Upper Gastrointestinal Research
Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

EFFECTS OF BARIATRIC SURGERY

Magdalena Plecka Östlund

Stockholm 2012

All previously published papers were reproduced with permission from the publisher.

The picture is reprinted with the kind permission from Jon Berkeley.

Published by Karolinska Institutet. Printed by Repro Print.

© Magdalena Plecka Östlund, 2012
ISBN 978-91-7457-621-4

Kunskap förändrar

Till Andreas, Bianca, Adrian och Junie

ABSTRACT

Globally, 500 million people are obese (body mass index [BMI] ≥30). In Sweden, 14% of the population is obese. Obesity is associated with an increased risk of mortality, cancer and several co morbidities. Bariatric surgery is the only treatment with documented long-term benefits, i.e. decreased mortality and co morbidities and sustainable weight loss.

The aim of the thesis was to clarify effects of clinically relevant aspects of bariatric surgery and make comparisons with the general population of corresponding age, sex and calendar period. The included studies are nationwide Swedish population based retrospective cohort studies, comparing defined outcomes before and after bariatric surgery.

Study I tested the hypothesis that the risk of obesity-related cancer decreases with increasing time after bariatric surgery. It included 13,123 patients who had undergone bariatric surgery in 1980-2006 in Sweden. Standardised incidence ratios (SIR) were calculated to assess risk. There was no overall decreased risk of cancer with increasing time after bariatric surgery (p for trend 0.4). Rather, the risk of colorectal cancer was increased with time after bariatric surgery (p=0.01).

In study II, the risk of in-hospital care for obesity related diseases before and after bariatric surgery in 13,273 patients during 1980-2006 was compared to a matched random sample of 132,730 individuals from the general population. Preoperative incidence rate ratios (IRR) and postoperative hazard ratios (HR) were calculated. The postoperative risk of diabetes, myocardial infarction, hypertension, stroke and angina remained increased compared to the general population. The risk estimates for diabetes (HR 1.2, 95% CI 0.9-1.7) and myocardial infarction (HR 0.8, 0.4-1.5) were lower after gastric bypass than after restrictive bariatric procedures (HR 2.8, 96% CI 2.5-3.1 and HR 1.6, 95% CI 1.4-1.9, respectively).

Study III assessed whether cholecystectomy is indicated as part of the bariatric surgery due to the known increased preoperative risk of gallstone formation. The need for cholecystectomy in a bariatric surgery cohort (n=13,443) during 1987-2008 was compared to the general population, and to two cohorts of patients who had undergone antireflux surgery (n=16,176) or appendectomy (n=154,751). An increased need for cholecystectomy after bariatric surgery was confirmed (SIR 5.5, 95% CI 5.1-5.8), but the absolute rate of cholecystectomy was low (8.5%) and the increased SIR after antireflux surgery (SIR 2.4, 95% CI 2.2-2.6) and appendectomy (SIR 1.7, 95% CI 1.6-1.7) indicated detection bias.

Study IV addressed the risk of hospital admission for psychiatric disorders, including substance- and alcohol abuse, before (IRR) and after (HR) bariatric surgery was compared to such admissions of the general population. The bariatric surgery cohort (n=12,277) during 1980-2006 was compared to a matched sample from the general

population (n=122,770). Patients undergoing bariatric surgery were more likely to be hospitalised for all studied diagnoses prior to surgery compared to the general population, e.g. IRR of depression was 2.8 (95% CI 2.5-3.0). After gastric bypass, there was an increased risk of inpatient care for alcohol abuse compared to those undergoing a restrictive surgical procedure (HR 2.3, 95% CI 1.7-3.2).

To conclude, bariatric surgery might not entail any reduced risk of obesity-related cancer with increasing time after surgery. The need for cholecystectomy following bariatric surgery was increased, but prophylactic cholecystectomy might not be generally recommended. Gastric bypass surgery seems to reduce the risk of inpatient care for diabetes and myocardial infarction, but increase the risk of inpatient care for alcohol abuse as compared to restrictive bariatric procedures.

LIST OF PUBLICATIONS

I. Magdalena Plecka Östlund, Yunxia Lu, Jesper Lagergren.

Risk of obesity-related cancer after bariatric surgery in a population-based cohort study.

Ann Surg *2010 Dec;252(6):972-6*

II. Magdalena Plecka Östlund, Richard Marsk, Finn Rasmussen, Jesper Lagergren, Erik Näslund.

Morbidity and mortality before and after bariatric surgery for morbid obesity compared to the general population.

Br J Surg *2011 Jun;98(2):811-6*

III. Magdalena Plecka Östlund, Urs Wenger, Fredrik Mattsson, Fereshte Ebrahim, Abrie Botha, Jesper Lagergren.

The need for cholecystectomy after bariatric surgery: A population-based cohort study.

Br J Surg *(in press)*

IV. Magdalena Plecka Östlund, Olof Backman, Richard Marsk, Dag Stockeld, Jesper Lagergren, Finn Rasmussen, Erik Näslund.

Increased alcohol dependence after gastric bypass surgery.

Submitted manuscript

TABLE OF CONTENTS

1 Introduction - obesity

1.1 Background 1
1.2 Definitions 1
1.3 Causes 2
1.4 Effects on health 3
  1.4.1 Co morbidity 3
  1.4.2 Mortality 6
1.5 Treatment 6
  1.5.1 Non-surgical treatment 6
  1.5.2 Surgical treatment 7
    1.5.2.1 Complications 12
    1.5.2.2 Weight outcome after surgery 14
    1.5.2.3 Postoperative mortality 15
2 Aims of the studies 17
3 Material and methods 19
3.1 Data Registers 19
  3.1.1 The National Patient Register 19
  3.1.2 The Cancer Register 19
  3.1.3 The Causes of Death Register 20
  3.1.4 The Register of the Total Population 20
  3.1.5 Population and Housing Censuses 20
4 Overview of the four studies 21
5 Statistical analyses 23
5.1 Standardised incidence ratios 23
5.2 Incidence rate ratios 23
5.3 Cox proportional hazards regression 23
6 Results 25
6.1 Study I 25
6.2 Study II 26
6.3 Study III 27
6.4 Study IV 28
7 Discussion 31
7.1 Methodological considerations 31
7.2 Population-based 31
7.3 Unexposed comparison cohorts 32
7.4 Sources of error 32
7.5 Validity 34
7.6 Statistical hypothesis testing 34
8 Findings and implications 35
9 Future perspectives 37
10 Conclusions 39
11 Populärvetenskaplig sammanfattning 41
12 Acknowledgements 45
13 References 49

LIST OF ABBREVIATIONS

AGB	Adjustable gastric banding
BPD + DS	Biliopancreatic diversion with duodenal switch
BMI	Body mass index (kg/m2)
CI	Confidence interval
CT	Computed tomography scans
DVT	Deep venous thromboembolism
EU	European Union
FTO	Fat-mass- and obesity-associated gene
GBP	Gastric bypass
GWAS	Genome wide association study
HR	Hazard ratio
IASO	International Obesity Taskforce
ICD-codes	International Classification of Diseases codes
IGF-1	Insulin-like growth hormone-1
IL-6	Interleukin-6
IRR	Incidence rate ratio
JIB	Jejunoileal bypass
MetS	Metabolic syndrome
NPR	National Patient Register
N	Number
NBHW	National Board of Health and Welfare (Socialstyrelsen)
NHD	The Department of Nutrition for Health and Development
PE	Pulmonary emboli
PIN	Personal Identity Number
PPI	Proton pump inhibitors
RR	Relative risk
SG	Sleeve gastrectomy
SIR	Standardized incidence ratio
SOS	Swedish Obese Subjects study
SOReg	Scandinavian Obesity surgery registry
SCB	Statistics Sweden (Statistiska centralbyrån)
T2DM	Diabetes mellitus type 2
TNF-α	Tumour necrosis factor-alpha
VBG	Vertical banded gastroplasty
v.s	versus
WHO	World Health Organization

1 INTRODUCTION – OBESITY

1.1 Background

It is no longer novel that overweight and obesity (body mass index [BMI] >25 and 30kg/m^2, respectively) among adults is a rapidly growing health problem worldwide, including Sweden. Globally, obesity has more than doubled since 1980 and is presently the fifth leading risk of death.[1] The co morbidities of overweight and obesity kill at least 2.8 million adults worldwide each year[1] and seem to reduce the average life expectancy by 22%.[2] The umbrella organization for worldwide obesity research, the International Obesity Taskforce (IASO), estimates in a new analysis from 2010 that 600 million adults are obese worldwide.[3] The World Health Organisation (WHO) has estimated that the attributed burden due to overweight and obesity is 44% for diabetes, 23% for ischemic heart disease and 7% to 41% for certain cancer types.[1]

In Sweden, approximately 50% of all men and 33% of all women aged 18-64 years are overweight or obese. This degree of overweight has remained stable for men and women since 2004, and 2008, respectively. About 14% of both men and women are obese, which reflects a more than 50% increase from 1980 to 2010.[4,5] The prevalence of overweight and obesity is still low in Sweden relative to other industrialised countries, however it is increasing in all age groups.[6] A study of morbid obesity in male Swedish conscripts indicates a 10-fold increase during the period 1969-2005.[7]

In the USA, the prevalence of obesity (BMI >30) has increased by 24% from 2000 to 2005. The prevalence of severe obesity, i.e. BMI over 40 and 50 has increased alarmingly by 50% and 75% respectively, during the same time period.[8] Overweight and obesity in adults are more common in groups with low socioeconomic status[9] and a shorter education.[9,10]

Studies have shown that children from low income families are more obese than their higher income counterparts, and that obesity prevalence decreases as the educational level of the head of the household increases.[11] A striking fact is that obesity is not easily preventable due to its complexity.

1.2 Definitions

When authorities began to realise there was a global epidemic increase of overweight and obesity, the term "globesity" emerged, emphasising the need to monitor and compare present and future weight development worldwide. The Department of Nutrition for Health and Development (NHD) at the WHO developed the WHO Global

Database on BMI to facilitate the monitoring of internationally comparable overweight and obesity numbers in a standardised manner.[12]

Consequently, BMI is currently frequently used to measure overweight and degree of obesity. Although BMI has limitations (it might not be accurate in measuring muscular or elderly [>65 years of age][13] individuals, and does not assess body fat distribution) it is non-invasive, easy to use and readily assessed.

BMI is calculated by dividing the individual's weight in kilograms by the square of their height in meters. A BMI≥25 is considered overweight, while obesity is defined as a BMI≥30. The terms "morbid obesity" and "super obese" are often used in clinical practice for people with BMI exceeding 35 and 50, respectively.

Since the estimation of BMI is predominantly based on the Caucasian populations the applicability of the cut-off points on other, non-Caucasian populations e.g. South Asians, has been discussed. Alternative measures such as waist-to-hip ratio, waist-to-height ratio and waist circumference focus on central adiposity and have been suggested to be particularly valuable in predicting cardiovascular risk. However, evidence is conflicting as to which measurement is best for predicting subsequent cardiovascular risk.[14]

In the 1950s, the American Metropolitan Life Insurance Company constructed ideal weight- and height tables for men and women. Excess body weight and excess body weight loss are often calculated based on these tables in American studies.[15] The WHO definition of BMI is presented in Table 1.[16]

Table 1 Classification of body mass index according to WHO.

Body mass index	***Classification***
18,5-24,9	Normal weight
25-29,9	Overweight
30-34,9	Class I obesity
35-39.9	Class II obesity
≥40	Class III obesity
≥50	"Super obese"

WHO=World Health Organisation

1.3 Causes

The aetiology of obesity is multifactorial; there are genetic and hereditary factors, but lifestyle and environmental changes are also important. In the past few years, the discovery of several genes associated with obesity has been made possible due to genome-wide association studies (GWAS),[17] through which a variant in the fat-mass- and obesity-associated (FTO) gene was identified.[18] It has been estimated that 16% of all adults, who are homozygous for the risk allele weigh 3kg more and are more likely to develop obesity than those without the allele. Despite the success of GWAS only about 20 genes are found to account for less than 5% of all monogenetic cases of severe obesity.[19]

It is suggested that the genetic predisposition might be of importance since not all individuals living in a so-called "obesogenic" environments become obese.[20] The implementation of these findings may finally result in genetic risk profiling and more customised therapeutic interventions, however this is not likely to be seen in the near future. An emerging body of evidence suggests that the response to metabolic challenges in postnatal life may be linked with environmental influences during foetal development.[21] A high maternal BMI in pregnancy and an above average BMI in childhood predispose of obesity in adulthood.[22]

Our lifestyle in general has changed dramatically over the last decades with increased sedentary behaviour, less manual work and less daily physical exercise. Food, being served in larger portions[23,24] with higher caloric density because of high fat content,[25] is now available virtually anywhere at any time. A slight imbalance between food intake and energy expenditure will result in a small increase of body mass over time, which ultimately will develop into overweight and obesity.[26]

There are several studies suggesting that the built environment can determine the exposure of risk factors for obesity. The availability of supermarkets is associated with a lower BMI, while availability of convenience stores is associated with a higher BMI.[27] There are fewer fast food chains, bars and convenience stores in wealthy neighbourhoods compared to poorer. Access to private transport is less common in poor neighbourhoods, which reduces the possibility of choosing cheaper and healthier foods available in supermarkets.[28] On the contrary, each additional hour spent in the car is associated with a 6% increase in the likelihood of obesity, while any kilometre walked per day is associated with a 5% decrease.[29]

1.4 Effects on health

Several co morbidities accompany obesity with different strengths of association. Far from all are included in this thesis, e.g. reduced fertility, obstructive sleep apnoea, pain in weight-bearing joints and gastro-oesophageal reflux, however other co morbidities are discussed in some more depth.

1.4.1 Co morbidities

A common co morbidity associated with obesity is ***diabetes mellitus type 2*** (T2DM).[30] The estimated prevalence of diabetes among adults worldwide was 285 million in 2010. By 2030 diabetes is expected to affect 439 million people.[31] T2DM seems to increase with the rising level of obesity.[32] The pathophysiology of T2DM and obesity is complex, but put simply, insulin sensitive tissues such as fat and muscle have the ability to store glucose whereas in prediabetes, when peripheral insulin resistance is present, this ability is impaired. The islet ß cells of the pancreas compensate for this by increasing insulin production. When this fails, T2DM develops.

After bariatric surgery (also called weight loss surgery, obesity surgery or metabolic surgery) for obesity most individuals improve or resolve obesity-related co morbidities such as T2DM. A recent review of 621 studies showed that diabetic patients had an overall 78% resolution, and 87% of cases of diabetes were either improved or resolved two years after bariatric surgery.[33] Patients who underwent biliopancreatic diversion/duodenal switch had the greatest percentage of such resolution (95%), followed by gastric bypass (80%), gastroplasty (80%) and adjustable banding (57%).[33] These remarkable effects on diabetes in obese patients have initiated the interest for surgical treatment for diabetic patients with a BMI<35, when traditional pharmaceutical treatment is insufficient for good metabolic control. [34,35]

The prospective Swedish Obese Subject study (SOS) compared conventional obesity treatment with surgical treatment, and reported an increase in glucose and insulin levels in the non-surgically treated patients, whereas an overall decrease was seen in the surgical group after 2 and 10 years of follow up.[36] The effect on diabetes resolution after surgery is not clear, but a possible endocrine mechanism has been suggested as an increase in gut hormones, known to effect glucose metabolism, is seen before a significant change in BMI takes place.[37,112]

High blood pressure is another common co morbidity linked with obesity. In a large American health survey, high blood pressure was the most common co morbidity in obese people, demonstrating an increase with escalating weight status.[32] The rise in blood pressure with obesity is explained by the release of angiotensinogen (a precursor of angiotensin) by the adipocytes, an increase in blood volume with the gain of body mass, and in response to a rise in blood viscosity. Adipocytes change the viscosity of the blood by releasing profibrinogen and plasminogen activator inhibitor 1, which may impair the fibrinolytic process.[38] A 10-year follow-up of women in the Nurses' Health Study and men in the Health Professionals Follow-up Study showed a relative risk of developing high blood pressure of 2.3 for women and 3.0 for men with a BMI of ≥35 compared with normal weight (BMI ≤25).[39] A meta-analysis of 134 studies found that approximately 62% and 79% of the cases achieved resolution or improvement in blood pressure after bariatric surgery, respectively.[40]

For a long time it has been clear that obesity is an independent risk factor for ***cardiovascular disease***.[41] Furthermore, obesity is associated with significantly increased cardiovascular related mortality.[42] The SOS study reported that the most common causes of death from cardiovascular disease in obese individuals were myocardial infarction, sudden death, and cerebrovascular damage.[43,44] Deaths in coronary artery disease events were reduced by 56% after bariatric surgery among operated patients as compared to non-operated controls.[45] The most recent report from the SOS study, with a mean follow-up time of 15 years, showed a reduced incidence of cardiovascular deaths and cardiovascular events in the surgically treated group.[46]

The ***metabolic syndrome*** (MetS) is a cluster of disorders that directly increase the risk of coronary heart disease, other forms of cardiovascular atherosclerotic diseases and T2DM. MetS comprises dyslipidaemia, elevated arterial blood pressure, deregulated glucose homeostasis, abdominal obesity or insulin resistance. There is, however, no general consensus regarding a strict definition of MetS.[47]

The World Cancer Research Fund and American Institute of Cancer Research reviewed the evidence for the association between obesity and ***cancer*** in 2007, and found convincing evidence for an increased risk of oesophageal adenocarcinoma, pancreatic-, colorectal-, postmenopausal breast- and kidney cancer.[48]

The mechanism of cancer genesis associated with obesity is not fully understood, but the hypothesis focuses primarily on metabolic and endocrine changes; in obesity the adipocytes produce increased levels of adipocytokines i.e. tumour necrosis factor- alpha (TNF- α), leptin and interleukin-6 (IL- 6), which have several different functions but seem to increase an unfavourable inflammatory state. Furthermore, adipocytes synthesise oestrogen in both men and women. The increase in release of sex hormones is linked to cancer. High concentrations of insulin-like growth hormone-1 (IGF-1) are seen in obese individuals. It is a peptide, which regulates cell proliferation, differentiation and inhibits apoptosis, which may contribute to tumour genesis.[49,50]

There are a number of studies highlighting the increasing numbers of different cancers associated with increasing BMI.[51-55] An increase of 5kg/m^2 in BMI, which is about 15kg for men and 13kg for women with an average BMI of 23, has been found to be strongly associated with oesophageal adenocarcinoma (relative risk [RR] 1.5), thyroid- (RR 1.3), colon- (RR 1.2) and renal cancer (RR 1.2), while a weaker positive association (RR < 1.2) has been found for rectal cancer, malignant melanoma, multiple myeloma, leukaemia, and non-Hodgkin lymphoma in men. In women, the association was strong for oesophageal adenocarcinoma (RR 1.5), endometrial- (RR 1.6), gallbladder- (RR 1.6), and renal (RR 1.3) cancer while a weaker positive association (RR < 1.2) was found for postmenopausal breast-, pancreas-, thyroid-, colon cancer, multiple myeloma, leukaemia, and non-Hodgkin lymphoma.[53]

About half of all the postmenopausal cancer cases among women in the United Kingdom seem to be attributable to overweight and obesity.[52] Excess body mass (BMI >25) accounts for about 5% of all cancers in the European Union (EU). By reducing the prevalence of overweight and obesity by 50% in the EU some 36,000 cancer cases could be avoided.[56]

Since substantial and sustained weight loss can be hard to achieve (without bariatric surgery), large epidemiologic data on the relation between weight loss and cancer are sparse. However, some cohort studies have reported an inverse association between weight loss and colon-,[57] postmenopausal breast-,[58] and non-metastatic high-grade prostate cancer.[59] There are data suggesting a reduction in cancer incidence in patients after bariatric surgery compared to non-operated controls.[60,61] The SOS study found a lower number of first-time cancer in the bariatric surgery cohort after inclusion in the study, in women but not in men.[62] Cancer specific mortality has been reported to decrease by 60% among operated obese patients compared to non-operated obese controls.[45]

1.4.2 Mortality

In light of the burden of the co morbidities accompanying obesity, it is not surprising that mortality is elevated in this condition. Death from all causes is increased in both sexes with a high BMI.[63,64] In the group with BMI>40 the relative risk of death were 2.6 for men and 2.0 for women compared to those with a BMI of 24-25. A significant risk of death from cardiovascular disease was found in all groups with a BMI>25 for women, and a BMI>27 for men.[65] For every 5kg/m^2 gained above BMI 25kg/m^2, the overall mortality is increased by an average of 30%.[66] The increased risk of BMI-related mortality tends to be greater in younger individuals, but the risk is increased for both men and women up to 75 years of age.[67] Several studies have shown a decrease in mortality after bariatric surgery compared with non-operated controls.[43,45,68-70] The BMI level associated with the greatest chance of longevity seems to be 23-25 for whites.[2] A 20 year old white man who is expected to live until the age of 78 is predicted to lose 13 years of his life if his BMI is >45.[2]

1.5 Treatment

1.5.1 Non-surgical treatment

Weight loss can be accomplished through a combination of physical activity, lifestyle modifications (diet) and drug treatment. All these options are difficult to adhere to, even for individuals of normal weight, and have a limited long-term effect.[71,72]

It appears that a modest amount of ***physical activity***, i.e. walking 30 minutes per day, may prevent weight gain. More exercise seems to increase weight loss even in the absence of reduced calorie intake. The effect of exercise quantity is established, but the effect of exercise intensity is not clear. There is a greater need for physical activity in the absence of dietary changes.[73] A randomised controlled study showed a dose-response association in weight and fat loss in groups with low-amount and high-amount exercise, while weight gain was found in not exercising controls.[73] The groups were instructed not to changes their diet. The results imply that sedentary overweight individuals would have to walk or jog 10-11 kilometres each week to prevent weight gain. It is considered that most individuals can achieve the low-exercise goals by walking for 30 minutes per day or jogging for 20 minutes per day.[73]

Lifestyle modifications or interventions usually include various diets with or without behavioural therapy. Weight loss ranging from -0.5 to -12kg is achieved by changes of dietary patterns suggested by i.e. Weight Watchers, low-fat non-reducing diets and meal replacements diets.[74] Studies of long-term lifestyle interventions are few and heterogeneous, making it difficult to generalise about the effectiveness. However, the conclusion in a recent systematic review was that diet alone and combined with exercise or behavioural therapy resulted in weight loss, improvement in metabolic syndrome (see page 5) and diabetes compared to no treatment controls for at least 2 years.[74]

Medical treatment is considered suitable for individuals with a BMI≥30, or a BMI≥27 combined with a co morbid condition, providing the individuals are unable to lose weight with lifestyle changes alone.[75]

The European Agency for the Evaluation of Medicinal Products suggests a placebo-subtracted weight loss of 10% for new drugs.[76] However, this has not been a requirement for drug approval and none of the drugs available on the market today meets these requirements.[77]

The only anti-obesity drug available in Sweden today is orlistat (Xenical®, Alli®). It is an inhibitor of gastrointestinal lipases, which prevents the intestinal absorption of ingested fat and is administered three times per day with meals. Its disadvantages include the adverse effects of fatty stools, faecal urgency and oily spotting occurring in 15-30% of cases.[78] Regardless of the amount of fat in the diet, the average percentage of inhibited fat absorption is not more than 36%.[79] The Swedish XENDOS study demonstrated improved weight loss (6kg versus 3kg) and reduction in T2DM incidence in the group receiving orlistat in combination with lifestyle changes, compared to a placebo combined with lifestyle changes over a 4-year period.[80] A recent meta-analysis showed an average weight reduction of 3kg among orlistat users compared to a placebo users.[78] To date, there are no large-scale studies that support a long-lasting effect of medication on obesity-related co morbidities.[81]

1.5.2 Surgical treatment

History

The name bariatric surgery derives from the Greek root *bar- ("weight")* and suffix *–iatr ("treatment")* and *–ic ("pertaining to")*. The history of surgical treatment for obesity started in the 1950s. The initial intestinal bypasses in the form of jejunocolic shunts were afflicted with severe complications such as liver conditions, electrolyte depletion, vomiting and anorexia.[82,83] The intestinal continuity was restored when the desired weight was achieved or when the complications became too severe. However, all the patients re-gained weight after restoring the continuity to the same level as before surgery, and this is why the technique was definitely abandoned.[84] Another technique that was used in the 1960s and early 1970s was the jejunoileal bypass, but it was also abandoned due to life threatening complications (described below). An American surgeon from the University of Iowa, Doctor Edward Mason, further developed the bariatric procedure by performing surgical stapling of the upper part of the stomach, thus creating a smaller pouch, which resulted in a reduced amount of food intake. Using a band to decrease the stomach size further developed this procedure.

Trends

The use of bariatric surgery has increased dramatically during recent years as a result of the increasing prevalence of obesity in combination with a lack of adequate non-surgical treatment alternative. Worldwide, the use of bariatric surgery has increased by 761% during a 10-year span from 1998 to 2008.[85] The most recent worldwide update on bariatric surgery estimated that during 2008, 4,680 surgeons performed 344,221 bariatric surgical procedures, and in the USA or Canada, 222,000 operations were performed by 1,625 surgeons.[85] In Sweden, approximately 700 bariatric procedures were performed in 1998 according to the National Patient Register. In 2010, the number was approximately 8000 as recorded in the Scandinavian Obesity surgery Register (SOReg).[86] This number of annual operations does not seem to meet the demand, and the updated Swedish NIOK report from 2009 estimated that 15,000 surgical procedures would be required annually in the coming years.[87]

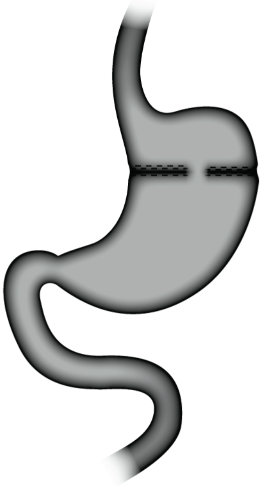
Indications

The indication for bariatric surgery in Sweden (as well as internationally) has historically been BMI≥40 or BMI≥35 with a co morbidity.[87] In Sweden, recently published guidelines for bariatric surgery recommend a BMI of 35 with or without co-morbidity for surgery although not all of the county councils in Sweden have accepted this modified BMI limit. Prior to primary bariatric surgery, the patient should have made serious attempts to lose weight. Individuals below 18 years of age are normally not treated surgically other than under strictly controlled conditions e.g. as part of research studies. The recommended upper age limit is 60 years[87,88] however it is suggested that patients over the age of 60 should not be discriminated based solely on their age, and a risk-benefit evaluation is of great importance in this age group.[88,89] One problem is that few controlled studies have addressed the effects of bariatric surgery in the age group over 60 years, which makes evidence-based recommendations difficult. Specific contraindications for bariatric surgery are non-compliant patients with mental or cognitive impediment, malign hyperphagia, on-going alcohol or drug abuse, and severe mental illness not responding to medication.[87] Although obesity is equally prevalent in men as in women, approximately 75% of the surgical candidates are women, which probably reflects that societies have a different view on obesity in men and women.[87,90]

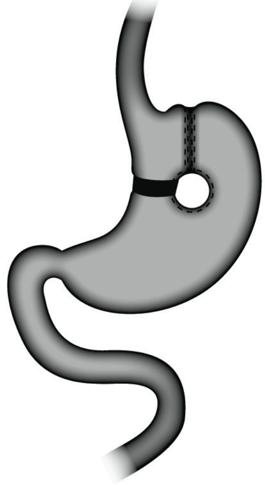
Surgical approach

The laparoscopic approach has with time become more favourable than open access surgery[91], and is now the dominating approach both in Sweden (95% in 2010)[86] and worldwide (>90% in 2008)[85], respectively. The laparoscopic approach reduces the risk of 30-day in-hospital morbidity and mortality compared to open surgery, but it is also associated with shorter in-hospital stay.[91,92] The currently used surgical procedures can be divided in two main categories: restrictive and malabsorptive. In practice there are combinations of the two. Some characteristics of the bariatric procedures are described below:

Restrictive procedures:

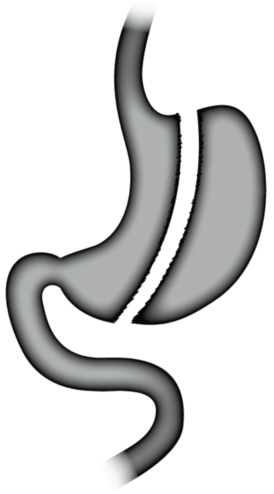


Horizontal gastroplasty is an old surgical procedure, which was abandoned in the 1980s. The stomach was divided into a small upper part and a large remnant by a suture or staple line, with a narrow channel between the pouches.[93] The size of the upper pouch and the width of the channel were modified in different ways,[94] but the failure- and revision rates were still high due to enlargement of the upper pouch, rupture or enlargement of the stoma.[95,96]



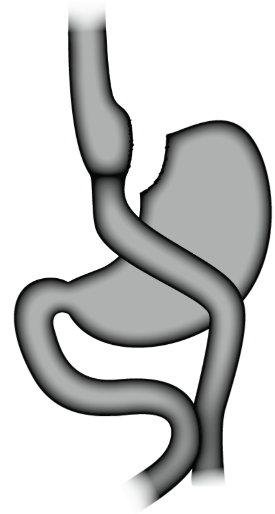
Vertical banded gastroplasty (VBG) represents a purely restrictive procedure where a small stomach pouch is created using a surgical stapling device.[97] A mesh or silicon band between the pouch and stomach remnant reinforces the stoma. The amount of food that can be consumed is limited and dilatation of the upper pouch may result in an earlier satiety, leading to weight loss.[97] Procedure-specific complications include band erosion, gastro-oesophageal reflux, vomiting, (refractory) ulcers, and enlargement of the pouch, stoma stenosis and staple line rupture.[98,99] Stoma stenosis, staple line rupture and insufficient weight loss often result in additional revisional surgery.[99,100] VBG has decreased in popularity because of the common need for revisional surgery and the introduction of gastric bypass, which is superior in terms of weight loss outcomes.[101-103]

Adjustable gastric banding (AGB) involves the placement of a horizontal adjustable band around the upper stomach, thus creating a small pouch. There is a balloon within the band, which can be adjusted by saline injected into a subcutaneous port, which is connected to the balloon. This device makes it possible to regulate the degree of constriction of the gastric pouch. AGB is the most common restrictive bariatric procedure worldwide accounting for 42% of all the weight loss surgical procedures. The trend of using AGB has decreased in Europe from 64% in 2003 to 43% in 2008, whereas in the USA and Canada, it has increased from 9% to 44% during the same time period.[85] There are few AGB being performed in Sweden.[86] AGB is afflicted with complications such as prolapse of the stomach through the band, band slipping, band dilatation, insufficient weight loss, gastro-oesophageal reflux disease and erosion of the band into the stomach wall.[104]



Sleeve gastrectomy (SG) is a more recently introduced procedure, which initially was recommended for super obese patients as a first-stage procedure in order to reduce co morbidities and decrease weight prior to the definite bariatric surgical procedure, e.g. biliopancreatic diversion with duodenal switch or gastric bypass. It is however, currently also being utilised as a primary single operation for obesity.[105] In this restrictive procedure a longitudinal gastrectomy is performed where the fundus is removed, leaving a tunnel-shaped remnant of the stomach with the pylorus left intact. The removal of the fundus seems essential for two reasons: the remaining stomach can easily expand with time after surgery resulting in weight regain if not properly removed, as well as the ghrelin-effect on appetite suppression. Ghrelin is a hormone that stimulates hunger and is produced by the cells lining the fundus.[106,107] Another suggested mechanism of SG on weight loss in SG is the rate of gastric emptying through various mechanisms although results are conflicting.[108] Complications such as gastro-oesophageal reflux are common.[105,109] The popularity for SG is slowly increasing, from 0% of all obesity procedures in 2003 to 5% in 2008.[85] Although, an increase of the procedure has been seen in Europe from 2003 to 2008,[85] it is rarely performed in Sweden.[86] There is a lack of large and long-term studies of SG.[110,107]

Restrictive (mainly) and malabsorptive procedures:



Gastric bypass (GBP) is created by stapling a small gastric pouch of the upper part of the stomach to restrict food intake, to which a jejunostomy is anastomosed. The major part of the stomach, duodenum and proximal jejunum is excluded from food intake. A jejunojejunostomy is conducted to restore continuity with the biliopancreatic limb. There is a post-prandial change in the release of gut hormones involved in glucose regulation[37] and the regulation of hunger and satiety[111,112]. This occurs by bypassing the above mentioned parts of the proximal intestine and by a more rapid stimulus of the distal gut. The changes seen after GBP on glucose homeostasis occur before the actual weight loss occurs suggesting a mechanism independent of weight loss. Marginal ulcers,[113] dumping[114] and internal hernias[115] are some of the problems following GBP. GBP is currently the most common bariatric procedure globally, accounting for 49% of all bariatric procedures. The use of GBP has increased from 11% in 2003 to 39% in 2008 in Europe, whereas GBP use has decreased in the USA and Canada from 85% to 51% during the same time period.[85] GBP presently accounts for 95% of all bariatric surgery in Sweden.[86]

Malabsorptive (mainly) and restrictive procedures

Biliopancreatic diversion (BPD), figure A, involves a distal gastrectomy and a Roux-en-Y reconstruction of a 200cm long food limb (alimentary), a 50cm long biliopancreatic limb (bile and pancreatic juices), and a 50cm common limb. The size of the gastric remnant is adjusted according to the patient's pre-operative excess weight, and other variables such as sex, age, eating habits and expected compliance.[116] BPD acts through two mechanisms for weight reduction. The restrictive mechanism for weight reduction is based on the smaller size of the stomach achieved through a distal gastrectomy, and a quick emptying into a distal segment of the small intestine through a wide gastroanastomosis. The malabsorptive mechanism is the biliopancreatic diversion that causes malabsorption, which helps maintain a lower weight.[116] *BPD with duodenal switch* (DS), figure B, is performed by a pylorus-saving sleeve gastrectomy combined with a duodenoileostomy. This procedure is reported to have fewer side effects, i.e. vomiting, diarrhoea[117] and fewer gastric ulcers.[118] The use of these procedures seems to have decreased worldwide, from 5% in 2003 to 2% in 2008.[85]

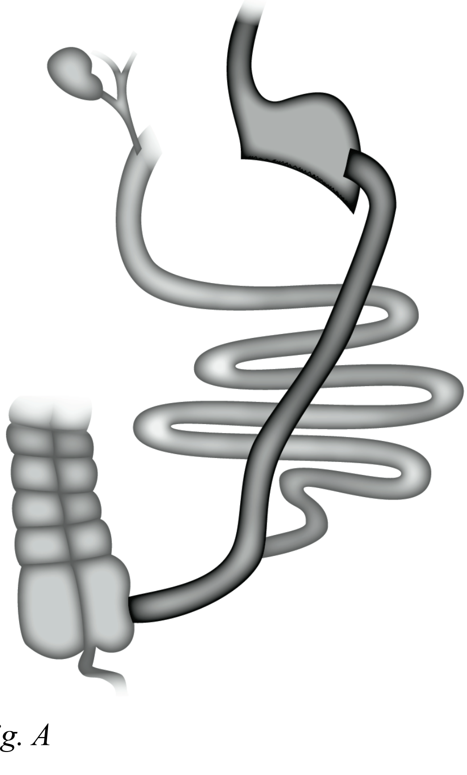


Fig. A

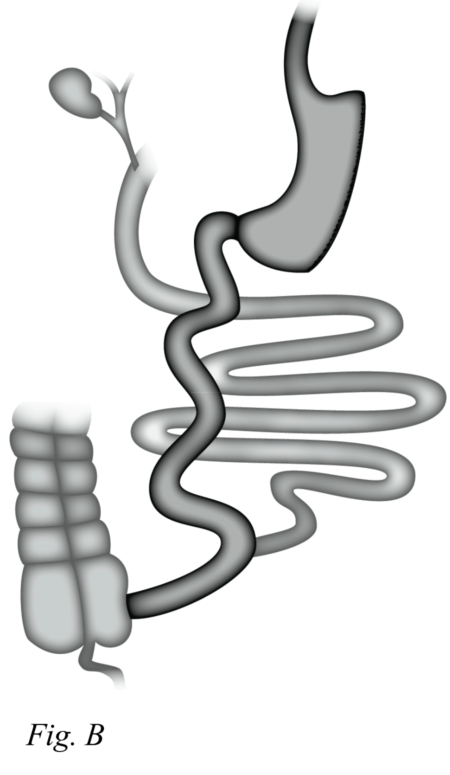
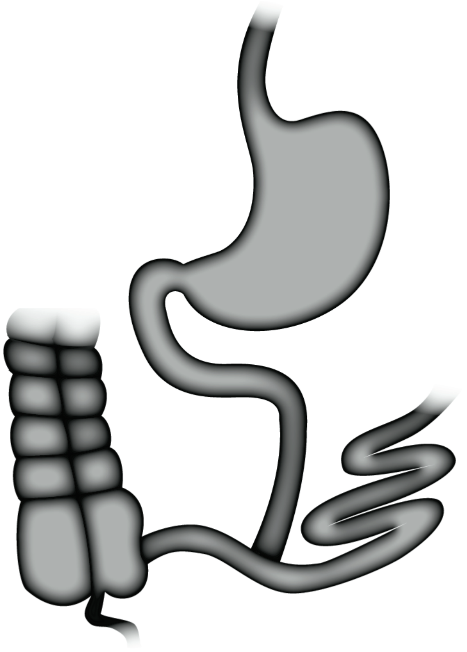


Fig. B

Malabsorptive procedures



Jejunoileal bypass (JIB) was used in the past but is now abandoned. JIB was a purely malabsorptive surgical procedure in which the stomach was left intact. The jejunum was transected 35cm distal to the ligament of Treitz, and the proximal end of the transected jejunum was anastomosed to the ileum 10cm proximal to the ileocecal valve, leaving out a blind-loop (figure). In effect, this procedure mimicked a short-bowel syndrome.[84] The weight loss was impressive, but the success was hampered by a multitude of life-threatening complications, i.e. electrolyte disturbance, liver and renal disease.[119] These complications resulted in a high frequency of bypass reversals.[120]

1.5.2.1 Complications

Each surgical procedure is afflicted with its specific complications, while some complications can occur no matter which surgical procedure is performed, e.g. wound infection, wound hematoma and urinary tract infection. Immediate complications are dealt with while the patient is still in the hospital, however, since the postoperative hospital stays might be short, early complications might go unnoticed. Immediate postoperative complications such as anastomotic-, or gastric leak, bleeding and pulmonary embolism are potentially lethal. GBP, the dominating weight loss procedure in Sweden, might be followed by some devastating complications.

Early (<30 days postoperatively) bleeding is reported in 0.7-3% of cases,[121,122] and is usually related to the staple lines. Therefore, it is not necessary to perform diagnostic examinations to localise the site of the bleeding. The bleeding can present as hematemesis, hematochezia, decrease in haemoglobin, tachycardia or hypotension. About 40% of staple line bleedings come from the gastric remnant, and the remaining comes from the gastrojejunal- (30%) or the jejunojejunal (30%) staple line.[123] Intraluminal bleeding (clot) can cause obstruction of the enteroanastomosis and distension of the gastric remnant. Early bleeding should be managed endoscopically or surgically depending on the clinical presentation and timing.

Late (>30 days postoperatively) bleeding is usually caused by marginal ulcers, often located on the site of the gastrojejunal anastomosis. A marginal ulcer can also result in a gastrogastric fistula or perforation. The pathogenesis of these ulcers is probably multifactorial, but exposure to acid from the gastric pouch probably contributes, despite the small size of the pouch.[124] Diabetes, tobacco smoking and gastric pouch length are associated with risk of marginal ulcer formation. The late bleeding can be treated endoscopically in combination with proton pump inhibitors (PPI).[113] Surgery, including resection of the ulcer with revision of the pouch or staple line, should be considered if the ulcer is refractory to medical therapy.[125]

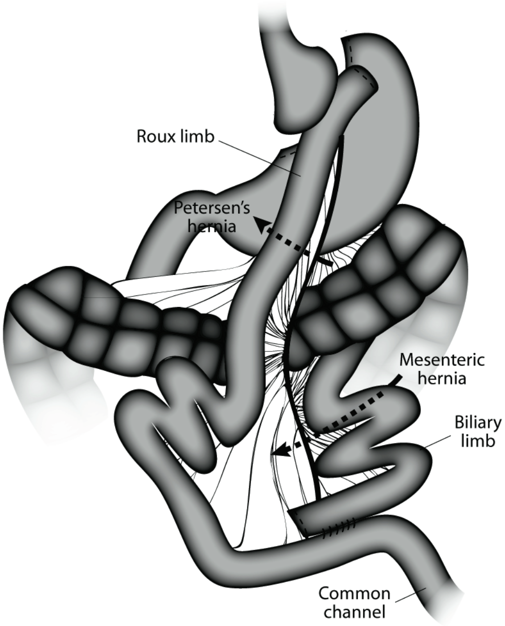
Anastomotic leaks occur in up to 4% of cases, depending on the type of approach: laparoscopic or open.[126,127] Independent risk factors include male gender, older age and diabetes.[126] The leakage is often located in the gastrojejunal (80%) anastomosis, and less frequently in the jejunojejunal anastomosis.[128,129] Early symptoms, which can be very vague and develop before abdominal pain is present, include tachycardia, tachypnea and fever. Suspicion of a leak prompts urgent intervention, either surgical exploration or abdominal computed tomography (CT) scan with oral contrast.[130] The latter should not delay an exploration, and a negative CT scan does not rule out a leak. The surgical aim of leak treatment is to correct the defect by means of stitching or stenting, and drainage.[130]

Thromboembolic events such as deep venous thrombosis (DVT) and pulmonary embolism (PE) are not uncommon despite the fact that patients are treated with routine prophylaxis and early postoperative mobilisation. These events are more likely to occur early after surgery. The literature on the subject is heterogenic, making it difficult to draw conclusions. It has been reported to occur in 0.2% to 4% of cases for DVT, PE or both in GBP patients.[131,132] A major risk factor for developing a thromboembolic event is obesity as well as abdominal surgery. Age above 50 years, history of tobacco smoking, previous DVT or PE and postoperative anastomotic leak are associated with an increased risk. A prophylactic inferior vena cava filter may be considered prior to surgery for patients with a history of DVT or PE or hypercoagulability diseases.[132]

Anastomotic strictures occur in 2-16% of patients within a mean time of 3 months after surgery, a concomitant marginal ulcer is common.[133-136] Symptoms associated with this complication are mainly epigastric pain or discomfort, vomiting, nausea and dysphagia.[134] Left untreated, the condition can cause severe dehydration with vitamin and mineral deficiency. Predisposing factors might be ischemia, acid and tension on the anastomosis.[135] The standard treatment is endoscopic balloon dilatation. Early stricture development is afflicted with more endoscopic dilatation sessions to obtain a sustained response.[135]

Internal hernias have an incidence of 0.2-16%[137-141] and can occur long after surgery.[138] There are three main sites for intestinal herniation: mesenteric, Petersen's, and mesocolic. The latter is specific to the retrocolic GBP. An antecolic GBP approach is most common, and the mesenteric hernia is adjacent to the jejunojejunostomy, whereas the Petersen's hernia involves the mesentery of the Roux limb and the mesentery of the transverse colon.[142] The afflicted patient presents with various degrees of colicky abdominal pain, which can be episodic but persist over time. The weight loss after surgery leads to loss of mesenteric fat, which can be the reason for the enlargement of the defects.[142] The laparoscopic method itself is afflicted with fewer intra abdominal adhesions, however the length of the roux limb might be of importance.[143] A CT scan with contrast or laparoscopy can be included in the diagnostic procedure.[141] Surgery aims to reduce the hernia and close the defects.

The overall frequency of complications after GBP seems to be lower in high-volume hospitals (defined in the USA as >100 cases/years) compared to low-volume (defined in the USA as <50 cases/year)[144] and decrease with time (and experience).[129]



With time after surgery the patients may encounter other medical problems including _gallstone formation._ Paradoxically, obesity[145,146,147] as well as a rapid weight loss[146] can be followed by an increased risk of gallstone formation. The overall postoperative symptomatic gallstone formation due to weight loss has been estimated to occur in 8% of the patients who undergo GBP, AGB or SG.[148] However, a 5-fold increased risk of developing symptomatic gallstones after bariatric surgery has been reported as compared to the general population.[149]

Dumping syndrome can be transient during the first postoperative year. It occurs 30-60 minutes after eating calorie-dense foods or liquids, i.e. high in sugar contents. Such food passes to the jejunum poorly digested, and causes hyper-osmolarity of the intestinal content by drawing fluid into it and distending the lumen. The symptoms are abdominal pain, nausea, tachycardia, sweating and light-headedness.[114,150]

Nutritional deficiencies are more common after malabsorptive procedures than restrictive. However, deficiencies can also develop in patients after restrictive procedures due to poor eating behaviour, food restrictions and food intolerance. The risk of developing nutritional deficiencies varies with the procedure as follows: adjustable gastric banding <sleeve gastrectomy <gastric bypass <biliopancreatic diversion.[151] Iron, vitamin B_{12}, vitamin B_9 (folate) and calcium deficiencies are

usually seen after bariatric surgery. Protein and fat-soluble vitamin deficiencies can occur after biliopancreatic diversion with a duodenal switch. This is explained mostly by the loss of acid action of the stomach and the bypassing of the duodenum and proximal jejunum.[152] Adequate supplementary vitamins and minerals counteract these deficiencies.[150,153]

1.5.2.2 Weight outcome after surgery

The established criterion of success in bariatric surgery is a >50% excess weight loss sustained for 5 years after surgery.[150] The excess weight equals to the total preoperative weight minus the ideal weight. The percentage of excess weight loss can be calculated by dividing the weight loss by the excess weight. The maximum weight loss reported in the SOS study was 32% in gastric bypass, 25% in vertical banding and 20% gastric banding 1-2 years after bariatric surgery.[154] The mean postoperative changes in body weight after 10, 15 and 20 years were 17%, 16% and 18%, respectively, despite the fact that only 13% of all the surgical procedures were gastric bypass procedures.[46] An up-to-date Cochrane review found that weight loss was greater after gastric bypass than vertical banded gastroplasty and adjusted gastric banding, but similar to isolated sleeve gastrectomy after a mean follow-up time of 2 years.[155]

1.5.2.3 Postoperative mortality

The postoperative risk of death is generally low after bariatric surgery. The 30-day mortality rate among patients operated with a gastric bypass or a laparoscopic adjustable gastric banding was 0.3% in an American observational multicentre study of 4,776 consecutive patients.[156] A meta-analysis in 2007 of open and laparoscopic approach and revisional surgery found an overall mortality at 30-day, and 31-day to 2 years of 0.3% and 0.4%, respectively.[157] The hazard ratio of overall mortality after 16 years of follow-up in the SOS study was 0.8 compared to non-operated controls and the 90-day mortality was 0.3%.[154] A Swedish retrospective cohort study of all patients who had undergone bariatric surgery during 1980-2005 reported a 30-day, 90-day and 1-year mortality of 0.2%, 0.3%, and 0.5%, respectively.[90,158] According to the Scandinavian Obesity surgery registry, the 30-, and 90-day mortality in Sweden between 2007 and 2011 was 0.05% and 0.1%, respectively.[86]

2 AIMS OF THE STUDIES

The overall aim of the thesis was to clarify some aspects of bariatric surgery, comparing those who have undergone such surgery to the general Swedish population.

The specific research questions were:

- Is the risk of obesity-related cancer reduced with time after bariatric surgery in those who have undergone bariatric surgery compared to the risk of the corresponding general population?

- How does the risk of admission to hospital for obesity-related co morbidities compare between those who have undergone bariatric surgery and the corresponding general population?

- What is the need for cholecystectomy in those who have undergone bariatric surgery compared to the corresponding general population and compared to patients who have undergone other abdominal surgical procedures?

- How does the risk of admission to hospital for alcohol abuse and psychiatric diseases compare between those who have undergone bariatric surgery and the corresponding general population?

3 MATERIAL AND METHODS

In Sweden, each citizen is assigned a unique 10-digit personal identity number (PIN) at birth, or when an individual decides to reside in Sweden for more than one year. Since 1947 the National Tax Board has maintained the PIN for all residents in Sweden. The PIN enables individual linkages between the different registers.[159]

3.1 Data registers

Several authorities handle the register linkages for health research purposes. The two major operators are Statistics Sweden (SCB) and the Swedish National Board of Health and Welfare (NBHW). The following data registers have been used in this thesis:

3.1.1 The National Patient Register

The National Board of Health and Welfare (NBHW) maintains the National Patient Register (NPR). Besides the PIN and patient information, it holds information on hospital, admission- and discharged dates, ICD-codes for diagnosis, and codes for surgical procedures. The National Patient Register was established in 1964-1965, and the nationwide coverage of in-patient care was 85% in 1983, and has been 100% since 1987.[160 161] The validity of the register was assessed by the NBHW in 1986 and 1990, and 99% of the admissions have registered main diagnoses.[160] The validity of the NPR is regarded as high, and it is highly suitable for large-scale population-based research.[161] The NPR has been used in all four studies included in this thesis.

3.1.2 The Cancer Register

This register was established in 1958 and is held by the NBHW. The register is based on the notification of malignant- and some benign tumours. It is mandatory for pathologists and physicians to report all cancer cases to the six regional cancer registries for coding and registration. The regional registries are responsible for verification and correction of the diagnoses, as well as correct coding as an aid to delivering the correct data to the NBHW. Currently, 99% of the cancer cases are verified morphologically, and the completeness of the register is considered as high. The small number of unreported cases has been more frequent in elderly patients and in soft tissue tumours, tumours of the nervous system and for leukaemia and lymphoma.[162] The Cancer Register is updated once a year, and was used in study I in this thesis.

3.1.3 The Causes of Death Register

This register began in 1952 and is held by the NBHW. It includes dates and underlying causes of all deaths among persons residing in Sweden the year they died, independent of where they died (in Sweden or abroad). Approximately 0.5% of the deaths do not have a recorded cause of death.[163] The most important source of uncertainty of the cause of death is the way they are reported by the physicians. Older patients usually have more chronic illnesses and co morbidities, and the definite cause of death might not be as obvious as for a younger patient. The register had a lag in registration of two years during the study period and was used in all studies in this thesis.

3.1.4 The Register of the Total Population

This register started in 1968 and is maintained by SCB. It contains information on Swedish residents and includes a number of variables, i.e. PIN, sex, age, name, address, marital status, citizenship, country of birth, immigration, emigration and date of death. This register was used in all four studies included in this thesis.

3.1.5 The Population and Housing censuses (Folk och Bostadsräkningar)

A population and housing census was performed by SCB every five years in Sweden between years 1960-1990.[164] The information was retrieved from questionnaires distributed to the entire population combined with information from different databases held by the SCB, such as the database of education attainment and employment. The variables partly differ between time periods, but all censuses contain information on sex, age, name, marital status, occupation, socioeconomic status and educational level.
This register was used for studies II and IV in this thesis.

4 OVERVIEW OF THE FOUR STUDIES

Table 1. Overview of the four studies comprising this thesis

	STUDY I	*STUDY II*	*STUDY III*	*STUDY IV*
Patients, Number	13,123	13,273	13,443	12,277
Men (%)	3,002 (23)	3,000 (22.6)	3,436 (25.6)	2,818 (22.9)
Women (%)	10,121 (77)	10,273 (77.4)	10,007 (74.4)	9,459 (77.1)
Controls	General background population	132,730 matched controls from the general background population	General background population Antireflux surgery cohort Appendectomy cohort	132,730 matched controls from the general background population
Study period	Jan 1st 1980- Dec 31st 2006	Jan 1st 1980- Dec 31st 2006	Jan 1st 1987- Dec 31st 2008	Jan 1st 1980- Dec 31st 2006
Data sources	NPR, Total Population Register, Cancer register	NPR, Total Population Register, Causes of Death Register, Population and Housing census	NPR, Total Population Register	NPR, Total Population Register, Causes of Death Register, Population and Housing census
Exposure	Bariatric surgery	Bariatric surgery	Bariatric surgery	Bariatric surgery
Outcome measure	Cancer	Cardiovascular co morbidities and diabetes	Cholecystectomies	Psychiatric co morbidities
Statistical analyses	Standardised incidence ratios	Cox proportional hazards regression	Standardised incidence ratios	Cox proportional hazards regression

NPR=the National Patient Register

Study design

All studies were nationwide Swedish retrospective population-based cohort studies. The study base was the Swedish population of 18 or 20 years and above. The bariatric surgery cohorts consisted of all patients who had undergone a defined obesity surgical procedure, as registered in the NPR during the period study period December 1st 1980 to January 31st 2008. The year 1980 was chosen as the start year due to the fact that bariatric surgery became more frequent in Sweden at that time and that the National Patient Register was more complete at that time compared to earlier years. At the time of writing and preparing the studies, most of the registers had been completed by 2008. The cohorts where followed up until the occurrence of a specific disease outcome, end of the study period, death or emigration, whichever came first. In studies II and IV, the age- and sex matched controls were given a pseudo surgery date, which corresponded to the date of surgery for the corresponding case participant. The person was considered as having an event if the diagnosis in question was detected in the NPR during the time frame from the date of their 18th birthday to the date of surgery or pseudo surgery; person-time was counted accordingly. The risk of hospitalisation was assessed before surgery by calculating incidence rate ratios (IRRs) and postoperative hazard ratios (HR) for the studied co morbidities.

5 STATISTICAL ANALYSES

5.1 Standardised incidence ratio

Standardisation is more an epidemiological method than a statistical one. When comparing morbidity between groups, one has to take into consideration that morbidity varies with age and sex. If the age-, and sex distribution differs between the groups they cannot be directly compared to each other. We have to standardise the results to make a valid the comparison. The relative risk of cancer (study I) and cholecystectomy (study III) were calculated as the standardised incidence ratio (SIR) with 95% confidence interval (CI). SIR was calculated by dividing the observed number of cases by the expected numbers. The expected numbers were assessed through the entire Swedish population of corresponding age, sex and calendar time. Thus our cohorts were divided into age-, sex-, and calendar year specific groups. The observed numbers of outcomes (cancer or cholecystectomy) that occurred in the cohorts were then obtained, and the observed incidence rates calculated. Person-years at risk were accumulated until the event under investigation (cancer in study I and cholecystectomy in study III), death, emigration or end of study period, whichever occurred first. By multiplying the observed person-time in the cohorts with the expected incidence rate in the total general population of corresponding age-, sex-, and calendar year, the expected numbers of cancers were calculated.

We assumed a Poisson distribution, i.e. a discrete probability distribution that expresses the probability of a given number of events occurring within a fixed interval of time, if these events occur with a known average rate and independently of the time since the last event. All prevalent cancer cases were excluded in study I as well as cancers detected during the first postoperative year. In study III, all patients who had previously undergone cholecystectomy were excluded.

5.2 Incidence rate ratio

In studies II and IV, the preoperative incidence rate ratios (IRR) were calculated with 95% CI. The cohort members and controls were followed in the NPR from the age of 18 years up until the date of surgery or pseudo surgery.

5.3 Cox proportional hazards regression

Cox regression was used to calculate HR with 95% CI for in-hospital care of co-morbidities (study II) or psychiatric diseases (study IV) while controlling for patient characteristics such as age at surgery or pseudo surgery, sex, socioeconomic status, educational level and preoperative occurrence of the diagnosis under study. To reduce the risk of detection bias in study II, the first year before and after surgery were excluded from analyses of myocardial infarction and stroke, and the first two years before and after surgery for angina pectoris, hypertension and diabetes in study II. In study IV, the first postoperative year and first two postoperative years were excluded to reduce detection bias.

6 RESULTS

6.1 Study I

Study I assessed the risk of obesity-related cancer after bariatric surgery. Tumour cases with an established association with obesity were included in the main analysis. These included cancer of the breast, prostate, colorectum, endometrium, kidney, oesophagus (adenocarcinoma only), liver, pancreas, gallbladder, non-Hodgkin's lymphoma and thyroid. The bariatric surgery cohort included 13,123 patients with a mean follow-up time of 9.0 years. Most cohort members were women (77%) and the most common surgical procedures were restrictive i.e. vertical banded gastroplasty or gastric banding. Approximately 47% were operated on in a low volume hospital.

In total, 296 new obesity-related cancer cases were found during follow-up. There was no trend of any augmented risk with increasing time after surgery (p for trend=0.4) and the overall risk of obesity-related cancer was not reduced in the bariatric surgery cohort (SIR 1.0, 95% CI: 0.9-1.2) compared to the corresponding background population.

To further investigate the risk of obesity-related cancer we examined groups consisting of at least 20 new cancer cases in each group, which were breast-, prostate-, colon-, endometrial- and kidney cancer.

There were a total of 85 breast cancer cases. The overall risk of breast cancer was decreased (SIR 0.5, 95% CI 0.4-0.7) as well as the risk among 35 patients who were followed-up for more than 10 years after bariatric surgery (SIR 0.6, 95% CI 0.4-0.8), but there was no trend with time after surgery (p for trend=0.6). Among the 23 patients who developed prostate cancer the SIR was 1.2 (95% CI 0.4-2.9) after 1-4 years, and decreased with increasing time to 0.7 (95% CI 0.3-1.3) when followed for more than 10 years. However, no trend with time was detected (p for trend=0.3). The SIR of colon cancer rather increased from 0.7 (95% CI 0.1-1.9) after 1-4 years to 2.1 (95% CI 1.3-3.2) after a follow-up time of 10 years, and the trend with time was statistically significant (p for trend=0.01). The risk of endometrial cancer (n=54) remained more than 2-fold increased during the entire follow-up period (p for trend=0.8). The risk for kidney cancer (n=24) was increased 3-fold after 10 years of follow-up, without any trend of a decrease after surgery (p for trend=0.4).

Table 2. Summary of cancer cases in study I.

OVERVIEW OF ALL CANCER CASES IN STUDY I				
	Number	*SIR*	*95% CI*	*P for trend with time after surgery*
All cancers	493	1.0	0.9-1.1	0.5
All obesity–related cancers	296	1.0	0.9-1.2	0.6
Breast cancer	85	0.6	0.4-0.7	0.6
Prostate cancer	23	0.8	0.5-1.3	0.3
Colon cancer	35	1.5	1.1-2.1	0.01
Endometrial cancer	54	2.2	1.6-2.8	0.8
Kidney cancer	24	2.7	1.7-4.0	0.4

SIR= standardized incidence ratio
CI=confidence interval

6.2 Study II

The 13,273 patients who underwent a primary bariatric surgery procedure in study II had a mean age of 40 years and a median follow-up time of 8.7 years. The operated cohort was compared compared with 132,730 age-, and sex matched controls from the general population. The socioeconomic position and educational level was lower in the operated cohort compared to the controls.

Overall, the pre- and postoperative risk of inpatient hospitalisation for the studied co morbidities, i.e. myocardial infarction, angina pectoris, stroke, hypertension and diabetes were higher in the operated group compared to the general population sample. For example, the risk of hospitalisation for diabetes was increased both preoperatively (IRR 4.1, 95% CI 3.7-4.6) and postoperatively (HR 2.4, 95% CI 2.2-2.7). An increased risk of hospitalisation for all studied co morbidities was seen preoperatively in the cohort of patients who underwent gastric bypass compared to those who underwent a restrictive surgical procedure. The risk estimates of in-hospital care for acute myocardial infarction (HR 0.8, 95% CI 0.4-1.5) and for diabetes (HR 1.2, 95% CI 0.9-1.7) were lower after gastric bypass surgery than after restrictive procedures (myocardial infarction HR 1.6, 95% CI 1.4-1.9 and diabetes HR 2.8, 95% CI 2.5-3.1).

Mortality after surgery was higher both before and after adjustment for potential confounding factors was conducted. The total surgical cohort, as well as the surgical subgroups, had a higher mortality compared to the general population sample. The mortality, including the 30-day mortality, was higher in the group who had undergone restrictive surgery compared to gastric bypass as presented in the table below.

Table 3. Summary of mortality in study II

MORTALITY IN STUDY II		
	Hazard Ratio (95% Confidence Interval)	
	Unadjusted mortality	*Adjusted mortality**
All surgery v.s general population	1.4 (1.3-1.5)	1.2 (1.2-1.3)
Gastric bypass v.s general population	2.2 (1.8-2.7)	1.8 (1.5-2.3)
Restrictive surgery versus general population	1.3 (1.2-1.5)	1.2 (1.1-1.3)
Restrictive surgery versus GBP	1.6 (1.3-2.0)	1.6 (1.3-2.0)

v.s=versus
*Adjusted for age at surgery, sex, socioeconomic status, educational level and preoperative co morbidity.
GBP=gastric bypass

A total of 766 deaths (6%) occurred in the surgery cohort, and 5,033 (4%) in the general population sample during the study period. The causes of mortality are presented in the table 4 below.

Table 4. Causes of mortality in study II.

MORTALITY CAUSE STUDY II		
	Surgery group	*Control group*
	N all (%)	N all (%)
Cancer	120 (0.9)	1600 (1.2)
CVD*	171 (1.3)	781 (0.6)
Accident	66 (0.5)	345 (0.3)
Suicide	34 (0.3)	145 (0.1)
Intoxication	11 (0.1)	123 (0.1)
Other	133 (1.0)	927 (0.7)
Missing data**	231 (1.8)	1112 (0.8)

*Cardiovascular disease
**The Causes of Death Register was complete until December 2004
N=number

6.3 Study III

The bariatric surgery cohort in study III comprised 13,443 patients with a mean age of 40 years. The need for cholecystectomy in the bariatric surgery cohort was compared with the need of the corresponding general background population by calculating SIR. The SIR of this cohort was compared to the SIR of a gastric bypass cohort consisting of 6,549 patients, an antireflux surgery cohort of 16,176 patients and to a cohort of 154,751 patients who had undergone appendectomy. Each of these cohorts was compared with its corresponding general population.

All cohorts were assessed for the overall postoperative need for cholecystectomy, as well as the need for imperative cholecystectomy i.e. a more acute need for cholecystectomy due to cholecystitis, jaundice, cholangitis or pancreatitis.

The need for cholecystectomy as well imperative cholecystectomy was increased 5 to 6-fold in the total bariatric surgery cohort and the gastric bypass cohort compared to the respective general background population. The SIRs for cholecystectomy and imperative cholecystectomy in the antireflux surgery cohort were 2.4 and 2.1, respectively, while the corresponding SIRs in the appendectomy cohort were 1.7 and 1.6, respectively. In all the cohorts, with exception for the appendectomy cohort, the need for a cholecystectomy peaked 7-12 months after surgery. The SIRs were similar between the sexes in all cohorts and for both types of cholecystectomy.

Table 5. Summary of cholecystectomies in study III.

The need for cholecystectomy in study III		
	Cholecystectomy Number (%)	***SIR (95% CI)***
Total bariatric surgery cohort	1,149 (8.5)	5.5 (5.1-5.8)
Total bariatric surgery cohort, imperative surgery	427 (3.2)	5.2 (4.7-5.7)
Gastric bypass surgery cohort	232 (3.5)	6.1 (5.3-6.9)
Gastric bypass surgery cohort, imperative surgery	89 (1.4)	6.1 (4.9-7.4)
Antireflux surgery cohort	695 (4.3)	2.4 (2.2-2.6)
Antireflux surgery cohort, imperative surgery	292 (1.8)	2.1 (1.8-2.3)
Appendectomy surgery cohort	4,345 (2.8)	1.7 (1.6-1.7)
Appendectomy surgery cohort, imperative surgery	1,727 (1.1)	1.6 (1.5-1.6)

SIR= standardized incidence ratio
CI=confidence interval

6.4 Results study IV

A total of 12,277 patients underwent primary bariatric surgery in study IV. These patients were compared to 122,770 matched subjects from the general population.

The total bariatric surgery cohort, which included both restrictive (vertical banded gastroplasty and gastric banding) and gastric bypass, had a higher risk of hospitalisation for all the studied co morbidities, i.e. psychosis, depression, substance abuse, suicide attempt and alcohol abuse before surgery compared to the general population sample.

Women had a higher preoperative risk of hospitalisation than men. The risk was of the same magnitude for all studied co morbidities after surgery, but an improvement was seen in the risk of hospitalisation for depression (IRR 2.8, 95% CI 2.5-3.0 and HR 1.9, 95% CI 1.7-2.2). There was no difference between men and women after surgery.

Overall, the risk of hospitalisation decreased after surgery for all studied co morbidities in the restrictive surgery cohort compared to the general population sample, while the opposite was seen in the gastric bypass cohort for the co morbidities substance abuse, suicide attempt and alcohol abuse.

When restrictive surgery was compared to gastric bypass surgery, the risk of hospitalisation was similar preoperatively in the two cohorts, but the postoperative risk was increased in the gastric bypass cohort for all studied co morbidities, except for psychosis (HR 0.7, 95% CI 0.3-1.5).

Table 6. The risk of substance abuse, suicide attempt and alcohol abuse before and after bariatric surgery compared to a general population sample in study IV.

The risk of substance abuse, suicide attempt and alcohol abuse before and after bariatric surgery in study IV

	Preoperative IRR (95% CI)			***Postoperative HR (95% CI)***		
	Substance abuse	Suicide attempt	Alcohol abuse	Substance abuse	Suicide attempt	Alcohol abuse
Restrictive surgery versus general population	1.9 (1.4-2.4)	2.7 (2.4-3.1)	1.5 (1.2-1.8)	1.4 (1.1-1.9)	2.4 (2.0-2.8)	1.3 (1.1-1.6)
Gastric bypass versus general population	2.5 (1.9-3.2)	2.7 (2.3-3.1)	1.6 (1.2-2.0)	3.8 (2.3-6.3)	4.1 (2.9-5.8)	4.0 (2.9-5.5)
Gastric bypass versus restrictive surgery	1.7 (1.3-2.5)	1.1 (1.0-1.4)	1.1 (0.8-1.4)	2.5 (1.6-4.0)	1.9 (1.4-2.6)	2.3 (1.7-3.2)

IRR=incidence rate ratio
HR=hazard ratio
CI=confidence interval

7 DISCUSSION

7.1 Methodological considerations

The Greek word 'epidemiology' literally means "the study of what is upon the people". It is the study of the occurrence of illness in a population in relation to different factors affecting the illness. Different study designs can be used to assess the occurrence of illness in a population.

A cohort study is an observational study of a defined group of individuals with a known exposure that is followed for a period of time to examine a specific outcome or disease possibly associated with the exposure. The basic requirement for cohort members is that they should be at risk of developing the outcome or disease which is to be measured i.e. they are free of the outcome/disease at the start of the follow-up period. The members who develop the studied outcome or disease, given that the outcome or disease can occur only once, or cannot be followed up e.g. because of death or emigration, are no longer at risk and exit from the cohort. In a cohort study, the exposure is already assigned to the members of the cohort, and the examiner "observes" the members for a specific outcome. In studies I-IV where the cohort comprised members who had undergone bariatric surgery (exposure), we observed them for cancer, cardiovascular co morbidities, cholecystectomies and psychiatric diseases (outcome/disease) during a defined period of time.

Since Sweden has a long-standing tradition of well-kept registers in combination with the PIN, loss to follow-up is not a major problem, which is otherwise a threat to many cohort studies. Cohort studies are generally well suited for studying unusual exposures, and the registers also make it possible to study outcomes with a long latency period. Furthermore, several outcomes can be studied in relation to one exposure. When the cohort members are chosen based on records of past exposure and the follow-up time is totally or in part in the past, the cohort is called a historical- or retrospective cohort. All the cohorts in this thesis are historical cohorts.

7.2 Population-based

A study is said to be population-based if the cohort members constitute a representative a truly random sample of all members in a defined and identified population.[165] Studies I-IV are population-based whereas the cohort members represent virtually all patients undergoing bariatric surgery in entire Swedish population, which is a well defined population. This again, is possible because of the complete Swedish registers and the PIN.

7.3 Unexposed comparison cohorts

The comparison cohorts in studies I and III were the entire background population of Sweden of the corresponding age, sex and calendar year to the bariatric surgery patients. In studies II and IV, the comparison population comprised of a random sample of age- and sex matched unexposed controls from the total background population. The key obstacle is to compare the exposed cohorts to the total background population, since the exposure (bariatric surgery) is aiming at reducing the obese state to a degree of a weight similar to that of the general population. One can argue that the optimal comparison cohorts should also be matched for BMI. This would, however, necessitate a randomisation among obese individuals to surgery or no surgery, which is not feasible. It is clear that as long as there is no alternative treatment for obesity with documented long-term effects on mortality and co morbidity, other than surgery, a randomised clinical trial would be unethical. Furthermore in study I, the low cancer incidence and long induction time makes prohibit the conduction of any theoretical randomised clinical trial.

7.4 Sources of error

The association between an exposure and an outcome can be the product of causality (true association), random errors or systematic errors. The aim of all studies is to obtain an accurate measurement, encountering as few errors as possible.
Most *systematic errors* can be categorised as selection bias, information bias or confounding. A systematic error is not dependent on study size. *Selection bias* occurs when the association between the exposure and the outcome is different between those who participate and those who do not participate in a study. A surgical cohort is, in general, afflicted by selection bias. The bariatric surgery candidates have chosen the operation themselves, which might make them different from those who do not choose such surgery. The surgeon might also select patients, i.e. those who are considered suitable for intervention. Furthermore, studies on this topic are often single-centre, single-hospital or based in high excellence institutions which obviously introduce selection bias. In contrast, the cohorts in this thesis are based on nationwide, complete registers, thus being considered population-based, a design that counteracts selection bias. *Information bias* can occur if the collected information is incorrect. The exposure and outcome can be misclassified in two principally different ways: differential or non-differential. Differential misclassification may arise when the exposure is misclassified depending on if the individual has the disease (outcome) or not. It can also occur when the disease (outcome) is misclassified depending on if the individual has been exposed or not. The risk of misclassification should be limited in the studies comprising this thesis, since they are based on robust NPR data. Non-differential misclassification on

the other hand, is unrelated to the exposure or disease. Such bias arises from misclassification of the exposure or outcome that is similarly distributes among case subjects and controls subjects. Such error is usually of minor concern in epidemiological studies, since it does not shift risk estimates in any unknown direction, but only dilutes the estimates towards a null result. Positive associations are therefore not explained by non-differential misclassification. One special type of differential misclassification of relevance for the present thesis is *biased follow-up* in which unexposed individuals are more likely to be under diagnosed for a disease than exposed individuals. Such bias is called *detection bias*. In an attempt to decrease the risk of detection bias, the following efforts were made:
Study I: The main outcome was the long-term effect of bariatric surgery. Moreover, the first year after surgery was excluded in the event of a new cancer being diagnosed during this period.
Study II: One year was excluded before and after surgery in the analyses in the cases of myocardial infarction and stroke, and 2 years for angina pectoris, hypertension and diabetes.
Study III: Detection bias was assessed by also evaluating other abdominal surgery cohorts than the bariatric surgery cohort.
Study IV: The first year preoperatively and 2 years postoperatively were excluded.
Furthermore, in studies II and IV some of the co morbidities might be under-reported, but not necessarily misclassified in the NPR i.e. diabetes, hypertension, angina pectoris, depression, and substance- and alcohol abuse. These conditions are usually handled by the primary outpatient clinics, and might not be recorded in the NPR unless it is a cause for inpatient care. In contrast, myocardial infarction, stroke and suicide attempt are conditions that usually urge the patient to seek inpatient care.

The International Classification of Diseases (ICD) was revised during the study period, which might be a source of misclassification. ICD version 8 (ICD-8) was used during 1969-1986, ICD-9 during 1987-1996 and ICD-10 from 1997 onwards. Moreover, the National Board of Health and Welfare revised The Swedish Classification of surgical procedures ("Klassifikationer av operationer") during the study period. The sixth version covered the period of 1963-1996 and the seventh version the period from 1997 and onwards.

Confounding is of central importance in any epidemiologic study; it refers to the mixing of effects. The definition of a confounding factor is one, which is associated with both the exposure and the outcome, but is not an intermediate link in the causal chain of events. Confounding can cause an over-, or underestimation of an effect. Confounding can be controlled in the study design or in the data analysis. In studies I and III, age, sex and calendar year were controlled for in the data design through standardisation. In studies II and IV, confounding by age and sex was controlled for by matching. Tobacco smoking habit is a potential confounder in studies, but unfortunately such data is not recorded in the NPR.

Random error is the error that remains when systematic errors have been eliminated. It is merely a random error or the variability of data that we cannot explain, but the risk of random errors can be decreased with an increase in sample size. The large sample sizes in the four studies included in this thesis should counteract substantial random errors. The *confidence interval* is a general guide to the amount of error or precision in a dataset. A wider confidence interval indicates lower precision. The confidence interval is an arbitrary level usually set to 95%, meaning that if the study could be replicated many times the correct value of the measure would be included within the confidence interval in 95% of the studies.

7.5 Validity

Internal validity describes how reliable the results of a study are. A study of high internal validity has few systematic errors. The internal validity is dependent on choosing the correct study design to answer the research question properly, correct data collection and analysis. External validity or generalizability is dependent on the internal validity, and further implies how well the study results may be applied to populations other than that under study.

7.6 Statistical hypothesis testing

The term statistical significance is based on the arbitrary p value, usually set to 0.05. The hypothesis testing of an analysis is based on the null hypothesis, which states that there is no relation between the exposure and outcome in whatever the comparison in the study is, e.g. if two drugs A and B were to be compared in a study, the null hypothesis states that there is no difference in the effect between drug A and drug B (RR=1). This would mean that the result is statistically significant in this example if p deviates from the null hypothesis, i.e. typically $p<0.05$ and the null hypothesis is to be rejected as false. The smaller the p value the more evidence there is against the null hypothesis. However, it does not automatically mean that the null hypothesis is true, it only implies it might be rejected.[165] Conversely, a $p>0.05$ indicates that the null hypothesis cannot be rejected. If the null hypothesis is falsely rejected, a *type 1 error* has occurred, meaning a difference is suggested ($R\neq1$) when there truly is none. A *type 2 error* would occur if the null hypothesis fails to be rejected although it should, meaning there is a difference but we might have failed to identify it.

8 FINDINGS AND IMPLICATIONS

Study I

Cancer risk

Contradictory to the hypothesis, this study did not identify any overall decreased risk of obesity-related cancer with increasing follow-up time after bariatric surgery compared to the general population. There were a total of 493 primary obesity-related cancers detected in a cohort comprising 13,123 patients. For specific obesity-related cancers, changes in trends with time after surgery were statistically significant only for colon cancer, and this trend showed rather an increase in risk with longer follow-up time after bariatric surgery. Although the specific obesity-related cancer groups were larger than any other previous studies, the limited number of cases and multiple testing might explain chance errors. It is possible that if this study were to be reproduced in the future, including a larger number of patients who had undergone gastric bypass and with a longer follow-up time, the outcome might be different. An inherent problem in studies of bariatric surgery in relation to risk of cancer is the long latency time. Nevertheless, this study indicates no decreased risk of cancer with longer follow-up after bariatric surgery.

Study II

Cardiovascular co morbidities and diabetes

This study shows, as expected, a higher preoperative incidence of acute myocardial infarction, angina pectoris, stroke, hypertension and diabetes mellitus in the bariatric surgery cohort compared to the general population sample. Generally, these increased risks remained after bariatric surgery. The preoperative burden of co morbid disease seemed to be somewhat increased in the group of patients undergoing gastric bypass compared to those treated with a restrictive procedure. After surgery, the risk of in-hospital care for diabetes and acute myocardial infarction was reduced in patients treated with gastric bypass compared to those treated with a restrictive procedure. The results may be explained by the fact that the gastric bypass procedure was more frequently used for the more ill and heavier patients in the 1980s and beginning of 1990s, as opposed to a restrictive surgical procedure. As a result of the gastric bypass procedure these patients might have had a better weight reduction and a higher degree of resolution of co morbid disease.

Study III

The need for cholecystectomy

This study confirmed the hypothesis of an increased need for cholecystectomy after bariatric surgery, but also the increased need in the other abdominal surgery cohorts, not associated with any increased risk of gallstone formation, indicated a level of detection bias after abdominal surgery in general. Since the need of cholecystectomy was higher in the bariatric surgery group than in the other surgery cohorts, detection bias would not explain the entire increase. Moreover, the need for more imperative cholecystectomy was also increased further suggesting it is not all due to detection bias. Patients are at a higher risk of developing gallstone disease after bariatric surgery compared to the general population. The crucial question is if the gallbladder should be removed prophylactically? The limited need for cholecystectomy on study III after bariatric surgery in combination with some of it being explained by detection bias, could be interpreted as indicating no need for routinely conducted prophylactic cholecystectomy.

Study IV

Psychiatric co morbidities

The results of this study support some earlier reports of an increased preoperative risk of psychiatric co morbidities and increased alcohol dependence after bariatric surgery. The risk of hospitalisation for the studied psychiatric co morbidities remained, on average, equally high after surgery for the whole bariatric surgery cohort as well as the restrictive surgery cohort separately. The risk of psychosis was, however, decreased after surgery, which might be explained by the fact that this diagnosis is likely to be verified at a younger age, and that few patients experience onset of psychosis later in life. The risk of in-hospital care for alcohol abuse after gastric bypass surgery is increased compared to those patients who had a restrictive procedure. The explanations for this might be the bypassing of the duodenum and proximal jejunum, as well as the fact that a larger portion of the stomach is bypassed. In these sites, alcohol is normally absorbed and metabolised by the enzyme alcohol dehydrogenase. Furthermore, alcohol is not portioned out from the stomach through the pylorus after bypass surgery, but is rather poured down to the small intestine, which contains small villi, which absorb liquids well. The information given to patients planned for gastric bypass should include the possibility of an increased risk of alcohol dependence.

9 FUTURE PERSPECTIVES

The increasing prevalence of obesity and the 300,000 obesity surgical procedures performed annually worldwide in combination with a limited scientific evidence of long-term effects of such surgery should encourage researchers to expand on this field of science. Bariatric surgery seems like a favourable treatment in the light of reduction of co-morbidities, lower mortality rates and a sustainable weight loss, but many questions remain unanswered. With time, the increase of obesity will probably result in an even higher demand for surgical intervention, given there is still no comparable alternative treatment. In such a scenario, the indications for surgery might have to be modified and tailored. Some questions to address might be: Who achieves the greatest benefits of bariatric surgery? At which BMI level could surgery be recommended? Is BMI the best measure for selecting patients for bariatric surgery? Which procedure is best for each patient?

A main issue is the understanding of the positive mechanisms of weight reduction by means of surgery; currently this is poorly understood. The complexities of the peptides, which are released after bariatric surgery, need further investigation. This may be the gateway to other surgical procedures or medical treatments in the future.

From a personal point of view, I would find it interesting to find out why there is such strong gender difference when it comes to bariatric surgery (approximately 75% women), as men and women are on average virtually equally obese. Perhaps this could be studied through a detailed questionnaire comparing obese men and women who would qualify for surgery with obese men and women who are candidates for surgery. Furthermore, how can we identify patients prior to surgery who have a substantially increased risk of developing psychiatric problems after surgery? The assessment of these conditions prior to surgery, in my clinical experience, is difficult. Finally, I am interested in the reason for the difference between obese individuals who develop co morbid diseases compared to those who are equally obese but do not?

10 CONCLUSIONS

- The overall long-term risk of obesity-related cancer might not be decreased with increasing follow-up time in those who have undergone bariatric surgery compared to the general population.

- The risk of diabetes and myocardial infarction seems to be reduced to the same levels as in the general population after gastric bypass surgery for morbid obesity, but the risk of mortality seems to remain increased.

- Bariatric surgery is followed by an increased need for cholecystectomy, but the individual's risk is limited and may be explained in part by detection bias, and prophylactic cholecystectomy might not be routinely recommended.

- Patients who undergo gastric bypass surgery seem to be more likely to be hospitalised for alcohol abuse compared to those treated with a restrictive procedure, which should be included in the preoperative information given to the patients.

11 POPULÄRVETENSKAPLIG SAMMANFATTNING

Fetma kan beräknas genom att dividera individens vikt (i kilogram) med längden (i meter) i kvadrat. Ett BMI mellan 18,5-24,9 är normalt däremot ett BMI över 30 innebär fetma. $BMI=vikt(kg)/ längd^2(m)$

Fetman (obesitas) i befolkningen har ökat markant de senaste 20 åren över hela världen. WHO har beräknat att 200 miljoner män och 300 miljoner kvinnor är feta. I Sverige är 14% av både männen och kvinnorna feta, vilket är mer än en fördubbling av förekomsten av fetma sedan 1980. Trots att fetma är i stort sett lika fördelad bland män och kvinnor är majoriteten av patienterna som opereras för sin fetma kvinnor (ca 75%). Faran med fetma är en okad risk för många sjukdomar t.ex. diabetes, högt blodtryck, hjärtinfarkt, flera cancerformer samt psykisk problematik. Fetma leder också till en genomsnittligt kortare livslängd.

Den mest effektiva behandlingen av fetma som finns att erbjuda idag är kirurgisk. Studier har visat att den viktnedgång som uppnås efter fetmakirurgi är långvarig och bestående till skillnad från viktnedgång som uppnås genom diet, läkemedelsbehandling eller en kombination av dessa. Den viktnedgång som kan åstadkommas kirurgiskt har långvariga och positiva effekter på många av följdsjukdomarna, något som alternativa behandlingsformen inte har lyckats dokumentera vid långtidsuppföljningar. Ungefär 80% av mycket feta (BMI≥35) med diabetes som behandlas med den idag vanligaste typen av kirurgiskt ingrepp, s.k. gastric bypass, blir av med sin diabetes.

Det grundläggande kravet för att komma ifråga för kirurgisk behandling i Sverige idag är att individen har ett BMI≥35. De idag mest använda kirurgiska ingreppen kan indelas i så kallade restriktiva eller en kombination av malabsorptiva-restriktiva ingrepp. Ett restriktivt ingrepp betyder att volymen (storleken) på magsäcken förminskas i syfte att förhindra ett stort födointag. Dessa operationsformer dominerade under 1980-1990-talen, men kom att ersättas alltmer av de malabsorptiva-restriktiva ingreppen, som är tekniskt mer krävande och innebär en förminskning av magsäcken i kombination med omkoppling av tunntarmen. Därmed kombineras effekten av minskat födointag genom en förminskning av magsäcken med ett minskat upptag av näringsämnen genom omkoppling av tunntarmen. Den idag vanligaste restriktiva operationen är gastrisk bandning medan den vanligaste malabsorptiva-restriktiva är gastric bypass. Den senare dominerar både i Sverige och internationellt, och utförs i majoriteten av fallen med titthålskirurgi.

Avhandlingens syfte var att belysa effekterna av fetmakirurgi ur olika kliniskt relevanta aspekter före och efter operation, jämfört med befolkningen i stort. Det stora patientmaterialet (ca 13 300 patienter) som har använts i samtliga fyra delstudier är baserat på Socialstyrelsens Patientregister där alla operationer och diagnoskoder registreras fortlöpande. Information om jämförelsegruppen, den svenska befolkningen, är hämtat från Registret över Totalbefolkningen som administreras av Statistiska Centralbyrån. Studieperioden sträcker sig mellan åren 1980 och 2008.

Studie I

Bakgrunden till studien baseras på det faktum att fetma leder till ökad risk för flertalet cancerformer bl.a. i prostata-, bröst-, livmoder-, njure och grovtarm. Studier visar att ju svårare (mer) fetma desto högre risk för cancerutveckling. Det svåra med att studera cancerrisk efter fetmakirurgi är den långa tid under vilken patienterna måste observeras för att cancern ska kunna identifieras samt behovet av en stor uppföljningsgrupp (kohort) för att antalet cancerfall ska bli tillräckligt stort för att slutsatser ska kunna dras. Det finns studier som pekar på att feta opererade har mindre risk för cancersjukdom än de feta som inte opereras, men dessa har varit relativt små och haft begränsad uppföljningstid. Syftet med studien var därför att belysa om risken för fetmarelaterad cancer minskar med tiden efter fetmakirurgi i en stor kohort med lång uppföljningstid jämfört med risken hos befolkningen. Studien fann ingen minskad risk för cancerutveckling med längre tid efter fetmakirurgi i jämförelse med befolkningen.

Studie II

Mot bakgrund av de många följdsjukdomar som oftare drabbar feta individer har flera studier undersökt graden av tillfrisknande från följdsjukdomarna efter fetmakirurgi och visat på att den är bättre hos opererade än hos icke-opererade feta individer. Studier visar också på mindre dödlighet framför allt i hjärtkärlsjukdomar bland de opererade jämfört med de som inte opereras för sin fetma. Därmed väcktes frågan hur denna jämförelse av feta opererade står sig i förhållande till insjuknandet i samma sjukdomar bland befolkningen. Studien analyserade risken för att bli inlagd för vård på sjukhus för akut hjärtinfarkt, kärlkramp, stroke, högt blodtryck och diabetes före och efter fetmaoperationen jämfört med motsvarande sjukdomar hos befolkningen. Resultaten från studien visade att risken för akut hjärtinfarkt och diabetes närmade sig samma risk som befolkningens hos de patienter som var opererade med gastric bypass till skillnad från dem som opererades med en restriktiv metod.

Studie III

Det finns bevis för att fetma orsakar en ökad förekomst av gallstensproduktion i gallblåsan. Paradoxalt nog medför också en snabb viktnedgång en ökad gallstensproduktion. Det pågår en debatt, framför allt i USA, om galloperationer ska genomföras i förebyggande syfte (profylaktisk) i samband med fetmaoperationen. Det saknas generell internationell konsensus. Det kan förehålla sig så att patienter som har genomgått fetmakirurgi blir mer utredda och att gallsten utan symtom identifieras oftare än hos andra individer. Denna kunskap kan medföra att patienter söker läkare och blir mer uppmärksamma på gallstensliknande besvär hos dessa patienter s.k. detektionsfel. För att utvärdera behovet av gallkirurgi på grund av gallsten efter fetmakirurgi och eventuell betydelse av detektionsfel genomförde vi studie III. Vi jämförde gallkirurgiförekomst efter fetmakirurgi med bakgrundsbefolkningen. Samtidigt analyserade vi behovet av gallkirurgi hos patienter som har opererats för svår halsbränna (reflux) och de som har opererats för akut blindtarmsinflammation I jämförelse med respective bakgrundsbefolkning. Resultaten visade en viss grad av detektionsfel hos de fetmaopererade patienterna, men att de ändå har ett ökat behov av gallstensorsakad gallkirurgi. Andelen som behövde gallkirurgi var dock inte hög och en del av ökningen kunde förklaras av detektionsfel, varför profylaktisk gallkirurgi inte allmänt kan rekommenderas denna patientgrupp.

Studie IV

Andra studier har rapporterat att fetmaopererade individer är överrepresenterade i missbruksprogram och att feta har mer psykiska besvär som ångest och depression samt att graden av psykisk ohälsa är relaterad till graden av fetma. Därför ville vi undersöka förekomsten av vård på sjukhus för de psykiska sjukdomarna; psykos, depression, självmord samt drog- och alkoholmissbruk före och efter operation jämfört med befolkningens risk. Resultaten visade att förekomsten av depression minskade efter operationen, men att de som opererades med gastric bypass till skillnad från de som opererades med restriktiv metod löpte en ökad risk för vård på sjukhus för alkoholmissbruk. Detta behöver beaktas när patienterna informeras om operationen.

12 ACKNOWLEDGEMENTS

Jag vill framföra mitt varmaste tack till alla som har bidragit till min avhandling, ett särskilt stort tack till:

Jesper Lagergren, min prisbelönte handledare och kollega. Det som utmärker dig är dina visioner som du omsätter i praktiken och din tillgänglighet som handledare. Det är få förunnat att som doktorand ha den bäste handledaren och att få vara en del av en forskargrupp av internationell rang. Tack för att du tog dig an mig.

Yunxia Lu, my co-supervisor, thank you for your patience with my statistical questions and your eminent statistical skills.

Erik Näslund, min bihandledare, för ultrasnabba e-mail och sms svar 24-7. Tack för all support på alla kongresser, samt för att du alltid delat med dig av dina stora kunskaper inom ämnet och för all uppmuntran genom åren.

Stefan Linder, min bihandledare, och kollega på avdelning 56, kirurgkliniken, Södersjukhuset. Tack för att du alltid tar dig tid att besvara mina frågor, för att du så frikostigt delar med dig av dina stora kliniska kunskaper och för en alltid så uppmuntrande inställning till allting trots hög arbetsbelastning.

Finn Rasmussen, medförfattare, tack för alla kloka råd, synpunkter och kritiskt granskande av mina delarbeten.

Irma Fredriksson, min mentor och min före detta rumskompis på kirurgkliniken, Södersjukhuset. Utan din geniala idé att ta kontakt med Jesper hade ingenting av detta blivit av. Ett stort, stort tack.

Richard Marsk, tack för att du så heroiskt har stått ut med mina galna STATA frågor och många e-mail.

Fereshte Ebrahim, på Epidemiologiskt Centrum, Socialstyrelsen, för snabb och professionell hjälp.

All my co-authors, for valuable comments and support.

All present and former members of UGIR, thank you so much for creating a welcoming, friendly atmosphere, a professional environment and for all sound advice. A special thank you to; **Fredrik Mattsson,** statistician, for your statistical help and good sense of humour. **Margrete Gellervik**, research secretary, for keeping track of me. **Eja Fridsta,** former research co-ordinator in UGIR, for a thorough work with the data collection. **Hedvig Löfdahl,** for many laughs, pep talks and general chitchat of non-scientific character in "our pre-dissertation room".

Claes Söderlund, min sektionschef på övre gastrointestinala sektionen, avdelning 56**,** Södersjukhuset, **Lennart Boström** verksamhetschef på kirurgkliniken Södersjukhuset samt **Staffan Törngren,** tidigare verksamhetschef på kirurgkliniken, Södersjukhuset, ett stort tack för att ni har gett mig möjligheten att forska och vidareutbilda mig under dessa år.

Mina kollegor på avdelning 56, Emma Sverdén, särskilt tack till dig "my roomie" för att du är du. Anders Sondén, Farshad Frozanpor, Lennart Engström, Angelica Pannes Diaz och Per Berggren för att ni är kollegiala och roliga att jobba med, och för allt ni lärt mig genom åren samt för att ni håller ställningarna under min frånvaro.

Alla mina kollegor på kirurgkliniken Södersjukhuset, tack för all hjälp och support, särskilt tack till **Anneli Linné,** för att du är en ovärderlig vän.

Administrativ personal på kirurgkliniken, Södersjukhuset. Agneta Lind Persson, Britt Keller, Danica Tesic, Kicki Svanbäck för er vänlighet och all hjälp med praktiska detaljer kring såväl semester, KID finansiering, placeringsschema som disputation.

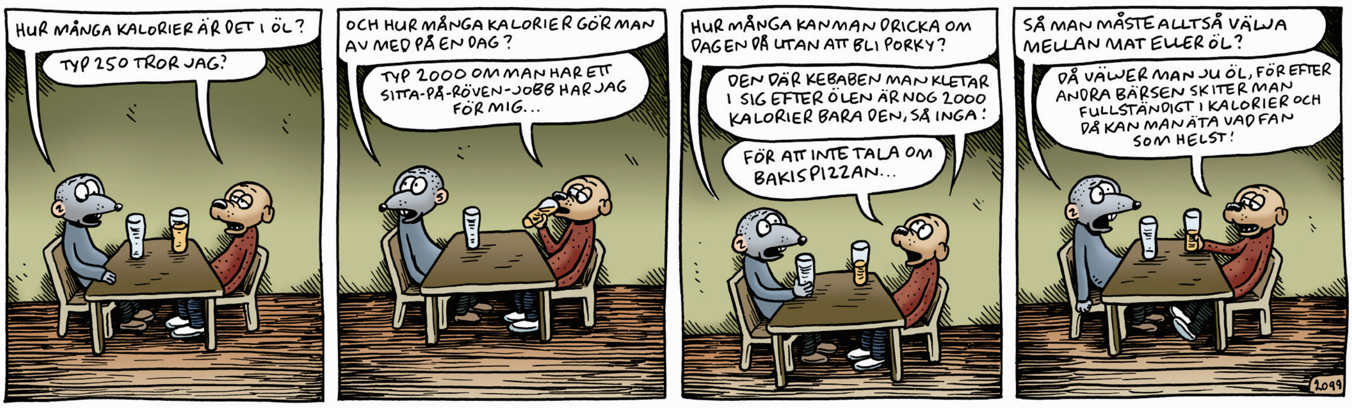
Forskarskolan för kliniker inom epidemiologi, Karolinska Institutet, stort tack till studierektor **Ylva Trolle Lagerros,** för din entusiasm och för en utbildning av hög klass. Särskilt tack till Helena Sackey, David Pettersson och Marcus Aly (samtliga från den bakre raden), för alla skämt och skratt, till och med under statistikveckorna (SIC!). Det har varit ett stort nöje att få tillgodogöra sig den här skräddarsydda forskarutbildningen i ert sällskap.

Min pappa **Andrzej,** för allt ditt stöd och för att du aldrig tvivlar på mig. Min bortgångna mamma **Zofia** som lärde mig att allting går att lösa och att tro på sig själv, mina svärföräldrar **Inger och Bo,** för all hjälp med barnlogistiken i ur och skur, min svåger **Daniel** och svägerska **Jenny,** för roliga resor och sena vin kvällar. My "sister" **Melanie** and her family; **Bruce, Jack** and **Griffin**, for encouragement, awesome shopping and lots of fun, I only wish we lived closer to each other.

Mina vänner, ingen nämnd och ingen glömd**,** tack för att jag har er och ert stöd samt för att ni så frikostigt har bjudit in hela klanen Östlund på frekventa middagar under vår "stugperiod" tillika min avhandlingsperiod. Ett särskilt stort tack till **Amy Williams**, för de operationsillustrationer du ritade och därmed räddade mig i sista sekunden.

Andreas, min man, du är det bästa som har hänt mig och du vet hur oändligt mycket jag älskar dig. Du är en klippa och min hjälte, tack för att du har stått ut!

Bianca, Adrian och Junie, våra gullungar, ni är det bästa här i livet och ni gör mig lycklig. Jag älskar er enormt mycket och jag är väldigt stolt över er.


HUR MÅNGA KALORIER ÄR DET I ÖL?
TYP 250 TROR JAG?
OCH HUR MÅNGA KALORIER GÖR MAN AV MED PÅ EN DAG?
TYP 2000 OM MAN HAR ETT SITTA-PÅ-RÖVEN-JOBB HAR JAG FÖR MIG...
HUR MÅNGA KAN MAN DRICKA OM DAGEN DÅ UTAN ATT BLI PORKY?
DEN DÄR KEBABEN MAN KLETAR I SIG EFTER ÖLEN ÄR NOG 2000 KALORIER BARA DEN, SÅ INGA!
FÖR ATT INTE TALA OM BAKISPIZZAN...
SÅ MAN MÅSTE ALLTSÅ VÄLJA MELLAN MAT ELLER ÖL?
DÅ VÄLJER MAN JU ÖL, FÖR EFTER ANDRA BÄRSEN SKITER MAN FULLSTÄNDIGT I KALORIER OCH DÅ KAN MAN ÄTA VAD FAN SOM HELST!
2099

Hämtad ur Rocky© Martin Kellerman/www.Kartago.se

13 REFERENCES

1. http://www.who.int/mediacentre/factsheets/fs311/en/index.html. WHO: WHO, 2011:Fact sheet # 311.
2. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003;289(2):187-93.
3. IASO.http://www.iaso.org/iotf/obesity/obesitytheglobalepidemic/.
4. http://www.fhi.se/PageFiles/10796/A2010-13-Levnadsvanor-lagesrapport-2010.pdf. Nationella folkhälsoenkäten. In: Folkhälsoinstitut S, editor, 2010.
5. Socialstyrelsen. Folkhälsorapport 2009. In: Socialstyrelsen, editor. 2009-126-71 ed, 2009.
6. Neovius M, Janson A, Rössner S. Prevalence of obesity in Sweden. *Obes Rev* 2006;7(1):1-3.
7. Neovius M, Teixeira-Pinto A, Rasmussen F. Shift in the composition of obesity in young adult men in Sweden over a third of a century. *Int J Obes (Lond)* 2008;32(5):832-6.
8. Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health* 2007;121(7):492-6.
9. Manhem K, Dotevall A, Wilhelmsen L, Rosengren A. Social gradients in cardiovascular risk factors and symptoms of Swedish men and women: the Goteborg MONICA Study 1995. *J Cardiovasc Risk* 2000;7(5):359-68.
10. Norberg M, Lindvall K, Stenlund H, Lindahl B. The obesity epidemic slows among the middle-aged population in Sweden while the socioeconomic gap widens. *Glob Health Action* 2010;3.
11. Ogden CL, Lamb MM, Carroll MD, Flegal KM. Obesity and socioeconomic status in children and adolescents: United States, 2005-2008. *NCHS Data Brief* 2010(51):1-8.
12. WHO Global database on body mass index. In: NHD, editor: http://apps.who.int/bmi/index.jsp?introPage=intro_1.html.
13. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 1995;141(12):1117-27.
14. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. *Eur J Clin Nutr*;64(1):16-22.
15. Montero PN, Stefanidis D, Norton HJ, Gersin K, Kuwada T. Reported excess weight loss after bariatric surgery could vary significantly depending on calculation method: a plea for standardization. *Surg Obes Relat Dis* 2011;7(4):531-4.
16. http://www.who.int/features/factfiles/obesity/facts/en/. WHO Fact sheet BMI. In: WHO, editor.

17. Vimaleswaran KS, Loos RJ. Progress in the genetics of common obesity and type 2 diabetes. *Expert Rev Mol Med*;12:1-27.
18. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;316(5826):889-94.
19. Razquin C, Marti A, Martinez JA. Evidences on three relevant obesogenes: MC4R, FTO and PPARgamma. Approaches for personalized nutrition. *Mol Nutr Food Res*;55(1):136-49.
20. Hetherington MM, Cecil JE. Gene-environment interactions in obesity. *Forum Nutr* 2010;63:195-203.
21. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115(3):e290-6.
22. Eriksson J, Forsen T, Osmond C, Barker D. Obesity from cradle to grave. *Int J Obes Relat Metab Disord* 2003;27(6):722-7.
23. Young LR, Nestle M. The contribution of expanding portion sizes to the US obesity epidemic. *Am J Public Health* 2002;92(2):246-9.
24. Smiciklas-Wright H, Mitchell DC, Mickle SJ, Goldman JD, Cook A. Foods commonly eaten in the United States, 1989-1991 and 1994-1996: are portion sizes changing? *J Am Diet Assoc* 2003;103(1):41-7.
25. Astrup A, Dyerberg J, Selleck M, Stender S. Nutrition transition and its relationship to the development of obesity and related chronic diseases. *Obes Rev* 2008;9 Suppl 1:48-52.
26. Levitsky DA, Pacanowski CR. Free will and the obesity epidemic. *Public Health Nutr*:1-16.
27. Powell LM, Auld MC, Chaloupka FJ, O'Malley PM, Johnston LD. Associations between access to food stores and adolescent body mass index. *Am J Prev Med* 2007;33(4 Suppl):S301-7.
28. Morland K, Wing S, Diez Roux A, Poole C. Neighborhood characteristics associated with the location of food stores and food service places. *Am J Prev Med* 2002;22(1):23-9.
29. Frank LD, Andresen MA, Schmid TL. Obesity relationships with community design, physical activity, and time spent in cars. *Am J Prev Med* 2004;27(2):87-96.
30. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003;289(1):76-9.
31. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*;87(1):4-14.
32. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999;282(16):1523-9.
33. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122(3):248-56 e5.

34. Rubino F, Kaplan LM, Schauer PR, Cummings DE. The Diabetes Surgery Summit Consensus Conference: Recommendations for the Evaluation and Use of Gastrointestinal Surgery to Treat Type 2 Diabetes Mellitus. *Ann Surg* 2009.
35. Ahn SM, Pomp A, Rubino F. Metabolic surgery for type 2 diabetes. *Ann N Y Acad Sci*;1212:E37-45.
36. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351(26):2683-93.
37. Rubino F, Gagner M, Gentileschi P, Kini S, Fukuyama S, Feng J, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. *Ann Surg* 2004;240(2):236-42.
38. Skurk T, Hauner H. Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 2004;28(11):1357-64.
39. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;161(13):1581-6.
40. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292(14):1724-37.
41. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67(5):968-77.
42. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007;298(17):2028-37.
43. Sjöström L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. *Int J Obes (Lond)* 2008;32 Suppl 7:S93-7.
44. Bjorge T, Engeland A, Tverdal A, Smith GD. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *Am J Epidemiol* 2008;168(1):30-7.
45. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357(8):753-61.
46. Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;307(1):56-65.
47. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Med*;9:48.
48. World Cancer Research Fund / American Institute for Cancer Research.

Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007: First published 2007 by the American Institute for Cancer Research 1759 R St. NW, Washington, DC 20009, 2007.

49. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4(8):579-91.

50. Pollak M. Insulin-like growth factor physiology and cancer risk. *European journal of cancer* 2000;36(10):1224-8.

51. Pischon T, Nothlings U, Boeing H. Obesity and cancer. *Proc Nutr Soc* 2008;67(2):128-45.

52. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;335(7630):1134.

53. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371(9612):569-78.

54. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348(17):1625-38.

55. Adams KF, Leitzmann MF, Albanes D, Kipnis V, Mouw T, Hollenbeck A, et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. *Am J Epidemiol* 2007;166(1):36-45.

56. Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. *Int J Cancer* 2001;91(3):421-30.

57. Rapp K, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, et al. Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. *Ann Oncol* 2008;19(4):641-8.

58. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006;296(2):193-201.

59. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev* 2007;16(1):63-9.

60. Adams TD, Stroup AM, Gress RE, K FA, Calle EE, Smith SC, et al. Cancer Incidence and Mortality After Gastric Bypass Surgery. *Obesity (Silver Spring)* 2009;17(4):796-802.

61. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. *Surg Obes Relat Dis* 2008;4(6):691-5.

62. Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol* 2009;10(7):653-62.

63. Engeland A, Bjorge T, Selmer RM, Tverdal A. Height and body mass index in relation to total mortality. *Epidemiology* 2003;14(3):293-9.

64. Freedman DM, Ron E, Ballard-Barbash R, Doody MM, Linet MS. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes (Lond)* 2006;30(5):822-9.

65. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;341(15):1097-105.
66. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373(9669):1083-96.
67. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *The New England journal of medicine* 1998;338(1):1-7.
68. Christou NV. Impact of obesity and bariatric surgery on survival. *World J Surg* 2009;33(10):2022-7.
69. Christou NV, MacLean LD. Effect of bariatric surgery on long-term mortality. *Adv Surg* 2005;39:165-79.
70. Flum DR, Dellinger EP. Impact of gastric bypass operation on survival: a population-based analysis. *J Am Coll Surg* 2004;199(4):543-51.
71. Jeffery RW, French SA. Preventing weight gain in adults: the pound of prevention study. *Am J Public Health* 1999;89(5):747-51.
72. Proper KI, Hildebrandt VH, Van der Beek AJ, Twisk JW, Van Mechelen W. Effect of individual counseling on physical activity fitness and health: a randomized controlled trial in a workplace setting. *Am J Prev Med* 2003;24(3):218-26.
73. Slentz CA, Duscha BD, Johnson JL, Ketchum K, Aiken LB, Samsa GP, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE--a randomized controlled study. *Arch Intern Med* 2004;164(1):31-9.
74. Brown T, Avenell A, Edmunds LD, Moore H, Whittaker V, Avery L, et al. Systematic review of long-term lifestyle interventions to prevent weight gain and morbidity in adults. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2009;10(6):627-38.
75. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *WMJ* 1998;97(9):20-1, 24-5, 27-37.
76. Agency EM. GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS USED IN WEIGHT CONTROL. London, 1 June 2006 CPMP/EWP/281/96 Rev.1.
77. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *Lancet* 2007;369(9555):71-7.
78. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* 2007;335(7631):1194-9.
79. Hauptman JB, Jeunet FS, Hartmann D. Initial studies in humans with the novel gastrointestinal lipase inhibitor Ro 18-0647 (tetrahydrolipstatin). *Am J Clin Nutr* 1992;55(1 Suppl):309S-13S.
80. Torgerson JS, Hauptman J, Boldrin MN, Sjöstrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27(1):155-61.

81. Aylwin S, Al-Zaman Y. Emerging concepts in the medical and surgical treatment of obesity. *Front Horm Res* 2008;36:229-59.
82. Lewis LA, Turnbull RB, Jr., Page IH. Effects of jejunocolic shunt on obesity, serum lipoproteins, lipids, and electrolytes. *Arch Intern Med* 1966;117(1):4-16.
83. Delena SA, Fechner RE, Brown H, Shelton EL, Jr. Reversible fatty liver with fibrosis following jejunocolic shunt. *South Med J* 1970;63(4):399-402.
84. Payne JH, DeWind LT. Surgical treatment of obesity. *Am J Surg* 1969;118(2):141-7.
85. Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg* 2009;19(12):1605-11.
86. Årsrapport SOReg 2010.
87. Ingmar Näslund et al. NATIONELLA INDIKATIONER FÖR OBESITAS-KIRURGI. 2009(2.0).
88. Blackburn GL, Hutter MM, Harvey AM, Apovian CM, Boulton HR, Cummings S, et al. Expert panel on weight loss surgery: executive report update. *Obesity (Silver Spring)* 2009;17(5):842-62.
89. Dorman RB, Abraham AA, Al-Refaie WB, Parsons HM, Ikramuddin S, Habermann EB. Bariatric Surgery Outcomes in the Elderly: An ACS NSQIP Study. *J Gastrointest Surg* 2011.
90. Marsk R, Freedman J, Tynelius P, Rasmussen F, Näslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. *Ann Surg* 2008;248(5):777-81.
91. Nguyen NT, Hinojosa M, Fayad C, Varela E, Wilson SE. Use and outcomes of laparoscopic versus open gastric bypass at academic medical centers. *J Am Coll Surg* 2007;205(2):248-55.
92. Weller WE, Rosati C. Comparing outcomes of laparoscopic versus open bariatric surgery. *Ann Surg* 2008;248(1):10-5.
93. Printen KJ, Mason EE. Gastric surgery for relief of morbid obesity. *Arch Surg* 1973;106(4):428-31.
94. Gomez CA. Gastroplasty in the surgical treatment of morbid obesity. *Am J Clin Nutr* 1980;33(2 Suppl):406-15.
95. Linner JH. Comparative effectiveness of gastric bypass and gastroplasty: a clinical study. *Arch Surg* 1982;117(5):695-700.
96. Olsson SA, Nilsson-Ehle P, Pettersson BG, Sorbris R. Gastroplasty as a treatment for massive obesity. A clinical and biochemical evaluation. *Scand J Gastroenterol* 1985;20(2):215-21.
97. Mason EE. Vertical banded gastroplasty for obesity. *Arch Surg* 1982;117(5):701-6.
98. Sugerman HJ, Kellum JM, Jr., DeMaria EJ, Reines HD. Conversion of failed or complicated vertical banded gastroplasty to gastric bypass in morbid obesity. *Am J Surg* 1996;171(2):263-9.
99. Marsk R, Jonas E, Gartzios H, Stockeld D, Granström L, Freedman J. High revision rates after laparoscopic vertical banded gastroplasty. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery* 2009;5(1):94-8.

100. van Gemert WG, van Wersch MM, Greve JW, Soeters PB. Revisional surgery after failed vertical banded gastroplasty: restoration of vertical banded gastroplasty or conversion to gastric bypass. *Obes Surg* 1998;8(1):21-8.
101. Hall JC, Watts JM, O'Brien PE, Dunstan RE, Walsh JF, Slavotinek AH, et al. Gastric surgery for morbid obesity. The Adelaide Study. *Ann Surg* 1990;211(4):419-27.
102. Balsiger BM, Poggio JL, Mai J, Kelly KA, Sarr MG. Ten and more years after vertical banded gastroplasty as primary operation for morbid obesity. *J Gastrointest Surg* 2000;4(6):598-605.
103. Olbers T, Fagevik-Olsen M, Maleckas A, Lönroth H. Randomized clinical trial of laparoscopic Roux-en-Y gastric bypass versus laparoscopic vertical banded gastroplasty for obesity. *Br J Surg* 2005;92(5):557-62.
104. O'Brien PE, Dixon JB. Weight loss and early and late complications--the international experience. *Am J Surg* 2002;184(6B):42S-45S.
105. Himpens J, Dobbeleir J, Peeters G. Long-term results of laparoscopic sleeve gastrectomy for obesity. *Ann Surg* 2010;252(2):319-24.
106. Weiner RA, Weiner S, Pomhoff I, Jacobi C, Makarewicz W, Weigand G. Laparoscopic sleeve gastrectomy--influence of sleeve size and resected gastric volume. *Obes Surg* 2007;17(10):1297-305.
107. Shi X, Karmali S, Sharma AM, Birch DW. A review of laparoscopic sleeve gastrectomy for morbid obesity. *Obes Surg* 2010;20(8):1171-7.
108. Papailiou J, Albanopoulos K, Toutouzas KG, Tsigris C, Nikiteas N, Zografos G. Morbid obesity and sleeve gastrectomy: how does it work? *Obes Surg* 2010;20(10):1448-55.
109. Bohdjalian A, Langer FB, Shakeri-Leidenmuhler S, Gfrerer L, Ludvik B, Zacherl J, et al. Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin. *Obes Surg* 2010;20(5):535-40.
110. Sarela AI, Dexter SP, O'Kane M, Menon A, McMahon MJ. Long-term follow-up after laparoscopic sleeve gastrectomy: 8-9-year results. *Surg Obes Relat Dis* 2011.
111. Borg CM, le Roux CW, Ghatei MA, Bloom SR, Patel AG, Aylwin SJ. Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. *Br J Surg* 2006;93(2):210-5.
112. Falken Y, Hellström PM, Holst JJ, Näslund E. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: role of gut peptides. *J Clin Endocrinol Metab* 2011;96(7):2227-35.
113. Azagury DE, Abu Dayyeh BK, Greenwalt IT, Thompson CC. Marginal ulceration after Roux-en-Y gastric bypass surgery: characteristics, risk factors, treatment, and outcomes. *Endoscopy* 2011.
114. Abell TL, Minocha A. Gastrointestinal complications of bariatric surgery: diagnosis and therapy. *Am J Med Sci* 2006;331(4):214-8.
115. Parakh S, Soto E, Merola S. Diagnosis and management of internal hernias after laparoscopic gastric bypass. *Obes Surg* 2007;17(11):1498-502.

116. Scopinaro N, Gianetta E, Adami GF, Friedman D, Traverso E, Marinari GM, et al. Biliopancreatic diversion for obesity at eighteen years. *Surgery* 1996;119(3):261-8.

117. Marceau P, Hould FS, Simard S, Lebel S, Bourque RA, Potvin M, et al. Biliopancreatic diversion with duodenal switch. *World J Surg* 1998;22(9):947-54.

118. Hess DS. Biliopancreatic diversion with duodenal switch. *Surg Obes Relat Dis* 2005;1(3):329-33.

119. Griffen WO, Jr., Bivins BA, Bell RM. The decline and fall of the jejunoileal bypass. *Surg Gynecol Obstet* 1983;157(4):301-8.

120. Requarth JA, Burchard KW, Colacchio TA, Stukel TA, Mott LA, Greenberg ER, et al. Long-term morbidity following jejunoileal bypass. The continuing potential need for surgical reversal. *Arch Surg* 1995;130(3):318-25.

121. Marsk R, Tynelius P, Rasmussen F, Freedman J. Short-term morbidity and mortality after open versus laparoscopic gastric bypass surgery. A population-based study from Sweden. *Obes Surg* 2009;19(11):1485-90.

122. Nguyen NT, Rivers R, Wolfe BM. Early gastrointestinal hemorrhage after laparoscopic gastric bypass. *Obes Surg* 2003;13(1):62-5.

123. Heneghan HM, Meron-Eldar S, Yenumula P, Rogula T, Brethauer SA, Schauer PR. Incidence and management of bleeding complications after gastric bypass surgery in the morbidly obese. *Surg Obes Relat Dis* 2011.

124. Siilin H, Wanders A, Gustavsson S, Sundbom M. The proximal gastric pouch invariably contains acid-producing parietal cells in Roux-en-Y gastric bypass. *Obes Surg* 2005;15(6):771-7.

125. Lee CW, Kelly JJ, Wassef WY. Complications of bariatric surgery. *Curr Opin Gastroenterol* 2007;23(6):636-43.

126. Fernandez AZ, Jr., DeMaria EJ, Tichansky DS, Kellum JM, Wolfe LG, Meador J, et al. Experience with over 3,000 open and laparoscopic bariatric procedures: multivariate analysis of factors related to leak and resultant mortality. *Surg Endosc* 2004;18(2):193-7.

127. Gonzalez R, Nelson LG, Gallagher SF, Murr MM. Anastomotic leaks after laparoscopic gastric bypass. *Obes Surg* 2004;14(10):1299-307.

128. Spyropoulos C, Argentou MI, Petsas T, Thomopoulos K, Kehagias I, Kalfarentzos F. Management of gastrointestinal leaks after surgery for clinically severe obesity. *Surg Obes Relat Dis* 2011.

129. Olbers T, Lönroth H, Fagevik-Olsen M, Lundell L. Laparoscopic gastric bypass: development of technique, respiratory function, and long-term outcome. *Obes Surg* 2003;13(3):364-70.

130. Durak E, Inabnet WB, Schrope B, Davis D, Daud A, Milone L, et al. Incidence and management of enteric leaks after gastric bypass for morbid obesity during a 10-year period. *Surg Obes Relat Dis* 2008;4(3):389-93.

131. Escalante-Tattersfield T, Tucker O, Fajnwaks P, Szomstein S, Rosenthal RJ. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2008;4(2):126-30.

132. Gonzalez R, Haines K, Nelson LG, Gallagher SF, Murr MM. Predictive factors of thromboembolic events in patients undergoing Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2006;2(1):30-5; discussion 35-6.

133. Ahmad J, Martin J, Ikramuddin S, Schauer P, Slivka A. Endoscopic balloon dilation of gastroenteric anastomotic stricture after laparoscopic gastric bypass. *Endoscopy* 2003;35(9):725-8.

134. Carrodeguas L, Szomstein S, Zundel N, Lo Menzo E, Rosenthal R. Gastrojejunal anastomotic strictures following laparoscopic Roux-en-Y gastric bypass surgery: analysis of 1291 patients. *Surg Obes Relat Dis* 2006;2(2):92-7.

135. Da Costa M, Mata A, Espinos J, Vila V, Roca JM, Turro J, et al. Endoscopic dilation of gastrojejunal anastomotic strictures after laparoscopic gastric bypass. Predictors of initial failure. *Obes Surg* 2011;21(1):36-41.

136. Matthews BD, Sing RF, DeLegge MH, Ponsky JL, Heniford BT. Initial results with a stapled gastrojejunostomy for the laparoscopic isolated roux-en-Y gastric bypass. *Am J Surg* 2000;179(6):476-81.

137. Cho M, Pinto D, Carrodeguas L, Lascano C, Soto F, Whipple O, et al. Frequency and management of internal hernias after laparoscopic antecolic antegastric Roux-en-Y gastric bypass without division of the small bowel mesentery or closure of mesenteric defects: review of 1400 consecutive cases. *Surg Obes Relat Dis* 2006;2(2):87-91.

138. Carmody B, DeMaria EJ, Jamal M, Johnson J, Carbonell A, Kellum J, et al. Internal hernia after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2005;1(6):543-8.

139. Champion JK, Williams M. Small bowel obstruction and internal hernias after laparoscopic Roux-en-Y gastric bypass. *Obes Surg* 2003;13(4):596-600.

140. Higa K, Ho T, Tercero F, Yunus T, Boone KB. Laparoscopic Roux-en-Y gastric bypass: 10-year follow-up. *Surg Obes Relat Dis* 2011;7(4):516-25.

141. Garza E, Jr., Kuhn J, Arnold D, Nicholson W, Reddy S, McCarty T. Internal hernias after laparoscopic Roux-en-Y gastric bypass. *Am J Surg* 2004;188(6):796-800.

142. O'Rourke RW. Management strategies for internal hernia after gastric bypass. *J Gastrointest Surg* 2011;15(6):1049-54.

143. Bauman RW, Pirrello JR. Internal hernia at Petersen's space after laparoscopic Roux-en-Y gastric bypass: 6.2% incidence without closure--a single surgeon series of 1047 cases. *Surg Obes Relat Dis* 2009;5(5):565-70.

144. Nguyen NT, Paya M, Stevens CM, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. *Ann Surg* 2004;240(4):586-93; discussion 93-4.

145. Mabee TM, Meyer P, DenBesten L, Mason EE. The mechanism of increased gallstone formation in obese human subjects. *Surgery* 1976;79(4):460-8.

146. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr* 1992;55(3):652-8.

147. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. *N Engl J Med* 1989;321(9):563-9.

148. Li VK, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. *Surg Endosc* 2009;23(7):1640-4.

149. Jonas E, Marsk R, Rasmussen F, Freedman J. Incidence of postoperative gallstone disease after antiobesity surgery: population-based study from Sweden. *Surg Obes Relat Dis* 2009.

150. Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Spitz AF, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Obesity (Silver Spring)* 2009;17 Suppl 1:S1-70, v.

151. Koch TR, Finelli FC. Postoperative metabolic and nutritional complications of bariatric surgery. *Gastroenterol Clin North Am* 2010;39(1):109-24.

152. Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. *Curr Opin Clin Nutr Metab Care* 2004;7(5):569-75.

153. Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, et al. Inter-disciplinary European guidelines on surgery of severe obesity. *Int J Obes (Lond)* 2007;31(4):569-77.

154. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007;357(8):741-52.

155. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. *Cochrane Database Syst Rev* 2009(2):CD003641.

156. Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361(5):445-54.

157. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 2007;142(4):621-32; discussion 32-5.

158. Sundbom M, Karlson BM. Low mortality in bariatric surgery 1995 through 2005 in Sweden, in spite of a shift to more complex procedures. *Obes Surg* 2009;19(12):1697-701.

159. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;24(11):659-67.

160. Kvalitet och innehåll i patientregistret, Utskrivningar från slutenvården 1964–2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997–2007. In: Socialstyrelsen, editor: Publicerad http://www.socialstyrelsen.se, juni 2009
Andra publiceringen, 23:e juni 2009: Korrigerad tabell 3, sid 17.

161. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
162. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009;48(1):27-33.
163. http://www.socialstyrelsen.se/register/dodsorsaksregistret/bortfallochkvalitet. Socialstyrelsen, Dödsorsaksregistret.
164. http://www.scb.se/Pages/List____257507.aspx. Folk- och bostadsräkningar, FoB: Statistiska centralbyrån, SCB.
165. Rothman KJ. *Epidemiology: an introduction*: Oxford University Press Inc., 198 Madison avenue, New York, New York 10016, 2002.