronounced effect on patients in the 75th percentile of preoperative BMI (>45.7 kg/m2) was seen, with a 15.2% and 13.6% higher total weight reduction after one and two years compared to the reference (25th percentile) for preoperative weight loss.

The risk for complications and mortality in relation to age after gastric bypass was evaluated in the second (II) paper (n = 47 600). In the entire cohort, the 30-days follow-up rate was 98.1% with a risk of any complication at 8.4%, whereas patients in the age-groups 50-54 years, 55-59 years and ≥ 60 years, had a significantly increased risk at 9.8%, 10.0%, and 10.2%, respectively, for any complication. In a multivariate analysis, the risk of major surgical complications such, as anastomotic leak, bleeding, and deep infections/abscesses, were all increased significantly by 14-41% for patients aged 50-54, years with a small but not significantly increased risk for those of an older age. The risk of medical complications

(thromboembolic, cardiovascular, and pulmonary complications) was significantly higher for patients ≥ 60 years with, a total mortality of 0.03%.

In the third (III) paper, the resolution of obesity-related comorbidities (type 2 diabetes, hypertension, dyslipidaemia, OSAS, and depression) after gastric bypass in relation to age over time (at one, two and five years, postoperatively) was evaluated (n=57,215). Resolution was defined as no longer in need of pharmacological (or CPAP) treatment. The follow-up rates for eligible patients were 89%, 69%, and 59 % at one, two, and five years, respectively, and 64 % in patients for those older than 60 at five years. The prevalence of most comorbidities at baseline was higher in patients over 60 years, compared to younger ones. For those 60 and above, a relative improvement compared to preoperative prevalence for diabetes, hypertension, dyslipidaemia, and OSAS of 45%, 10%, 24, and 62%, respectively, was seen at five years.

In the fourth (IV) paper, health-related quality of life (SF-36 and OP) was evaluated at one, two and five years after gastric bypass, and the same cohort as in paper III was used. Further, in all age groups, the mental aspects of QoL (MCS) returns nearly to baseline after five years, compared to PCS and OP, with a maintained improvement up to five years after surgery. In conclusion, patients over 60 had an improvement in parity with younger individuals with regard to MCS, PCS and OP.

In summary, an association was found between a preoperative low caloric diet and a subsequent weight loss before surgery, and a better maintained weight loss up to two years after surgery. This is particularly evident for those with the highest levels of BMI. Gastric bypass in the elderly (≥ 60 years) exhibits an increased, but acceptable, risk for complications and mortality compared to younger patients. Further, the elderly have good resolutions, although not in the same range as younger patients, of obesity-related comorbidities, and good effects on health-related quality of life, comparable to younger individuals, up to five years after gastric bypass.

Taken together, these result support that a preoperative weight loss, in line with the association to a reduced risk of complications, entails a better maintained weight loss as well. Furthermore, elderly have a good effect on obesity-related comorbidity and health-related quality of life, with acceptable but increased surgical risk.

List of scientific papers

I. Gerber P, Anderin C, Gustafsson UO, Thorell A.
Weight loss before gastric bypass and postoperative weight change: data from the Scandinavian Obesity Registry (SOReg).
Surg Obes Relat Dis. 2016 Mar-Apr;12(3):556–562.

II. Gerber P, Anderin C, Szabo E, Näslund I, Thorell A.
Impact of age on risk of complications after Gastric Bypass: a cohort study from the Scandinavian Obesity Surgery Registry (SOReg).
Surg Obes Relat Dis 2018, 14(4):437–444.

III. Gerber P, Gustafsson UO, Anderin C, Thorell A.
Impact of Age on Obesity-related Comorbidity After Gastric Bypass: a cohort study from the Scandinavian Obesity Surgery Registry (SOReg).
Annals of Surgery 2021. In Press.

IV. Gerber P, Gustafsson UO, Anderin C, Johansson F, Thorell A.
Impact of age on Quality of Life after Gastric Bypass. Data from the from the Scandinavian Obesity Surgery Registry (SOReg).
Manuscript

Contents

List of abbreviations

BMI	Body Mass Index
CT	Computer Tomography
DS	Duodenal Switch
EWL	Excess Weight Loss
EBMIL	Excess BMI Loss
GB	Gastric Banding
HGP	Horizontal Gastroplasty
MRI	Magnetic Resonance Imaging
PCS	Physical Component Summary Score
LCD	Low Calorie Diet
LRYGP	Laparoscopic Roux-en-Y Gastric Bypass
MCS	Mental Component Summary Score
OP	Obesity-Related Problem Scale
RYGB	Roux-en-Y Gastric Bypass
SBU	Statens beredning för medcinsk utvärdering (The Swedish Council on Technology Assessment in Health Care)
SF-36	The Short Form (36) Health Survey
SOReg	Scandinavian Obesity Surgery Registry
SOS	Swedish Obese Subjects
TBWL	Total Body Weight Loss
VBG	Vertical Banded Gastroplasty
VLCD	Very Low Calorie Diet

1. Introduction

The global increase in the prevalence of obesity is a major health concern worldwide, mainly due to obesity-related comorbidities and mortality (8). Obesity is also associated with reduced health-related physical as well as mental quality of life compared to the general population (9). According to National Health and Nutrition Examination Survey (NHANES) data, the prevalence of obesity in the US was relative stable during the 60s and 70s but saw an increase from 13% to 34% between 1989 and 2008, as well as a further increase thereafter. Today, well over 1.9 billion adults worldwide over 18 years of age are classified as overweight (BMI 25.0-29.9) of which 650 million are obese (BMI ≥30) (2, 4, 10). In data from NHANES, the prevalence for obesity in US (2013-2014), was 35.2% and 40.5% for men and women, respectively (11). The same trend is seen in younger individuals (6-18 years) in US, with an increase from 15% in 1971-74 to almost 26% in 1988-1994. Even further, the rate of obesity in 10-years-olds in Sweden has risen to 3% since the millennium compared to <1% in the 80s (3, 4, 11).

Conservative treatment for obesity, including life-style changes (mainly diet regimens and physical activity), is associated with unsatisfactory long-term results (12). Due to the well-documented effects of surgical treatment of obesity (sustained weight loss, resolution of comorbidities, and mortality rates over time) (4), the number of operations has increased worldwide during the last decades (13, 14).

A commonly used definition of successful weight loss is EWL ((Weight initial - Weight postop) / (Weight initial - Weight ideal)) *100) ≥ 50%. However, the Swedish national registry for bariatric surgery (Scandinavian Obesity Surgery Registry, SOReg) uses other ways of reporting weight loss, such as total percentage weight loss or EBMIL (Excess BMI Loss). For example, data from SOReg indicates that approximately 10% of patients fail to achieve ≥50% excess weight loss two years after gastric bypass (15). Further, in Sweden we recommend a two to three-week period of low calorie diet (LCD, 800-1,200 kcal/day) or very low calorie diet (VLCD, < 800 kcal/day) prior to surgery (15). This has been shown to reduce liver and intraabdominal fat volume, as well as reducing the risk of postoperative complications, especially in patients with high BMI (6, 16).

With increasing life expectancy in most populations worldwide, the number of bariatric procedures in patients over 60 years increases, despite prevailing recommendations (17).

Thus, between 1999 and 2005 older patients accounted for 2.7% of the total number of procedures, compared to almost 10% during the period 2009-2013 (1-3). To what extent patients over 60 years should be recommended bariatric surgery from a risk-benefit perspective is a matter of debate.

1.2 Etiology

Obesity is a consequence of an excess of food intake in relation to the an individual's needs – in other words an imbalance between the intake and need of calories causes obesity (18). However, the degree of energy intake is complex and influenced by genetic, cultural, and social factors (11, 19). For instance, in a Danish study an increased risk for obesity between the age of 10-20 was related to parenteral neglect. Kuwaiti women, for example, (60% prevalence of obesity) and consanguinity (relationship) of 55% indicate that both cultural and genetic factors have a risk influence (19). Further, a Finnish twins study indicated a genetic association of obesity up to 80% (11), as well as effects on metabolism. Today it is generally accepted that somewhere in the range of 50% of obesity is correlated to genetic factors (11). Moreover, in some endocrine disorders (e.g. hypothyroidism, Cushing), variations in energy metabolism and gastrointestinal microbial diversity might also increase the risk of obesity as well (20, 21). Additionally, several pharmacological agents might also induce obesity (anti-psychotic, anti-depressive and anti-epileptic drugs), as well as insulin and corticosteroids, and psychiatric disorders such as psychosis itself also entail an increased risk for obesity, as well as ADHD (11). Other, more uncommon, syndromes are associated with severe obesity such as Prader Willi syndrome, *MC4R* syndromes, and fragile X or Bardet-Biedl's syndrome (11, 22).

1.3 Definitions

1.3.1 Definition of obesity

The most used definition of obesity is Body Mass Index (BMI), calculated as: weight/length^2 (weight in kilograms and length in metres), Table 1. According to WHO the definitions for overweight and obesity are BMI > 25 and >30 kg/m^2, respectively (10). Despite several limitations, BMI still constitutes a useful measure of overweight and obesity, although one important limitation is the lower BMI cut-off limits for Asian ethnicity (BMI > 23 moderate increased risk, and BMI > 27.5 increased risk) (23). Another is that BMI does not allow discrimination between amount of muscle and fat, which might differ between young and old, as well as between sedentary and wellexercised individuals. The strengths are that only height and weight is needed for calculation of BMI and the cut-offs are similar for both sexes (10), and BMI allows, for most adult individuals, an adequate estimation of the degree of obesity to be used in daily clinical practice (24, 25).

Table 1: Classification of overweight/obesity in relation to health consequences (10, 11)

Classification	BMI (kg/m²)	Health consequences
Underweight	<18.5	Low risk
Normal range	18.5-24.9	Normal risk
Overweight	≥25.0	Slightly elevated risk
Obese	≥30.0	Slightly to moderate elevated risk
Obese class I	30.0-34.9	Moderate elevated risk
Obese class II	35.0-39.9	Elevated risk
Obese class III	≥40.0	Very high risk

Other clinically useful means to classify degree of obesity include waist-to-hip ratio, waist circumference, abdominal sagittal diameter, as well as waist-height (26, 27). Examples of more complex and resource-consuming measures are the bioelectrical impedance measure (BIA), magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DEXA), where the two latter methods are more often used for research purposes (26). Although these techniques are more accurate than measuring BMI, they are still considered too expensive and complicated for use in daily clinical practice (28).

Table 2: Different methods for determination of degree of obesity (26, 29)

Method	Definition	Pros	Cons
BMI	Body Mass Index BMI (kg/m²)	Easy, standardised, well known, research data available	Does not distinguish between body fat and lean body mass, less valid for elderly
Waist Circumference	Circumference of waist as measured between lowest rib and iliac crest	Easy, correlated with body fat, some research	Not standardised, difficult for BMI >35
Waist-to-Hip Ratio	Dividing circumference of hip and waist (hip cm/waist cm)	Correlates to body fat, inexpensive, research	Risk of systematic error: measure difficulties, difficult for BMI >35
Waist-to-Height Ratio (WtHR)	Waist circumference divided by height	Easy, good predictor of cardiovascular disease	Risk of systematic error
Bioelectric Impedance (BIA)	Use electrical impulse, impedance. Calculate body fat and fat-free mass	Safe, fast, easy, portable	Calibration difficult, ratio of body fat influenced by for example various illnesses
Underwater Weighing (Densitometry)	Weight in air and under water. Formula estimate body volume, body density, fat percentage.	Accurate	Time, requires water, not for children or older adults and individuals with BMI >40
Air-Displacement Plethysmography	Body volume estimate based on air pressure	Fast, safe, children, older adult, pregnant, BMI >40	Expensive, labour-consuming
Dual Energy X-ray Absorptiometry (DEXA)	Estimates fat-free mass, fat mass, and body mineral density	Accurate	Expensive, not pregnant, BMI >35 (might be problem)
CT scan or MRI		Accurate	Expensive. Time consuming

1.3.2 Definition of weight loss

The gold standard measure for weight loss is yet to be determined (30). The most common measures include per cent excess weight-/BMI loss (% EWL, % EBMIL) defined as percentage loss of the overweight and excess BMI, respectively, total body weight loss in kilograms or percentage of total weight lost (%TBWL) (15, 30, 31). Patients with a lower preoperative BMI more easily achieve a higher % EWL compared to those with higher BMI, where % TBWL better describes the weight loss in comparison between different preoperative BMI classes.

Table 3: Different methods for measuring weight loss(15, 30, 31). (Weight ideal = weight corresponding to BMI 25)

Definition		**Calculate**
Δ BMI	Change BMI	BMI initial – BMI postoperatively
% EWL	% Excess Weight Loss	(Weight initial - Weight postop)/ (Weight initial - Weight ideal) *100
% EBMIL	% Excess BMI Loss	(Δ BMI / (BMI at surgery – 25)) *100
TBWL	% Total Body Weight Loss	(preoperative Weight – actual Weight) *100/ preoperative Weight)

1.4 Consequences of obesity

1.4.1 Health – mortality

Obesity is one of the major reasons for premature death (8, 32). Thus, obese individuals have a shorter life expectancy of six to nine years compared to people with normal weight (8, 33, 34). One study concluded that males and females > 40 years with a BMI > 30 kg/m² have 4.2 and 3.5 years shorter expected lifetime , respectively, compared to those with BMI below 30 kg/m^2 (33). In the US alone it has been estimated that almost 15% of the deaths in the year 2000 were related to excess weight (35).

1.4.2 Health – comorbidities

Individuals with a BMI above 35 kg/m^2, Table 1, have a higher risk of cardiovascular disease compared to normal weight individuals. Hypertension is almost three times as common in the obese compared to individuals with normal BMI, and obesity is also associated with higher prevalence of dyslipidaemia and type 2 diabetes mellitus (36-38). The metabolic syndrome (MetS) is defined by IDF (International Diabetes Federation) as the presence of: 1) central obesity (waist >80 and >94 cm in women and men, respectively) and 2) at least two of the following: TG >1.7 mmol/l, HDL <1.3 mmol/l (women) and <1.0 mmol/l (men), pharmacologically treated hypertension or blood pressure >130/80 mmHg and elevated blood glucose concentrations or diabetes (39, 40). Obesity is the main cause for both metabolic syndrome and type 2 diabetes, and each of the above criteria of the metabolic syndrome increases the risk of cardiovascular disease five-fold compared to controls (40).

Obstructive sleep disorder as well as osteoarthritis is associated with obesity, and obesity-associated obstructive sleep apnoea is related to increased morbidity and mortality (41). Furthermore, since obese individuals are at increased risk of osteoarthritis, an early diagnosis is important in order to enable proper treatment strategies (42), including weight loss, which has been shown to markedly improve function and to reduce pain and inflammation (43).

1.4.3 Health – other issues

Although numerous factors might influence fertility, an association between obesity and infertility has been reported. Weight reduction dramatically improves fertility and pregnancy outcomes, including reduced risk of miscarriage, gestational diabetes, hypertension, and preeclampsia (44).

From large cohort studies, a correlation between obesity and increased risk of various types of cancer has been established (45, 46). The relative risk for endometrial cancer and oesophageal adenocarcinoma is reported as high and a modestly increased relative risk for renal and pancreatic adenocarcinoma, hepatocellular cancer, gastric cardia cancer and multiple myeloma has also been reported. Furthermore, slightly increased (near normal) risk has been reported for colorectal cancer, postmenopausal breast-, gallbladder-, ovarian- and thyroid cancer (47). Bariatric surgery has been shown to effectively reduce these risks, in particular for female (gynaecological) malignancies (48), with indications of a reduced overall risk of 33% of developing any sort of cancer after bariatric surgery, and an even stronger reduction for obesity-associated cancer of >40 % (such as postmenopausal breast-, colon-, endometrial- and pancreatic cancer) (49).

There is also an association between obesity and deteriorated physical, as well as mental, aspects of self-reported quality of life, and depression is more prevalent in individuals with obesity compared to the normal population (9, 50-52). Some reports also indicate that the stigma of obesity in itself is related to poor health (46, 53). A well-validated quality of life (QoL) instrument provides a standardised way to measure and compare patients' health related QoL (HR-QoL) due to obesity over time (54).

1.4.4 Older patients

In the US, obesity also displays an increased prevalence also in elderly but to a decreasing extent in the highest ages. Thus, it has been reported that individuals in the groups 65-74 years, 75-84 years and >85 years, individuals with a BMI >30 accounts for 25%, 17% and 9.9% respectively (55). The same trend is seen in Spain, where the prevalence of individuals with BMI >40 was 19% in the group 65-69 years compared to 13 % in those >80 years (56). Interestingly, it has been reported that individuals over 65 with obesity do not suffer from higher risk for short term mortality (≤ 1 year) compared to those with normal or moderately increased BMI in the short term (≤ 1 year) (55). This finding is in line with the debated "obesity paradox", which states that the elderly with a higher BMI might in fact have a lower mortality risk in situations of severe illness, including when treated in the ICU (55, 56). There seems to be an U- or J-shaped mortality risk in relation to BMI, where the increased risk starts at BMI >35 (57). In line with the "obesity paradox", there are indications that the "optimal" weight increases with age. This suggests that although there is an increased risk for cardiovascular disease in the elderly, the obesity itself might reduce the mortality risk compared to individuals with a lower BMI (58). This is contradicted by recent data, which indicate that even obese older individuals (> 75 years) are at increased risk for mortality compared to those with a normal BMI of around 25 kg/m² (33). For the elderly there might be a stronger correlation between waist-hip ratio and mortality than between BMI and mortality (57). Furthermore, an inverse association between BMI and health-related quality of life has been reported, with a lower BMI being related to a better quality of life for older individuals as well (57). On the other hand, older individuals have shown to be more prone to suffer from "sarcopenic obesity" ("sarx" = flesh and "penia" = lack), with a relatively low proportion of muscle mass (59). It has been reported that sarcopenic patients might be prone to the same risks as patients with a higher BMI regarding, for example functional disability, morbidity, and mortality (55).

1.5 Obesity treatment modalities

1.5.1 Diets and conservative treatment

Numerous diets and diet recommendations have been used for the treatment of obesity. VLCD (very low calorie diet) <800 kcal/day and LCD (low calorie diet) 800-1,100 kcal/day are the most studied alternatives for restriction of daily calorie intake (6, 15). Although long-term follow-up data are sparse, some studies report that use of VLC or LC, high-protein, and Mediterranean diets might result in sustained weight loss of around 3 kg up to five years after commencement of the treatment (60-62). In the short term, energy restricted diets have been found to result in weight loss of 14-38 kg (63). Data from The National Weight Control Registry, including 2,886 participants (with eligibility criteria 13.6 kg weight loss maintained ≥1 year) showed a mean weight loss of 31.3, 23.8 and 23.1 kg at one, five, and 10 years and >87% had a maintained total weight loss of ≥10% at five and 10 years (64). From the same registry and with the same eligibility criteria, a comparison between surgical (n=72) vs a non-surgical (n=137) group over two years was made and showed no significant difference in weight regain over this period (3.7±11.9 vs 5.2±10.8 kg, p=0.998) and therefore concluded that weight loss might be sustained with non-surgical methods including behavioral therapy (65). However, the reported effects of conservative treatment in older individuals ≥60 years are modest, and there is no strong evidence to support such strategies in the elderly (66).

1.5.2 Physical exercise

Restricting calorie intake is more efficient for losing weight compared to exercise alone (67), but the combination of the two is likely the best way to achieve weight loss, when studied in the short term. The weight loss has been reported to be in the same range for combined exercise and calorie restriction vs calorie restriction alone (~1.0 kg/week) (67). There might be a dose-response relation between the duration of exercise and weight loss, where exercise >200 minutes/week was reported to induce a weight loss of 13.1 kg compared to 3.1 kg with <150 minutes of exercise/week at 18 months follow-up (60, 67). However, physical activity of less than 150 minutes/week has reported not to induce weight loss, and therefore a duration of physical activity of at least 200 minutes/week might be needed for the maintenance of the lost weight (67, 68). Interestingly, a 12-week programme of aerobic exercise has been shown to induce weight loss in the range of 5-10% without any complementary diet restrictions (67). Accordingly, ACSM (American College of Sports Medicine) recommends that exercise programmes should exceed 225 minutes/week to induce and maintain weight loss (67). Moderate physical activity in the range of 150-250 minutes/week corresponding to an energy equivalent of 1,200-2,000 kcal/week has been reported to prevent weight gain (68). In a randomized controlled trial (RCT) that included individuals >65 years, a combination of exercise and calorie restriction was found to be superior compared to diets or calorie restriction alone (69).

1.5.3 Pharmacological treatment

Medical treatment of obesity has historically included agents such as thyroid hormone, amphetamine, and chemical congeners of amphetamine. Although some effects in terms of weight loss were reported, the severity of side-effects, such as cardiovascular death, stroke, and depression, was unacceptable. In Sweden there are three drugs approved for treatment of obesity. Orlistat (Xenical, Beacita), is a gastrointestinal lipase inhibitor with proven effects on diabetes (70) and weight-loss of up to four years after starting treatment. Liraglutide is a glucagon-like-peptide 1 (GLP-1) analogue, which has a central acting appetite reducing effect. Finally, Mysimba is a combination of bupropion/naltrexone affecting both opioid receptors and the noradrenaline/dopamine system in the central nervous system (70, 71). These agents have been shown to be associated with a weight loss in the range of 5-19% of total body weight after one year. Further, an RCT showed promising results with Semaglutide (in a one/week administration), with a total weight loss of around 15% at up to 68 weeks (72). New strategies acting on the melanocortin system or mimicking GLP-1 effects have been evaluated and used with variable success. A combination of different drugs or agents might be a promising approach to reduce obesity in the future (73, 74). A recent cohort study comparing bariatric surgery with medical treatment revealed a better outcome for surgery when hypertension, diabetes, and dyslipidaemia was followed up after to seven years (75).

1.5.4 Endoscopic treatment

The use of intragastric balloon with or without fluid has been reported to be associated with good outcomes in the short term, with weight loss in the range of 10% after six months. However, adverse effects such as nausea, vomiting, bloating, and some rare but serious complications (intestinal obstruction and oesophageal perforation), and the obvious weight regain after removal, has limited its use (76). Electrical, laparoscopically implanted, devices are currently available. These stimulators include vagal nerve blockade (electrodes that are placed on the anterior and posterior vagal trunk and when activated intended to reduce gastric emptying rate) and gastric stimulators (also several electrodes that reduce the gastric emptying rate). However, these techniques have shown from modest to quite promising results in the range of 3.2-17% TBWL (Total Body Weight Loss) up to at least one year (76). A transabdominal gastric emptying system (Aspire Assist) has also been reported to induce weight loss in the same range but only short term. Alternative endoscopic procedures are the duodenojejunal bypass liner (EndoBarrier) and gastroduodenojejunal bypass sleeve; where the former is a 60 cm long fluoropolymer sleeve placed into the duodenum where the nutrients “bypass” the covered mucosa, and the latter is also a coated polymer sleeve, which is longer than the EndoBarrier. Both of these have been shown to be associated with a TBWL in range of 10-13% in short-term studies (76, 77).

1.5.5 Bariatric surgery from its beginning to today

The expression bariatric surgery (baros = “weight”) is claimed to have been coined by the physician Raymond E. Dietz, 1961 (78), and the first bariatric procedure, a jejuno-ileal bypass, was performed by Kremen in 1954. This technique was modified several times and eventually a modified “Roux-en-Y” developed in parallel with other techniques, such as various banding methods. With the introduction of laparoscopic surgery, Roux-en-Y gastric gypass became the golden standard technique (79). Pure restrictive approaches including the development of banding techniques, for example, vertical banded gastroplasty (VBG) and adjustable gastric banding. Scopinaro developed a malabsorptive technique, biliopancreatic diversion, which eventually evolved into the duodenal switch (79). The most commonly used technique today is the sleeve gastrectomy, which was initially used as a first stage procedure of the duodenal switch.

The number of bariatric surgical procedures has increased over recent decades. During 2013, almost 470,000 bariatric procedures were performed globally, of which 45% were Roux-en-Y gastric bypass (RYGB), 37%, sleeve gastrectomy (SG), and 10% adjustable gastric banding (AGB) while no other single procedure exceeded 2.5% (80). In Sweden in 2019, less than 5,000 procedures were performed, evenly distributed between gastric bypass (47%) and sleeve gastrectomy (48%), and around 20 biliopancreatic diversions with duodenal switch (BPD-DS) (81), and a few single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) for some patients. Previously commonly performed procedures, such as gastric banding (GB) and vertical banded gastroplasty (VBG) have been completely abandoned in Sweden due to its high rates of complications needing revisional surgery (80, 81).

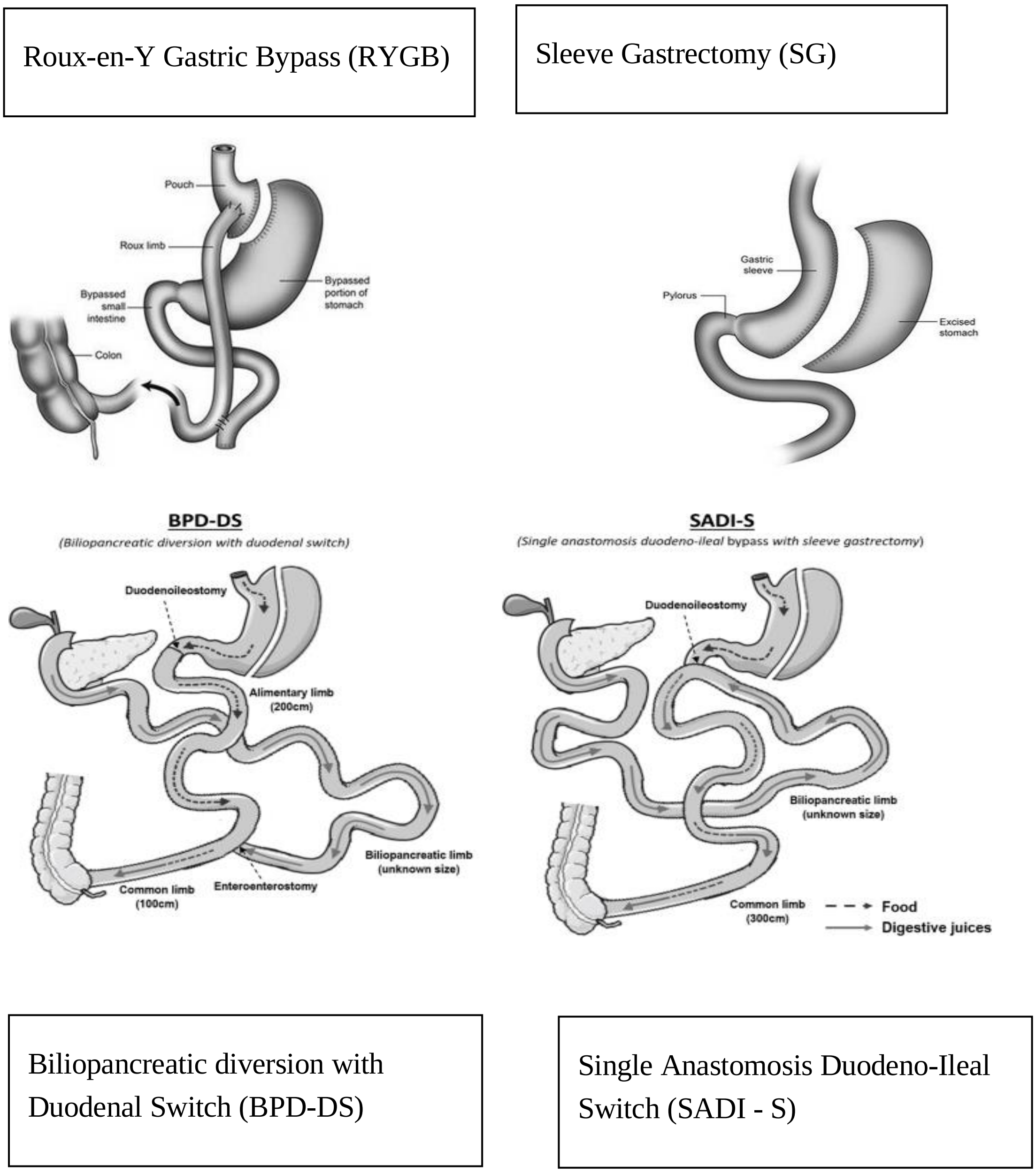

Figure 1 The bariatric procedures currently in use in Sweden.

1.6 Indications for bariatric surgery

Indications for bariatric surgery are still mainly based on the 1991 NIH consensus document [48]. In Sweden, the general and most used criteria are:

- BMI >35 kg/m2
- Age >18 years
- Previously serious weight-reducing attempts
- Stable psychosocial context
- Informed and understanding the risks and consequences of bariatric surgery
- Motivated, both regarding the operative procedure and follow-up programme
- Acceptable risk

At a first glance, indications seem straightforward. Still, the complexity of patient selection becomes obvious when considering the various risks, certainly in older patients. According to the NIH Guidelines, the patient must be both physical and psychological suitable and thoroughly informed, with realistic expectations and an understanding of the postoperative course (82). The role of a psychologist and/or psychiatrist is crucial in the selection process to ensure that mentally disadvantaged patients are identified (82). We also know that improved preoperative preparation might avoid several post-operative problems (5, 6). The expected post-operative weight loss should be addressed in a way that motivates attainment of preoperative weight loss recommendations (82-84). Still, the main reason to recommend bariatric surgery is to improve health and to reduce the medical consequences of obesity due to comorbidities (85).

1.7 Risks with bariatric surgery

1.7.1 Overall

Mortality after surgery was evaluated in a couple of studies including one study of 304,515 patients undergoing bariatric procedures and rates were reported higher in ages > 50 years OR 3.8 (2.8-5.0), male sex OR 1.7 (1.2-2.2), chronic renal failure OR 2.7 (1.6-4.5) and open procedure OR 5.6 (4.4-7.2) (86, 87). The risk of any complication within 30 days after bariatric surgery has been reported to vary between 1-23% depending on surgical procedure (77). In the Scandinavian Obesity Surgery Registry (SOReg) the most commonly reported early complication was postoperative bleeding (2%), infection (1%), anastomotic leakage (1%), and minor wound complications (1%) (88-94). Total rates of postoperative medical complications, such as thromboembolic events, cardiovascular or pulmonary complications, were reported in less than 1% of patients. Other complications include urinary tract infection (0.4%) (89, 95) and stomal ulceration and/or stricture in the range of 0.7% (95).

Long-term complications after bariatric surgery include stomal ulceration, dumping and internal hernia with a total reported risk up to 16%. A large Swedish multicentre RCT shows that closure of the mesenteric defect reduces the risk of internal hernia by approximately 67% over time (96). Depending on the surgical procedure performed, nutritional deficiencies such as for thiamine, vitamin B12, vitamin D, as well as for iron, zinc, copper and magnesium have been reported at varying rates (97). The surgical procedure associated with the highest risk for such deficiencies is biliopancreatic division, but deficiencies for micronutrients are also seen after gastric bypass, as well as sleeve gastrectomy. Other problems include, for example, gallstone formation, excess of skin due to weight loss (71), and chronic abdominal pain (98). Today an increased awareness regarding sleeve gastrectomy and if there is any associated increased risk of Barrett’s oesophagus and with an increased risk of Oesophageal cancer exists as well.

1.7.2 Weight loss before surgery

Nowadays, a preoperative weight loss prior to bariatric surgery is recommended, although there has previously been a lack of lack of high-quality evidence for the clinical effects (6). In a recent review, a correlation between VLCD and decrease in hepatic volume was reported (99), verified by, for example, one study showing that 80% of reduction of the liver volume occurred within the first two out of 12 weeks with VLCD (5). Although some studies support the use of weight loss prior to bariatric surgery in terms of reduced rates of complications and improved weight loss over time, there is an inconsistency regarding reported effects on operating time, intraoperative complications, such as blood loss, and length of stay (83, 84, 100). A retrospective analysis of prospectively registered data from the Scandinavian Obesity Surgery Registry comprising over 22,000 patients demonstrated a total risk reduction of postoperative complications in the range of 13-18% in patients who lost weight preoperatively as compared to those who did not (6). These results were confirmed in a multicentre RCT (7). Pharmacological measures or an intragastric balloon have been proposed to be more effective than a strict low calorie diet in reducing liver volume prior to bariatric surgery, although the use of low calorie diets might be preferred due to the higher level of evidence and practical applicability (101). The length of the preoperative low caloric diet is debated, with a variation between two and four weeks (6, 16, 83, 101). There is no strong evidence to support four weeks compared to two weeks, since the average reduction in liver volume is markedly reduced after two weeks (5, 101).

1.7.3 Surgical risk – the elderly

Although increasing age is often considered a risk factor for inferior outcome after surgery, the number of older patients undergoing bariatric surgery has increased during the last decade. There are conflicting data in the literature regarding the safety of bariatric surgery in older patients, with reported limited increased risk of complications (102), but also an increased risk of mortality from 65 years and above (103, 104). Whereas one study reported that age > 65 years as an independent risk factor for medical complications after sleeve gastrectomy (OR, 1.75 (1.04-2.96)) (105), as compared to another review, that concluded that age by itself should not exclude patients from being considered for surgery (106).

Furthermore, a recent study implies that bariatric surgery is also safe in patients over 75, although this conclusion was based solely on 19, presumably selected, patients (107).

1.8 Why operate?

1.8.1 Weight loss

In general, patients lose in the range of 60-70% of their excess weight during the first two years after bariatric surgery (81, 108). Both sleeve gastrectomy and gastric bypass seems to be relatively comparable, although the latter has been reported to exhibit a better outcome regarding weight loss in the short- and long term, with approximately 25% of TBW loss still remaining up to 10 years after (81, 109, 110). The large matched controlled SOS (Swedish Obese Subjects) study (data covering 20 years) reports maintained weight loss in the range of 25-30% at 15 years for gastric bypass (13, 111), supported by data of long-term weight loss in the range of 20-25% TBW up to 20 years after (112). Even patients with BMI >50 seem to have comparable outcomes regarding total weight loss to those below after up to five years (113).

1.8.2 Reduction of mortality

In the SOS study, a reduction in overall mortality (25% after 15 years, Hazard Ratio 0.76 (0.59-0.99)) was found in patients undergoing bariatric surgery compared to controls (94). This is in corroboration with another report where a reduced mortality was shown in surgically-treated patients of 40% (37.6 vs 57.1 per 10,000, p<0.001), after a mean follow-up of 7.1 years (114). In another study, (mean follow-up 7.2 years) comparing surgery with non-surgery groups of patients in age-cohorts (<35, 35-44, 45-54 and >55 years) , a significantly lower odds for total mortality was found in patients undergoing surgery for all age groups above 35 years but not in patients below 35 years (115). In a French study, where patients were followed for seven years, a lower mortality was recorded in patients who received a gastric bypass (hazard ratio 0.64 (0.52-0.78)) or sleeve gastrostomy (hazard ratio 0.38 (0.29-0.50)) as compared to non-operated match controls (116).

1.8.3 Obesity and comorbidity after bariatric surgery

After 15 years follow-up, in the previously mentioned SOS study, a reduction in myocardial infarction of 27%, as well as marked improvements in the incidence and resolution of diabetes, was also demonstrated (94). Today, there are well-documented positive effects in obesity-related comorbidities such as diabetes, hypertension, dyslipidaemia and sleep apnoea in both gastric bypass and sleeve gastrectomy (medium-term follow-up, <5 years) (117, 118). Very obese patients with a BMI >50 have been reported to improve in comorbidities in the same range as those with lower BMI, although the risk reduction for cardiovascular event was not confirmed (113). At short-term follow-up (< 3 years) there are comparable data reported regarding resolution/improvement of comorbidities after sleeve gastrectomy, compared to gastric bypass, for type 2 diabetes, hypertension, dyslipidaemia and obstructive sleep apnoea (119).

1.8.4 Quality of life

Health-related quality of life is reported to improve after bariatric surgery regardless of surgical technique (120). For global QoL as assessed by SF-36, there are improvements reported in the short and long term (up to 12 years). Interestingly, the beneficial effects on mental aspects were not maintained for more than one year (121-123). The most pronounced effect is seen in the physical component summary score (PCS) (123-125), with an improvement often maintained up to five years. For obesity specific QoL, as assessed by the OP scale in SOReg, sustained improvements have been repeatedly reported (81). Further, a long-lasting weight reduction is correlated to an improvement in health-related quality of life, including obesity specific scale (OP) and in rates of depression up to 10 years after bariatric surgery (126).

1.8.5 A variety of benefits

Obstructive sleep disorder and osteoarthritis have both been shown to effectively improve after surgically-induced weight loss (41-43, 48). Further, bariatric surgery has a positive effect regarding, for example, gestational diabetes and preeclampsia as well as malformations (127), although the surgical weight reduction induces the risk of malnutrition, such as anaemia and vitamin D- deficiency, as well as some other nutrients, and a risk of surgical complications due to the bariatric procedure per se (127). In comparisons between strict diet regimes and physical exercise, bariatric surgery is superior (128).

1.8.6 Benefits and risk in older patients undergoing bariatric surgery.

In parallel with increasing age in the general population, the number of patients at higher age undergoing bariatric surgery has increased. Globally, patients over 60 represented around 10% of those operated during the period 2009-2013 (1, 2). Although older patients are burdened with a higher degree of morbidity, the rate of complications after surgery has been reported to be acceptable (129). However, increased rates of adverse outcomes from as early as 55 years of age are seen, with a significant increased risk (OR 1.05 (1.02-1-07)) for patients >65 years (130). In one study of older (>65 years) compared to younger (18-64 years) patients operated on with sleeve gastrectomy or gastric bypass a higher 30-day mortality in the older patients was found in the former, whereas no difference was found in the later (131). In another review, low rates of mortality and surgical complications were reported in older patients, and sometimes an even a lower risk compared to younger individuals (102). In the light of the overall relatively low rates of morbidity in the older group of patients, the general trend today seems to be accepting bariatric surgery even in the elderly (131, 132).

But when recommending bariatric surgery to older patients, the presumably somewhat higher risks need to be justified and compared to the beneficial effects.

Patients > 60 years have repeatedly been reported to have somewhat lower weight loss compared to younger patients, although the difference seems to decrease over time (102, 133). Accordingly, long-term results up to 10 years after bariatric surgery have been reported as comparable between patients of various ages (baseline <40, 40-54 and >55 years) with a maintained weight loss in all groups of around 30% of TBW (134).

In a meta-analyses, comprising >6,000 patients in 15 studies, a resolution of diabetes, hypertension and dyslipidaemia in the range of 61-100%, 50-91% and 38-60% was found, although follow-up rates were low (102). This is in corroboration with additional findings regarding short- and midterm (≤ 5 years) resolution of comorbidities up to five years in older patients (135). In another study with patients >75 years, a sustained weight loss as well as improvements in both diabetes and hypertension were reported after bariatric surgery (107).

In the short term, self-reported QoL improves also for patients >65 years (136) and the improvement seems to be in the same range or even better compared to younger patients (134).

Taken together, although somewhat conflicting, the available data today suggest that older patients seem to be at slightly higher risk for adverse outcome after bariatric surgery compared to younger individuals. However, with improved surgical care, rates of morbidity and mortality seem to be acceptably low, suggesting that older patients should not necessarily be withheld from surgery, at least not solely based on a certain age. More data on beneficial effects in older patients are therefore needed. We need better evidenced-based knowledge as to what extent this group of patients should be recommended for bariatric surgery.

2. Aims

The aims of the thesis were to study first postoperative weight loss in relation to a preoperative weight loss before bariatric surgery and, second the effect of age as a factor in bariatric surgery. The task was pursued as follows:

I

Is preoperative weight loss associated with improved postoperative weight loss over time, and is this dependent on preoperative body mass index (BMI)?

II

What is the specific impact of age on the risk of complication for patients undergoing laparoscopic gastric bypass? Is there any difference between various age groups in the rate of complications and mortality using data from a large population-based registry?

III

What is the specific impact of age on the resolution of obesity-related comorbidities for patients undergoing laparoscopic gastric bypass? Is there any difference between various age groups regarding specific comorbidities?

IV

What is the specific impact of age on quality of life after gastric bypass, and does QoL after surgery differ between elderly and younger patients?

3. Methods

Table 4 illustrates an overview of the different cohorts from SOReg. All studies involve retrospective analyses of prospectively collected data.

Table 4. Overview of studies I – IV, design, patents (n), respective cohort, exposure, and outcome

Study	Design, cohort	Patients (n)	Data extracted	Exposure	Outcome
I	Retrospective	20,564	1 Jan 2008 – 30 Nov 2011	Preoperative weightloss	Postoperative weightloss
II	Retrospective	47,660	1 May 2007 – 16 Oct 2016	Age	Complications
III	Retrospective	57,215	1 May 2007 – 31 Dec 2018	Age	Comorbidites
IV	Retrospective	57,215	1 May 2007 – 31 Dec 2018	Age	Health-related quality of life

3.1 Scandinavian Obesity Surgery Registry (SOReg)

The Scandinavian Obesity Surgery Registry (SOReg) is a nationwide well-validated (<2% incorrect values) quality registry for bariatric surgery, with a 98% registration rate (137). The registry was established in 2007 and is financially supported by the Swedish National Board of Health and Welfare and approved by the Swedish Surgical Society. Patient data are registered preoperatively (upon procedure decision), at day of surgery, and at six weeks. Further follow-up is at one, two, and five years after surgery, and nowadays 10 years.

3.2 Cohorts

All patients included in cohorts were operated on with primary gastric bypass, excluding other bariatric procedures.

The cohort in the first paper (I) consisted of all patients operated on between 1 January 2008 and 30 November 2011, with a follow-up period of at least two years. First 20,654 patients were identified, but due to missing data on weight (preoperatively, one, and two years) 10,380 patients were excluded and 704 patients due to errors in data; thereafter 9,570 patients remained for analyses. The preoperative weight reduction was calculated by the difference at decision for surgery and at the time of surgery. Weight loss was described as relative difference (%) of total body weight at one and two years after surgery. A stratification was made with percentiles based on relative preoperative weight loss as well as BMI at the time of decision for surgery.

The second paper (II) consisted of 47,660 patients operated on between 1 May 2007 and 16 October 2016. The six-week follow-up rate was 98.1%. Data included age, gender, different co-morbidities, smoking, access (laparoscopic, open, or converted from open to laparoscopic surgery), weight and BMI at the time of a definitive procedure plan. Postoperative complications (as registered in the SOReg's database) at 30 days was divided into 'any postoperative complication', specific surgical complications including anastomotic leak, bleeding, deep infection/abscess, minor wound complication, and 'medical complication' (thromboembolic event, cardiovascular or pulmonary complication). Postoperative bleeding was defined as bleeding after surgery with significant impact on haemoglobin concentration, or a detectable bleeding requiring intervention under general anaesthesia, and/or the need for blood transfusion. The entire cohort was divided into five-year intervals, with separate groups for all patients ≥60, ≥70, and < 20 years. The rates of complications within each age group were analysed separately and compared with the complications in the total cohort.

The patients included in the third paper (III) were operated on 1 May 2007 and 31 December 2018, with a total of 57,226 patients (2,687 ≥ 60 years). An age stratification in line with paper II was performed. Further patients followed up at each date - one, two and five years - were included. Comorbidities, registered in SOReg are defined related to obesity when in active treatment for type 2 diabetes mellitus, hypertension, dyslipidaemia, and depression, as well as ongoing treatment for obstructive sleep apnoea syndrome (OSAS).

In the fourth (IV) paper we stratified the patients as in paper III and used the same criteria for follow-up. Health related quality of life was registered for SF-36 and OP preoperatively and at one, two, and five years postoperatively. The weight loss was separately analyzed up to five years postoperatively.

3.3 Health-related quality of life measurements

Two different quality of life instruments, SF-36 (Short Form 36 Health Survey) and Obesity-related Problem scale (OP), are used in SOReg.

3.3.1 Short Form Health Survey (SF-36)

SF-36 is a validated global instrument for estimating health-related quality of life and measures a variety of mental and physical dimensions. The instrument consists of 36 questions, divided into eight dimensions of health-related quality of life (HRQoL), with a summary of these eight dimensions into a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score, established on a computer-based calculation.

A higher value equals better quality of life, and the value for each dimension is weighted based on given answers, with a value between 0 and 100, where zero equals the worst possible outcome and 100 the best. PCS is a combination of the dimensions Physical Function, Role-Physical, Bodily Pain, and General Health, whereas MCS combines Vitality, Social Function, Role-Emotional and Mental Health. In SF-36 data on age- and sex-matched controls is also available for comparison as well (137, 138).

3.3.2 Obesity-related Problem scale (OP)

The Obesity related Problem scale (OP) is a Swedish validated obesity-specific instrument to measure an individual’s QoL in relation to obesity. OP consists of eight questions about psychosocial problems related to obesity and facing bariatric surgery. It is expressed on a scale from 0 to 100 but has the reverse direction compared with SF 36, i.e. a higher value indicates a worse quality of life. OP is a disease-specific quality of life instrument and is therefore seldom used in non-obese individuals (81, 139).

3.4 Statistics

Exposure was defined as preoperative weight loss (paper I) and age (papers II-IV) and outcome was weight loss at one and two years after surgery (paper I), complications and mortality within 30 days after surgery (paper II), resolution of comorbidities over time (paper III), and development of health-related quality of life over time (paper IV).

Results are presented as percentages, median (range), odds ratio (OR), percentiles and 95% confidence interval (CI) when appropriate. A two-tailed t-test was used for crude group comparisons of continuous variables, and a Chi-square test for binary variables. Baseline characteristics were analysed to determine the univariate predictors of the different outcome variables.

The co-variates included in the multivariate analysis were chosen according to stepwise logistic modelling where a p-value < 0.15 was considered relevant. The relevant covariates were BMI, age, gender, and occurrence of diabetes (papers I – II), and for papers III and IV covariates were preoperative weight, smoking, gender, diabetes, and hypertension.

A multiple linear regression model was used to quantify the relationship between pre- and postoperative weight loss (paper I). The logistic regression model was used to estimate odds ratios for postoperative relative weight loss in relation to preoperative relative weight loss (paper I), to estimate odds ratios for various postoperative complications in relation to age (paper II), to estimate odds ratios for mean resolution at various outcome of comorbidity after gastric bypass in relation to age with the entire cohort of patients as reference (paper III), and to estimate odds ratios for each age group in relation to the total mean change of MCS, PCS, and OP at one, two, and five years after surgery (paper IV). The health-related quality of life outcomes (SF-36 and OP) in absolute number were analyzed with repeated measurement ANOVA over one, two, and five years.

A linear trend analysis was performed using age as a continuous variable in relation to "any complication" as the dependent variable (paper II). Further, a sensitivity analysis was performed (papers III and IV), comparing patients' baseline data with or without five years follow-up data. Using logistic regression, independent predictors at baseline for reaching five years follow-up were identified. All data were analysed using STATA® Version 12.0 and 13.1.

3.5 Ethics

All studies were approved by the Regional Ethics Committee, EPN 2011 1624-31-1

4. Results

4.1 Paper I

Patients had a median preoperative weight loss of 6 kg from date of decision to surgery (mean 7.9 weeks), and a BMI decrease from 42.0 to 40.1. The preoperative weight loss was divided into different percentiles and median weight change percentages are presented in **Table 5**, with the median weight change in the entire cohort being -4.5%.

Table 5. Preoperative relative weight change, in percentiles and % (n = 9,570).

Weight loss	Number of cases	Weight change in %	Weight change in % (Median)
25th percentile	2,396	> -0.9	0
50th percentile	4,783	-0.9 - -6.9	-4.5
75th percentile	2,391	≤ -7.0	-8.6

With the 25th percentile as reference, there was a 42 % (OR 1.42, 95% CI 1.28-1.57) and 139% (OR 2.39, 95% CI 2.10-2.72) increased probability of losing more weight the first year in 50th and 75th percentile, with corresponding values at two years of 35% and 88%, **Table 6.** Further, the division into preoperative BMI percentiles revealed that the heaviest group (BMI > 45.7 kg/m^2) had a more pronounced postoperative weight loss compared to patients with lower BMI. Thus, at one and two years postoperatively, patients in the 75th percentile of preoperative weight loss displayed 15.2 and 13.6 % increased weight reduction, respectively, compared to patients within the 25th percentile.

Table 6. Postoperative relative change loss in relation to preoperative relative weight loss. The probability of weight loss and the 25th percentile is reference.

Preop. Weight Loss	OR	Lower	Upper	Postop. Weight Change Median (%)	Weight Change Compared to Ref. (%)	
1 year after surgery						
25th percentile (ref)	1.00			-29.82	-	
50th percentile	1.42	1.28	1.57	-31.31	-5	p<0.001
75th percentile	2.39	2.10	2.72	-33.33	-11.8	p<0.001
2 years after surgery						
25th percentile (ref)	1.00			-30.70	-	
50th percentile	1.35	1.23	1.51	-32.33	-5.3	p<0.001
75th percentile	1.88	1.66	2.12	-33.79	-10.1	p<0.001

4.2 Paper II

In this paper (n = 47,660) with 2,137 patients over 60, the age-related risk of complications and mortality are given in **Table 7**, with a total frequency of any complication within 30 days at 8.4% and an increased risk in the age groups 50-59 and ≥60 years around 15%, **Table 8**.

Further a non-statistically significant increased risk of “any complication” was noted between 60-69 years, and a corresponding reduction for younger individuals at 14-23% compared to the total cohort. With a linear trend analysis, the significantly higher risk for any complication in older patients was confirmed ($p<0.001$).

Table 7. Age interval and corresponding median BMI (Body Mass Index), rates of complications (%) and mortality (‰), values for all patients (All). BMI = (kg/m^2). *** Any. = Any compl., Leak = Anastomotic leak, Bleed = Postop.bleeding, Infect. = Deep Infection/abscess Wound = Minor wound compl., Medi. = Any medical compl, Mort = Mortality*

Age group	Number	BMI	Any **	Leak **	Bleed.**	Infect.**	Wound**	Medic.**	Mort. ‰
All	47660	42.3	8.4	1.1	2.0	0.9	1.0	0.9	0.3
≥70	30	41	3.3	0	3.3	0	0	0	0
65-69	370	41.4	10.9	2.7	1.1	1.6	1.6	3.5	2.7
60-64	1737	41.8	10.2	1.4	2.2	1.3	2.2	1.5	1.2
≥60	2137	41.7	10.2	1.6	2.0	1.3	2.1	1.8	1.4
55-59	3903	41.5	10.0	1.9	2.6	1.2	1.2	1.2	0
50-54	5354	41.5	9.8	1.5	2.3	1.2	1.2	1.1	0.6
45-49	7106	41.8	8.4	1.1	2.5	1.0	1.0	0.9	0.4
40-44	7920	42.2	8.1	0.9	2.0	0.8	0.9	1.0	0.1
35-39	7153	42.4	7.9	0.9	1.9	0.7	1.0	0.7	0.4
30-34	5543	43.1	8.0	1.0	1.6	0.7	0.8	0.7	0.4
25-29	4510	43.2	7.7	0.7	1.6	0.6	1.0	0.6	0
20-24	3325	43.4	7.2	0.8	1.2	0.5	0.3	0.6	0
<20	709	43.9	6.4	0.4	0.6	0.3	0.6	0.6	0

Anastomotic leak (1.1%), **Table 7,** exhibit a reduced risk of 37% in those between 25-29 years, and a corresponding increased risk (36-109%) for age groups 50-54, 55-59 and 65-69 years, **Table 8**. Further postoperative bleeding (2.0%) showed a significant increased risk only in the age groups 45-49 and 55-59, with a significant reduction for those below 25 years. Deep infection/abscess (0.9%) had an age-correlated increased risk, and a non-significant increase was noticed from the age of 45. For superficial wound infections (1.0%), there was a significant increased risk for all patients ≥60 years (102 %) and the age group 60-64 years (114 %), compared to the youngest age groups (age group 20-24 and <20 years), who displayed a reduction of 68% and 43% respectively, **Table 8**. Medical complications (0.9%) showed an significant increased risk for age groups ≥60 and 65-69 years (OR 1.82 and 3.43, respectively) with crude incidence of 1.8 and 3.5%. The overall mortality rate was low, at 0.03%, **Table 7**, and no deaths within 30 days after surgery were reported in the age groups below 30 years (8,544 patients). In the age groups ≥60, 60-64 and 65-69 years the mortality rate was between 0.12-0.27 %.

Table 8. The odds ratio (OR) in relation to different complications and age groups. ** Not possible to predict. No complication registered in this age group, ** Any. = Any compl., Leak = Anastomotic leak, Bleed = Postop.bleeding,, Infec. = Deep Infection/abscess Wound = Minor wound compl., Any Med. = Any medical compl.*

Age	Number	Any**	Leak**	Bleed**	Infec.**	Wound**	Any Med.**
All (ref.)	47 660	1	1	1	1	1	1
≥70	30	0.33 (0.04-2.45)	*	1.43(0.19-10.56)	*	*	*
65-69	370	1.29 (0.87-1.69)	2.09(1.10-4.00)	0.45 (0.17-1.21)	1.55 (0.68-3.52)	1.45 (0.64-3.30)	3.43(1.94-6.08)
60-64	1737	1.16 (0.99-1.36)	1.10 (0.72-1.67)	0.99 (0.71-1.38)	1.30 (0.84-2.01)	2.14 (1.52-3.02)	1.43(0.95-2.16)
≥60	2137	1.16 (1.00-1.34)	1.27 (0.89-1.82)	0.89 (0.65-1.22)	1.34 (0.90-1.99)	2.02 (1.46-2.79)	1.82(1.29-2.58)
55-59	3903	1.17 (1.05-1.31)	1.72 (1.34-2.22)	1.26 (1.02-1.56)	1.33 (0.97-1.82)	1.18 (0.87-1.60)	1.22(0.89-1.66)
50-54	5354	1.17 (1.06-1.29)	1.36 (1.07-1.73)	1.14 (0.94-1.38)	1.41 (1.07-1.85)	1.23 (0.94-1.61)	1.20(0.91-1.59)
45-49	7106	0.98 (0.89-1.07)	0.98 (0.77-1.25)	1.24(1.05-1.47)	1.13 (0.87-1.47)	0.98 (0.76-1.27)	0.99(0.76-1.29)
40-44	7920	0.96 (0.88-1.05)	0.79 (0.61-1.01)	1.01 (0.85-1.20)	0.92 (0.70-1.21)	0.95 (0.74-1.22)	1.16(0.91-1.49)
35-39	7153	0.94 (0.86-1.04)	0.88 (068-1.14)	0.97 (0.81-1.17)	0.79 (0.58-1.07)	1.03 (0.80-1.33)	0.80(0.59-1.08)
30-34	5543	0.96 (0.87-1.07)	0.95 (0.72-1.27)	0.84 (0.67-1.05)	0.84 (0.60-1.18)	0.73 (0.53-1.01)	0.75(053-1.06)
25-29	4510	0.93 (0.83-1.05)	0.63 (0.43-0.91)	0.85 (0.66-1.09)	0.78 (0.53-1.15)	1.07 (0.78-1.46)	0.68(0.45-1.01)
20-24	3325	0.86 (0.75-0.99)	0.83 (0.56-1.23)	0.66 (0.47-0.91)	0.64 (0.39-1.04)	0.32 (0.17-0.58)	0.73(0.46-1.14)
<20	709	0.77 (0.57-1.06)	0.41 (0.13-1.29)	0.30 (0.11-0.82)	0.36 (0.88-1.42)	0.57 (0.21-1.53)	0.69(0.26-1.84)

4.3 Paper III

This paper (n= 57,215) included 2,687 patients over 60, with a loss to follow-up at 11%, 31%, and 41% at one, two, and five years after surgery. A total of 8,152 patients (14.3%) were treated for diabetes, with increased prevalence in patients of higher age. For example, the prevalence was 2.9% and 39% in age groups 20-24 and ≥60 years, respectively. The prevalence for diabetes was 6.4%, and a near 50% remission rate for those over 60 at five years, although lower compared with younger patients. The odds ratio for remission of diabetes was reduced with increasing age, **Figure 2,** and the OR compared to all patients was statistically significantly higher in the age groups 30-34, 35-39, and 40-44 years, at one year after surgery, compared to a lower OR in all age groups over 60 (except ≥70). Those differences were still present at two years, while nearly the only significant differences remaining at five years was higher OR in patients 30-35 years and lower OR in patients ≥60 years, **Figure 2.**

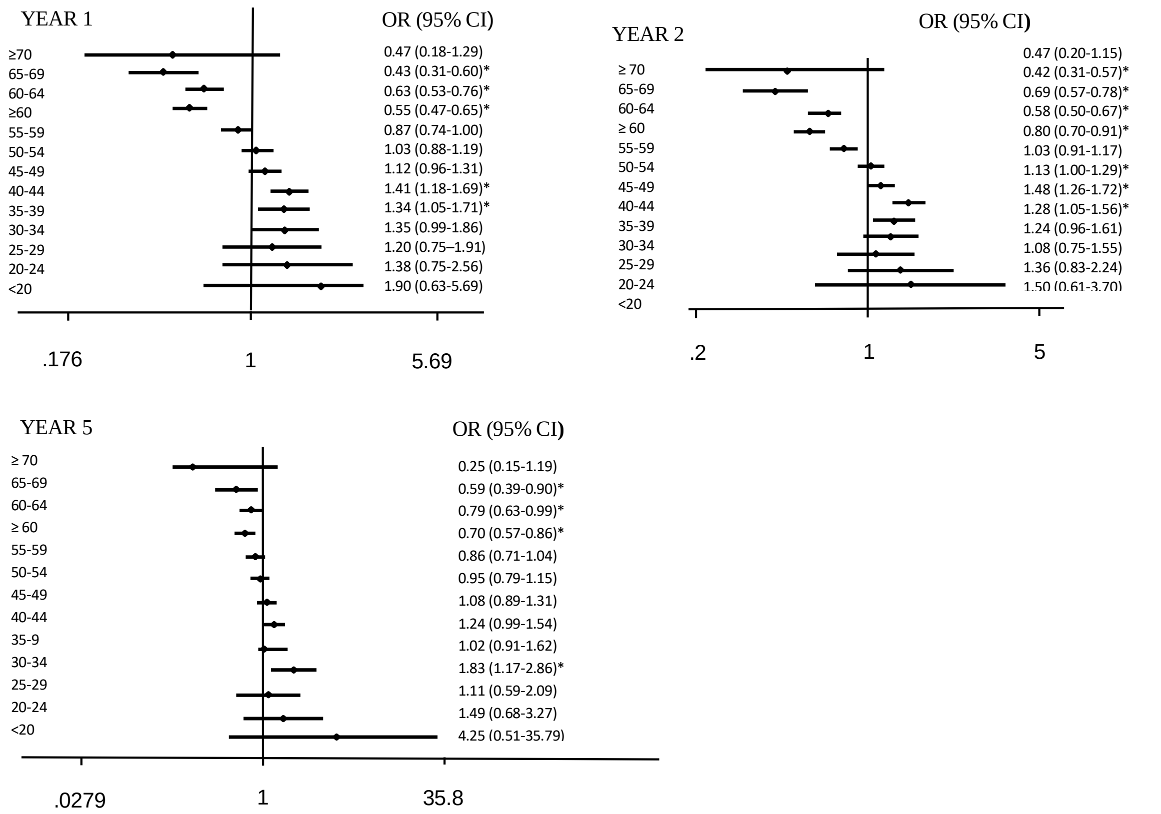

Figure 2. Odds ratio (95% CI) to achieve resolution of diabetes at 1, 2 and 5 years after gastric bypass in the various age groups compared to all other patients(reference). Asterisk (*) indicates statistically different from reference.

In the entire cohort at baseline, 14,610 patients (25.5%) had pharmacological treatment for hypertension, with a reduced prevalence at one, two, and five years to 16.8, 17.5 and 19.9%, respectively (0<0.001) and a significant reduction in all age groups, except those >70 years at one and five years. Elderly patients (≥60 years) had a lower relative reduction in the prevalence of hypertension, 10% at five years, compared to those below 30 with near 50% reduction (p<0.001). Further, most patients between 50 and 69 years exhibit a lower OR for remission compared to all other patients, whereas OR was higher in patients below 45 years at up to five years after surgery. The prevalence of dyslipidaemia was 9.9 % (n= 5,644) and reduced by approximately 40-45% at year five. Although an age-related increased prevalence was seen, the reduction in relative terms was similar across age groups. The OR for resolution of dyslipidaemia exhibited a similar pattern with lower and higher OR in older and younger patients, at one and two years, respectively. However, at five years only patients aged 55-59 years had a lower OR and those between 30 and 39 years had higher OR for resolution of dyslipidaemia compared to the entire cohort of patients, **Table 9.** For OSAS, the preoperative prevalence was 9.9% (n= 5,639) with a reduction by approximately 75% at one, two and five years. The reduction was less pronounced in older patients, but statistically significant at all follow-up times in all age groups except for patients <20 and > 70 years. Further, the likelihood for significantly higher or lower OR in younger and older patients, respectively, was less pronounced in patients with OSAS compared to those with diabetes or hypertension, **Table 9**. Depression, compared to other diagnoses, was more evenly distributed across the various age groups. The preoperative prevalence of 15.1 % was significantly reduced at one and two years, although increased at five years after surgery. A trend towards better maintained resolution at five years was seen in the older groups of 55-59, >60, and 60-64 years.

Table 9. Odds ratio to achieve resolution of hypertension, dyslipidaemia, obstructive sleep apnoea syndrome (OSAS) and depression at 1,2 and 5 years after gastric bypass. Asterisk (*) indicates statistical, difference compared to reference (All patients) (p<0.05, NA, analysis not possible due to low numbers).

Hypertension	**1 year**	**2 year**	**5 year**	**Dyslipidemia**	**1 year**	**2 year**	**5 year**
≥70	0.64 (0.29-1.40)	0.40 (0.15-1.08)	0.38 (0.84-1.76)	≥70	0.90 (0.29-2.80)	0.38 (0.10-1.47)	0.34 (0.04-3.30)
65-69	0.70 (0.55-0.89)*	0.53 (0.40-0.70)*	0.39 (0.26-0.59)*	65-69	0.73 (0.53-1.01)	0.52 (0.36-0.76)*	0.79 (0.50-1.25)
60-64	0.58 (0.51-0.65)*	0.55 (0.47-0.63)*	0.49 (0.40-0.59)*	60-64	0.68 (0.57-0.81)*	0.82 (0.66-1.01)	0.83 (0.64-1.08)
≥60	0.58 (0.52-0.65)*	0.52 (0.46-0.60)*	0.45 (0.37-0.53)*	≥60	0.68 (0.58-0.80)*	0.70 (0.58-0.85)*	0.80 (0.63-1.01)
55-59	0.70 (0.64-0.77)*	0.68 (0.61-0.76)*	0.63 (0.55-0.73)*	55-59	0.74 (0.64-0.85)*	0.69 (0.58-0.81)*	0.71 (0.58-0.88)*
50-54	0.81 (0.74-0.88)*	0.85 (0.76-0.94)*	0.92 (0.80-1.05)	50-54	0.97 (0.85-1.12)	0.93 (0.79-1.10)	1.02 (0.82-1.28)
45-49	1.06 (0.97-1.15)	1.11 (1.00-1.23)*	1.21 (1.06-1.39)*	45-49	1.20 (1.04-1.39)*	1.28 (1.07-1.53)*	1.14 (0.90-1.44)
40-44	1.34 (1.21-1.48)*	1.53 (1.36-1.73)*	1.41 (1.20-1.65)*	40-44	1.20 (1.00-1.45)*	1.41 (1.12-1.78)*	1.20 (0.90-1.61)
35-39	2.23 (1.93-2.58)*	2.06 (1.72-2.45)*	2.65 (2.11-3.33)*	35-39	1.54 (1.16-2.03)*	1.45 (1.02-2.08)*	1.61 (1.03-2.53)*
30-34	2.79 (2.25-3.46)*	2.49 (1.92-3.22)*	2.57 (1.78-3.71 *	30-34	3.23 (2.00-5.26)*	4.01 (2.10-7.63)*	4.68 (1.63-13.40)*
25-29	4.14 (2.84-6.05)*	6.51 (3.71-11.44)*	4.86 (2.36-10.02)*	25-29	2.27 (1.23-4.18)*	3.12 (1.20-8.09)*	2.62 (0.76-9.00)
20-24	4.18 (2.27-7.73)*	5.49 (2.51-12.00)*	5.10 (2.01-12.91)*	20-24	5.22 (1.58-17.18)*	4.91 (1.13-21.31)*	4.23 (0.52-34.61)
<20	7.00 (1.53-32.01)*	14.64 (1.87-114.61)*	NA	<20	NA	NA	NA
OSAS	**1 year**	**2 year**	**5 year**	**Depression**	**1 year**	**2 year**	**5 year**
≥70	0.57 (0.13-2.55)	0.52 (0.86-3.15)	1.09 (0.11-10.58)	≥70	NA	NA	NA
65-69	0.72 (0.45-1.12)	0.69 (0.41-1.15)	0.37 (0.21-0.65)*	65-69	1.27 (0.73-2.21)	0.91 (0.44-1.88)	1.50 (0.70-3.20)
60-64	0.63 (0.51-0.78)*	0.65 (0.50-0.85)*	0.64 (0.47-0.89)*	60-64	1.04 (0.80-1.34)	1.03 (0.75-1.41)	0.92 (0.60-1.40)
≥60	0.63 (0.52-0.77)*	0.64 (0.50-0.81)*	0.54 (0.40-0.72)*	≥60	1.08 (0.85-1.36)	1.00 (0.75-1.34)	1.05 (0.73-1.53)
55-59	0.84 (0.70-1.00)	0.83 (0.66-1.03)	0.95 (0.71-1.27)	55-59	1.00 (0.84-1.18)	1.22 (1.00-1.50)*	1.20 (0.92-1.56)
50-54	0.92 (0.78-1.08)	0.86 (0.70-1.06)	1.36 (1.00-1.83)*	50-54	1.01 (0.87-1.16)	0.99 (0.83-1.18)	1.01 (0.79-1.28)
45-49	1.03 (0.87-1.22)	1.03 (0.84-1.27)	0.74 (0.57-0.98)*	45-49	0.93 (0.81-1.05)	0.83 (0.71-0.98)*	0.81 (0.65-1.00)
40-44	1.16 (0.95-1.41)	1.33 (1.03-1.71)*	1.00 (0.72-1.40)	40-44	0.90 (0.79-1.02)	0.88 (0.74-1.04)	0.88 (0.70-1.10)
35-39	1.15 (0.91-1.46)	1.35 (0.98-1.85)	1.85 (1.16-2.95)*	35-39	1.11 (0.97-1.27)	0.96 (0.81-1.15)	0.99 (0.79-1.25)
30-34	1.79 (1.27-2.52)*	1.41 (0.91-2.17)	3.23 (1.37-7.61)*	30-34	0.94 (0.80-1.11)	1.09 (0.89-1.33)	1.06 (0.80-1.41)
25-29	2.03 (1.24-3.31)*	2.31 (1.23-4.31)*	2.43 (0.95-6.26)	25-29	1.03 (0.86-1.24)	1.05 (0.82-1.33)	1.25 (0.91-1.72)
20-24	7.56 (1.82-31.39)*	3.52 (0.82-15.10)*	1.78 (0.40-8.04)*	20-24	1.14 (0.90-1.45)	1.47 (1.08-2.00)*	1.27 (0.86-1.87)
<20	NA	NA	NA	<20	2.53 (1.44-4.44) *	2.53 (1.26-5.07)*	4.13 (0.33-3.89)

4.4 Paper IV

4.4.1 Mental Component Summary

For mental health (Mental Component Summary (MCS) of SF-36), an improvement was seen in the total cohort up to two years, **Figure 3.** Patients in the age group ≥60 rate their preoperatively MCS higher compared to the total cohort (46.2 vs 43.5, p<0.001), and had a higher MCS at one, two, and five years after surgery compared to the entire group. Those below 30 years have a step rise up to two years, with a maintained improvement up to five years, compared to those between 30 and 60 years with a worse outcome at five years compared to preoperatively. The OR for those below 30 years indicates a better mean relative change at one, two, and five years, compared to those between 40 and 59 years in the range of 3-11%, 9-15% and 8-12%, respectively ($p<0.001$). The oldest, ≥60 years, have a vague non-significant trend towards lower odds compared to the mean relative change in the entire cohort.

4.4.2 Physical Component Summary

The global physical health, PCS, improved both within each age group as well as the entire cohort as a total, **Figure 3**, with all age groups approaching their respective SF-36 age-reference after surgery (140). Those over 44 had a lower preoperatively PCS compared to the entire cohort, with a maintained trend at five years after surgery. For the age groups ≥60, 60-64 and 65-69 years, an improvement in PCS was seen at five years after surgery in absolute numbers from preoperative values at 32.3, 32.3, and 32.4 compared to 41.0, 41.9, and 38.1 ($p<0.001$), although not equal to younger groups. The improvement was, in general, more pronounced for younger patients. This was shown in a multivariate analysis, with statistical significance for patients below 20 and over 60 with an increased (1.42) and decreased (0.82) OR for change in PCS compared to the entire cohort, respectively.

4.4.3 Obesity-Related Problem Scale

In Obesity related Problem scale measurement, **Figure 3**, the entire cohort exhibits an improvement up to five years (18.8, 21.3, and 26.2, vs 64.1 before surgery, $p<0.001$), where the oldest (≥60, except ≥70) seemed to suffer least from their obesity according to OP, with a preoperatively score of 55.3, 56.4, and 51.1 ($p<0.001$), respectively. The age groups ≥60 and 60-64 have an improvement of the OP score at one, two, and five years to 15.9 vs 15.8, 16.6 vs 16.2, and 22.2 vs 21.8 (compared baseline, $p<0.001$), respectively. In most age groups over 40, the relative changes seem better compared to younger age groups and a total improvement in OP is maintained up to five years after surgery, **Figure 3**. The improvement in OR starts from 40 years, and age groups between 40-59 mostly exhibit a non-significant increased chance (in relation to the mean relative chance) compared to the total group in the ranges of 5-12%, 2-19%, and 7-11% at one, two and five years respectively ($p<0.001$). For all the age groups ≥ 60 years, the improvement is small and non-significant.

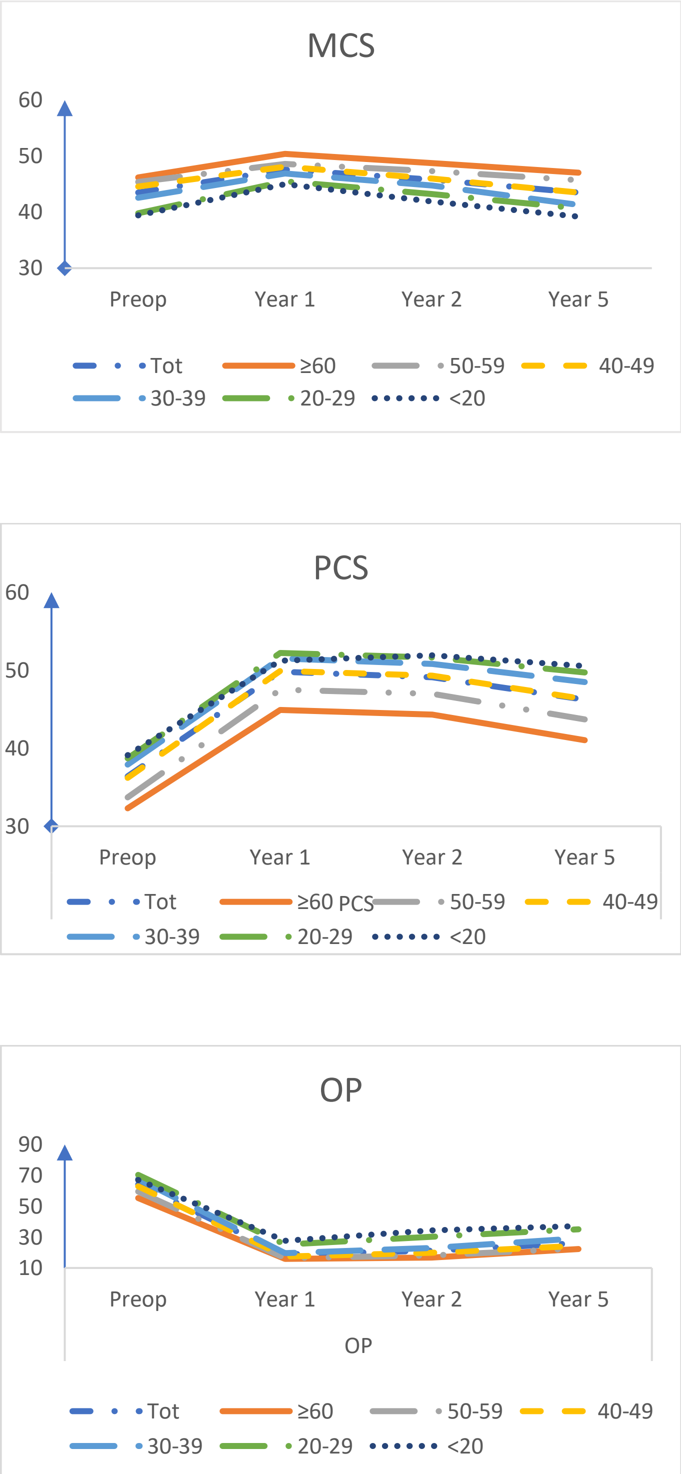

Figure 3 Health related quality of life: MCS, PCS and OP preoperatively, years one, two, and five after surgery. Age groups (>60 years, 50-59 years, 40-49 years, 30-39 years, 20-29 years and <20 years).

5 Discussion

5.1 Methodological considerations and limitations

In this thesis, data from the Scandinavian Obesity Surgery Registry, SOReg, were analysed in all included studies. In SOreg (validated to ≥97.8% correct values), data on bariatric surgery are registered perioperatively with, today, a ten- year follow up. We chose to analyse patients operated on with primary gastric bypass only, in order to homogenise outcome. The cohorts were stratified in line with each specific aim, thereby to better describe the associations between exposures (preoperative weight loss and age) and outcomes (postoperative weight loss, complications, comorbidities, and health related quality of life).

5.1.1 Validity

A high validity of data is needed to perform credible studies, and it is often divided into *1) internal validity (study population)* – study design and statistics and, 2) *external validity (generalisability)* – requires internal validity for the ability to generalise and is dependent on study population and design. High *internal* validity indicates few systematic biases and a high statistical precision. In our cohorts, papers I-IV, the precision might be considered high, with a low frequency of *random errors* – where a repetition with similar study design, cohorts and based on the same registry a likewise outcome could be assumed indicating a high validity. However, there is still a risk of *systematic bias*, where an inference at any stage of the process might lead to results that systematically deviate from the true values because of *selection bias, misclassification,* or *confounding.*

5.1.2 Precision

With large cohorts, the risk for impact of *random errors* decreases and there might be conditions for high *precision (reproducibility)*. Furthermore, with a validated registry such as SOReg, the risk for *random error* might be considered low, this is especially true for paper I and II. Where the risk of *random error,* also were reduced through the use of sensitivity analyses in paper III and IV. Due to the pure size of the cohorts in all our studies, the risk of *random errors* could be considered low, as well.

Related to precision are t*ype 1 errors (α -error)* - reject the null hypothesis incorrectly (level of significance), and *type 2 errors (β-error)* - accept the null hypothesis incorrectly (power). A *type 1 error* might be considered in *paper I,* since there may be no association between preoperative weight loss and postoperative weight loss, instead be explained by the fact that we only studied those who followed recommendations (recommended diet and follow-up). A *type 2 error* is possible in *paper II* where the rate of complications might be higher because our results could partly be explained by selection bias, i.e. the process of selecting those over 60 is skewed (only the most physically fit are selected for surgery), which might also be applied to *paper III and IV*. The risk of a *type 2 error* must, despite this, be considered as low due to the large size of the cohorts, even for the age groups up to 70 years, especially for studies two to four.

5.1.3 Selection bias

There is a risk for selection bias in all our studies, where a comparison between different types of surgical treatment and/or strictly conservative treatment could lead to different results. For example, although all patients voluntarily chose to be operated with bariatric surgery in general, we only selected those who received gastric bypass surgery, which might have an impact in our results. A different outcome cannot be ruled out if sleeve gastrectomy had been chosen. Moreover, with loss to follow-up, the risk of inducing a selection bias must be considered since only patients reaching one, two, and five years were included in the analyses. The sensitivity analyses in papers III and IV were conducted to address this problem, showing similarity between groups with and without five year follow-up. On the other hand, in *paper I,* all patients with two years' data were included, and with a total number of patients of > 9,000 patients the risk of selection bias might be considered low. Most of the patients in *paper II* (n > 47,000) reached six weeks follow-up, and our data indicates complications equal or even better compared to other studies (8, 103), therefore this could indicate a valid selection and near the true values. In the last two studies, *papers III and IV*, there was a significant dropout over time (one, two, and five years) addressed by a sensitivity analysis (see above), which give some support for our conclusion. Throughout, paper II-IV, it is important to consider the premises under which patients ≥60 years were chosen for surgery.

5.1.4 Information bias

Information bias is a measurement or classification error during data collection or registration, where misclassification is usually described as *differential misclassification (the risk of error differs across groups)* or *non-differential misclassification (the risk of error is equal)*. There is always a risk for misclassification and despite a well-validated registry (141) and cohorts of this size (n=9,000–57,000 patients), errors can occur. The validation in SOReg:s is based on random checks, where the most common errors are incorrect registration of weight, height, complication, and/or comorbidity (137, 141). This, taken together, suggests that the risk of information bias may be low in all our papers (I-IV), especially with a registry as well validated as SOReg.

5.1.5 Confounding factors

Confounding factors are of the utmost importance in cohort studies. There might be a common causal factor that affects both exposure and outcome, and that fully or partially explains the relations between those. Three ways of addressing confounding factors is in the study design or analyses, are so called meaningful multiple regression or identification with DAG (Directed Acyclic Graph) or stratification of data. In our studies we have consistently chosen gastric bypass avoiding the problem with stratified surgical procedures, thereby refining both study design and analysis accordingly. The possible confounding factors have been addressed with stepwise logistic modelling with meaningful covariates chosen accordingly. Throughout all papers, the confounders were included logistic regressions. In *paper I,* for instance BMI was considered a confounder, interfering in the analysis of preoperative weight loss and the postoperative outcome. This was addressed both with a regression analysis and by the stratification in percentiles of preoperative BMI. Further selected confounders in *paper I* were age, gender, and diabetes; in *paper II,* they were BMI, gender and diabetes, and *paper III-IV* preoperative weight, smoking, gender, diabetes, and hypertension. In *papers II-IV* a stratification was performed regarding age into different age groups, which made a comparison between different ages and outcomes possible.

5.1.6 Generalisability

With addressed internal validity, the condition for external validity exists in our material, although there is some concern regarding selection bias, the possibility to generalise is given.

5.2 General discussion

In the first paper (I), an association between pre- and postoperative weight loss up to two years after surgery was found. One difficulty is the definition of weight loss and our choice was weight loss as the percentage of total body weight, due to it is relative uniformity in relation to different degrees of preoperative BMI (compared to percent excess weight loss or BMI-loss, – with a wider variation between different BMI categories). Nowadays a preoperative low caloric diet (LCD/VLCD) is usually considered mandatory before bariatric surgery (6, 84, 137), at least in Sweden, although both positive (142-146) and negative (147-150) effects have been found between a preoperative weight loss and a postoperative weight development. In two different RCTs, there was no difference in the postoperative weight loss between those assigned to preoperative diet and those without diet restrictions (151). In our material the most pronounced effect of a preoperative weight loss was seen in the patients in the higher range of BMI (>45.7 kg/m^2), with the highest odds ratios compared reference. Although no causality relation can be established, this suggests a "dose-response" relationship between pre- and postoperative weight loss. The reason for a better postoperative weight loss for the groups with a better preoperative loss in weight is not fully understood. However, the results after surgery must not necessarily be explained by the fact that those patients are more prone to follow recommendations and procedures, but rather a result of the preoperative weight loss itself.

In the second paper (II), we found a low rate of complications and mortality at 30 days after surgery, although there was age-increased risk. This is in line with previous findings (102, 152, 153). For almost all surgical complications, the risk was increased from the age of 50 years, whereas for medical complications the increase was noted from 60 years and upwards. The fact that the group of patients over 60 constitutes of a small number of probably highly selected patients might explain the non-significance numbers in odds ratios for complications compared to, for example the age group 50-54. The relatively low frequency (8.4%) of complications, compared to other studies (106, 152, 154), might partly be explained by the increasing volumes of bariatric surgery and the improvements in laparoscopic techniques over time. Even mortality rates of 0.03% in the total cohort of our material, and 0.14% for those over 60, is low compared to other reports (103, 104, 152, 155, 156), which regarding the elderly might lead to a selection problem (bias). Although a selection bias might constitute a problem, it should be emphasized that despite the current conditions in choosing elderly (≥ 60) individuals for bariatric surgery, our results indicates that it must be considered safe.

In the third paper (III), we found that older patients (≥ 60) also have a marked and sustained improvement in obesity-related comorbidities after RYGB. Most age groups display a slightly increased prevalence of various comorbidities between years two and five after surgery, although the pattern is relatively constant between age groups, indicating a probability for "relapses". Older patients show a substantial improvement in obesity-related diseases. These results could be hampered by the fact that older individuals have probably been under medical treatment for a longer duration and with higher doses compared to the younger patients. The odds ratios for resolution of most comorbidities in the range of 30-50% (compared to the total cohort) indicates an age-specific difference, where a correlation between the duration of diabetes type 2 and resolution after surgery is known (157). The outcome for hypertension after bariatric surgery is modest, even compared to others (158), with lower remission rates for elderly compared to younger patients. However, an improvement even for the elderly must be considered due to a lower use of medication. For dyslipidaemia and OSAS, a similar pattern to other studies is seen, with a reduction five years after operation, even for those over 60. No obvious relation to depression between ages is seen (159), and in line with other studies, the effect of surgically induced weight loss on depression seems to be modest (160, 161).

In the fourth paper (IV), health-related quality of life measurements, SF-36 and OP, improved for older individuals almost in the same range as younger ones. Further, our material confirms the known beneficial effects of bariatric surgery, in especially in the physical aspect of health-related quality of life, even for older individuals. However, the mental aspect (MCS) had more of a short duration improvement (<2 years), also described by others (125, 162, 163). The physical aspect of health-related quality of life, mostly addressed by PCS and OP, where a more pronounced and maintained effect up to five years after surgery was noticed. Obesity and its consequences on the mental aspects of health-related quality of life with stigmatisation is well known (50, 126, 163), as well as the correlation to anxiety and depression compared to a normal population (163), where conservative strategies have inferior outcomes compared to bariatric surgery both in the short and long run (123, 124, 126, 164). The mental aspect could probably be summed up in "you are the same person in the long run", though no obvious difference between elderly and younger patients was shown up to five years after the operation.

5.3 Clinical implications

No absolute causality has been demonstrated between age and outcome after bariatric surgery in relation to complications, comorbidities, and health-related quality of life, furthermore an association between preoperative weight loss and postoperative outcome of weight has been shown.

Patients with compliance to the preoperative diet and a preoperative weight loss might have a better postoperative outcome regarding weight loss. One important observation is that patients in higher ranges of BMI have the most pronounced effect regarding weight loss after surgery, indicating that compliance might not be the sole explanation. Together with the knowledge of reduced perioperative complications after a preoperative weight loss, this emphasizes the importance of following those recommendations with the positive consequence of a safer surgery and better outcome.

Further, the risk of severe complications and mortality for older patients are slightly increased compared to younger individuals after surgery, or in the same range. Comorbidities, although to a somewhat lower extent than for younger patients, for individuals over 60 display major benefits in terms of resolution up to five years after gastric bypass, with improvement in health-related quality of life for older individuals as well.

When we sum up the risk of morbidity and mortality, and correlate this to the beneficial effects on comorbidities and health related quality of life, older patients (≥ 60 years) should not be denied bariatric surgery based solely on chronologic age.

6 Conclusions

With the use of a preoperative low calorie diet and a subsequent weight loss, we saw a better maintained weight loss up to two years after surgery. Individuals with the highest BMI levels showed an even better outcome. These findings are in line with previously reports of reduced risk of complications after a preoperative weight loss.

The elderly (≥ 60 years) have a slightly increased, but still acceptable, risk for complications and mortality compared to younger patients after gastric bypass.

The elderly (≥ 60 years) have a good resolution, of obesity-related comorbidities, such as diabetes, hypertension, dyslipidaemia, OSAS and depression up to five years after gastric bypass.

The elderly (≥ 60 years) experience beneficial effects regarding health-related quality of life, to the same extent and often comparable to younger individuals, up to five years after gastric bypass.

The elderly (≥ 60 years) experience the beneficial effects of gastric bypass and should therefore not be denied surgery as an alternative for the treatment of obesity.

7. Future perspectives

This thesis is partly based on previous work in preoperative weight loss and outcomes thereafter, as well as the Swedish guidelines for those over 60 to obtain bariatric surgery. Our results imply that a preoperative weight loss has advantage before bariatric surgery, and older individuals over 60 experience the beneficial effects of bariatric surgery with slightly increased, but acceptable risk. This undoubtedly creates new questions that need to be addressed in further studies.

Of interest is the outcome over time after a preoperative weight loss before bariatric surgery, especially regarding comorbidities and health-related quality of life over time. Nevertheless, there is still an uncertainty regarding the underlying mechanism for the effects of a preoperative diet; is it possible to find a sufficient explanatory model? Does the outcome after a preoperative weight loss in sleeve gastrectomy differ compared to after gastric bypass?

Finally, is there any upper age limit for bariatric surgery? How do elderly patients over 70 respond to bariatric surgery – both in the short as well long term? Should surgical strategies vary between older and younger individuals (for example sleeve gastrectomy vs gastric bypass), and do those strategies affect outcomes regarding complications, comorbidity, and health-related quality of life?

Tentative future research questions could therefore be:

- does a preoperative weight loss have an effect on comorbidity after bariatric surgery?
- is there an age limit – exceeding 70 years?
- different bariatric methods – for those over the age of 60 years?
- should selection strategies differ between older and younger patients?

8. Populärvetenskaplig sammanfattning

Globalt föreligger sedan länge en pandemi med fetma där kirurgi som behandlingsmetod visat sig vara överlägsen andra metoder. I princip all kirurgi mot fetma som genomförs i Sverige registreras i det skandinaviska registret för obesitaskirurgi, SOReg (Scandinavian Obesity Surgery Registry). Inför kirurgi mot fetma, så rekommenderas i Sverige, såväl som internationellt, en viktnedgång, vilket också visat sig ge fördelar både avseende utförandet av själva kirurgin och minskad komplikationsrisk. Det är oklart om denna rutin gynnar viktutveckling över tid. Vidare har en osäkerhet förelegat kring behandling av patienter över 60 år med kirurgi mot fetma, vilket baseras på de i Sverige gällande riktlinjerna. Trots denna osäkerhet har över 3000 bariatriska ingrepp (operationer) genomförts inom denna patientgrupp sedan starten av SOReg. Vi har därför valt att studera ålderns betydelse för utfallet efter fetmakirurgi (gastric bypass) med avseende på komplikationer, samsjuklighet och hälsorelaterad livskvalitet.

Utifrån rekommendationen kring en viktnedgång före operation, så har vi studerat hur detta påverkar utfallet beträffande viktnedgång efter kirurgi (delarbete I). Vi fann att de med största viktnedgång inför operation liksom de allra tyngsta (högst BMI), uppvisar den bästa viktnedgången upp till två år efter kirurgi. Avseende riskerna vid kirurgi mot fetma så ökar dessa med stigande ålder, men är i jämförelse acceptabla även för de över 60 år. Dessutom ökar riskerna snarast redan från 50 års ålder (delarbete II). Därutöver verkar äldre ha god effekt på fetma-relaterad samsjuklighet i form av förbättring (minskad sjuklighet) i diabetes, högt blodtryck, höga blodfetter, sömnapné och behandlad depression (delarbete III), om än inte i lika hög utsträckning som yngre. Äldre uppvisar också en god effekt efter kirurgi mot fetma på hälsorelaterad livskvalitet (SF36 - MCS o PCS, och OP) i paritet med yngre individers (delarbete IV).

Sammantaget kan fetmakirurgi rekommenderas till individer över 60 år med god effekt på samsjuklighet och livskvalitet med acceptabla risker. Vidare verkar en viktnedgång före kirurgi mot fetma, i enlighet med minskad risk, vara gynnsamt för en bibehållen viktnedgången efter operation.

9. Acknowledgements

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