

From DEPARTMENT OF MEDICINE  
Karolinska Institutet, Stockholm, Sweden

**SEVERE OBESITY IN YOUNG ADULTS**

**- CHARACTERIZATION AND TREATMENT  
OUTCOMES WITH EMPHASIS ON  
MENTAL HEALTH ASPECTS**

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**Karolinska  
Institutet**

Stockholm 2018

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Published by Karolinska Institutet.

Printed by E-print AB

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ISBN 978-91-7831-104-0

# Severe obesity in young adults - Characterization and treatment outcomes with emphasis on mental health aspects

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*“Inside you vault opens behind vault endlessly.  
You will never be complete, that's how it's meant to be.”*

Tomas Tranströmer, *Romanesque Arches*, *New Collected Poems*



## ABSTRACT

**Background:** Obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) is associated with a range of physical and psychiatric comorbidities and premature mortality. Young adulthood (here 16-25 years) constitutes a vulnerable period for weight gain, poor weight loss results, and mental health problems. Up to 8.3% of Swedish young adults are classified as obese. In spite of the fact that the peak incidence for obesity occurs during young adulthood, this age period has been generally overlooked in clinical obesity research, particularly in regard to obesity-related mental health problems.

**Aim:** To characterize severe obesity (BMI  $\geq 35$  kg/m<sup>2</sup>) in young adulthood (16-25 years) with emphasis on mental health aspects, and to study long-term outcomes (weight loss, adverse events, loss-to-follow-up and health-related quality of life [HRQL]) in young (18-25 years) vs older ( $\geq 26$  years) adults after Roux-en-Y gastric bypass (RYGB).

**Methods:** In Study I, we used cross-sectional self-reported questionnaire data on obesity-related comorbidities, mental health, self-esteem, lifestyle and health-related quality of life; physical fitness tests; biochemical data on micronutritional deficiencies; and anthropometry from n=165 young adults, aged 16-25 years who were about to start treatment at the Karolinska University Hospital Obesity Center. In Study II, we compared cross-sectional questionnaire patient data (n=121 treatment-seekers to the Obesity Center, 18-25 years) on mental distress, self-reported suicide attempts, physical/psychosomatic symptoms, and quality of life with data on n=363 normal-weight responders to the Stockholm Public Health Cohort 2010 who were individually matched 3:1 for age, gender and socioeconomic status. For Studies III-IV, we frequency matched n=3,531 young (18-25 years) to n=17,137 older (26-74 years) patients in the Scandinavian Obesity Surgery Registry for BMI, gender and year of surgery to compare weight loss, adverse events, loss-to-follow-up and changes in HRQL between matching groups.

**Results:** In Study I, we found consistent indications of poor mental and obesity-related health problems (up to 55%), high levels of cardiometabolic risk factors (up to 82%) and micronutritional deficiencies (48%) in treatment-seeking young adults (mean BMI 39.2 kg/m<sup>2</sup> [SD: 5.2], 80% women). In Study II, we found an increased risk of mental distress (adjusted relative risk [RR]=1.76, 95% CI: 1.38-2.24), suicide attempts (adjusted RR=2.04, 95% CI: 1.06-3.95), physical/psychosomatic symptoms (adjusted RR=1.59-2.95) and poor quality of life (range of adjusted RR=1.97-6.61) in obese treatment-seekers (mean BMI 39.8 kg/m<sup>2</sup> [SD: 5.3], 81% women) compared to population controls (mean BMI 22.4 kg/m<sup>2</sup> [SD: 4.0], 81% women). In Study III, a total of n=369 young (37.0% of eligible) and n=2,210 older (46.1%) adults were followed-up 5 years after RYGB. Young adults displayed higher weight loss (31.8% vs 28.2%) at 5 years, more long-term adverse events (any kind of adverse events between 2-5 years: 20.3% vs 12.7%, adjusted OR=1.72, 95% CI: 1.29-2.31; serious adverse events between 2-5 years [Clavien-Dindo  $\geq 3$ b]: 14.1% vs 6.9%, adjusted OR=2.06, 95% CI: 1.45-2.92) and higher loss-to-follow-up throughout the study period (range of adjusted

RR=1.16-2.13), all,  $p < 0.001$ . In Study IV,  $n=138$  young (20.7% of those eligible) and  $n=1,021$  older (31.8%) adults were available for follow-up 5 years post-RYGB. Both young and older adults displayed clinically relevant improvements in physical HRQL 5 years after RYGB compared to baseline values, while no change or deterioration in mental HRQL was observed in both groups. Older adults generally experienced greater HRQL improvements than the young adults in adjusted analyses.

**Conclusion:** Treatment-seeking young adults with severe obesity constitute a vulnerable patient group with a wide array of obesity-related comorbidities, particularly mental health issues. While we found promising weight loss results and improvements in physical HRQL in young adults 5 years after RYGB, there were also higher numbers of long-term adverse events, drop-outs and generally poor improvements in HRQL in young vs older adults. Future research needs to address the impact of mental distress on the development and treatment of obesity in young adults. Studies on the significance of and the etiology behind our data showing more serious adverse events and higher loss-to-follow-up in the younger RYGB-patients are needed.

**Key words:** Young adult, obesity, mental health, RYGB, weight loss, adverse event, loss-to-follow-up, HRQL.



## LIST OF SCIENTIFIC PAPERS

- I. Dreber H, Reynisdottir S, Angelin B, Hemmingsson E. Who is the treatment-seeking young adult with severe obesity? – A comprehensive characterization with emphasis on mental health. PLoS One. 2015 Dec 22;10(12):e0145273
- II. Dreber H, Reynisdottir S, Angelin B, Tynelius F, Rasmussen F, Hemmingsson E. Mental distress in treatment-seeking young adults (18-25 years) with severe obesity compared with population controls of different body mass index levels: cohort study. Clin Obes. 2017 Feb;7(1):1-10.
- III. Dreber H, Thorell A, Torgerson J, Reynisdottir S, Hemmingsson E. Weight loss, adverse events and loss-to-follow-up 5 years after Roux-en-Y gastric bypass in young (18-25 y) versus older ( $\geq 26$  y) adults: a Scandinavian Obesity Surgery Registry Study.  
*Submitted*
- IV. Dreber H, Thorell A, Reynisdottir S, Hemmingsson E. Health-related quality of life 5 years after Roux-en-Y gastric bypass in young (18-25 y) versus older ( $\geq 26$  y) adults: a Scandinavian Obesity Surgery Registry Study.  
*Submitted*

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## LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AMOS	Adolescent Morbid Obesity Surgery Study
ASRS	ADHD Self-Report Scale
BMI	Body mass index
CI	Confidence interval
EQ-5D	EuroQol-5D
EWL	Excessive weight loss
GBP	Gastric bypass
GHQ-12	Twelve item General Health Questionnaire
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HRQL	Health-related quality of life
IRR	Incidence rate ratio
KSQ	Karolinska Sleep Questionnaire
OP	Obesity-related Problems scale
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
RSES	Rosenberg Self-Esteem Scale
RYGB	Roux-en-Y gastric bypass
SF-36	Short Form Health Survey SF-36
SOReg	Scandinavian Obesity Surgery Registry
SOS	Swedish Obese Subjects
T2DM	Diabetes mellitus type 2
WHO	World Health Organization



# 1 INTRODUCTION

Obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) is one of the major drivers behind today's global burden of disease <sup>1,2</sup>, and is estimated to account for 10-13% of deaths in the European region <sup>3</sup>. Obesity may develop at any time in life, although certain age periods have been pinpointed as more or less vulnerable to weight gain. Young adulthood, i.e. the period between adolescence and independent adulthood, has been identified as one such high-risk period. Young adulthood constitutes the fastest weight-gaining period in life, mainly through the profound physiological and psychosocial changes that take place during these years <sup>4-8</sup>. Notably, weight gain during young adulthood is a better predictor of cancer and mortality than weight gain in later adulthood <sup>9,10</sup>.

In 2007, a separate section for young adults (here defined as 16-25 years) with obesity was opened at the Obesity Center (Överviktscentrum) at the Karolinska University Hospital. The Obesity Center was the first, and is still the only, clinic in Sweden to provide specialized care for this vulnerable patient group. The specific focus on young adults with obesity is rare also in an international perspective.

Throughout their clinical work, the clinicians at the Obesity Center have observed numerous and serious psychosocial issues among the young adult patients. Moreover, the clinicians were frequently faced with the major dilemma of whether young adults who displayed poor behavioral weight reduction should be referred for bariatric surgery. This dilemma arose because young adults had seldom been included in the major studies that showed health benefits after bariatric surgery. Given the unique traits of the young adulthood period, we hypothesized that we could not rely on generalization of results from adult samples.

Despite clear findings from population cohorts on the risks of obesity in young adulthood, including premature mortality and an increased incidence in cardiovascular disease <sup>11-19</sup>, we found that young adults had generally been overlooked in clinical obesity research compared to children and older adults <sup>20</sup>. We were thus faced with a patient group at risk but without age-specific guidelines to refer to.

The research questions in the present thesis emanate from the above mentioned clinical perceptions and were developed in collaboration with clinicians at the Obesity Center at the Karolinska University Hospital.



## 2 LITERATURE REVIEW

### 2.1 OBESITY

#### Definition

Obesity is defined by the World Health Organization (WHO) as an excess of body adiposity with negative health consequences<sup>21</sup>, and was declared a disease by the American Heart Association in 2013<sup>22</sup>. The positive association between obesity and pathology was, however, recognized by Hippocrates as early as 400 BC when he acknowledged that “Corpulence is not only a disease itself, but the harbinger of others”.

The definition of excess adiposity at the population level is based upon BMI (weight [kg] divided by height [m]<sup>2</sup>), and is defined as BMI  $\geq 30$  kg/m<sup>2</sup> in adults, while the cut-off in <18 year-olds, is at plus two standard deviations of BMI for age and sex<sup>21 23 24</sup>. BMI displays a J-shaped association with all-cause mortality<sup>25</sup>, and obesity is classified into class I (30.0-34.9 kg/m<sup>2</sup>), class II (35.0-39.9 kg/m<sup>2</sup>) and class III ( $\geq 40.0$  kg/m<sup>2</sup>) obesity<sup>26</sup>. BMI  $\geq 35$  kg/m<sup>2</sup> is defined as severe obesity. At an individual level, BMI may inaccurately assess excess adiposity since skeletal muscle mass is not taken into account in the BMI calculation. Moreover, fat distribution (central/peripheral fat deposits) is more strongly associated with obesity-related morbidity than BMI<sup>27</sup>, and ethnic- and age-dependent variations in BMI-related comorbidities exist<sup>28 29</sup>, which together further complicate the applicability of BMI. Despite the above-mentioned limitations, the concept of BMI is generally used in clinical work, while more precise measurements of adiposity such as magnetic resonance scanning are not applicable in a clinical setting given the high frequency of obesity in today’s society.

Obesity is increasing worldwide with no signs of levelling off. Globally, the prevalence has nearly doubled compared to 1980<sup>5</sup>. In total, 12% of adults and 5% of children worldwide are classified as obese<sup>5</sup>. The peak prevalence for obesity is 60-64 years among women, and 50-54 years among men<sup>5</sup>. In Sweden, 15% of Swedish 16- to 84-year-old men and women were classified as obese in 2016 according to self-reported data, indicating an increase from 11% in 2011<sup>30</sup>. According to a study from 2008<sup>31</sup>, the cost of obesity in Sweden totals SEK 3,600 million (equivalent to 1.9% of the Swedish Gross Domestic Product) spent on health care.

#### Pathogenesis

Obesity is a consequence of the individual’s susceptibility to environmental triggers that lead to caloric overconsumption relative to his/her bodily needs in terms of activity level and metabolism<sup>32</sup>. Why calories may supersede need is suggested to largely be a consequence of ingested calories per se, rather than due to differences in calorie activity depending on dietary source<sup>33 34</sup>. Energy homeostasis is delicately controlled by neurohormonal inner pathways in concordance with external signals that trigger hunger, and satiety signals to defend against weight change irrespective of present weight (set-point theory)<sup>35-37</sup>.

External signals include the changing global food environment and an increased availability and affordability of energy-dense nutrition in the last 40 years, which is proposed to account for the recent sharp rise in incidence and prevalence of obesity<sup>38</sup>. Conflicting evidence exists as to what degree decreased physical activity actually contributes to the upshift in energy homeostasis given that the major change in decreased energy output occurred before the rise in the obesity epidemic<sup>39</sup>. Instead, physical activity is suggested to play a significant role in weight maintenance and regulation in calorie intake, rather than by direct contribution to caloric imbalance per se<sup>40</sup>.

Other external factors such as endocrine disruptors, infections, ambient temperature and antibiotics are suggested to change and disturb the internal homeostasis, thereby contributing to long-term energy storage surplus<sup>41-43</sup>, via for example hypothalamic inflammation<sup>44-45</sup>. Moreover, behavioral factors including sleep deprivation, smoking cessation and time discounting are also suggested to play a role in flipping the energy homeostasis and thereby impacting on weight status<sup>46-48</sup>. Importantly, there is a strong association between obesity and socioeconomic status, with a positive association in developing countries and an inverse relationship in developed countries (applies to both children and adults), although the exact mechanisms for this are still to be revealed<sup>49-51</sup>.

The recent steep rise in obesity prevalence supports a multifactorial pathogenesis, rather than a single gene, as the causative agent in creating a positive energy balance and ultimately obesity. Single identifiable obesity-prone genetic mutations are rare<sup>52</sup>, but studies on monogenetic twins display around 70% concordance on fat mass and dizygotic twins display around 32% concordance<sup>53</sup>, together supporting a partly genetic etiology of obesity. Hereditary traits may predispose to obesity via external triggers and effects on hunger, satiety and food intake<sup>53</sup>. For example, a certain gene polymorphism may predispose to food palatability, eating for reasons other than hunger, and physical activity dependent effects on weight<sup>54</sup>.

Once obesity has manifested in an individual, compensatory processes counteract weight loss, thereby favoring long-term excess adiposity (the set-point theory)<sup>36-37-55</sup>. Here, hormonal responses, such as leptin deficiency and the recently launched theory of an osteocyte pathway are suggested to contribute<sup>56-57</sup>. Considering these modern theories of obesity pathogenesis, obesity is today regarded as a two-stage disease: one step with a sustained positive energy balance (accumulation of fat mass), and another that resets the body weight set-point at a higher-than-before value (maintaining fat mass)<sup>33</sup>. Which of these two stages come first is, however, part of current research discussion.

Given the multifactorial pathogenesis of obesity, obesity was recently reevaluated as having a common phenotype with heterogeneous etiologies, rather than the previously prevailing “one-disease” approach<sup>58</sup>. Possibly, this new perspective on obesity may clarify the differing roles of genetics, demographics and life style in the pathogenesis of excess adiposity.



## **Obesity-related mortality and morbidity**

Obesity is clearly associated with low quality of life <sup>59</sup>, and physical, psychiatric as well as social consequences of obesity may contribute to limitations in everyday life:

Obesity is associated with premature mortality according to repeated pooled, prospective studies, and cardiovascular diseases constitute the major part of obesity-related mortality and morbidity <sup>25 60-62</sup>. Diabetes mellitus type 2 (T2DM) was identified as the second leading cause of obesity-associated *mortality*, while chronic kidney disease was identified as the second leading cause of obesity-associated *morbidity* <sup>5 63</sup>.

Cancer incidence has been positively associated with BMI according to several meta-analyses <sup>64-66</sup> with relative risks (RR) of 1.2-1.5 for each 5 kg/m<sup>2</sup> increase in BMI when compared to the risk in normal weight individuals (esophageal, breast, renal, thyroid, colon and endometrial cancer) <sup>64</sup>.

Besides cardiovascular diseases and cancer, obesity-related diseases include osteoarthritis, infertility, polycystic ovary syndrome, sleep apnea, anxiety and depression among others <sup>67-69</sup>. Despite clear associations between obesity and the above-mentioned disorders/symptomatology at a population level, obesity must be viewed as a highly heterogeneous disorder in individual patients because specific BMI levels are by no means directly correlated to disease levels. Instead, obesity-related comorbidities are suggested to be conditioned on visceral/peripheral fat, adiposopathy, physical activity levels and nutritional quality, rather than body weight per se <sup>27</sup>.

## **Obesity treatment: Behavioral weight reduction, pharmacotherapy and bariatric surgery**

Obesity treatment aims to provide the patients with strategies to reduce their total caloric surplus, either by lifestyle interventions, low-calorie diets, pharmacological treatments and/or bariatric surgery. Weight loss  $\geq 5\%$  is considered to affect physical health in a clinically positive way <sup>70</sup>.

### *Behavioral weight reduction and low-calorie diets*

Sustained life style interventions, i.e. lowering caloric intake and increasing energy output, may together lead to weight loss <sup>71 72</sup>, although the variability between individuals is large <sup>58</sup>.

Intensive support and monitoring are proven to sustain 5% weight loss up to 8 years after intervention <sup>72</sup>. Notably, no difference in long-term weight loss has been observed between different kinds of diet regimens <sup>73 74</sup>, and recent research failed to demonstrate positive associations for interactions between genes, insulin secretion or effects of certain dietary compositions <sup>34</sup>.

Besides weight loss, (intensive) lifestyle interventions displayed other positive side effects on health such as improved cardiovascular biomarkers, reduced incidence of T2DM and lower

liver fat, depression rates, urinary incontinence, knee pain, sleep apnea and need for antidiabetic medications (from the Look AHEAD and Diabetes Prevention Program studies) among others <sup>71 75-80</sup>.

Lifestyle interventions may also be supplemented by low or very low calorie diets, which, according to a meta-analysis resulted in 5.0-6.3% weight loss at a mean of 1.9 years after completing the low calorie diet <sup>81</sup>.

### *Pharmacotherapy*

Three anti-obesity drugs have been approved in Sweden for patients with BMI  $\geq 30$  kg/m<sup>2</sup> or BMI  $\geq 27$  kg/m<sup>2</sup> together with obesity-related comorbidities: orlistat, naltrexone/bupropion and liraglutide.

Orlistat (launched in 1999) acts by inhibiting pancreatic lipase, whereby the uptake of fatty acids is reduced by 30%. The total weight reduction is about 10.2% after 1 year if combined with lifestyle interventions (vs 6.2% in placebo group); patients on Orlistat regained less weight during year 2 and also showed higher reductions in cardiometabolic risk markers than patients who switched to placebo <sup>82</sup>.

Recently, two new anti-obesity agents were approved in Sweden: 1) the combined pill with naltrexone/bupropion, and 2) liraglutide. Naltrexon is an opioid receptor antagonist, while bupropion is a dopamine/norepinephrine reuptake inhibitor, together giving sustained decrease in appetite. The average weight loss for patients on naltrexone/bupropion was 9.3% compared to 5.1% on placebo <sup>83</sup>, and a HbA1c-level  $\leq 7.0$  was reached in 44.1% (on naltrexone/bupropion) vs 26.3% on placebo after 56 weeks <sup>84</sup>.

Liraglutide is a GLP-1 analogue, which acts via neuronal pathways to slow down gastric emptying and increase satiety <sup>85</sup>. At 56 weeks, weight loss was 5.8 kg more for patients on liraglutide vs placebo, and 3.8 kg more than those on Orlistat. Furthermore, blood pressure and the prevalence of metabolic syndrome and prediabetes were lower in the active treatment group <sup>86</sup>. All-cause mortality has been proven reduced in patients on Liraglutide compared to placebo (HR [hazard ratio] =0.85, 95% CI [confidence interval]: 0.74-0.97) <sup>87</sup>.

Combined interventions with medications and lifestyle changes demonstrate more weight loss compared to medication or lifestyle changes alone <sup>88</sup>. However, discontinuation of pharmacological treatment is common in real-life settings <sup>89</sup> and novel pharmacological anti-obesity agents are continuously needed.

### *Bariatric surgery*

Bariatric surgery is without comparison the most efficient weight loss strategy to date <sup>90-93</sup>. Criteria for bariatric surgery in Sweden varies throughout the country secondary to local obesity guidelines and diverse economical compensation schemes. However, a majority of surgical centers apply the following criteria for bariatric surgery: BMI  $\geq 35$  kg/m<sup>2</sup>, age  $\geq 18$

years, previous adherence to weight loss strategies, stable psychosocial situation and high motivation to undergo life style changes associated with bariatric surgery.

Bariatric surgery includes any technique that reduces the stomach size by changing the anatomy (gastric bypass [GBP], gastric sleeve, biliopancreatic diversion with duodenal switch) or by inserting a restrictive band into the ventricle (gastric banding). The present thesis includes studies (Studies III-IV) on GBP which accounts for 64% of surgical interventions in Sweden (2016)<sup>94</sup>. In total, 5,500 surgical interventions were performed in Sweden in 2016 (irrespective of mode of surgery), and numbers are decreasing from the peak of 9,000 surgical interventions/year in 2011<sup>94</sup>.

## **Gastric bypass**

### *Surgical techniques*

In GBP, the stomach is stapled and reduced into a pouch, leading to restriction of food intake. The pouch is connected to the jejunum, thereby by-passing the upper small intestine, which results in malabsorption and secondary weight loss. Roux-en-Y gastric bypass (RYGB) is the most common variant of GBP and the GBP-modality of choice in Sweden. In RYGB, the small intestine is divided 45 cm below the lower stomach outlet and formed into an Y-configuration, allowing the contents from the small pouch to drain into the upper part of the small intestine, thereby enabling uptake of nutrients along the passage of most of the small intestine. Close to 100% of the RYGBs in Sweden are performed using the antecolic, antegastric technique according to Lönroth et al<sup>95</sup>.

### *Positive effects*

When developed, GBP was assumed to lead to weight loss mainly through mechanical malabsorption and a faster transition of ingested food. However, research found that modifiers of neurohormonal circuits, including gut hormones, bile acids, vagal signaling and intestinal microbiota appeared to account for the main weight loss<sup>96-98</sup>. Moreover, the physiologic complication of dumping syndrome causes weight loss post-GBP via gastrointestinal and vasomotor symptoms secondary to an osmotic shift of fluids from the intravascular compartments into the intestines after food intake<sup>99</sup>.

Meta-analyses display a mean weight loss after GBP in adults with BMI  $\geq 40$  kg/m<sup>2</sup> of 20-30 kg up to 10 years after surgery<sup>93</sup>. Mortality (OR=0.48, 95% CI: 0.35-0.64), cardiovascular adverse events (OR=0.54, 95% CI: 0.41-0.70), myocardial infarction (OR=0.46, 95% CI: 0.30-0.69) and stroke (OR=0.49, 95% CI: 0.32-0.75) were all reduced compared to non-surgical controls in meta-analyses with follow-up data up to 14 years after bariatric surgery<sup>100</sup>. In a recent randomized controlled trial (RCT) of patients from a 2-year lifestyle-intensive intervention program with/without RYGB, 23% of surgery patients compared to 4% of non-surgery patients had achieved the endpoint of HbA1c  $\leq 7.0\%$ , low-density lipoprotein cholesterol  $\leq 100$  mg/Dl and systolic blood pressure below 130 mm hg (as recommended by the American Diabetes Association) 5 years after surgery<sup>101</sup>. A comparison of patients with

severe obesity on either surgical treatment or specialized medical treatment displayed favorable 6.5-year data for the surgically treated with a greater likelihood of remission of hypertension (RR=2.1, 95% CI: 2.0-2.2) and diabetes (RR=3.9, 95% CI: 2.8-5.4)<sup>102</sup>. Micro- (HR=0.44, 95% CI: 0.34-0.56) and macrovascular (HR=0.64, 95% CI: 0.54-0.85) complications of T2DM as well as cancer incidence (only in women, HR=0.58, 95% CI: 0.44-0.77) were also reduced in GBP patients compared to obese controls (Swedish Obese Subjects Study [SOS])<sup>103 104</sup>.

Positive effects of bariatric surgery were also seen for pregnancy outcomes in Swedish registry studies, such as a reduced risk of gestational diabetes and excessive fetal growth<sup>105</sup>. However, gestation was shorter and there was an increased risk of small-for-gestational-age after bariatric surgery vs population controls<sup>105</sup>.

Nonetheless, diminishing effects over time warrant longer follow-ups<sup>101</sup>. Data on healthcare costs and utilization after bariatric surgery revealed both net savings compared to non-bariatric samples<sup>91</sup> and short-term increases in total expenditures, while long-term drug expenditures were lower for the surgically vs non-surgically treated obese patient group<sup>106</sup>.

#### *Negative side effects*

Albeit the obvious positive effects on weight loss and resolution of comorbidities, the negative side effects of GBP must be mentioned: Mortality after GBP is low in Sweden, estimated to 0.05% within 30 days after surgery<sup>107</sup>. Short-term (within 6 weeks of surgery) adverse events (any kind, see below) occur in about 6% of operations, and serious short-term adverse events (grade  $\geq 3b$  according to the Clavien-Dindo classification<sup>108</sup>) occur in about 3% of operations<sup>94</sup>. Short-term adverse events are primarily related to intraoperative factors or perioperative care and include leakages from any of the anastomoses or the small bowel (1.8% of GBP-patients), staple line bleeding (2.1%), wound dehiscence (0.1%), small bowel obstructions due to edema for example, bleeding clot, stenosis or ischemia (1.0%), stricture (0.2%), ulcer (0.5%), venous thromboembolism (0.1%), cardiovascular complications (0.2%), pulmonary complications (0.7%) and urinary tract infections (0.4%)<sup>109</sup>. Long-term adverse events between 6 weeks and 5 years affected 13.2% of patients, including perforation (0.2% of patients), bowel obstruction due to internal hernia, adhesion, anastomotic stricture and intussusception (5.2%); wound dehiscence (1.3%) and ulcer (1.8%) according to Swedish registry data<sup>94</sup>. The risk of long-term incisional hernia clearly diminished after the introduction of laparoscopic techniques, although the overall rate of complications was not affected<sup>110</sup>.

Lately, the issue of chronic abdominal pain post-RYGB has been highlighted<sup>111</sup>, which affects about one third of patients. Besides surgical side effects, there are rising concerns about psychiatric adverse events, including problematic use of alcohol (HR=2.3, 95% CI: 1.7-3.2 for before vs after surgery) and increased prescription of psychotropic medication and opioids (RR=1.3, 95% CI: 1.2-1.4 for surgery vs medical intensive therapy), which might be secondary to the augmented risk for post-surgical chronic abdominal pain<sup>102 111-115</sup>. In a

recent Swedish registry study, the HRs for alcohol abuse (HR=2.7, 95% CI: 2.4-3.2), other substance use disorders (HR=3.2, 95% CI: 2.5-4.0), depression (HR=3.2, 95% CI: 2.8-3.7) and suicide attempt (HR=2.9, 95% CI: 2.4-3.4) in a GBP cohort compared to the reference population during a follow-up period of up to 8.6 years, call for attention <sup>113</sup>. Likewise, the GBP cohort displayed increased risks for all of the above-mentioned diagnoses (incidence rate ratios [IRR] of 2.6-7.7) after surgery, while the control group displayed increased IRR only for alcohol abuse, other substance use disorders and depression (IRR=1.4-2.3). In another nationwide Swedish registry cohort of GBP patients, a diagnosis of depression prior to surgery displayed a HR of 52.3 (95% CI: 30.6-89.2) for depression after surgery compared to GBP patients without depression before surgery <sup>114</sup>. Similarly, self-harm prior to surgery displayed a HR of 36.6 (95% CI: 25.5-52.4) for self-harm after surgery compared to patients with no history of self-harm <sup>114</sup>. Faster absorption and a higher peak in ethanol concentration post-RYGB is suggested to account for the increased risk of alcohol abuse after bariatric surgery <sup>116</sup> and may, hypothetically, also impact on post-surgical suicide rates. Meanwhile, discontinuation of medications, lower absorption of psychotropic medications post-surgery, inadequate weight loss and changes in the release of gut hormones may explain the etiology behind other psychiatric side effects <sup>117</sup>. The question of whether increasing psychiatric adverse events are a direct result of surgery or are cohort effects, remains to be answered.

Together, the lower absorption of nutrients and bypassing the acid-producing part of the ventricle, clearly increases the risk of malnutrition, notably iron, vitamin B12 and vitamin D deficiency <sup>118</sup>. Supplementation pre-surgery in accordance with the Nordic guidelines, and continuous yearly monitoring is therefore essential <sup>119</sup>.

In conclusion, GBP is considered a generally safe procedure, and for the average morbidly obese patient, the health risks associated with obesity outweigh the risks of surgery <sup>120</sup>. However, as accounted for above, a number of long-term unexpected side effects have emerged. A careful evaluation of benefits as well as potential harmful side effects at the individual patient level is increasingly necessary as more side effects are being discovered.

## **2.2 YOUNG ADULTHOOD**

### **- The transition from adolescence to independent adulthood**

Young adulthood has recently gained attention as a period of unique medical value in regard to physiological and sociological changes, which differentiate it from adolescence and older adulthood. Neurologically, young adulthood includes developments in limbic structures and the prefrontal cortex that favor changes in pleasure seeking and affect emotional regulation, sleep patterns, reward-seeking behavior (which promote risk-taking) as well as advancements in abstract and logical thinking, decision-making, impulse control and future planning <sup>121</sup>. Socially, young adulthood is a period of transition from dependence to independence; from

living with family members and going to school, to building a household, achieving self-sufficiency and becoming a responsible citizen, i.e. markers that define adulthood <sup>122-124</sup>.

## **Definitions of young adulthood**

The question of whether young adulthood is a distinct developmental period, such as adolescence, is under continuous debate because the above-mentioned social patterns do not appear globally. Accordingly, the years in between adolescence and independent adulthood are defined by different terms and age spans depending on setting. Contemporary definitions include the following:

- WHO defines “adolescence” as 10 to 19 years old, and “youth” as 15 to 24 years old <sup>125</sup>.
- United Nations defines “youth” as a “period of transition from dependence of childhood to adulthood’s independence and awareness of our interdependence as members of a community”, defined chronologically as the period between 15 and 24 years <sup>126</sup>.
- The Swedish Public Health Authority (Folkhälsomyndigheten) defines youth as 14 to 19 years old and young adults as 20 to 29 years old <sup>127</sup>.
- The Stockholm County Council defines young adults as 16 to 25 years old.
- In research, terms such as youth, young adults, emerging adults and early adults are used interchangeably.

In this thesis, the terms “young adult / young adulthood” were chosen due to the initial request from the Stockholm County Council to the Obesity Center to provide “specialized obesity treatment for *young adults (16-25 years)*”.

## **Young adults in the western 21<sup>st</sup> century**

### **- Social and medical challenges**

The transition to adulthood in modern western society is considered to be prolonged due to shifting social norms and economic realities, including economic hardship and higher unemployment rates among uneducated youth in particular <sup>128</sup>. Likewise, increasing numbers of young people pursue university education and thereby postpone a financially independent adult life <sup>129 130</sup>. Secondary delays in partnership and parenthood combined with an acceptance of prolonged individual freedom adjourn what is traditionally seen as independent adult life.

Previous views of young adults as being free from disease are shifting and becoming more nuanced. In this respect, the “Lancet Commission on Adolescent Health and Wellbeing” (2016) recently stated that young adults have been largely neglected in welfare systems and society compared to children and older adults <sup>131</sup>.

According to a WHO study of 50 countries, the health of young adults improved only half as much as for younger children, mainly due to road and work-related injuries<sup>132</sup>. The distribution of young adults' health hazards is changing, with a growing number of chronic diseases due to higher survival rates from childhood and a higher incidence of metabolic cardiovascular diseases (e.g. obesity-related comorbidities) at younger ages. In Sweden, mortality in the 15 to 29 years age group has remained constant since the middle of the 1990s, whereas mortality has been decreasing in all other age groups<sup>133</sup>.

Swedish healthcare statistics as well as national questionnaires reveal an increasingly higher prevalence of mental health problems in Swedish young adults since the 1990s; particularly among women, immigrants and individuals with low socioeconomic resources<sup>134-136</sup>.

Anxiety, depressive and substance abuse disorders account for the main rise in mental illness prevalence<sup>135</sup>. Importantly, young adults constitute the only age group in Sweden that did not experience a decrease in numbers of committed suicides since 1980<sup>137</sup>, and the peak incidence of mental illnesses takes place during young adulthood<sup>138</sup>. High unemployment rates among young adults has been discussed as one explanation behind the increasing rates of mental health issues in this age group<sup>139 140</sup>.

Possibly, the failed transition of healthcare for adolescents with chronic diseases to adult healthcare is partly to blame for the poor health outcomes described above<sup>141</sup>. The young adult's risk-taking behavior and tendency to challenge authorities have been discussed as possible mechanisms behind such failures of care continuity between age groups<sup>142</sup>.

### **Young adulthood - a critical period for the development of obesity**

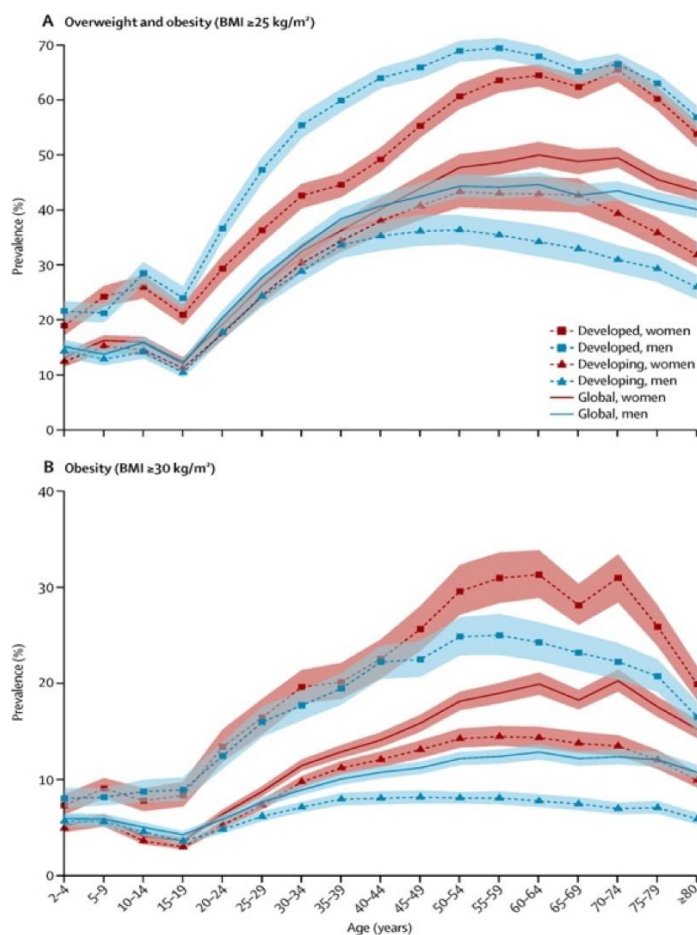
As shown in **Figure 1**, young adulthood has been highlighted as a critical period for the development of obesity<sup>4 5 20 143 144</sup>.

In the westernized world, 8.3% of women and 8.9% of men aged 15-19 years, and 13.2% of women and 12.2% of men aged 20-24 years were classified as obese in 2013 (extracted data, **Figure 1**)<sup>4</sup>. In Swedish self-reported data, 3.5% of women and 3.0% of men aged 16-19 years, and 8.3% of women and 7.7% of men aged 20-24 years were classified as obese in 2015<sup>145</sup>. Obesity in Swedish young adults increased almost 175% between 2002 and 2010 (self-reported data)<sup>146</sup>. In Stockholm, 3% of 18-24-year-old men and women had a BMI  $\geq 30$  kg/m<sup>2</sup> in 2015, which is a statistically significant reduction compared to 5% in 2011<sup>147</sup>. BMI trajectories from childhood into young adulthood demonstrate that obesity in early childhood and adolescence clearly predicts obesity in young adulthood<sup>148-150</sup>. Likewise, obesity in young adulthood clearly predicts obesity in later adult life<sup>151</sup>.

Physiologically, the surge in obesity incidence may be explained by increased total body fat and decreased insulin sensitivity secondary to the influx of sex and growth hormones during adolescence<sup>152-155</sup>. Child-bearing puts young adult women at further risk of weight gain<sup>156</sup>.

Alongside physiological contributors, young adults' changing social habitats are believed to influence weight status: Critical life points such as leaving home, starting university or a job

career may predispose to obesity-prone behavior due to for example monetary deficiencies, poor cooking skills and an urge for independency expressed via new (unhealthy) life style behaviors<sup>20 144 157-160</sup>. Declining rates of eating together as a family and home-cooking may leave the young adult without skills to prepare their own meals, leading to frequent eating-out<sup>20 157 161 162</sup>. Moreover, the young adults' urge to lead an independent life is the target of fast food and soft drink marketing<sup>20</sup>. The declining rates of physical activity seen throughout the late teens may also promote the development of obesity<sup>144 163</sup>. Herein, recent data reported that Swedish young adults are more sedentary in every-day life than elderly  $\geq 85$  years<sup>164</sup>. Moreover, social norms tend to be important health determinants, in particular in young adults<sup>165</sup>, and adolescent body dissatisfaction with secondary dieting and dietary restraint have been associated with obesity development in later adolescence<sup>166</sup>. In addition, weight-teasing and parental weight-related concerns are associated with increasing weight in young adulthood<sup>167</sup>.



**Figure 1.** Prevalence of overweight and obesity and obesity alone, by age and sex, 2013. Reprinted with permission. Ng M et al. *Lancet* 2014; 284(9945):766-81



## Physical, mental and social consequences of obesity in young adulthood

### *Physical comorbidities*

Obesity-related cardiovascular comorbidities are generally not yet present in young adulthood<sup>168</sup>, although abnormal levels of cardiovascular markers may exist<sup>169-172</sup>. Other obesity-related health problems such as polycystic ovary syndrome<sup>173</sup>, stress urinary incontinence in midlife<sup>174</sup> and functional limitations<sup>175</sup> are positively associated with BMI in this age group, and young adults with obesity rate their general health worse than their normal weight counterparts (OR=4.5, 95% CI: 2.9-7.0)<sup>176</sup>.

Prospective longitudinal studies (Harvard Growth Study<sup>14</sup>, Swedish conscription data<sup>15</sup>, Danish conscription data<sup>16</sup>, US National Health Interview Survey<sup>19</sup>, national Israeli data<sup>18</sup><sup>177</sup>) found an approximately doubled to tripled risk of all-cause mortality in later adulthood if overweight/obese in adolescence/young adulthood compared to if normal weight.

Moreover, longitudinal data display a positive association between obesity in young adulthood and future risk for fatty liver disease, metabolic syndrome, and T2DM, irrespective of metabolic disturbances at baseline<sup>12</sup><sup>178</sup>, and a recent Swedish study displayed a positive association between BMI in young men (conscription data) and future adult heart failure with a HR=9.2, 95% CI: 6.6-12.9, if BMI  $\geq 35$  kg/m<sup>2</sup> compared to those with normal weight at baseline<sup>11</sup>.

Concerning health risks associated with *weight gain* in young adulthood, the comprehensive American CARDIA study (the Coronary Artery Risk Development in Young Adult Study) reported that young adults with changing BMI displayed a progression of metabolic risk markers, while young adults with stable BMI levels had minimal progression regardless of baseline BMI<sup>179</sup>. Likewise, young adults who continuously gained weight displayed an increased risk of future cardiovascular disease, independently of initial weight status. In contrast, initially overweight (BMI: 25.0-29.9 kg/m<sup>2</sup>) displayed higher levels of risk factors compared to initially normal weight<sup>180</sup>.

### *Mental health*

Existing studies on coexisting obesity and mental health problems primarily included mood disorders, and research was mainly conducted on community samples or clinical cohorts with bariatric surgery patients.

Cross-sectional community studies display both positive (range of odds ratio [OR]: 1.0-2.6)<sup>181-190</sup> and no<sup>176</sup><sup>187</sup><sup>191-195</sup> or inverse<sup>196</sup> associations between obesity and mood disorders or BMI and depressive symptoms in young adults/adolescents. A few studies displayed positive associations in men<sup>197</sup><sup>198</sup> or women<sup>183</sup><sup>187</sup> only.

In treatment-seeking, non-bariatric patients, the only cross-sectional study on mental health prior to this thesis found a higher prevalence of mood disorders in German patients with obesity (mean BMI 42.4 kg/m<sup>2</sup>) compared to their population counterparts (mean BMI 29.8

kg/m<sup>2</sup>, 43% vs 17%). However, generalization of results is limited due to a low participation rate (n=47), no adjustment for covariates and diverging BMI levels between patients and population controls <sup>199</sup>.

In bariatric cohorts, young adults were included in studies primarily aimed at studying adolescents (i.e. <18 years of age), and results have seldom been stratified by age groups. A systematic review of psychosocial status in adolescent candidates for bariatric surgery found that 30-68% of candidates had moderate to severe depression and 25% had an anxiety disorder <sup>200</sup>.

Concerning bidirectional, longitudinal associations of obesity and mood disorders (largely population studies), some studies on mood disorders in adolescence/young adulthood and subsequent weight gain and/or obesity (up to late adulthood) found a positive association (range of OR=1.5-3.8) <sup>195 201-206</sup>, while others found an inverse <sup>207</sup> (B=-0.38 in CES-D score vs BMI level) or no <sup>176 187 208-211</sup> association. A few studies found positive associations only in previously overweight, but negative associations in previously lean <sup>212</sup>. A systematic review of depression in childhood/adolescence (age 6-19) and obesity later in life displayed ORs of 1.9-3.5 with 95% confidence intervals varying between 1.0 and 5.8 <sup>213</sup>.

A number of studies on longitudinal associations on obesity and mood disorders found significantly different results between genders with positive associations in females but not in males <sup>195 201 203 205 206</sup>, while one study found contrasting results with a positive association in males only <sup>207</sup>.

Longitudinal studies on obesity in adolescence/young adulthood and mood disorders/depressive symptoms later in life also displayed mixed results with positive <sup>188 195 214-217</sup> (range of OR=1.3-5.9) no <sup>187 191 218 219</sup> or inverse (each 5-kg/m<sup>2</sup> increase in BMI, decreased the risk of suicide by 15%) <sup>220</sup> associations. In a meta-analysis of longitudinal associations between obesity at baseline and depressive disorder at follow-up, which covered all ages, the odds for depressive disorders at follow-up were higher in <20 year olds compared with older participants (OR=1.7 vs. 1.3) <sup>67</sup>. A few studies displayed positive associations in females only <sup>195 217 221</sup>.

In summary, previous research suggests that comorbid mood disorders and obesity clearly exist in young adults, although the associations are far from clear. The mixed results between studies may be secondary to failures of defining subtypes of mood disorders, given that some subtypes are suggested to be associated with underweight (melancholic depression), while others are associated with overweight (atypical depression, juvenile onset depression) <sup>182 222</sup>. Generally, comparison of results on comorbid obesity and mood distress/disorders in young adults was limited due to heterogeneous use of measurements of obesity as well as mental health. The community studies enrolled few participants with obesity (compared to numbers of normal weight) and, frequently, a distinction between underweight and normal weight participants was lacking <sup>223</sup>.

Shared biological and lifestyle modifying pathways, weight gain secondary to negative side effects of antidepressant treatment, peer victimization, inaccurate weight perception, shame and binge eating have been discussed as possible explanatory factors for why obesity and mental distress co-occur in adolescence/young adulthood<sup>224</sup>. Moreover, since obesity and mood disorders are both common states, they may co-occur by chance alone, as discussed by McElroy et al<sup>222</sup>.

Concerning mental health problems other than mood disorders, obesity in young adulthood has been positively associated with childhood attention deficit hyperactivity disorder (ADHD) and behavioral problems<sup>225-227</sup>, while no clear associations have been found between obesity and later schizophrenia<sup>228</sup>.

### *Social consequences*

Socioeconomic hazards of obesity on the individual level in young adulthood have primarily been described by Gortmaker et al, who clearly showed that individuals who were classified as obese in adolescence were less likely to get married, had lower household incomes and fewer years of education in young adulthood, irrespective of baseline socioeconomic status<sup>229</sup>. Negative stereotypes of obese students as being lazy, societal discrimination and parental weight stigmatization have been discussed as possible explanations<sup>230 231</sup>.

### **Weight management in young adults**

Behavioral weight reduction programs have displayed poor results and/or shorter weight loss maintenance in young compared to older adults<sup>232-234</sup>. Given the specific traits of young adults as described above, including difficulties with planning, an urge to be “disease-free” and frequently moving houses, it is not surprising that traditional weight reduction programs fail. However, the fact that young adulthood is a period of changing habits, may also be used as an opportunity to empower the young adult to start adhering to a healthier lifestyle. Research has found that young adults’ motivation to seek and stay in obesity treatment differs from that of older adults, and that traditional obesity treatment seldom has accounted for such differences<sup>233 234</sup>. For example, social appearance was an important motivator in young adults, while older adults pursued weight loss to achieve health benefits<sup>234</sup>.

Evidence on young adults’ performance in weight reduction is, however, limited. Attrition, and difficulties in attracting young adults to trials, are general obstacles to reliable results in the young adult age group in obesity research, as well as in other medical fields.<sup>235-237</sup>

A systematic review of 14 behavioral weight loss trials in young adults displayed 3.0 kg weight loss (95% CI: 1.5-4.4) (up to 52 weeks of follow-up)<sup>235</sup>, and the only significant change in risk factors was an improvement in HDL cholesterol<sup>235</sup>.

Likewise, young adults have seldom been included in bariatric surgery trials and/or results have generally not been stratified by 18-to-25-year-olds. Consequently, long-term results are lacking, and outcomes besides weight loss have rarely been reported. Lennerz et al provided

2-year results on n=47 18-to-21-year-olds and reported -16.2 BMI units weight loss along with reductions in comorbidities such as T2DM and hypertension <sup>236</sup>. For comparison, the Swedish Adolescent Morbid Obesity Surgery Study (AMOS) on n=81, 13-to-18-year-olds with a mean BMI of 45.5 kg/m<sup>2</sup> found significant weight loss (-13.1 BMI units), normalized glucose homeostasis (81%), remission of T2DM (in 3/3 patients), normalized blood pressure (100%) and normalized aspartate aminotransferase levels (100%) 5 years after RYGB <sup>238</sup>. However, after 5 years, 25% of surgical patients had undergone additional abdominal surgery, 72% displayed a micronutritional deficiency and they had consumed more healthcare than adolescent non-surgical controls with obesity <sup>238</sup>.

Concerning side effects of bariatric surgery in young cohorts, a recent study found that externally caused mortality was higher for patients <35 years undergoing bariatric surgery vs severely obese in conservative treatment (HR=2.53, 95% CI: 1.27-5.07) <sup>239</sup>, possibly caused by suicide as discussed above. Young age was also associated with an increased risk of problematic alcohol use after surgery <sup>115</sup>. Moreover, Zeller et al followed n=14 adolescents after bariatric surgery into young adulthood, whereof n=11 presented with pre-surgery mental health symptoms outside the normal range <sup>240</sup>. Post-surgery, mental health trajectories varied greatly between individuals with n=5 out of n=11 displaying remission and n=6 displaying persistent symptomatology, while no new cases of poor mental health were observed <sup>240</sup>.

Given young adults' low adherence to medical treatments in general, obesity professionals express concerns about young adults, in particular in regard to adherence to vitamin supplementation after surgery. This has, however, not yet been thoroughly investigated.

### **2.3 GAPS IN KNOWLEDGE**

Firstly, parts of the reviewed literature were based on adolescent research as data on young adults were lacking. Obviously, this lack clearly highlights a general need for young adult data in order to evaluate whether and how young adults with obesity differ from their younger and older counterparts. This method of reasoning is, however, based on the assumption that young adulthood per definition is a unique age period with specific needs.

The knowledge base of young adults with obesity is generally based on community samples, which may differ from clinical cohorts, and generalization of results from community settings to clinical cohorts may not be applicable <sup>241</sup>.

Notably, young adults are pushed towards bariatric surgery due to poor results in behavioral treatment despite the fact that results of surgery in the young are yet to be published.

Finally, there is a relative mismatch of research on physical vs psychiatric comorbidities in young adults with obesity, given that the incidence of mental illness peaks at 25 years, and that worrying tendencies of serious psychiatric adverse events including alcohol abuse after bariatric surgery in younger cohorts in particular have been observed.

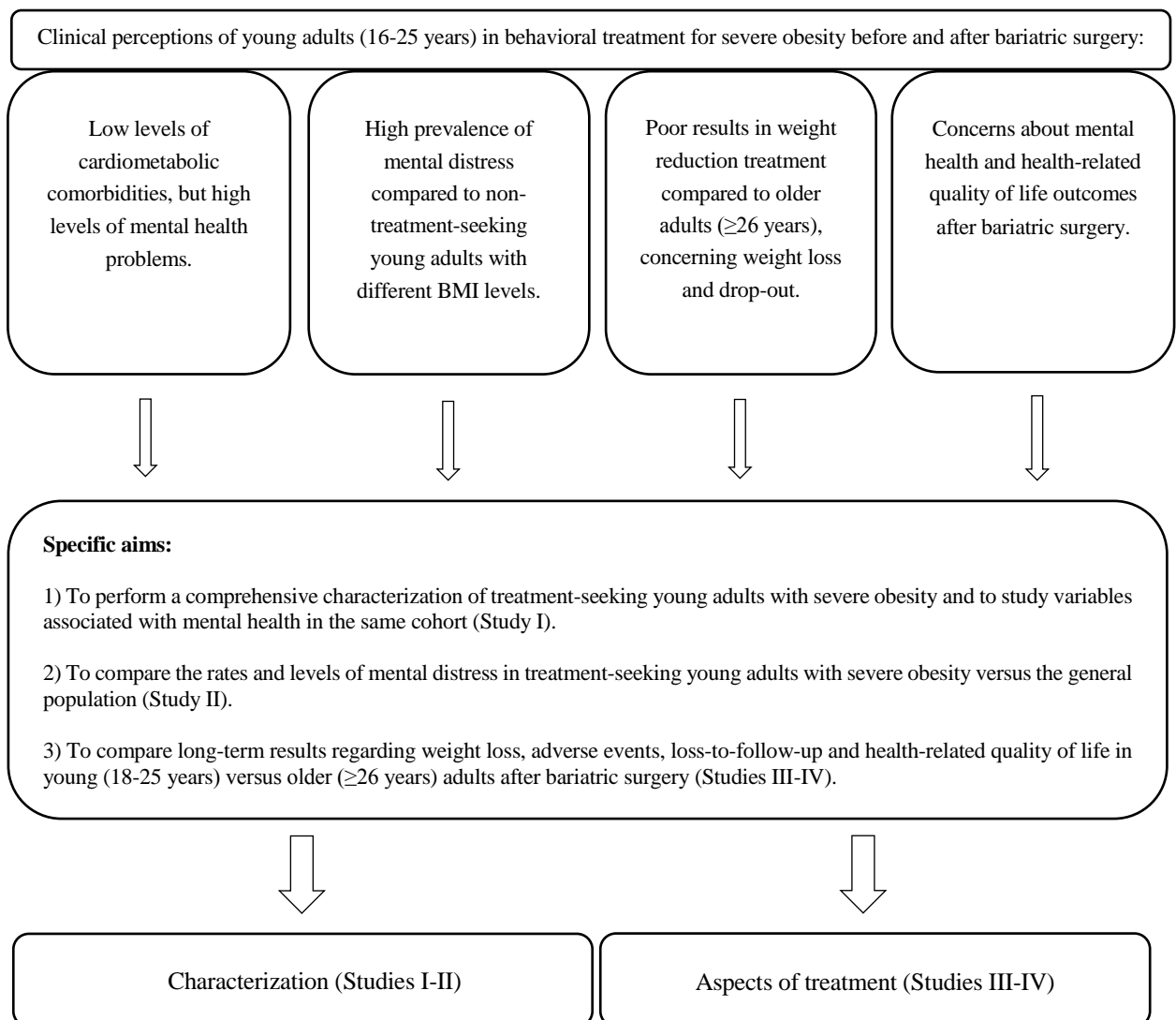
### 3 AIMS AND RESEARCH QUESTIONS

#### 3.1 OVERALL AIM

The overall aim of the thesis was to enhance the knowledge on treatment-seeking young adults with severe obesity concerning comorbidities and treatment outcomes in order to improve clinical decision-making.

#### 3.2 SPECIFIC AIMS

**Figure 2** presents the development of the specific research questions addressed in this thesis. All research questions were developed in collaboration with clinicians at the Obesity Center.



**Figure 2.** Overview of the development of Studies I-IV.

### 3.3 RESEARCH QUESTIONS

Five research questions were developed to examine the specific aims as presented above. These five research questions in turn framed the thesis into two main areas of interest, (1) characterization and (2) treatment of young adults with severe obesity. Both research areas involved aspects of mental health.

1. What sociodemographic and life style factors characterize young adults (16-25 years) with severe obesity who seek behavioral weight reduction treatment, and what is the prevalence of obesity-related comorbidities, cardiometabolic risk factors, micronutritional deficiencies, mental health problems and issues in health-related quality of life (HRQL) in the same cohort? (Study I)
2. What variables are associated with mental distress in young adults (16-25 years) with severe obesity who seek behavioral weight reduction treatment? (Study I)
3. What is the prevalence of mental distress in young adults (18-25 years) with severe obesity who seek behavioral weight reduction treatment compared to population controls with different BMI levels? (Study II)

→ *Studies I-II: Characterization*

4. What are the (5-year) outcomes of Roux-en-Y gastric bypass in young (18-25 years) vs older ( $\geq 26$  years) adults concerning weight loss, adverse events and loss-to-follow-up? (Study III)
5. What is the level of HRQL before and 5 years after Roux-en-Y gastric bypass in young (18-25 years) vs older ( $\geq 26$  years) adults? (Study IV)

→ *Study III-IV: Aspects of treatment*

## 4 METHODS

**Table 1** presents an overview of study I-IV including specific aims, study design, study setting and main measures.

### 4.1 STUDY SETTING

Studies I-II were based on clinical data collection from the Obesity Center at the Karolinska University Hospital (Studies I-II) and population control data from the Stockholm Public Health Cohort (Study II). Studies III-IV were based on registry data from the Scandinavian Obesity Surgery Registry (SOReg).

#### **The Karolinska University Hospital Obesity Center (Studies I-II)**

The Obesity Center at the Karolinska University Hospital provides individualized behavioral weight reduction treatment including individual coaching sessions based on cognitive behavioral therapy and acceptance cognitive therapy, group sessions, motivational interviewing, and physical activity training. The professional team includes obesity-trained physicians, nurses, physiotherapists, occupational therapists and psychotherapists. Patients  $\geq 18$  years who fulfill the criteria for bariatric surgery may be evaluated by a physician for referral to bariatric surgery centers.

Since 2007, young adults (16-25 years) are offered specialized obesity care according to the “youth friendly service” concept<sup>242</sup>, including a greater focus on patient autonomy and to a lesser extent the family involvement that pediatric treatment is generally based on. Compared to older adults ( $\geq 26$  years), treatment of young adults is focused on more concrete problem-solving, and the young adults are contacted for several years after drop-out in order to facilitate re-connection with the Obesity Center and thus continuation of treatment. In 2012, a compulsory pre-bariatric surgery care program for 18-to-25-year-olds was incorporated into the Stockholm Regional Obesity Treatment Guidelines, which were to be delivered by the Obesity Center. Since 2015, the Obesity Center also provides post-bariatric surgery care for young adults.

Referral requirements to the young adult section are: age 16-25 years and BMI  $\geq 35$  kg/m<sup>2</sup> or BMI  $\geq 30$  kg/m<sup>2</sup> together with obesity-related comorbidities except for current eating disorders according to DSM-IV criteria<sup>243</sup> (these patients are referred directly to eating disorder specialist clinics). The young adult patients may be referred to the Obesity Center from primary care physicians, hospital-based physicians (mainly pediatricians) and school nurses throughout Stockholm City County.

**Table 1.** Overview of specific aims, design, study setting and main measures for Studies I-IV.

Study:	Specific aim:	Design and study setting:	Main measures:		
			Matching variables:	Main outcomes:	Covariates:
I	(1) To perform a comprehensive characterization of sociodemographic factors, lifestyle factors, obesity-related comorbidities, cardiometabolic risk factors, micronutritional deficiencies, mental health issues and HRQL in treatment-seeking young adults with obesity and (2) to study variables associated with mental health in the same cohort.	Cross-sectional cohort study.	-	BMI, occupation, nationality, socioeconomic status, sexuality, VO <sub>2</sub> max, smoking, alcohol drinking, sleep impairment, obesity-related comorbidities and medications/treatments, cardiometabolic risk factors and micronutritional status, insomnia, suicidal behavior, depressive and anxiety symptomatology, ADHD symptomatology, self-esteem, SF-36, Obesity-related Problems scale.	BMI, age, gender, socioeconomic status, hazardous alcohol drinking, insomnia, insulin resistance, social support.
		Obesity Center.			
II	To compare the rates and levels of mental distress in treatment-seeking young adults with obesity vs the general population with different BMI levels.	Cross-sectional, matched, cohort study.	Age, gender, socioeconomic status.	Mental distress, depression, suicidal behavior, physical/psychosomatic symptoms, quality of life.	Age, gender, socioeconomic status, smoking, hazardous alcohol drinking, physical disease, sexual orientation, social support.
		Obesity Center and Stockholm Public Health Cohort.			
III	To compare weight loss, adverse events and loss-to-follow-up in young (18-25 years) vs older ( $\geq 26$ years) adults up to 5 years after Roux-en-Y gastric bypass.	Prospective registry-based observational matched cohort study.	BMI, gender, year of surgery.	Weight loss, adverse events, loss-to-follow-up.	BMI, gender, year of surgery, obesity-related comorbidities, surgical access, duration of surgery, surgical volume, concurrent surgery.
		SOReg.			
IV	To compare HRQL between and within young (18-25 years) vs older ( $\geq 26$ years) adults 5 years after Roux-en-Y gastric bypass.	Prospective registry-based observational matched cohort study.	BMI, gender, year of surgery.	SF-36, Obesity-related Problems scale.	SF-36, Obesity-related Problems scale at baseline, obesity-related comorbidities, weight loss at 5 years, adverse events, surgical access.
		SOReg.			

**Abbreviations:** HRQL, health-related quality of life; BMI, body mass index; ADHD, attention deficit hyperactivity disorder; SF-36, Short Form-36; SOReg, Scandinavian Obesity Surgery Registry



## **The Stockholm Public Health Cohort (Study II)**

Since 2002, the Stockholm Public Health Cohort prospectively collects self-reported data every fourth year on a random sample of Stockholm citizens aged 18 years and above. Data are collected by postal or web-based questionnaires, and include anthropometry, demography, lifestyle habits, physical and psychosocial work environment, and mental health. Data from 2010 were included in the present thesis, and the response rate for the total cohort that year was 57% with generally lower rates in participants <45 years of age. Drop-out was more frequent in men than women, in younger than older responders, in non-native than native Swedes and in responders of low than high socioeconomic status. A detailed description of the cohort was published by Svensson et al <sup>244</sup>.

## **The Scandinavian Obesity Surgery Registry (Studies III-IV)**

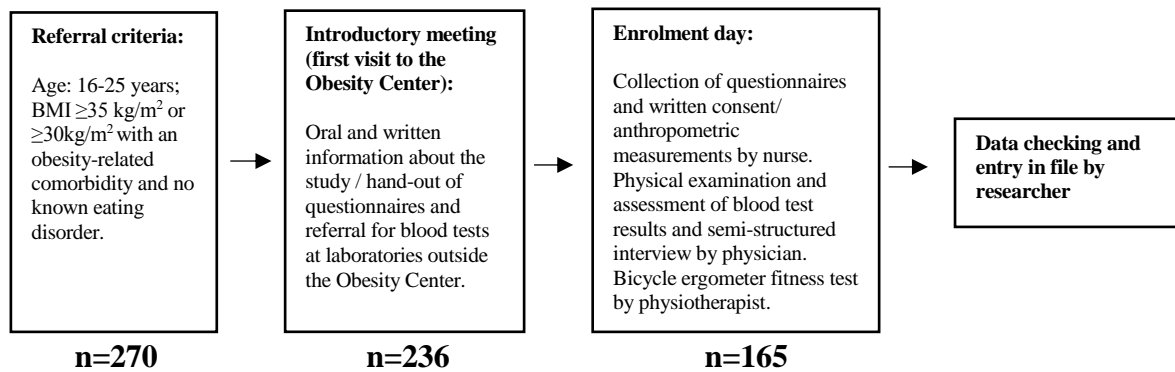
The Scandinavian Obesity Surgery Registry (SOReg, <http://www.ucr.uu.se/soreg/>) is a quality and research registry, financed by the Swedish Association of Local Authorities and the National Board of Health and Welfare, and has been running in its present form since 2007. SOReg covers all bariatric surgery centers in Sweden, irrespective of financing source <sup>245</sup>. The registry covers surgery-related technicalities, procedures, anthropometry, adverse events and HRQL. Data are collected by a nurse or surgeon approximately 1 month before surgery, on the day of surgery, and at 6 weeks/1 year/2 years/5 years/10 years post-operatively as part of standard care either by a physical visit, telephone or email. Mortality data in SOReg are cross-matched with the Swedish Population Register. A detailed description of the registry was published by Hedenbro et al <sup>246</sup> and annual follow-ups are published with public access at the SOReg homepage (<http://www.ucr.uu.se/soreg/>).

For 2007-2010, the coverage was 80-90% for all bariatric procedures in Sweden. From 2011 and onwards, the coverage was 97% <sup>107</sup>. According to regular audits with random comparisons of the patient medical records and the Swedish Population Register, 96.7-98.6% of SOReg data was correctly registered <sup>246 247</sup>. Routines for follow-up may differ between operating centers due to differences in economical compensation schemes throughout Sweden, albeit all participating centers are pledged to register for at least 1 year.

## **4.2 RECRUITMENT**

### **Study I**

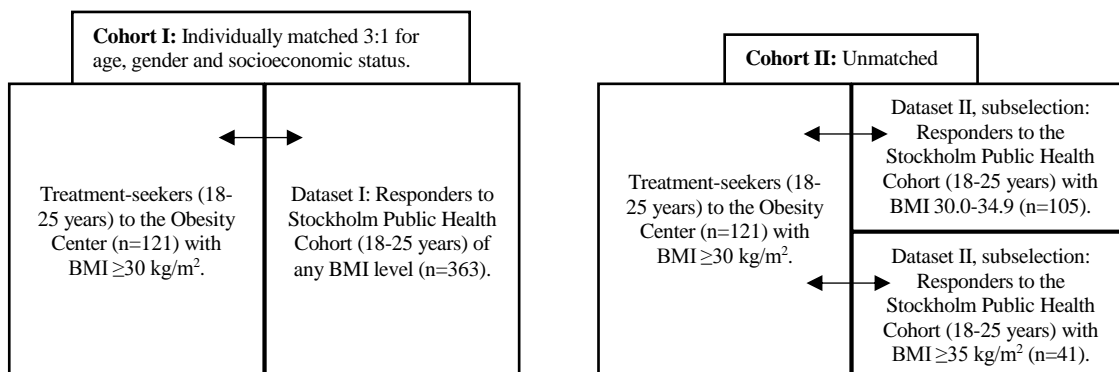
Only enrollees to the Obesity Center were included in Study I. Patients with eating disorders, language barriers or intellectual disabilities were excluded from participation. Data and consent were collected at the second visit to the Obesity Center. See **Figure 3** for an overview of the data collection process. Eighty-seven percent (n=236) of those accepted for clinic enrollment met the study inclusion criteria, and 70% (n=165) of eligible patients participated.



**Figure 3.** Overview of data collection and numbers of participating patients in Study I. Abbreviations: BMI, body mass index; n, numbers.

## Study II

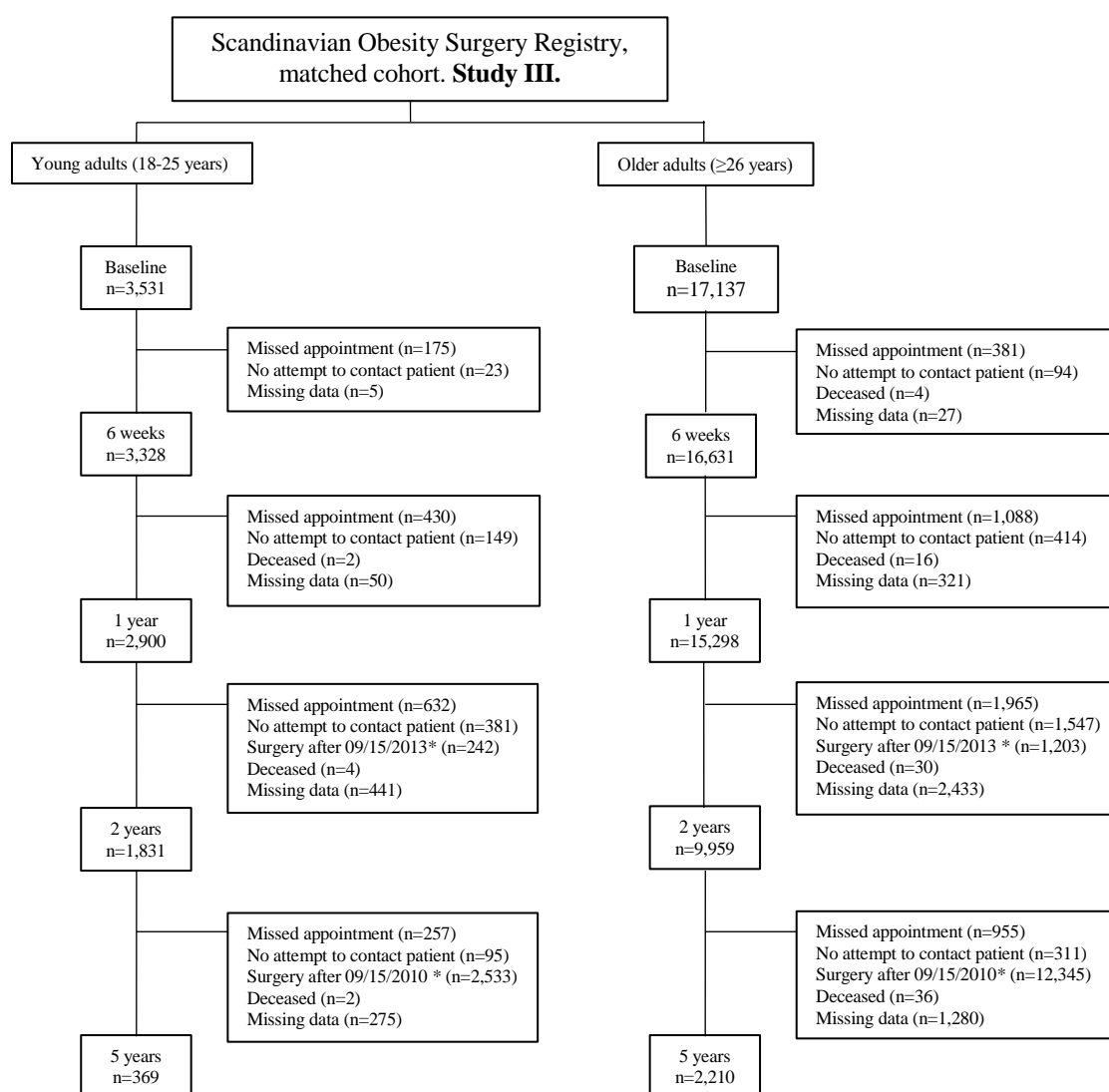
Data on treatment-seekers aged 18-25 years who enrolled in Study I were included in Study II together with two datasets of responders to the Stockholm Public Health Cohort from 2010. The first dataset consisted of responders with any BMI level that were individually matched 1:3 with treatment-seekers for age, gender and socioeconomic status. The second dataset consisted of all responders aged 18-25 years with BMI  $\geq 30$  kg/m<sup>2</sup> (matching here would have resulted in insufficient statistical power). Responders with obesity were categorized as having obesity class I or severe obesity. **Figure 4** presents an overview of the two cohorts. Seventy-nine percent (n=212) of 270 patients who were accepted for enrollment to the Obesity Center during the study period met the inclusion criteria, whereof 57% (n=121) participated in the study. A selection of questions from the Stockholm Public Health Cohort questionnaire was included in the questionnaire that was handed out to the treatment-seekers in order to obtain the same items for treatment-seekers and controls.



**Figure 4.** Overview of cohort I and II in study II. Abbreviations: n, numbers; BMI, body mass index.

## Studies III - IV

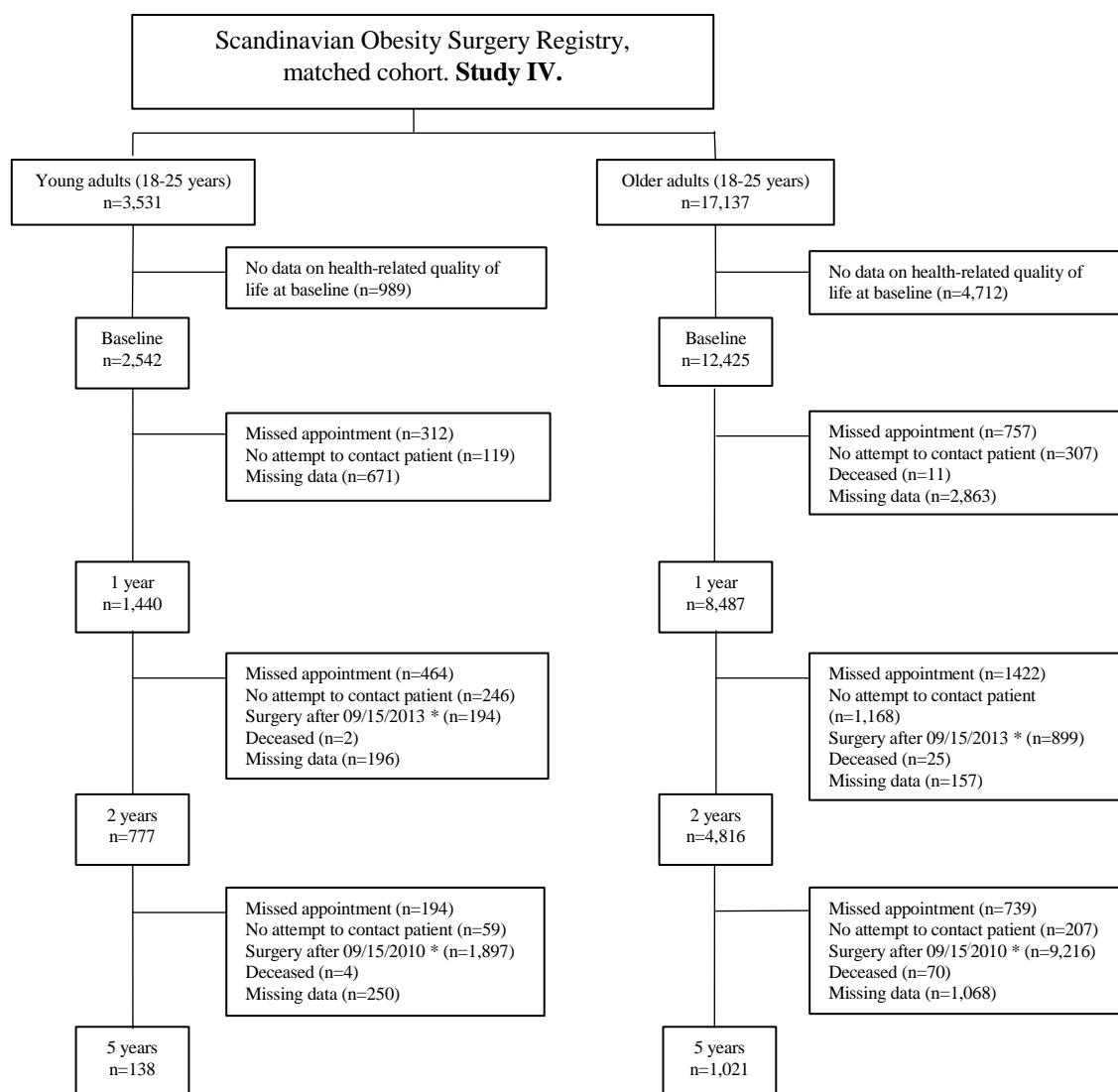
Studies III-IV included only patients who were registered in SOReg and who had undergone RYGB. Young adults (18-25 years, n=3,531) who were included between May 2, 2007 (the initiation of SOReg) and December 30, 2013 were frequency matched to older adults ( $\geq 26$  years, n=17,137) for BMI, gender and year of surgery. Patients were followed up 6 weeks, 1, 2 and 5 years after RYGB. The last day of data entry was September 15, 2015, which is why all included patients were not eligible for 2- and 5-year follow-up. Data were extracted on Feb 8, 2016. See flowchart in **Figure 5** for details.



**Figure 5.** Study III flow chart. Numbers (n) of young (18-25 years) and older ( $\geq 26$  years) adults, matched for body mass index at baseline, gender and year of surgery, at baseline, and 6 weeks, 1, 2 and 5 years after Roux-en-Y gastric bypass.

\* Not eligible for 2- and 5-year follow-up.

The cohort in Study III constituted the population base also for Study IV. However, since data on the main outcome for Study IV (HRQL) were missing for a number of entries, the original cohort was reduced to n=2,542 young (18-25 years) and n=12,425 older ( $\geq 26$  years) adults at baseline. In Study IV, the patients were followed up at 1, 2 and 5 years after RYGB. See flowchart in **Figure 6** for details.



**Figure 6.** Study IV flow chart. Numbers (n) of young (18-25 years) and older ( $\geq 26$  years) adults, matched for body mass index at baseline, gender and year of surgery, at baseline, and 1, 2 and 5 years after Roux-en-Y gastric bypass.

\* Not eligible for 2- and 5-year follow-up.

### 4.3 MAIN MEASURES

The included measures are used interchangeably as either matching variables, main outcomes and/or covariates throughout Studies I-IV depending on study design and aim. **Table 1** presents the measures included in Studies I-IV including the specific purpose (matching

variable/main outcome/covariate) of each measure per study. A brief description of each included main measure in Studies I-IV is presented below.

### **Anthropometric variables (Studies I-IV)**

For Study I and for treatment-seekers in Study II, weight, height and waist circumference were measured in light clothing by a trained nurse using a digital calibrated scale and a wall-mounted stadiometer. The population controls in Study II self-reported weight and height. For Studies III-IV, weight, height and waist circumference were measured either by healthcare staff at physical appointments, or self-measured and reported by the patient via email or telephone. For Studies III-IV, weight loss was reported as percentage weight loss, loss of BMI units and excessive weight loss (EWL, proportion of preoperative BMI  $\geq 25$  kg/m<sup>2</sup> lost).

### **Socioeconomic status (Studies I-II)**

Socioeconomic status was reported in Study I and was included as a matching variable in Study II. In both studies, socioeconomic status was measured using a question on economic strain: “Did you experience any difficulties coping with private expenditures during the last year?”.

### **Lifestyle (Studies I-IV)**

In Study I, cardiorespiratory fitness in terms of VO<sub>2</sub>/kg \* min was assessed using Åstrand’s submaximal bicycle ergometer test and categorized into very poor, poor, average and fair, taking gender and age into account <sup>248</sup>.

Smoking was included as a self-reported measure in Studies I-IV. Alcohol intake was also self-reported in Studies I-II, and values were summarized as units alcohol/week (1 unit=12 g of 100% alcohol <sup>249</sup>) or hazardous drinking (weekly consumption of 14 units for men and 9 units for women, or consumption of 5 units for men or 4 units for women on the same occasion <sup>249</sup>).

Sleep impairment during the past 3 months was measured in Study I by the self-reported 18-item Karolinska Sleep Questionnaire (KSQ) which covers insomnia, disturbed sleep, nightmares, snoring and daytime sleepiness on a 6-item Likert scale <sup>250</sup>.

### **Obesity-related comorbidities, cardiometabolic risk factors and micronutritional status (Studies I-IV)**

For Studies I-II, present and life-time incidence of obesity-related comorbidities and corresponding medications and treatments were collected through items in the questionnaire and by the physician’s examination including checking the patient records. In Studies III-IV, obesity-related comorbidities were restricted to current pharmacological treatment for diabetes type 2, hypertension, dyslipidemia, depression, and/or usage of continuous positive airway pressure treatment for sleep apnea. For Study I, cardiometabolic

risk factors and micronutritional status were assessed using blood samples including fasting p-glucose, b-HbA1c, total cholesterol, p-LDL cholesterol, p-HDL cholesterol, p-triglycerides, p-alt, s-ferritin, total iron binding capacity, b-HB, s-25-OH-vitamin-D 25, b-folate, s-cobalamin and s-zinc. Age-adjusted cut-offs for metabolic risk factors were applied. Insulin resistance was calculated using the HOMA index <sup>251</sup>.

### **Mental health and quality of life (Studies I-IV)**

Mental health and quality of life were evaluated using validated questionnaires including the Hospital Anxiety and Depression Scale (HADS) <sup>252</sup>, the Rosenberg Self-Esteem Scale (RSES) <sup>253</sup>, and the Adult ADHD Self-Report Scale (ASRS) <sup>254</sup> in Study I; the General Health Questionnaire-12 (GHQ-12) <sup>255</sup> and separate questions on physical/psychosomatic symptoms in Study II <sup>256</sup>; EuroQol-5D (EQ-5D) <sup>257</sup> and separate questions on previous suicidal behavior in Studies I-II <sup>256</sup>; and the Obesity-related Problems scale (OP) <sup>258</sup> and Short Form Health Survey-36 (SF-36) <sup>259</sup> in Studies I and IV:

The 14-item Likert HADS scale is used for detection of both anxiety and depressive symptomatology in outpatient adolescents and adults. The items are scored 0-3 points each and summarized into one anxiety measure and one depressive measure; thereafter they are categorized according to: no impairment ( $\leq 7$  points), subclinical impairment (8-10), and clinical impairment ( $\geq 11$ ). Patients above the subclinical cut-off should be considered for further clinical evaluation <sup>260</sup>.

The 10-item RSES is scored using a 4-point Likert scale to detect low self-esteem. The most widely used cut-off for low self-esteem is  $< 15$  points <sup>253</sup>.

ASRS assesses symptoms of concentration and hyperactivity associated with ADHD in patients  $\geq 16$  years old. The responses of the 6-item questionnaire are summarized into a score of 0-6 points: a score of  $\geq 4$  points indicates ADHD symptomatology <sup>254</sup>.

The 12-item GHQ is used to detect psychiatric symptomatology in surveys or clinical settings <sup>261</sup>. GHQ-12 may be scored using either the Likert (0-3 points/item which are summarized into a continuous score of 0-36 points) or the GHQ (one point / positive reply is summed up to a maximum score of 12 points) scoring methods. While there is no cut-off for mental distress using the Likert scale, a cut-off of  $\geq 3$  points is used with the GHQ scale <sup>255</sup>.

Questions on physical/psychosomatic symptoms were retrieved from the Stockholm Public Health Cohort questionnaire and included “Are you bothered by any of the following symptoms? Headache/hyperacusis/urinary incontinence/acid reflux/fatigue/tinnitus”, with the possible responses of “no”, “yes, mild” and “yes, severe” <sup>256</sup>.

EQ-5D measures five dimensions of quality of life: mobility, hygiene, daily activities, pain and anxiety. There are three possible levels (no/some/extreme problems) and together the dimensions are converted into an index score, which is summarized differently across

countries. The British time-trade-off method was used in Studies I-II. EQ-5D is mostly used in community settings. A low score is associated with impairment of quality of life <sup>257</sup>.

Suicidal behavior was measured using two separate questions: “Have you ever had suicidal thoughts” and “Have you ever tried to commit suicide?”. Possible responses were “yes,  $\geq 1$  year ago”, “yes,  $< 1$  year ago”, “yes, last week” or “no, never” <sup>256</sup>. The questions were repetitively used in the Stockholm Public Health Cohort and were initially developed by the National Centre for Suicide Research and Prevention of Mental Ill-Health and were also repetitively included in the Swedish national public health questionnaire. The responses were found to correlate well with self-rated health, mental distress and anxiety, among others <sup>262</sup>.

OP includes questions on obesity-related limitations in eight activities of daily living such as buying clothes and swimming, and was frequently used in Swedish obese samples, including bariatric cohorts such as the SOS study <sup>263</sup>. A summary score of 0-100 is calculated, with lower scores indicating better psychosocial functioning and categorized as: mild ( $< 40$  points), moderate (40-59 points) or severe ( $\geq 60$  points) psychosocial impairment <sup>258</sup>.

SF-36 measures HRQL using 36 questions on functional physical and mental health in the last 4 weeks. The responses are summarized into eight domains each ranging from 0 to 100, with 100 indicating optimal health. A summary component score of mental and physical health is calculated, with a score of 50 indicating the population mean <sup>259</sup>.

#### *Methodological considerations on the construct of questionnaires*

The construct of questionnaires necessitates some deliberation to reduce the risk of drawing false conclusions. I will here therefore discuss certain questionnaire properties that were considered when selecting questionnaires for Studies I-IV: the level of reliability and validity and the risk of response bias.

Measurements of *reliability* and *validity* are central when validating a new questionnaire. High reliability means that the results are consistent between  $\geq 2$  measurements, and high validity means that the questionnaire measures what it is intended to measure. Reliability and validity may preferably be evaluated for different populations and languages.

Internal consistency and test-retest variability are two ways of evaluating reliability. Internal consistency reflects to what extent the items are correlated to each other. High internal consistency means that responders replied in a similar way to items of similar meanings. Thus, internal consistency is low if a respondent replies yes to both “I love food” and “I hate food”. Internal consistency is measured by Cronbach’s alpha and ranges between negative infinity and one. A score  $\geq 0.9$  equals excellent internal consistency <sup>264</sup>. Test-retest variability refers to what extent a responder replies in a similar way if asked to repeat his/her responses. Test-retest variability is assessed by Pearson’s product-moment correlation coefficient. The larger the coefficient, the more stable the responses and thus better test-retest variability.

Validity refers to the content and construct validity. A content-valid questionnaire indicates that the included items are representative for what the questionnaire is designed for and intended to assess. When constructing a new questionnaire, the content validity may for example be evaluated by an expert in the field. A questionnaire of high construct validity means that inferences may be drawn from the responses to actual behavior or other pre-existing measurements. For example, a score that indicates high levels of leg pain, should correlate to difficulties walking. Construct validity is measured by correlation coefficients with  $\geq 0.5$  points indicating high correlation between constructs<sup>265</sup>.

Concerning validation of the questionnaires in the present thesis, HADS, RSES, GHQ-12 and SF-36 were validated in  $\geq 16$ -year-olds<sup>261 266 267-269</sup>. ASRS was constructed for  $\geq 16$ -year-olds, although validated in  $\geq 18$ -year-olds only<sup>270</sup>. OP was used in 16-to-17-year-olds<sup>271</sup>, but validated for  $\geq 18$ -year-olds. KSQ and EQ5D were validated in  $\geq 18$ -year-olds. The separate questions were tested within the Stockholm Public Health Cohort ( $\geq 18$ -year-olds), but not properly validated. HADS, RSES, ASRS, OP and EQ5D had been extensively used in clinical care at the Obesity Center before the initiation of Studies III-IV, and we thus had real-life experience from using them in the population that we were to study.

*Response bias* may arise secondary to miscommunication between the responders and the researchers, misunderstanding of the questions, problems with recalling necessary information, lack of motivation to undergo the survey, contextual cuing (e.g. that the respondent tends to think more about his/her health if surveyed in a hospital setting than in everyday life), socially desired responding and language barriers, among others. Such response biases may cause repeated tendencies to respond in specific patterns, which may distort the data. Response bias must therefore be considered when deciding how and in what setting responders will answer the questionnaire. In clinical obesity research, impression management secondary to desire to undergo bariatric surgery is of particular concern.

### **Adverse events (Study III)**

An adverse event was defined as a postoperative course that was aberrant from the normally expected course. Adverse events were registered in SOReg by a surgeon if a complication occurred, and otherwise by a nurse (i.e. in the case of negative responses). An adverse event that occurred between surgery and 6 weeks was registered at 6 weeks, and an event that occurred between 6 weeks and 1 year was assessed at 1 year etc.

Adverse events included post-surgery complications such as leak, bleeding, abscess, wound complications, port-related complications, cardiovascular complications, venous thromboembolism and urinary tract infection. Long-term complications included ileus, anastomotic stricture, stomal ulcer, perforation, hernia, anemia/malnutrition requiring intervention or other non-specified surgery-related adverse events such as biliary stones. The Clavien-Dindo classification of the severity of adverse events was added on May 1, 2010. Clavien-Dindo 2-3a, i.e. adverse events requiring medication or intervention under local anesthesia, were classified as significant, and Clavien-Dindo 3b-5 (including mortality due to



a complication), i.e. adverse events requiring an intervention under general anesthesia, were defined as serious.

### Loss-to-follow-up (Study III)

Loss-to-follow-up was categorized as “Missed appointment”, meaning that the patient was invited to a follow-up visit (physical visit/telephone/email) but did not turn up; “No attempt to contact patient”, meaning that the caregiver had not invited the patient to follow-up; and “Total loss-to-follow-up”, meaning those mentioned above plus missing data and deceased.

### Uncategorized variables (Studies I-IV)

Variables not classified into any of the above categories included employment status (Studies I-II); sexual orientation and social support (Studies I-II), all measured by items from the Stockholm Public Health Cohort; nationality (Study I), measured by questions on country of birth and parents’ country of birth; surgical access (Studies III-IV), categorized as laparoscopic, open or converted; duration of surgery in minutes (Study III); and high-volume center (Studies III-IV), defined as a surgery center that in a certain year performed more than the median number of RYGB surgeries for that specific year. The above mentioned non-surgical variables were not validated; however, they had been frequently used and found applicable in previous Stockholm Public Health Cohorts <sup>256</sup>.

## 4.4 STATISTICAL ANALYSES

### Background to statistical tests included in Studies I-IV

The statistical analyses used in Studies I-IV are accounted for in **Table 2**; below, I briefly discuss the background for using each test in the respective study.

**Table 2.** Statistical analyses used in Studies I-IV.

Statistical analysis	Study I	Study II	Study III	Study IV
Chi <sup>2</sup> -test		x	x	x
Independent samples t-test	x	x	x	x
Mann-Whitney U test		x	x	x
Paired samples t-test	x			
Paired samples sign test				x
Multiple regression	x	x		x
Logistic regression			x	
Poisson regression		x	x	
Linear mixed effects models			x	

*Chi<sup>2</sup>-test* (used in Studies II-IV) was used to test whether there was an association between two independent categorical variables, and the *independent samples t-test* (Studies I-IV) was used when testing whether there was a difference in mean between two independent groups

on a normally distributed continuous variable. The difference in distribution between two non-normally distributed independent samples was analyzed using the *Mann-Whitney U test* (Studies II-IV). The *paired samples t-test* (Study I) was used to test whether there was a difference between two measurement points in a normally distributed variable in the same sample. In a non-normally distributed sample with different distributions between the two dependent samples, the *paired samples sign test* (Study IV) was applied.

*In multiple regression* (Studies I-II, IV) a dependent continuous variable (the outcome) is studied in relation to independent continuous or categorical variable(s) which are linearly related to the dependent variable. The multiple regression analysis will estimate a linear equation in terms of:  $Y = \beta_0 + \beta_1X_1 + \beta_2X_2 \dots + \beta_pX_p + \epsilon_i$ , where Y is the dependent variable,  $\beta_0$  is the constant,  $\beta$  is the regression coefficient, X is the independent variable(s) and  $\epsilon_i$  is the error term.

*Logistic regression* (Study III) was used to calculate the probability of an independent variable falling into one of two categorical variables. Logistic regression was used to study ORs between groups. Odds is calculated by dividing the probability of X to occur, with the probability of X not to occur written as  $P/(1-P)$ . OR is calculated by dividing the odds of an exposed group with the odds of an unexposed group written as  $(a/b)/(c/d)$ . OR approximates and may be interpreted as relative risk in samples with infrequent prevalence of the outcome (approximately <10%), but overestimates the relative risk in samples with large (approximately  $\geq 10\%$ ) prevalence of the outcome<sup>272</sup>.

*Poisson regression* (Studies II-III) is generally used to predict count data (the dependent variable) in relation to independent variables, and to determine the percentage difference in counts of the dependent variable between categorical independent variables, or in relation to one unit's step up/down of continuous variables. Poisson regression thus calculates the risk ratio (relative risk), i.e. the risk of X occurring in an exposed group vs X occurring in another group, written as  $a/(a+b) / c/(c+d)$ . However, Poisson regression may also be used to analyze dichotomous data and may as such be an alternative to logistic regression in samples with large frequencies of the outcome<sup>272 273</sup>.

*Linear mixed effects models* (Study III) handle correlated data, such as repetitive measurements, and data that are unbalanced (i.e. included subjects do not display the same numbers of observations, and the observations are made at different times). Linear mixed effects models are therefore an advantage in datasets with missing data (see below). Moreover, the mixed effects approach, taking random and fixed effects into account, may describe the unique "behavior" of each variable (individual) that is included in the analysis. Accordingly, all data are not to be fitted into one single regression line (which is seldom accurate when depicting real-life data), but instead one line per individual.

All statistical tests were two-sided and calculated with 95% CI. A p-value <0.05 was considered statistically significant. All data were analyzed using SPSS version 22-23.

The clinical relevance of the differences/changes in HRQL (Study IV) was measured by effect size, Cohen's  $d$  (average score<sub>group1</sub> – average score<sub>group2</sub>/pooled standard deviation)<sup>274</sup>. Effect size was categorized into negligible (<0.2), weak (0.2-0.5), average (0.5-0.8) and large changes (>0.8).

### **Missing data**

Missing data is common in real-life settings in medical research, and particularly so in longitudinal studies. Missing data increase the risk for biased results. Traditional statistical analyses of longitudinal data, such as repeated measures ANOVA, may lose power when handling unbalanced data, as subjects with missing data will be discarded from the analyses (listwise deletion/completers only analyses). One way to handle this is to impute data (Study III-IV) which allows subjects with incomplete data to be included in the analyses.

There are a number of ways to impute data, such as “*baseline carried forward*” (Study III-IV), where the baseline value of the variable for each subject is imputed for all missing data entries. In “*last observation carried forward*” (Study III-IV), the last entered data point before the missing value is imputed. In “*multiple imputation*” several different hypothetical complete datasets are created by predicting the missing values by means of predefined variables from the original dataset. Missing data in the original file are thereafter replaced by the new datasets. Eventually, the results of the analyses with imputed data are compared with the results of the original analyses with missing data<sup>275</sup>. Since the new dataset is dependent on the complete cases, the results of multiple imputation are generally similar to results in completers-only analyses.

Modern statistical methods in terms of *mixed models* (Study III, see above) use the full dataset, irrespective of whether data are missing or not. However, unbiased results are created only if data were missing at random, since mixed models will make use of the complete data when estimating means.

In order to detect any crucial differences between missing and complete data, the baseline (or other) variables in data that were missing are generally compared with the baseline variables in data that were not missing (Studies III-IV) using appropriate tests as described above.

### **Matching**

Matching is a statistical technique which is used to reduce bias when comparing independent groups<sup>276</sup>. The aim of matching is to create a dataset with the same values in one or several confounders in all matching groups. Matching is generally achieved on an individual basis, i.e. that each individual in group A has the same value of the confounding variable(s) as a paired individual in group B (Study II). Alternatively, the proportion of the confounding variable is the same across groups A and B, so-called frequency matching (Studies III-IV).



## 5 ETHICAL CONSIDERATIONS

Swedish healthcare policies should be built on the four basic principles of medical ethics: autonomy, beneficence, non-maleficence and justice. These principles are intended to guide clinicians through medical decision-making to provide what is regarded as beneficial health services for the whole population. In this chapter I consider the above-mentioned principles in the light of the present thesis.

*Autonomy*, meaning that an informed, adult, person is able to decide for him/herself about his/her life as long as the decision does not conflict with other people. In a medical setting, autonomy means that a patient may refuse or accept treatments, and that his/her decision must be respected by the healthcare workers. Hence, the patient preferably needs reliable information on positive as well as negative effects of a specific treatment before he/she is able to decide whether he/she wants to undergo that specific treatment. Results from children and adults have generally been applied to young adults, without examining what needs may be specific to the young adult population. A central theme of this thesis is to shed light on young adults, i.e. to acknowledge young adults as independent individuals and not as random “above 18 years old people”. Here, I argue that fulfilled autonomy cannot be achieved unless young adults are addressed as an independent age group. Without considering whether a treatment option differs in outcome between certain age periods, and the lack of research on whether this is the case, the patient is left non-informed on age-specific outcomes. Increased autonomy is becoming more important as a means of improving Swedish healthcare services, since reports show that Swedish patients feel less involved in decision-making compared to other OECD countries<sup>277</sup>.

When discussing autonomy, one may argue against the use of the term “young adult” since this term may imply that the young person does not “stand alone” from the adult age group. “Young” is here related to “adult”, and thereby linguistically dependent on another age group. As discussed in the introduction, the terminology for people in between adolescence and mature adulthood varies and, in hindsight, we could have considered the terminology in a broader perspective in order to fully acknowledge the uniqueness of our patient group.

*Beneficence* - doing what is best for the patient – is clearly not achieved unless treatment options are thoroughly evaluated. Obviously, research on treatment effects, for example Studies III-IV, contribute such data. However, what is considered as “medical good quality” according to medical professionals, may not be as important from a patient’s perspective. For example, weight loss has historically been the overall aim in general obesity medicine, while patients with obesity may be suffering more from obesity stigma, than body fat per se. With such a perspective, “doing what is best for the patient” might be to focus on self-acceptance instead of eating less calorie-dense food. Therefore, in hindsight, inclusion of patients’ narratives in the present thesis would have enhanced the picture of severe obesity in young adulthood.

The concept of beneficence is closely linked to *non-maleficence* – i.e. do no harm (“primum non nocere”). Studies on adverse events are therefore as important as studies on positive treatment effects (Study III). However, one may argue that the ethical concept of “do no harm” only includes intentional overt actions or adverse events which are necessary to achieve the positive effects. Such acceptance of harmful actions is theorized as “the double effect doctrine” (Thomas Aquinas, *Summa Theologica* II-II, Qu. 64, Art.7). In this perspective, unknown and unintentional adverse events of bariatric surgery are accepted if the intention with surgery is “good” and if the “good” outweighs the “bad”. Consequently, to know whether good outweighs bad, one must study what might be “bad” in addition to what is supposed to be “good”, such as weight loss and resolution of comorbidities.

*Justice* means that health care should allocate the resources in a fair manner because resources are scarce. In Swedish healthcare, priority should be offered according to medical needs, meaning that patients with serious needs should be served before those with less serious needs. Importantly, having a “need” of something, means that this “something” has a predominantly positive effect on the need so that the need is consequently reduced <sup>278</sup>. Hence, a fair decision on who should be served first cannot be made unless we know the treatment outcome, which consequently makes evaluations of treatments a central issue.

Importantly, to know whether treatment effects actually do good or harm, results must be reliable, meaning that the methodology must be accurate and thoroughly discussed. Consideration of “limitations and strengths” is obviously central in all medical research.

All studies in the present thesis were approved by the Stockholm Ethical Review Board: 2012/1154-31/4 (Studies I-II) and 2012/1217-31/5 (Studies III-IV)

## 6 RESULTS

### 6.1 RESULTS OF CHARACTERIZATION / RESEARCH QUESTIONS 1-3 (STUDIES I-II)

A total of n=165 young adult (16-25 years) treatment-seekers to the Obesity Center were included in Study I. Mean age was 19.7 years (SD: 2.7), 80% (n=132) were women, mean BMI was 39.2 kg/m<sup>2</sup> (SD: 5.2), and 17% (n=28) were categorized as having obesity class I, 41% (n=68) as obesity class II and 41% (n=67) as obesity class III and above.

Sociodemographic and lifestyle factors, obesity-related comorbidities and risk factors, micronutritional deficiencies, mental health and HRQL of the treatment-seeking young adults are presented in **Table 3-4**.

A multivariate regression analysis of anxiety and depressive symptomatology as measured by HADS demonstrated independent associations between anxiety symptomatology and pain (B=2.4) and low self-esteem (B=0.25; R<sup>2</sup>=0.33, p <0.001); and between depressive symptoms and cardiorespiratory fitness (B=0.18), poor psychosocial functioning (B=0.031) and low self-esteem (B=0.23; R<sup>2</sup>=0.38, p <0.001), when adjusted for age, gender, economic strain, hazardous alcohol drinking, insomnia, insulin resistance and social support.

In Study II, a total of n=121 young adult (18-25 years) treatment-seekers with obesity were included. Mean age was 20.8 years (SD: 2.3), 81% (n=98) were women, and mean BMI was 39.8 kg/m<sup>2</sup> (SD: 5.3). An individually matched population cohort included n=363 young adults, with a mean age of 20.8 years (SD: 2.3), 81% (n=294) were women and mean BMI was 22.4 kg/m<sup>2</sup> (SD: 4.0), all, p <0.05 for difference in matching variables between patients and controls. Five percent (n=18) of the population controls were classified as obese. While the two groups differed on percentage of tobacco smokers (25% in treatment-seekers, 16% in population controls), heterosexual orientation (83% vs 91%) and presence of social support (88% vs 94%), there was no statistical difference between groups in any of the other baseline characteristics (nationality, single household, occupation, hazardous alcohol drinking).

The frequencies of mental distress in treatment-seekers vs population controls for any BMI level are presented in **Table 5**.

In the second part of Study II we included n=146 unmatched young adult (18-25 years) population controls from the Stockholm Public Health Cohort with BMI  $\geq 30$  kg/m<sup>2</sup> for comparison with the same treatment-seekers as in the first part (n=121). A total of n=105 controls had obesity class I (BMI 30.0-34.9 kg/m<sup>2</sup>) with a mean BMI of 32.1 kg/m<sup>2</sup> (SD: 1.3), a mean age of 21.4 years (SD: 2.2), and 50% (n=52) of them were women. A total of n=41 controls had severe obesity with a mean BMI of 39.7 kg/m<sup>2</sup> (SD: 5.3) a mean age of 21.8 years (SD: 2.3) and 78% (n=32) of them were women.

**Table 3.** Sociodemographic and life style factors, obesity-related comorbidities and risk factors, and micronutritional deficiencies in n=165 young adult (16-25 years) treatment-seekers with severe obesity.

Variable	Treatment-seekers
<b>Sociodemographic factors, % (n)</b>	
Occupation	
<i>Students</i>	64 (106)
<i>Employed</i>	20 (33)
<i>Unemployed</i>	10 (17)
<i>On sickness benefit ≥30 consecutive days</i>	3 (5)
Economic strain last year	19 (31)
Born in Sweden	87 (143)
Second-generation immigrant	19 (31)
<b>Lifestyle factors, % (n)</b>	
Poor or very poor cardiorespiratory fitness (n=90)	92 (90)
Daily tobacco smoker	22 (36)
Hazardous alcohol drinker	17 (27)
Sleep impairment (insomnia)	54 (88)
<b>Obesity-related comorbidities, % (n)</b>	
Diabetes mellitus type 2	3 (5)
Hypercholesterolemia	3 (5)
Hypertension	2 (4)
Polycystic ovary syndrome (women only)	10 (13)
Non-alcoholic fatty liver disease	1 (2)
Obstructive sleep apnea	0 (0)
≥1 cardiometabolic obesity-related disease (any of those above)	16 (26)
Asthma	21 (35)
Hypothyroidism	7 (11)
<b>Cardiometabolic risk factors</b>	
Fasting p-glucose, mmol/l; mean (SD)	5.4 (1.5)
HbA1c, mmol/mol; mean (SD)	35.1 (7.1)
Impaired fasting plasma-glucose (6.1–6.9 mmol/l) <sup>a</sup> ; n (%)	3 (5)
Increased p-glucose (≥7 mmol/l) <sup>c</sup> ; % (n)	2 (3)
Insulin, mIU/l; mean (SD)	26.6 (20.9)
Insulin resistant according to the HOMA index	82 (129)
Total cholesterol, mmol/l; mean (SD)	4.5 (0.9)
LDL cholesterol, mmol/l; mean (SD)	2.8 (0.7)
HDL cholesterol, mmol/l; mean (SD)	1.1 (0.2)
Fasting triglycerides, mmol/l; mean (SD)	1.3 (0.6)
≥1 plasma lipid abnormality <sup>b</sup> , % (n)	62 (98)
ALT, μkat/L; mean (SD)	0.5 (0.5)
Elevated ALT <sup>c</sup> , n (%)	22 (35)
<b>Micronutritional deficiencies, % (n)</b>	
Depleted iron stores (serum-ferritin <12 μg/L or total iron binding capacity > 400 μg/dL)	17 (27)
Iron-deficiency anemia (depleted stores or early functional iron deficiency and Hb <120 g/L (men) or <130 g/L (women))	0 (0)
S-cobalamin (<100 or <150 pmol/l) <sup>d</sup>	8 (12)
B-folate (<305 nmol/l)	7 (10)
S-25-OH-vitamin-D (<25 nmol/l)	35 (55)
S-zinc (<10.7 μmol/l)	7 (11)
≥1 micronutritional insufficiency	43 (68)
≥1 micronutritional deficiency	48 (76)

Abbreviations: n, numbers; HOMA, homeostatic model assessment; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase.

<sup>a</sup> As defined by the World Health Organization.

<sup>b</sup> According to the Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents<sup>279</sup>.

<sup>c</sup> According to Schwimmer et al<sup>280</sup> and Mårtensson et al<sup>281</sup>.

<sup>d</sup> Reference values according to Beckman Coulter Inc (DxI, low cut-off) and Roche Diagnostics (Modular E120, high cut-off).



**Table 4.** Psychiatric disorders, psychiatric medication, self-reported suicide attempts, mental health and health-related quality of life in n=165 young adult (16-25 years) treatment-seekers with severe obesity.

Variable	Treatment-seekers
<b>Psychiatric disorder, % (n)</b>	
Depressive episode	13 (22)
Anxiety disorder	12 (20)
ADHD	13 (21)
Dyslexia	20 (33)
Other neurodevelopmental disorders	5 (8)
Eating disorder not otherwise specified	1 (2)
≥1 psychiatric disorder	29 (47)
<b>Medication for any psychiatric disorder, % (n)</b>	21 (35)
<b>Suicide attempts, % (n)</b>	
Never	88 (145)
>1 year ago	9 (15)
<1 year ago	3 (5)
<b>HADS Anxiety subscale, total score; mean (SD)</b>	7.8 (4.6)
Normal (score ≤7); n (%)	53 (87)
Subclinical (score 8 to 10); n (%)	21 (35)
Clinical (score ≥11); n (%)	26 (42)
<b>HADS Depression subscale, total score; mean (SD)</b>	5.3 (4.1)
Normal (score ≤7); n (%)	73 (120)
Subclinical (score 8 to 10); n (%)	17 (28)
Clinical (score ≥11); n (%)	10 (17)
<b>Rosenberg Self-Esteem Scale, total score; mean (SD)</b>	16.2 (6.9)
Low self-esteem (score ≤15); n (%)	42 (69)
<b>Obesity-related Problems scale, total score; mean (SD)</b>	63.7 (28.1)
Mild impairment (score ≤39); n (%)	19 (32)
Moderate impairment (score 40 to 59); n (%)	25 (42)
Severe impairment (score ≥60); n (%)	55 (91)
<b>Positive screening for ADHD using ASRS; n (%)</b>	37 (61)
<b>Short Form Health Survey-36</b>	
Physical component score; mean (SD)	45.7 (11.2)
Mental component score; mean (SD)	35.8 (13.9)

Abbreviations: n, numbers; ADHD, Attention deficit hyperactivity disorder; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; ASRS, adult ADHD self-report scale.

Treatment-seekers displayed more mental distress than the population controls with obesity class I or severe obesity as measured by GHQ-12 (Likert scoring: 14.9 points in treatment-seekers vs 11.5 points in controls with obesity class I and 10.2 points in controls with severe obesity; GHQ scoring: 3.8 points vs 2.3 and 2.1 points, all,  $p \leq 0.017$  when adjusting for age, gender, socioeconomic status and BMI). Treatment-seekers also displayed more anxiety symptomatology (as measured by the EQ-5D anxiety item) compared to controls with class I obesity (RR=1.78, 95% CI: 1.33-2.38) or severe obesity (RR=1.71, 95% CI: 1.28-2.30). The frequencies of depression, suicidal ideation and suicide attempts did not display any statistically significant differences across patient vs control groups (all,  $p \geq 0.33$ ).

**Table 5.** Mental distress as measured by the General Health Questionnaire-12, depression; lifetime suicidal behavior; quality of life; and present physical/psychosomatic symptoms in n=121 young adults (18–25 years) seeking behavioral weight reduction treatment for severe obesity and n=363 normal weight controls (18-25 years) from the Stockholm Public Health Survey, matched individually in a 1:3 ratio for age, gender and socioeconomic status.

Variable	Treatment-seekers	Population controls	Difference or RR (95% CI) <sup>a</sup>
<b>General Health Questionnaire</b>			
<b>GHQ-12 (Likert scoring <sup>b</sup>), mean (SE)</b>	15.5 (0.57)	10.8 (0.34)	4.55 (3.24, 5.86)
<b>GHQ-12 (GHQ scoring <sup>c</sup>), mean (SE)</b>	3.9 (0.30)	2.2 (0.17)	1.75 (1.08, 2.42)
<b>Mental distress (GHQ scoring <math>\geq 3</math>), % (n)</b>	52 (63)	30 (109)	1.76 (1.38, 2.24)
<b>Positive responses to GHQ-12-items: % (n)</b>			
‘Able to concentrate’	67 (81)	80 (287)	0.83 (0.72, 0.94)
‘Lost much sleep’	27 (33)	19 (68)	1.56 (1.07, 2.26)
‘Playing a useful part’	63 (76)	81 (292)	0.78 (0.67, 0.91)
‘Capable of making decisions’	81 (98)	91 (328)	0.90 (0.82, 0.99)
‘Under strain’	34 (41)	25 (89)	1.37 (0.99, 1.89)
‘Could not overcome difficulties’	36 (43)	23 (84)	1.53 (1.12, 2.08)
‘Enjoy normal activities’	63 (76)	83 (297)	0.78 (0.67, 0.90)
‘Able to face up to problems’	70 (81)	86 (309)	0.85 (0.67, 0.98)
‘Feeling unhappy and depressed’	40 (48)	26 (92)	1.53 (1.13, 2.08)
‘Losing confidence in yourself’	35 (42)	17 (60)	2.26 (1.59, 3.21)
‘Thinking of self as a worthless person’	37 (45)	15 (54)	2.81 (1.97, 4.01)
‘Feeling reasonably happy’	64 (77)	85 (308)	0.74 (0.64, 0.85)
<b>Depression <sup>d</sup>, % (n)</b>	22 (32)	8 (27)	2.18 (1.34, 3.55)
<b>Suicidal ideation, % (n)</b>	41 (50)	19 (69)	1.98 (1.43, 2.73)
<b>Suicide attempt, % (n)</b>	12 (14)	6 (20)	2.04 (1.06, 3.95)
<b>EQ5D, mean (SE)</b>	0.64 (0.019)	0.86 (0.011)	-0.23 (-0.27, -0.18)
<b>Some or extreme problems with: % (n)</b>			
Mobility	22 (26)	4 (14)	6.61 (3.15, 13.84)
Hygiene	3 (3)	1 (2)	2.91 (0.54, 15.81)
Daily activities	32 (39)	6 (22)	5.70 (3.27, 9.90)
Pain	68 (82)	30 (109)	2.17 (1.75, 2.68)
Anxiety	85 (103)	42 (149)	1.97 (1.69, 2.29)
<b>Physical/psychosomatic symptoms: % (n)</b>			
Headache	59 (71)	38 (138)	1.59 (1.29, 1.95)
Hyperacusis	33 (40)	14 (51)	2.19 (1.51, 3.19)
Urinary incontinence	16 (20)	6 (21)	2.74 (1.44, 5.23)
Acid reflux	41 (49)	14 (50)	2.95 (2.02, 4.30)
Fatigue	79 (95)	43 (155)	1.80 (1.53, 2.12)
Tinnitus	26 (31)	21 (74)	1.10 (0.75, 1.61)

Abbreviations: GHQ-12, General Health Questionnaire-12; RR, relative risk; SE, standard error.

<sup>a</sup> Matched and adjusted for age, gender, socioeconomic status, tobacco smoking, hazardous alcohol drinking, physical disease, sexual orientation and social support.

<sup>b</sup> Min–max (0–36).

<sup>c</sup> Min–max (0–12).

<sup>d</sup> Self-reported lifetime physician-diagnosed depression.

## 6.2 RESULTS OF ASPECTS OF TREATMENT / RESEARCH QUESTIONS 4-5 (STUDIES III-IV)

### Participants’ characteristics in Study III

A total of n=3,531 young (18-25 years) and n=17,137 older ( $\geq 26$  years) adult RYGB patients from SOReg, frequency matched for gender, BMI and year of surgery, were included in Study III. In the young adult age group, mean age was 22.2 years (SD: 2.1), 81.6% (n=2,882) were women and mean BMI was 43.7 kg/m<sup>2</sup> (SD: 5.4). In the older adult age group, mean

age was 42.6 years (SD: 9.6), the age range was 26-74 years, 82.0% (n= 14052) were women and mean BMI was 43.4 kg/m<sup>2</sup> (SD: 5.0). No clinically relevant differences were observed in matching variables between matching groups, although there was a statistically significant difference in BMI between groups (p <0.001). A total of n=369 young (37.0% of eligible) and n=2,210 older (46.1%) adults were included in the 5-year analysis. See flow chart in **Figure 5** for details.

Both young and older adults with complete data displayed higher baseline BMI (44.5 kg/m<sup>2</sup> vs 43.6 kg/m<sup>2</sup> in young adults, 43.8 kg/m<sup>2</sup> vs 43.3 kg/m<sup>2</sup> in older adults) and fewer comorbidities than those with missing data at 5 years (15.2% vs 23.1% in young adults, 44.0% vs 54.1% in older adults). Among older adults, smoking was more common (18.6% vs 13.7%), and age was higher (43.2 years vs 42.5 years) in completers vs those with missing data (all, p <0.01).

### **Weight loss**

Young adult completers lost less weight during the preoperative low-calorie diet period than older adult completers (5.2% vs 5.6% of preoperative weight, p <0.001). In the subsequent follow-ups, young adult completers displayed higher percentage weight loss and a more pronounced change in BMI slope than older adult completers up to 5 years post-RYGB in crude and adjusted (for gender, year of surgery, comorbidity at baseline [yes/no], surgical access [laparoscopic/open], duration of surgery [minutes], surgical volume [high/low] and concurrent surgery [yes/no]) analyses, all, p <0.001 (**Tables 6-7** and **Figure 7**). A sensitivity analysis on percentage weight loss and change in BMI slope with listwise deletion data and last observation carried forward data supported our results (all, adjusted with the above mentioned co-variates, p <0.05) while the analysis with baseline carried forward data displayed lower percentage weight loss in young vs older adults at 1 (28.0% vs 28.6%), 2 (19.3% vs 20.5%) and 5 (11.5 vs 13.1%) years after RYGB compared to baseline (all, adjusted with the above mentioned co-variates, p <0.05). The mixed models analysis with baseline carried forward data displayed no statistically significant difference in change in BMI slope between young and older adults (**Table 7**).

Five years post-RYGB, EWL was higher (75.6% [SD: 27.2] vs 68.2% [SD: 25.9], and successful weight loss (EWL ≥50%) was more common (85.6% vs 76.0%) in young compared to older adult completers (both, crude, p <0.001, **Table 6**).

**Table 6.** Body weight, body weight lost and excessive weight loss 1, 2 and 5 years after Roux-en-Y gastric bypass <sup>a</sup> in 3,531 young (18-25 years) and 17,137 older (26-74 years) adults matched for body mass index, gender and year of surgery.

	1 year		2 years		5 years	
	Young adult (n=2,900)	Older adult (n=15,298)	Young adult (n=1,831)	Older adult (n=9,959)	Young adult (n=369)	Older adult (n=2,210)
<b>Body weight, kg; mean (SD)</b>	82.7 (16.9)	83.3 (16.1)	81.5 (16.7)	82.4 (16.5) *	87.1 (19.0)	88.7 (18.4)
<b>BWL, %, mean (SD)</b>	34.6 (7.6)	32.0 (7.5) **	35.4 (8.5)	32.6 (8.8) **	31.8 (10.5)	28.2 (10.1) **
<b>BWL category, % (n)</b>						
<b>Weight gain</b>	0.0 (1)	0.0 (2)	0.0 (2)	0.1 (11)	0.5 (2)	0.5 (11)
<b>0.0-14.9% BWL</b>	1.3 (37)	1.4 (212)	1.7 (31)	2.5 (251) *	7.6 (28)	9.1 (202)
<b>15.0-29.9% BWL</b>	24.4 (709)	37.4 (5,716) **	22.1 (405)	33.8 (3,771) **	28.7 (106)	45.4 (1,004) **
<b>30.0-39.9% BWL</b>	50.6 (1,468)	46.6 (7,127) **	43.7 (800)	43.0 (4,286)	42.5 (157)	32.9 (727) **
<b>≥40.0% BWL</b>	23.6 (685)	14.6 (2,241) **	32.3 (592)	20.5 (2,040) **	20.6 (76)	12.0 (266)
<b>BMI &lt;25 kg/m<sup>2</sup>, % (n)</b>	23.3 (675)	15.8 (2,416) **	27.6 (505)	19.5 (1,938) **	16.3 (60)	10.0 (221) **
<b>%EWL, mean (SD)</b>	84.2 (22.2)	78.7 (21.7) **	85.7 (23.1)	79.9 (23.3) **	75.6 (27.2)	68.2 (25.9) **
<b>EWL ≥50%, % (n)</b>	94.3 (2,734)	92.0 (14,059) **	93.4 (1,708)	90.3 (8,973) **	85.6 (316)	76.0 (1,680) **

Abbreviations: n, number; SD, standard deviation; BWL, body weight lost; BMI, body mass index; EWL, excessive weight loss.

<sup>a</sup> Compared to preoperative weight (approximately 4 weeks before surgery including 2-3 weeks of low calorie diet).

\* p <0.05 for difference in young vs older adults.

\*\* p ≤0.001 for difference in young vs older adults.

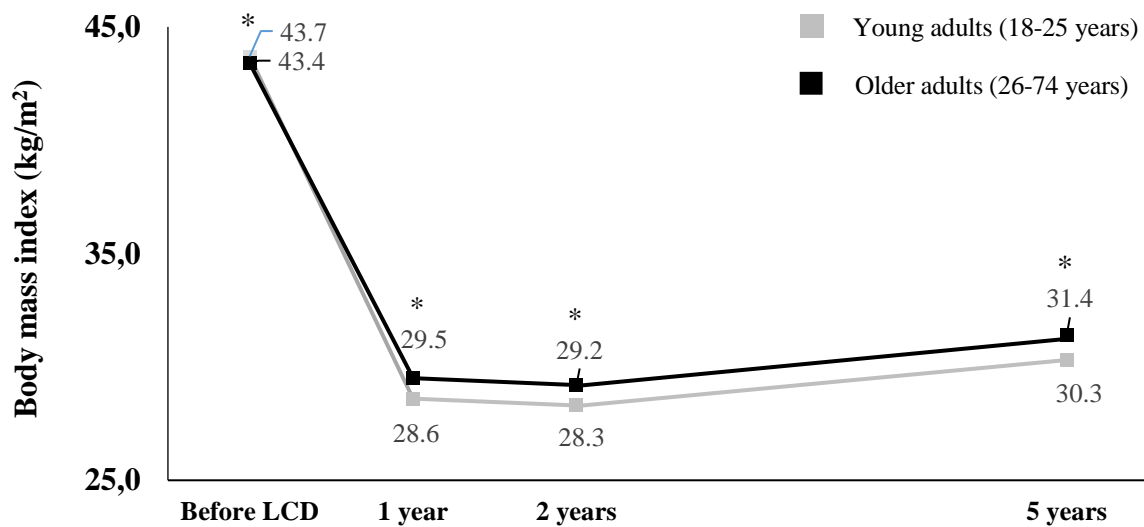
**Table 7.** Effects of matching group in 998 young adults (18-25 years) and 4,792 older (26-74 years) adults (patients eligible for 5-year follow up within the study period); on the intercept and the slope of body mass index 5 years after Roux-en-Y gastric bypass for completers (full information maximum likelihood), in listwise deletion (LiDe), and when imputing data by using baseline carried forward (BCF) and last observation carried forward (LOCF). Matching groups were adjusted for gender, year of surgery, comorbidity (yes/no), surgical access (laparoscopic/open), duration of surgery (minutes), surgical volume (low/high) and concurrent surgery.

Parameter/effect	Completers	p-value	LiDe <sup>a</sup>	p-value	BCF	p-value	LOCF	p-value
<b>Intercept-intercept <sup>b</sup></b>	40.8	<0.001	39.9	<0.001	39.7	<0.001	41.7	<0.001
<b>Slope-intercept <sup>c</sup></b>	-0.53	<0.001	-0.22	<0.001	-0.21	<0.001	-0.23	<0.001
<b>Young adults on intercept</b>	0.49	<0.001	0.55	0.002	0.29	<0.001	0.35	<0.001
<b>Young adults on slope</b>	-0.077	<0.001	-0.051	<0.001	0.0094	0.062	-0.011	<0.001

<sup>a</sup> N<sub>Young adults</sub>=232, N<sub>Older adults</sub>=1525

<sup>b</sup> Predicted body mass index at baseline for older adults.

<sup>c</sup> Predicted change in body mass index per month for older adults.



**Figure 7.** Body mass index in young (18-25 years) and older (26-74 years) adults before surgery / low calorie diet and 1, 2 and 5 years after Roux-en-Y gastric bypass.

Abbreviations: LCD, low calorie diet.

N<sub>Young adults</sub>: Before LCD = 3,531, 1 year = 2,900, 2 years = 1,831, 5 years = 369.

N<sub>Older adults</sub>: Before LCD = 17,137, 1 year = 15,298, 2 years = 9,959, 5 years = 2,210.

\*  $p < 0.05$  unadjusted and when adjusted for body mass index at baseline, gender, year of surgery, comorbidity (yes/no), surgical access (laparoscopic/open), duration of surgery, surgical volume and concurrent surgery.

## Adverse events

**Figure 8** displays percentages of adverse events (any/significant/serious) in young and older adults, respectively. Intraoperatively and between 0 to 6 weeks after surgery, adverse events of *any kind* were less frequent in young vs older adults (OR=0.74, 95% CI: 0.58-0.93 and OR=0.79, 95% CI: 0.69-0.92 respectively). However, when adjusted for co-variates (baseline BMI, gender, year of surgery, comorbidity at baseline [yes/no], surgical access [laparoscopic/open], duration of surgery [minutes] and centre volume [low/high]), there was no significant difference between groups in percentages of adverse events of any kind intraoperatively (adjusted OR=0.87, 95% CI: 0.68-1.12) or at 6 weeks (OR=0.91, 95% CI: 0.79-1.06). At the subsequent follow-ups, young adults reported higher rates of any type of adverse events between 6 weeks and 1 year (adjusted OR=1.45, 95% CI: 1.24-1.70), between 1 and 2 years (adjusted OR=1.40, 95% CI: 1.18-1.66) and between 2 and 5 years (adjusted OR=1.72, 95% CI: 1.29-2.30) in crude and adjusted values, all,  $p < 0.001$  than older adults. See **Figure 8** for crude data including p-values for adjusted analyses.

The frequency of *significant* adverse events (Clavien Dindo 2-3a) was the same in young and older adults throughout the study period (all,  $p \geq 0.20$ ) independent of adjustment for covariates. For short-term *serious* adverse events (between surgery and 6 weeks post-RYGB), young adults displayed fewer adverse events than older adults (crude OR=0.73, 95% CI:

0.56-0.95, and adjusted OR=0.76, 95% CI: 0.58-1.00). However, young adults displayed more long-term serious adverse events (Clavien Dindo  $\geq 3$ ) in crude and adjusted values between 6 weeks and 1 year (adjusted OR=1.71, 95% CI: 1.36-2.13), between 1 and 2 years (adjusted OR=1.44, 95% CI: 1.15-1.80) and between 2 and 5 years (adjusted OR=2.06, 95% CI: 1.45-2.92), all,  $p < 0.001$  than the older adults.

When including all eligible (for 2- and 5 years follow-up) baseline patients in an intention-to-treat analysis of any adverse events between the same assessment points as above, the results of fewer short-term (crude data) but more any adverse events (crude and adjusted data) in the young were attenuated but still significant (data not shown). For serious adverse events, the 2-year data were borderline significant ( $p=0.062$ ) while the 1- and 5-year data were significant.

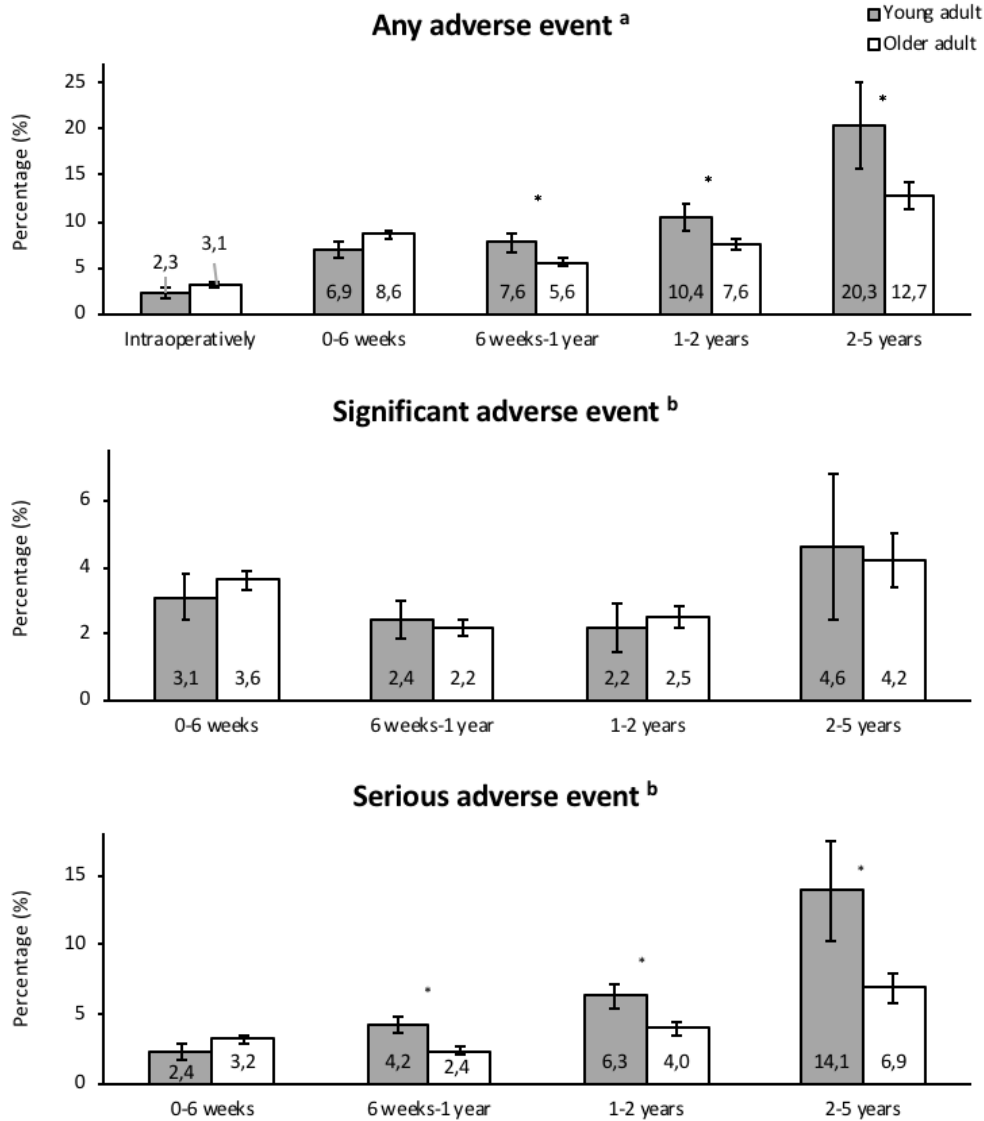
However, when analyzing completers (i.e. only those with 5-year data) with at least one adverse event of any kind between baseline (intraoperatively) and 5 years post-RYGB in completers, we found no difference between young and older adults in crude or adjusted values (24.5% vs 24.5%,  $p=0.97$ ; adjusted OR=1.12, 95% CI: 0.95-1.32,  $p=0.18$ ).

In a classification of specified adverse events between matching groups, ileus (2.7% vs 1.5% at 6 weeks - 1 year, 5.0% vs 3.0% at 1-2 years and 10.3% vs 5.0% at 2-5 years) and “other adverse events” (3.4% vs 2.1% between 6 weeks and 1 year, 3.7% vs 2.4% between 1 and 2 years and 7.9% vs 3.6% between 2 and 5 years) were more common in young adults, while hernia was more common in older adults (0.1% vs 0.5% between 6 weeks and 1 year, 0.3% vs 0.8% between 1 and 2 years and 0.3% vs 1.9% between 2 and 5 years), all  $p < 0.05$ .

### **Loss-to-follow-up**

Young adults consistently displayed higher risks for “missed appointment” (adjusted range of RR=1.25-2.13) and “total loss-to-follow-up” (adjusted range of RR=1.16-1.89; all,  $p < 0.001$ ) compared to older adults at all assessments throughout the observation period of 5 years.

Moreover, younger patients were less often contacted for follow-up appointments 1 to 5 years post-RYGB (adjusted range of RR=1.18-1.50, all,  $p \leq 0.010$ ). Detailed data on loss-to-follow-up are displayed in **Table 8**. Adjusted values were not materially different from crude values.



**Figure 8.** Percentage of any, significant (Clavien-Dindo 2-3a = complication requiring pharmacological treatment or intervention under local anesthesia) and serious (Clavien-Dindo  $\geq$ 3b = complication requiring intervention under general anesthesia) adverse event in young (18-25 years) and older (26-74 years) adults intraoperatively, between surgery - 6 weeks, between 6 weeks - 1 year, between 1-2 years and between 2-5 years after Roux-en-Y gastric bypass. Error bars represent 95% confidence intervals.

<sup>a</sup> N<sub>Young adults</sub> intraoperatively=3,531, 6 weeks=3,328, 1 year=2,900, 2 years=1,830, 5 years=369.

N<sub>Older adults</sub> intraoperatively=17,137, 6 weeks=16,630, 1 year=15,280, 2 years=9,946, 5 years=2,210.

<sup>b</sup> Registrations only after May 1, 2010: N<sub>young adults</sub> 6 weeks=2,657, 1 year=2,601, 2 years=1,734,

5 years=369. N<sub>older adults</sub> 6 weeks=13,288, 1 year=13,422 2 years=9,575, 5 years=2,202.

\* p < 0.05 when adjusted for body mass index at baseline, gender, year of surgery, comorbidity at baseline, surgical access (laparoscopic/open), duration of surgery, center volume (low/high).

**Table 8.** Relative risk of loss-to-follow-up (missed appointment, no attempt to contact patient and total loss-to-follow-up) at 6 weeks, 1, 2 and 5 years after Roux-en-Y gastric bypass in 3,531 young (18-25 years) compared to 17,137 older (26-74 years) adults matched for body mass index at baseline, gender and year of surgery.

	Young adult	Older adult	Adjusted RR (95% CI), p-value <sup>a</sup>
<b>6 weeks, % (n)</b>			
Visits	94.3 (3,328)	97.0 (16,631)	
Missed appointment <sup>b</sup>	5.0 (175)	2.2 (381)	2.13 (1.77-2.57), <0.001
No attempt to contact patient	0.7 (23)	0.5 (94)	1.08 (0.68-1.71), 0.74
Total loss-to-follow-up <sup>c</sup>	5.7 (203)	3.0 (506)	1.89 (1.60-2.23), <0.001
<b>1 year, % (n)</b>			
Visits	82.1 (2,900)	89.3 (15,298)	
Missed appointment <sup>b</sup>	12.2 (430)	6.3 (1,088)	1.81 (1.62-2.02), <0.001
No attempt to contact patient	4.2 (149)	2.4 (413)	1.50 (1.24-1.81), <0.001
Total loss-to-follow-up <sup>c</sup>	17.9 (631)	10.7 (1,839)	1.57 (1.44-1.71), <0.001
<b>2 years, % (n) <sup>d</sup></b>			
Visits	55.7 (1,831)	62.5 (9,959)	
Missed appointment <sup>b</sup>	19.2 (632)	12.3 (1,965)	1.47 (1.36-1.60), <0.001
No attempt to contact patient	11.6 (381)	9.7 (1,544)	1.18 (1.06-1.31), 0.002
Total loss-to-follow-up <sup>c</sup>	44.3 (1,458)	37.5 (5,975)	1.20 (1.15-1.25), <0.001
<b>5 years, % (n) <sup>d</sup></b>			
Visits	37.0 (369)	46.1 (2,210)	
Missed appointment <sup>b</sup>	25.8 (257)	19.9 (955)	1.25 (1.11-1.40), <0.001
No attempt to contact patient	9.5 (95)	6.5 (311)	1.33 (1.07-1.65), 0.010
Total loss-to-follow-up <sup>c</sup>	63.0 (629)	53.9 (2,582)	1.16 (1.10-1.23), <0.001

Abbreviations: RR, relative risk; CI, confidence interval; n, numbers.

<sup>a</sup> Adjusted for body mass index at baseline, gender, year of surgery, comorbidity at baseline, surgical access (laparoscopic/open), duration of surgery, center volume (low/high).

<sup>b</sup> Patient was contacted by care provider but did not turn up at planned appointment.

<sup>c</sup> “Missed appointment”, “no attempt to contact patient”, loss-to-follow-up of unknown reason (=missing data) and deceased.

<sup>d</sup> Includes only patients who were eligible for follow-up at 2 years ( $n_{\text{young adults}} = 3,289$ ,  $n_{\text{older adults}} = 15,934$ ) and 5 years ( $n_{\text{young adults}} = 998$ ,  $n_{\text{older adults}} = 4,792$ ).

## Participants’ characteristics in Study IV

A total of  $n=2,542$  young (18-25 years) and  $n=12,425$  older ( $\geq 26$  years) adult RYGB patients from Study III were included in Study IV. In the young adult age group, mean age was 22.2 years (SD: 2.2), 82.1% ( $n=2,087$ ) were women and mean BMI was  $43.6 \text{ kg/m}^2$  (SD: 5.4). In the older adult age group, mean age was 42.6 years (SD: 9.6), the age range was 26-74 years, 81.9% ( $n=10,177$ ) were women and mean BMI was  $43.4 \text{ kg/m}^2$  (SD: 5.0).

Concerning differences in baseline variables among patients from the SOReg cohort (in Study III) with vs without HRQL data at baseline (included vs non-included in Study IV), there were fewer smokers (13.4% vs 15.0%), more patients with depression (15.8% vs 14.5%) and more open procedures (3.9% vs 2.8%) among included vs non-included older adults, while no differences were found between included/non-included young adults.

A total of  $n=138$  young (20.7% of eligible) and  $n=1,021$  older (31.8%) adults were included in the 5-year analysis (see flowchart in **Figure 6**). A missing data analysis revealed statistically significant differences in baseline descriptives between those with missing vs those with complete data at the 5-year follow-up (for young adults: laparoscopic access:



98.2% vs 94.2%; for older adults: 42.5 years old vs 43.8 years old at baseline; 168.1 cm vs 167.5 cm; 18.4% vs 14.6% men; any comorbidity: 53.7% vs 45.2%; sleep apnea: 10.2% vs 8.2%; laparoscopic access: 85.7% vs 97.1%; all,  $p < 0.05$ ). Also, HRQL-baseline levels were lower in missing vs complete data for certain variables in young (physical function, social function, physical component score) and older adults (physical role, bodily pain, general health, vitality, social function, physical component score and OP) all,  $p < 0.05$ . In Study IV 5-year weight loss in young and older adults were 32.3% and 27.6% respectively ( $p < 0.001$ ).

### Health-related quality of life

A total of 70.8% ( $n=1,793$ ) of young and 63.5% ( $n=7,874$ ) of older adults were categorized as having severely impaired psychosocial functioning (OP score) at baseline ( $p < 0.001$ ). Five years after RYGB, young adults displayed average to large improvements ( $ES \geq 0.5$ ) in physical functioning, physical component score and OP, while older adults displayed average to large ( $ES \geq 0.5$ ) improvements in physical functioning, role physical, general health, physical component score and OP as presented in **Table 9-10** (all,  $p \leq 0.001$ ). Concerning the mental domains of SF-36; weak, negligible or no 5-year changes were observed in any of the age groups as presented in **Table 10** (all,  $p < 0.55$ ).

**Table 9.** Physical domains of Short Form-36 and between-groups effect sizes up to 5 years after Roux-en-Y gastric bypass in  $n=2,542$  young (18-25 years) vs  $n=12,425$  older (26-74 years) adults.

Variable, mean (SD)	Young adult	Older adult	p-value <sup>a</sup>	Effect size <sup>a</sup>
<b>Physical functioning, baseline</b>	64.7 (20.7)	58.5 (22.6)	<0.001	0.15
1 year	93.0 (14.3) **	88.4 (18.0) **	<0.001	0.28
2 years	91.8 (14.5) **	87.7 (19.1) **	<0.001	0.24
5 years	87.1 (17.2) **	81.5 (22.9) **	0.027	0.28
Effect size (baseline - 5 years)	1.18	1.01		
<b>Role physical, baseline</b>	59.1 (37.5)	55.3 (39.6)	<0.001	0.10
1 year	90.7 (23.9) **	86.6 (29.6) **	<0.001	0.15
2 years	85.7 (30.0) **	84.0 (32.3) **	0.835	0.05
5 years	74.2 (38.8) *	75.7 (37.7) **	0.647	0.04
Effect size (baseline - 5 years)	0.40	0.53		
<b>Bodily pain, baseline</b>	61.0 (27.4)	52.6 (27.5)	<0.001	0.63
1 year	80.8 (24.5) **	74.1 (28.0) **	<0.001	0.25
2 years	75.3 (28.1) **	72.0 (29.2) **	0.006	0.12
5 years	68.1 (34.0) *	63.0 (31.5) **	0.071	0.16
Effect size (baseline - 5 years)	0.06	0.35		
<b>General health, baseline</b>	52.2 (22.3)	54.7 (22.2)	<0.001	0.11
1 year	77.7 (19.0) **	79.3 (20.3) **	<0.001	0.08
2 years	73.1 (22.3) *	76.1 (22.2) **	<0.001	0.13
5 years	61.7 (25.8) **	66.5 (25.2) **	0.039	0.19
Effect size (baseline - 5 years)	0.39	0.50		
<b>Physical component score, baseline</b>	40.7 (10.0) **	36.8 (10.9)	<0.001	0.37
1 year	53.4 (7.1) **	50.7 (9.3) **	<0.001	0.33
2 years	52.2 (8.3) **	50.2 (9.8) **	<0.001	0.22
5 years	47.1 (11.3) **	45.3 (12.4) **	0.171	0.15
Effect size (baseline - 5 years)	0.60	0.73		

Abbreviations: SD, standard deviation.

$N_{\text{young adults}}=1,440$  (1 year), 777 (2 years), 138 (5 years).

$N_{\text{older adults}}=8,487$  (1 year), 4,816 (2 years), 1,021 (5 years).

Effect size categories: negligible (<0.2), weak (0.2-0.5), average (0.5-0.8), large (>0.8).

<sup>a</sup> Between-group differences.

\*\* Within-group difference compared to baseline,  $p \leq 0.001$

\* Within-group difference compared to baseline,  $p < 0.05$

**Table 10.** Mental domains of Short Form-36, Obesity-related Problems scale and between-groups effect sizes up to 5 years after Roux-en-Y gastric bypass in n=2,542 young (18-25 years) vs n=12,425 older (26-74 years) adults.

Variable, mean (SD)	Young adult	Older adult	p-value <sup>a</sup>	Effect size <sup>a</sup>
<b>Vitality, baseline</b>	42.9 (21.8)	44.3 (23.4)	<0.001	0.06
1 year	64.6 (21.7) **	67.9 (23.6) **	<0.001	0.15
2 years	57.8 (24.8) **	63.1 (25.4) **	<0.001	0.21
5 years	48.1 (27.3)	52.1 (27.2) **	0.118	0.15
Effect size (baseline - 5 years)	0.21	0.31		
<b>Social functioning, baseline</b>	67.5 (27.7)	70.9 (27.8)	<0.001	0.12
1 year	86.4 (21.1) **	87.4 (21.5) **	<0.001	0.05
2 years	81.6 (24.1) **	84.7 (23.6) **	0.001	0.13
5 years	73.9 (29.1)	77.3 (27.5) **	0.203	0.12
Effect size (baseline - 5 years)	0.23	0.23		
<b>Role emotional, baseline</b>	63.6 (40.4)	71.8 (38.5)	<0.001	0.21
1 year	81.8 (33.8) **	85.5 (31.3) **	<0.001	0.11
2 years	77.6 (36.4) **	82.2 (34.3) **	0.001	0.13
5 years	70.6 (41.1)	73.8 (39.8)	0.426	0.08
Effect size (baseline - 5 years)	0.17	0.05		
<b>Mental health, baseline</b>	62.7 (20.6)	69.2 (20.5)	<0.001	0.32
1 year	75.9 (19.7) **	79.8 (19.9) **	<0.001	0.20
2 years	71.1 (22.1) **	76.7 (21.7) **	<0.001	0.26
5 years	68.2 (22.8) *	69.8 (23.9)	0.285	0.07
Effect size (baseline - 5 years)	0.25	0.03		
<b>Mental component score, baseline</b>	40.7 (12.6)	45.4 (12.5)	<0.001	0.37
1 year	46.0 (12.1) **	49.0 (12.0) **	<0.001	0.25
2 years	43.5 (13.1) **	47.2 (13.0) **	<0.001	0.28
5 years	40.9 (14.0)	43.5 (14.4) **	0.008	0.18
Effect size (baseline - 5 years)	0.02	0.14		
<b>Obesity-related Problems scale, median (IQR), baseline</b>	75.0 (33.3)	70.8 (35.7)	<0.001	0.20
1 year	20.8 (33.4) **	12.5 (29.2) **	<0.001	0.34
2 years	29.2 (45.9) **	12.5 (33.3) **	<0.001	0.45
5 years	39.6 (45.8) **	20.8 (45.8) **	<0.001	0.40
Effect size (baseline - 5 years)	1.11	1.34		

Abbreviations: SD, standard deviation; IQR, interquartile range.

N<sub>young adults</sub>=1,440 (1 year), 777 (2 years), 138 (5 years).

N<sub>older adults</sub>=8,487 (1 year), 4,816 (2 years), 1,021 (5 years).

Effect size categories: negligible (<0.2), weak (0.2-0.5), average (0.5-0.8), large (>0.8).

<sup>a</sup> Between-group differences.

\*\* Within-group difference compared to baseline, p ≤0.001

\* Within-group difference compared to baseline, p <0.05

Older adults displayed larger improvements in physical role, general health, vitality, social functioning, physical component score and OP than their younger counterparts as displayed in the multiple regression analysis of change (5 years post-RYGB vs baseline) in each of the HRQL components (all, adjusted p ≤0.036, **Table 11**). A sensitivity analysis that included baseline and last observation carried forward data did not materially alter these findings (data not shown).

**Table 11.** Effect of matching group (1=young adults) on 5-year change in Short Form-36 and Obesity-related Problems scale in n=138 young (18-25 years) and n=1,021 older (26-74 years) adults (i.e. eligible patients).

<b>Variable <sup>a</sup></b>	<b>Unadjusted model Beta (95% CI)</b>	<b>p-value</b>	<b>Adjusted model Beta (95% CI) <sup>b</sup></b>	<b>p-value</b>
<b>Short Form-36</b>				
<b>Physical functioning</b>	-2.6 (-6.9, 1.8)	0.25	-2.0 (-5.5, 1.5)	0.27
<b>Physical role</b>	-9.0 (-17.7, -0.44)	0.039	-7.2 (-14.0, -0.47)	0.036
<b>Bodily pain</b>	-2.2 (-8.2, 3.8)	0.47	-2.0 (-7.4, 3.4)	0.47
<b>General health</b>	0.72 (-4.3, 5.8)	0.78	-6.6 (-10.9, -2.3)	0.02
<b>Vitality</b>	-3.8 (-9.2, 1.7)	0.17	-6.2 (-10.9, -1.4)	0.011
<b>Social functioning</b>	-5.3 (-11.5, 0.90)	0.094	-5.7 (-11.0, -1.4)	0.026
<b>Role emotional</b>	0.56 (-8.3, 9.5)	0.90	4.7 (-12.0, 2.7)	0.21
<b>Mental health</b>	2.4 (-2.2, 7.0)	0.30	-1.3 (-5.4, 2.8)	0.54
<b>Physical component score</b>	-2.1 (-4.3, 0.064)	0.057	-2.1 (-4.0, -0.14)	0.036
<b>Mental component score</b>	0.06 (-2.9, 3.0)	0.99	-2.04 (-4.7, 0.58)	0.13
<b>Obesity-related Problems scale</b>	5.3 (-0.64, 11.3)	0.08	13.6 (8.7, 18.4)	<0.001

Abbreviations: CI, confidence interval.

<sup>a</sup> For Short Form-36, a negative coefficient denotes that the change (5-year levels vs baseline) was smaller in young vs older adults. For Obesity-related Problems Scale, a positive coefficient denotes that the change was smaller in young vs older adults.

<sup>b</sup> Adjusted for health-related quality of life component at baseline, comorbidity (yes/no), weight loss at five years, adverse events (yes/no) and surgical access (laparoscopic/open).



## 7 DISCUSSION

Here I will endeavor to address the five research questions stated above and place the results in the context of previous research to discuss clinical implications of the main findings and suggest areas for future research.

### 7.1 MAIN FINDINGS ON CHARACTERIZATION (STUDIES I-II)

We found that a total of 47-85% of young adult treatment-seekers to a specialized obesity unit had anxiety symptomatology, 27% had depressive symptomatology, 37% had ADHD symptomatology, 42% had low self-esteem, 12% had a history of suicide attempts, 55% had severe impairment in psychosocial functioning and 52% had mental distress. A total of 29% had  $\geq 1$  psychiatric diagnosis, including depression (13%), ADHD (13%) and other neurodevelopmental disorders (5%). We found plasma lipid abnormalities in 62%, insulin resistance in 82%, poor cardiorespiratory fitness in 92% and a micronutritional deficiency in 48% of the treatment-seekers.

The design of Study II allowed us to compare our results from treatment-seekers with those in population controls with different BMI levels. Herein, we found that the treatment-seekers experienced approximately doubled RR for mental distress, depression, anxiety and suicidal behavior compared to individually matched population controls. For physical/psychosomatic symptoms, including urinary incontinence and acid reflux, the RR almost tripled for treatment-seekers vs population controls. We also found that treatment-seekers displayed significantly more mental distress and lower quality of life than population controls with class I obesity or severe obesity.

Moreover, we found that anxiety symptomatology in treatment-seeking young adults with obesity was associated with pain and low self-esteem, while depressive symptomatology was associated with physical inactivity, low self-esteem and low psychosocial functioning.

#### **Other research:**

##### *Mental health in young adults with obesity*

Although Study I was not designed to compare results with a control group, a review of reference literature indicates that compared to population data the participants in Study I display poor health, particularly in regard to mental health: Normative HADS scores for Swedish 16-23-year-olds were 3.8-7.0 for anxiety and 2.5-4.0 for depression (7.8 and 5.3 in Study I)<sup>282</sup>, and normative SF-36 in the same study group was 52-55 (physical component score) and 39-51 (mental component score) (46 and 36 respectively in Study I)<sup>282</sup>. Normative scores varied between genders and mode of response (email/telephone). Self-esteem as measured by RSES was higher (i.e. better) in U.S. reference controls (Swedish reference data were not found) than in the present study (22.3 vs 16.2 points)<sup>283</sup>. A total of 15% of Swedish 18- to 24-year old women and 10% of Swedish 18- to 24-year old men had been either

hospitalized in a psychiatric ward and/or prescribed psychiatric medication in 2016 (mainly for depression and anxiety) (extracted data)<sup>284</sup>, which may be (non-statistically) compared with 21% on psychiatric medication in our patient group. Interestingly, a Swedish case control study on validation of GHQ-12 found that a Likert score  $\geq 14$  points and a GHQ score  $\geq 4$  points discriminated well between healthy individuals and affective disorders<sup>285</sup>. Accordingly, our data of 15.5 (SD: 0.57) using Likert scoring and 3.9 (SD: 0.30) using GHQ scoring in treatment-seekers highlight possible psychiatric distress in young adults with obesity that needs further evaluation.

The few previously published studies on mental health in young adults with obesity also found a higher prevalence of mental distress (assessed via standardized psychiatric interview) in German treatment-seekers with obesity compared to population controls: 23% vs 10% for depression, and 40% vs 14% for anxiety<sup>199</sup>. Meanwhile, 31.5% of American teenagers undergoing bariatric surgery had a psychiatric diagnosis<sup>286</sup>, i.e. rates that were similar to the present findings.

Despite a repetitive bidirectional relationship between obesity and mental distress, as discussed in the introductory chapter, the role of mediators, moderators and direct cause-effect links between the two states continue to be obscure. Previous data generally proposed BMI to be repetitively positively associated with the level of mental distress (in contrast to the results of the regression analysis in Study I). Moreover, educational attainment, body image, binge eating, physical health and psychosocial characteristics such as self-esteem, hostility, anger, sadness and maladaptive schemas have been associated with both obesity and mental distress<sup>287</sup>. Inflammation is suggested to be another mechanism through which obesity and depression may coexist<sup>288</sup>. However, data on associations between obesity and mental distress have generally been cross-sectional, which does not reveal whether any of the above-mentioned correlates are possible targets in obesity care.

#### *Cardiometabolic health in young adults with obesity*

In addition to poor mental health indices, a majority of the treatment-seekers in our study displayed high-risk levels of cardiometabolic markers including lipid abnormalities, insulin resistance and elevated alanine aminotransferase levels. Previous prevalence studies of cardiometabolic risk markers in youth have generally included patients on waiting lists for bariatric surgery, i.e. patients who were generally worse off than those in behavioral treatment, and have reported levels that were similar to our results: The American Teen-LABS consortium reported that 50.4% had dyslipidemia, 26.1% had impaired fasting glucose, 71.1% had increased HOMA levels and only 5.0% were free from any cardiovascular risk marker<sup>289</sup>.

In non-bariatric treatment-seeking cohorts, youths with severe obesity vs overweight displayed significantly more abnormal levels of lipids (58.5% of those with severe obesity vs 45.8% of those with overweight), alanine aminotransferase (81.4% vs 55.4%) and insulin resistance (82.1% vs 55.6%)<sup>170</sup>. Community studies found lower frequencies of

cardiometabolic risk factors in youth with severe obesity than is the case in the present thesis (dyslipidemia in 10.8-30.0%, abnormal levels of HbA1c in 13.2%); however, they found a clear positive association between the severity of obesity and cardiometabolic risk markers<sup>172</sup>.

The present findings are serious given that cardiometabolic risk markers generally track into adulthood and severely increase the risk of future cardiovascular morbidity and mortality, independently of future BMI levels<sup>290 291</sup>.

### *Micronutritional deficiencies in young adults with obesity*

When comparing our results with data from a Danish population study of 18-to-25-year-olds (although not statistically tested), our results indicate that the treatment-seeking young adults in Study I suffer from lower vitamin D levels than Danish controls of different BMI levels (35% vs 19.3% had vitamin D deficiency, and 45% vs 30.1% had vitamin D insufficiency, using the same cut-offs)<sup>292</sup>. The Danish study also found an association between poor vitamin D levels and obesity, as has been found in other age groups<sup>292 293</sup>. Hypovitaminosis D has been linked to obesity via low dietary intake, increased uptake of vitamin D in the fat cells, low sun exposure and secondary low conversion to active vitamin D and reduced hepatic synthesis of vitamin D secondary to steatosis<sup>294</sup>. Iron status was similar in our population as that in an Australian sample of 18- to 25-year old women with obesity, low ferritin levels (<15 µg/l) were found in 16.7%. The association between low iron levels and obesity has been explained by low dietary intake and the obese inflammatory state<sup>295</sup>. Moreover, previous studies of obese populations showed disparate results regarding deficiencies in folate (0.0-63.2%) and vitamin B12 (5.1-20.0%)<sup>296</sup>. Micronutritional abnormalities in young ages are of major concern given the associations with osteomalacia (hypovitaminosis D), cognitive deficits (hypoferrremia) and fatal pregnancy outcomes (low folate), among others<sup>297-299</sup>.

## **7.2 MAIN FINDINGS ON ASPECTS ON TREATMENT (STUDIES III-IV)**

Five years after RYGB, we found statistically significantly more weight loss (31.8% vs 28.2%), fewer short-term (in crude data) but more long-term (in crude and adjusted) adverse events (e.g. 20.3% vs 12.7% between 2 to 5 years post-surgery), higher loss-to-follow-up throughout (63.0% vs 53.9%) and generally smaller improvements in HRQL in young (18-25 years) vs older (26-74 years) adults. Moreover, we found clinically relevant improvements in physical HRQL in young adults up to 5 years after RYGB, while their mental HRQL did not differ from baseline levels.

## Other research:

### *Age-dependent effects on weight loss*

Our findings of statistically significantly more weight loss in the young completers support previous publications that showed increased BMI loss 60 months post-RYGB in young (<35 years) compared to older patients when grouped in age quartiles<sup>300</sup>, and higher weight loss 2 years after gastric banding in women aged 20-45 years old compared to 55-to-65-year-old women (about 10% more EWL)<sup>301</sup>. Conversely, behavioral weight loss trials report less weight loss in young (<35 years) compared to older adults ( $\geq 35$  years, 4.3 vs 7.7 kg, 6-month trial)<sup>233</sup>. Given the poor weight loss in young adults in behavioral treatment (-2.4 kg according to a systematic review of up to 12 months follow-up)<sup>235</sup>, our results clearly suggest that Roux-en-Y gastric bypass provides the most efficient weight loss treatment to date for this age group; this is also supported by the few and smaller previous studies of similar age groups<sup>302</sup>.

There are several plausible explanations for the favorable weight loss in the younger patients: redistribution in fat mass accumulation over the life course may change lipolysis and insulin regulation, and therefore also the potential for weight loss<sup>301 303 304</sup>. For example, fat mass lost after RYGB was mainly found to consist of subcutaneous adipose tissue, which is more prevalent in younger ages<sup>304</sup>. Furthermore, brown adipose tissue declines with age, possibly contributing to higher energy expenditure and thus favoring weight stability after RYGB in the young<sup>305</sup>. Faria et al discussed that the age-effect is due to better glucose control or lower contamination by organic pollutants in the visceral fat in the young<sup>306</sup>. Moreover, one study reported lower energy intake in young (<35 years) compared to older patients ( $\geq 35$  years) after RYGB<sup>307</sup>, which could contribute to the lower weight in the young post-RYGB.

Hypothetically, obesity could differ in terms of genetics and metabolic activity in young compared to older adults secondary to earlier onset of obesity and/or shorter duration of being obese given the recent rise in obesity incidence during late adolescence<sup>4 52</sup>, which together may influence energy expenditure post-RYGB.

Although a statistical difference was found in weight loss between young and older adult completers, the clinical relevance of the difference is not obvious. Thus, our findings may not necessarily be used as an argument to advance RYGB-surgeries to as young ages as possible. Rather, the present results indicate that age seems to be a predictor to weight loss, and that young age does not exclude from surgery.

Loss-to-follow-up is a common problem in obesity surgery research<sup>308</sup>, meanwhile sensitivity analyses have seldom been used/reported for. The present findings on weight loss with different conclusions depending on which analysis we used (i.e. higher percentage weight loss in the older adults in the baseline carried forward analysis but the opposite in the other ones), highlight the need for reporting weight loss data by the usage of different



sensitivity analyses to make the analysis more transparent as long as follow-up is not complete.

#### *Age-dependent effects on adverse events*

Ageing was previously regarded as a risk factor for adverse events post-RYGB primarily in short-term studies<sup>309</sup>. For example, Morgan et al reported a positive association between age as a linear variable and adverse events up to 1 year after RYGB in 31-to-54-year-olds<sup>310</sup>. Possibly, the low numbers of young adults in the study by Morgan et al explain the divergence between theirs and our data, since the association between age and adverse events post-RYGB is not necessarily linear. Moreover, patients with unspecified adverse events were not recorded in the study by Morgan et al, leading to under-reporting of, for example, abdominal pain that required surgical exploration; in our study this would have been reported as a serious adverse event.

In addition, we stratified adverse events by intraoperative events, 6 weeks, 1 year etc., while Morgan et al collapsed their data into one measurement (0-1 year). Although our study was not designed for collapsing all data on adverse events into one measurement period (since this allow for diverse and uncontrolled loss-to-follow-up between groups within the observation period), it is however notable that our results in the collapsed analysis did differ from the main analysis and showed no differences in number of adverse events in young vs older adults. Possibly, age influences the risk of adverse events differently in the short vs long-term, with a higher risk of adverse events in older patients shortly after surgery (due to e.g. cardiovascular co-morbidities), and a higher risk of long-term adverse events in younger patients. If so, a comparatively high number of adverse events among the older patients shortly after surgery may impact on 1-year outcomes, which in that case could explain the diverging results between our study and that of Morgan et al with 1-year data. Aligning with this, age <50 years was found to be predictive of adverse events up to 30 days after bariatric surgery in a recent SOReg study<sup>309</sup>. Furthermore, RYGB-related self-reported symptoms (surgical, medical, nutritional) leading to healthcare contact after surgery were more common in patients younger than 35 years of age in a Danish cohort with a median of 4.7 years follow-up after surgery<sup>311</sup>. Moreover, Stenberg et al showed that increasing age was negatively associated with small bowel obstruction 3 years after RYGB<sup>312</sup>.

Possibly, young adults' psychological vulnerability may predispose to surgical exploration of undefined pain and thus higher frequencies of adverse events, since depression and stress have been linked to postoperative pain syndromes<sup>313</sup>.

#### *Age-dependent effects on loss-to-follow-up*

Previous research on age as a predictor for adherence post-RYGB reports both negative<sup>314</sup><sup>315</sup> and no<sup>316</sup> associations; however, comparisons of data are limited due to the heterogeneity of definitions of loss-to-follow-up between studies. Possibly, young adults' preoccupation with peer sameness, low perception of future health hazards and an urge for living independent

lives, as well as frequent moves between houses/changing cities may predispose to higher loss-to-follow-up in young vs old<sup>317 318</sup>. Interestingly, cognitive impairments and depressive symptoms, which are frequent in the obese young adult patient group, have been linked to low adherence<sup>319-321</sup>.

While a number of studies found positive associations between adherence and weight loss as well as lower complication rates<sup>322 323</sup>, the importance of long-term follow-up, including effects on weight loss, adherence to dietary regimens and vitamin substitution is largely unknown.

### *Health-related quality of life*

Physical and mental HRQL 1 year after RYGB in young as well as older adults in Study IV approached Swedish norm levels (physical component score: 53.4 [SD: 7.1] for young RYGB patients vs norm levels of 53.4 [SD: 6.8], and 50.7 [SD: 9.3] in older RYGB patients vs norm levels of 51.2 [SD: 8.5]; mental component score: 46.0 [SD: 12.1] in young RYGB patients vs norm levels of 49.8 [SD: 9.5], and 49.0 [SD: 12.0] in older RYGB patients vs norm levels of 50.2 [SD: 10.0]) but deteriorated below norm levels both 2 and 5 years after surgery. With the exception of studies on adolescent RYGB patients, HRQL has seldom been reported in detail for younger cohorts: In the Swedish AMOS study on 13-to-18-year-olds undergoing RYGB, the physical component score was improved 5 years after RYGB (48.3 at 5 years vs 44.1 at baseline,  $p < 0.001$ ) while there was no statistically significant difference in mental component score (44.7 vs 41.6,  $p < 0.66$ )<sup>238</sup>. Studies that collapsed all patients  $\geq 18$  years into one group generally found clear long-term improvements in physical HRQL while mental HRQL displayed diverging results<sup>324</sup>.

The few studies to date on the effect of age on changes in HRQL after RYGB reported an inverse association between age and physical function as well as bodily pain (both SF-36 variables)<sup>325</sup>. Possibly, poorer baseline physical function in the older participants may explain why previous data diverged from our results, since low HRQL levels allow for greater changes. Importantly, and aligning with the discussion on age-dependent effects on weight loss, the clinical relevance of the differences in HRQL between young and older adults is not clear.

## **7.3 CLINICAL IMPLICATIONS**

Obesity care clearly involves not only weight loss per se, but also management of obesity-related comorbidities and symptoms. However, traditional obesity care has focused on cardiovascular obesity-related diseases and may thus have dismissed other relevant aspects in the care of the young adult patient who has not yet developed such comorbidities. For example, symptoms such as urinary incontinence, fatigue and headache, found to be prevalent in Studies I-II, may affect young adults' every-day life more than increased levels of lipids, glucose etc. and should thus be addressed by obesity professionals alongside

cardiovascular preventive efforts. Additionally, a change in perspective with more focus on present symptoms and less on future risks may increase young adults adherence to obesity care, since young adults generally search weight loss treatment primarily for psychosocial reasons while future cardiovascular diseases are of little motivational value <sup>234</sup>.

### **Coexisting obesity and mental distress in young adults – a challenge for healthcare**

Although there is not yet any straightforward explanation as to why obesity and mental distress co-occur, we know from research and clinical practice that treating mental distress may influence weight status and vice versa. For example, eating may relieve mental distress <sup>326</sup> and thus weight gain will continue as long as the stressors are not appropriately targeted. This is why a thorough mental health examination is essential when initiating a weight loss program. High levels of mental distress have the potential to impair treatment outcomes because successful behavioral treatment relies upon cognitive restraint which, in turn, is dependent on mental well-being. Therefore, obesity professionals should pay continuous attention to signs of mental distress and the severity of pre-existing mental illness throughout the treatment period. This is particularly important given that the incidence of mental illness peaks during young adulthood and pre-symptomatology (for example undefined anxiety) may therefore develop during treatment (to a defined psychiatric disease) which in turn may impact upon obesity treatment <sup>138</sup>. Moreover, weight gain is a common side effect of psychiatric medications <sup>224</sup>, which may lead to undertreatment of psychiatric diseases in patients with obesity which, in turn, may impair weight management further.

Importantly, obesity and mental illness were together highlighted as the two main public health issues and challenges in Sweden in 2017 <sup>30</sup>. Pinpointing shared phenomenological characteristics, such as physical inactivity (as were shown to co-vary with mental distress in Study I), overeating (as in atypical depression) and sleep disturbances may constitute one way of treating both diseases simultaneously <sup>327</sup>. Likewise, pinpointing shared external factors in preventive efforts, such as poor socioeconomic status, unemployment and stigma may target obesity as well as mental distress at the same time, and thus serve as another way of handling obesity and mental issues. In addition, evidence is emerging that both depression and obesity improve when treated with naltrexone/bupropion, and may help when treating both disorders <sup>328</sup>. However, the question of how to handle comorbid obesity and mental distress is clearly challenging in today's healthcare organization, because psychiatry and obesity professionals seldom operate in the same clinic.

Given the high prevalence of both obesity and mental distress, the two may co-occur by chance <sup>222</sup>. If so, we cannot expect accompanying mental health problems to improve directly secondary to weight loss, as opposed to cardiovascular obesity-related comorbidities (as observed in the lack of long-term improvements in mental HRQL in Study IV despite profound weight loss) <sup>327</sup>. Likewise, weight loss may not necessarily follow mental health improvements. Instead, standard care treatment of both mental health problems and obesity together with knowledge on how pharmacotherapy impacts on weight status is probably necessary in order to improve the overall health of these patients.

Given that an increasing amount of evidence supports increasing levels of psychiatric adverse events post-RYGB, particularly in young adults with previous mental ill-health<sup>114</sup>, the present findings of high levels of mental distress in treatment-seekers clearly call for attention, and support a thorough mental health examination before referral to bariatric centers, together with close follow-up after surgery. Whether the follow-up should be part of standard surgical follow-up, or part of routine psychiatric/general practice is however not as clear, since data have so far not revealed whether bariatric surgery directly affects mental health or whether the results are due to cohort effects, given the lack of controlled studies.

Importantly, although mental distress is frequent in young adults with obesity, obesity per se in this age groups does not automatically implicate mental health problems in all patients. To falsely apply mental distress on patients secondary to their physical appearance may be counterproductive and cause stigma as discussed by Brandheim<sup>329</sup>.

### **Bariatric surgery or not, and when is the right time to intervene?**

The increasing rates of obesity in young adulthood, together with the clear augmented risks of future cardiovascular disease and premature death in this age group, is not only of clinical but also of major societal concern, given the high socioeconomic burden of long-standing obesity. Effective treatment is therefore highly warranted and bariatric surgery is clearly the most effective weight loss treatment to date with secondary positive effects such as less pain and improved physical function. However, the potential concomitant increased risks of surgical (particularly long-term, as displayed in Study III), micronutritional and psychiatric (as found in previous studies) adverse events constitute major drawbacks, creating a considerable treatment dilemma for clinicians. If the young adult is offered solely lifestyle modification, obesity is likely to continue. Meanwhile, bariatric surgery is associated with worsened mental health status (importantly, research does not yet show a clear cause-effect relationship), for some with fatal outcomes, or leads to even more serious micronutritional deficiencies than those observed before surgery.

It is reasonable to hypothesize that improved follow-up of patients after surgery may overcome aspects of these fears, although there is not yet enough scientific evidence to support this. Enhanced follow-up could, for example, include multidiscipline assessments including repetitive blood tests for micronutritional deficiencies and thorough mental health assessments by psychiatrists. Whether intensified follow-up regimens could counteract surgical adverse events is however less obvious. Importantly, and in light of the findings in the present thesis, cognitive impairment and depression have been associated with poor adherence post-RYGB<sup>320</sup>, and should be targeted when designing post-bariatric care programs for young adults.

The lack of long-term quantitative and qualitative data on bariatric surgery in young adults is a concern given that young adults differ in terms of brain and psychosocial maturity as well as psychological vulnerability from their older counterparts, on whom the long-term bariatric studies in general so far have been conducted<sup>103</sup>. Meanwhile, young adults are pushed

towards bariatric surgery because behavioral treatment requires continuous effort. The pros and cons of bariatric surgery for young adults therefore warrant reflection and individualized, patient-centered timely decisions; this poses a clear challenge for the clinician while bariatric surgery recommendations largely are based on studies on adults. For example, as long as the young adult remains in the obesogenic environment where he/she grew up, it is plausible to assume that the risk for weight gain post-RYGB is augmented, in which case it may be better to postpone surgery until the young adult is living an independent adult life with the capability to make own decisions on food choices etc. On the other hand, bariatric surgery with successful weight loss may increase the chances of the young adult finding a job given better psychosocial and physical functioning; this might be the missing link in the young adults' journey to independence from his/her obesogenic childhood environment. Hypothetically, bariatric surgery in adolescence, before the BMI surge in young adulthood, may constitute a more appropriate timing<sup>238</sup>. Recent studies reporting higher resolution of cardiovascular abnormalities in young vs older adolescents post-RYGB further promote such a hypothesis<sup>330</sup>, and should be taken into account when developing guidelines for young adults with obesity.

Moreover, our data align with data from well-known trials on adolescents, such as AMOS (as discussed in the introductory chapter) and the American FABS-5+ Study on n=74 13-to-21-year-olds with a mean-baseline BMI of 58.5 (SD: 10.5) kg/m<sup>2</sup> who displayed a 29.2% change in weight 8 years after surgery<sup>331</sup>. Consequently, and importantly, we found promising results with similar weight loss outcomes in our real-life data as in trial-controlled environments on younger cohorts.

## **7.4 METHODOLOGICAL CONSIDERATIONS**

### **Limitations in study design**

The main limitation of Studies I-II was the cross-sectional design, which did not allow for causal inferences. The lack of a control group in Study I limited the possibilities to relate the data to other patient groups; however, we overcame this in Study II. Moreover, we did not include variables on stigma, bullying and eating disorders when assessing mental health, which are common mediators/moderators in the association of obesity and mental distress. We had disappointing clinical experiences (unreliable findings) from using such questionnaires and therefore decided to exclude those variables. This may in turn have limited the comprehensive approach and the regression analysis of Study I.

In Studies III-IV we used registry data, which may be associated with a number of limitations: Firstly, data entry may diverge between participating clinics due to differences in motivation and training of those who are responsible for data entry. Secondly, due to differences in economical compensation schemes in the Swedish healthcare system, follow-up regimens may differ between clinics, and could cause biased results. This assumption could not be statistically tested, but the registry was visually inspected by the researchers with

this consideration in mind, and we found no obvious differences in percentages of young vs older adults between clinics, nor between high vs low volume centers. Moreover, well-known confounders of the outcomes, which were not included as variables in the registry, could not be adjusted for, and thus limited our analyses, possibly leading to underestimation or overestimation of odds ratios and relative risks.

The nature of SOReg did not allow for detailed background data on the adverse events but the large numbers of data entries enabled us to study rare events. Since planning Study III, closure of mesenteric defects has been found to clearly reduce the risk of ileus after RYGB<sup>312</sup>, which consequently could not be accounted for in Study III. Concerning Studies III-IV stratification of results by more than one age group would have revealed more detailed information about the association between age and outcomes. However, we also analyzed age as a linear variable, and found weight loss to be linearly negatively associated with ageing (data not shown) further strengthening our results of age-dependent weight loss post-RYGB.

## **Bias**

Bias refers to a systematic error whereby the calculated value might not be representative for the parameter that it is meant to estimate. *Sampling bias* refers to when individuals are excluded not completely at random; this results in a sample that is not representative of the population it is intended to estimate resulting in a biased estimated prevalence. Thereby, the *external validity* of the study may be impaired. In Study I we excluded certain patients (cognitive impairments and language barriers) beforehand, thereby risking a biased sample. Furthermore, the inclusion rate of 57% of treatment-seekers in Study II might be regarded as low whereby the external validity of the results might be affected. Likewise, certain individuals are underestimated in the Stockholm Public Health Cohort due to lower participation rates, such as non-native Swedes, who may bear an increased risk of mental distress as well as BMI. However, we found that the level of the main outcome for mental distress in Study II, GHQ-12, approximated the level of GHQ-12 in normative data on young adults (9.2 [SD: 5.5] vs 10.8 [SD: 5.8] in population controls), which increases the generalizability of the study<sup>261</sup>

*Misinformation bias* refers to bias due to measurement errors. Measurement errors which are the same in all included participants is referred to as *non-differential misclassification* and may lead to both under- and overestimations. For example, the reference values for Åstrand's test (Study I) are based upon normal weight individuals while overweight individuals' cardiorespiratory fitness is generally underestimated. Moreover, smoking and alcohol use (Studies I-IV) were repetitively found to be underestimated in self-reports, indicating another type of measurement error<sup>332,333</sup>. Socioeconomic status (Studies I-II) is generally measured by income/educational level, or employment status. However, those measurements were not suitable since our cohort mainly consisted of students, whose disposable income may underestimate their socioeconomic status. Similarly, using educational level or employment grade as a measurement of socioeconomic status is not appropriate since some participants had not yet finished their education, or started working life. Given the well-known difficulties

with assessing socioeconomic status in the present age group, we decided to use economic strain as a proxy for economic status, which, as accounted for above, is by no means a complete measurement.

Certain diseases in Study I may have been underdiagnosed or misdiagnosed, for example non-alcoholic fatty liver disease which necessitates liver biopsy for accurate diagnosis. To optimize the accuracy of the self-reports, a physician evaluated the responses together with the patient and against the patient's health record. Moreover, we did not screen for malabsorption, which may account for some of the micronutritional deficiencies in Study I. Patients may have forgotten to fast the night before the blood samples, leading to an overestimation of mean values of glucose and lipids. We endeavored to overcome this error by checking the fasting status with every patient.

Misclassification could differ between observation groups, due to the use of self-reports vs objective measurements of anthropometrics in Study II, called *differential misclassification*. Self-reports of weight and height (Studies II-IV) are known to underestimate body weight and overestimate body height, thereby risking underestimation of BMI<sup>334</sup>.

Another possible differential misclassification was found in Study IV regarding "impression management", i.e. socially desired responses, which was previously found to differ between age groups<sup>335</sup>.

*Attrition* was a major risk factor for bias in Studies III-IV, since those with complete data are not necessarily representative for the baseline cohort. Notably, we found differences between missing and non-missing data in baseline variables, which warrant caution when interpreting our results. Given the higher drop-out rates in young vs older adults, results on weight loss and adverse events may have been skewed since young adults hypothetically attended only in cases of unacceptable adverse events, and thus may have caused an overestimation of adverse events in the young. We tried to overcome the risk for attrition bias either by using linear mixed models (Study III) or data imputation (Study III-IV) when analyzing weight loss and adverse events, however these statistical methods are by no means complete in reducing the risk of attrition bias.

### **Data/statistical limitations**

Historically, there has been a long-standing debate on whether Likert scales should be treated as categorical or continuous scales and accordingly be analyzed by parametric or non-parametric statistics<sup>336</sup>. In Studies I-II & IV we analyzed GHQ-12, HADS, EQ5D and SF-36 as continuous variables since these questionnaires may be treated as collections of several items which together produce, at least empirically, interval data which *approximate* continuous data<sup>336 337</sup>. In Study IV we performed the non-parametric equivalent and found that the results did not differ materially from the results of parametric tests.

Unfortunately, certain baseline variables such as smoking were not mandatory in SOReg. Therefore, we could not include these as covariates in the completer's analyses without risking the loss of more values and thus low statistical power.

Frequency matching in Studies III-IV resulted in interpretation problems due to the large number of drop-outs, particularly in Study IV as about one third of participants lacked HRQL data and could thus not be included in the study. Consequently, matching was not properly valid for Study IV and the results must therefore be carefully evaluated. Ideally, matching on an individual basis could have partially overcome this problem.

Study IV included a relatively large number of statistical tests (**Tables 9-11**), which inherently increase the risk of chance findings and thus type I errors.

### **Strengths**

The main strength of this thesis was the focus on clinical aspects of young adults with obesity who are notorious for low participation and high drop-out rates in trials. Inclusion was possible via the cross-sectional design of Study I and the use of data from the Obesity Center, which specializes in young adults with obesity. In Studies III-IV, the use of high-quality registry data with 5-year follow-up enabled us to analyze close to 100% of Swedish 18-to-25-year-olds who had undergone RYGB during the specific observation period, and thus provided us with real-life data as opposed to data in controlled environments/trials.

The main methodological strength throughout Studies I-IV was the use of validated generic and disease-specific questionnaires that measured a wide array of mental health aspects. In Study II we successfully included population controls with obesity and severe obesity, which is rare in an international perspective.



## 8 CONCLUSION

The overall conclusions of the present thesis are:

- Treatment-seeking young adults (16-25 years) with obesity displayed indications of poor mental health, high frequencies of cardiovascular risk markers and micronutritional deficiencies.
- Mental distress in treatment-seeking young adults (16-25 years) with obesity was independently associated with pain, low self-esteem, poor cardiorespiratory fitness and poor psychosocial functioning.
- Treatment-seeking young adults (18-25 years) with obesity displayed approximately doubled RR for mental distress compared to normal weight population controls, and significantly more mental distress than population controls with class I obesity or severe obesity.
- Young adults (18-25 years) displayed effective weight loss that was at least equal to older adults (26-74 years) but experienced more long-term adverse events and were less frequently followed-up, up to 5 years after RYGB, compared to older adults.
- Young adults (18-25 years) displayed improved physical HRQL but no or weak changes in mental HRQL 5 years after RYGB compared to baseline levels.
- Young adults (18-25 years) displayed smaller 5-year changes in physical role, general health, vitality, social functioning, physical component score and psychosocial functioning after RYGB than older (26-74 years) adults.

## 9 FUTURE RESEARCH

To further improve the care of young adults with severe obesity, I propose the following areas to be addressed in future research:

- Expansion of the significance of mental distress on weight loss outcomes and adherence to weight loss strategies.
- Exploration of the etiology behind the present findings of higher rates of long-term adverse events in young vs older adults: Detailed data from patients' health records may complement registry data to evaluate what symptoms are manifested behind the variable "serious adverse event" in the present thesis. Future studies need to address the high attrition rates in young adults if we are to draw more reliable conclusions on particularly adverse events than was possible in the present thesis.
- Trials aimed at improving young adults' follow-up rates post-RYGB and improved understanding of the significance of follow-up on outcomes. Digital follow-up has shown promising results in young adults if combined with face-to-face visits in behavioral weight management and should be evaluated also in bariatric medicine for patients who prefer non-physical meetings or live far away from the operating clinic<sup>323 338</sup>. Standardized reporting of sensitivity analyses in longitudinal obesity research with large drop-outs may support the reader to interpret data in a less unbiased way than what is possible with completers' analyses only.

## 10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Patienter inom åldersgruppen ”unga vuxna” (här 16-25 år) saknas generellt i klinisk fetmaforskning, trots att de tidiga vuxenåren utgör en klar riskperiod för att insjukna i fetma. Istället har vårdriktlinjer för unga vuxna baserats på forskning på barn och äldre åldersgrupper, vilket kan riskera att kliniska problem som är specifika för unga vuxna med fetma inte uppmärksammas i behandlingen.

Syftet med den aktuella avhandlingen var att karaktärisera unga vuxna (16-25 år) som är vårdsökande för fetma, speciellt med avseende på psykisk ohälsa (karaktäriseringsstudier, studie I-II), samt att jämföra långtidseffekter av magsäckskirurgi mellan yngre (18-25 år) och äldre ( $\geq 26$  år) vuxna med avseende på viktnedgång, komplikationer, uppföljningsgrad och livskvalitet (behandlingsstudier, studie III-IV).

I studie I undersökte vi förekomst av fetmarelaterade följsjukdomar, psykisk ohälsa, självkänsla, livsstilsfaktorer och livskvalitet; konditionsnivå och labbdata över näringsämnen samt metabola riskfaktorer bland 165 unga vuxna som sökte vård för fetma på en specialistklinik i Stockholm. I studie II jämförde vi enkätsvar över psykisk ohälsa, självmordsförsök, fysiska/psykosomatiska symtom och livskvalitet mellan 121 unga vuxna som sökte vård på samma fetmaklinik som i studie I, med data från individer som besvarat en regelbundet återkommande folkhälsoundersökning (Folkhälsoenkäten). I studie III-IV jämförde vi unga (18-25 år) och äldre ( $\geq 26$  år) vuxna i det närmast heltäckande fetmakirurgiregistret (Scandinavian Obesity Surgery Registry) med avseende på viktnedgång, komplikationer, uppföljningsgrad och livskvalitet upp till fem år efter magsäckskirurgi.

I studie I fann vi indikationer på att unga vuxna som söker fetmabehandling har höga nivåer av psykiska hälsoproblem och riskmarkörer för framtida hjärt-kärlsjukdom samt generella vitaminbrister. I studie II fann vi en nästan fördubblad risk för psykisk ohälsa, självmordsförsök, psykosomatiska symtom och låg livskvalitet bland unga som är vårdsökande för fetma jämfört med normalviktiga individer som besvarat Folkhälsoenkäten. I studie III fann vi att unga vuxna uppvisade en statistiskt säkerställd större viktnedgång fem år efter magsäckskirurgi jämfört med äldre vuxna (31.8% vs 28.2% viktnedgång). Dock var risken för allvarliga kirurgiska komplikationer dubbelt så hög bland de yngre jämfört med de äldre patienterna 2-5 år efter magsäckskirurgi (14.1% vs 6.9%), och uppföljningsfrekvensen var upp till nästan hälften så komplett i den yngre jämfört med den äldre gruppen under hela observationsperioden. Både yngre och äldre patienter hade fått en påtagligt förhöjd fysisk livskvalitet upp till fem år efter magsäckskirurgin, och förbättringen var störst i den äldre gruppen. Dock noterades ingen kliniskt relevant förbättring i mental livskvalitet i någondera av åldersgrupperna.

Avhandlingen diskuterar de aktuella resultaten i en klinisk kontext såsom hur hög samsjuklighet mellan fetma och psykisk ohälsa bland unga vuxna kan hanteras i den kliniska vardagen samt kring magsäckskirurgins för- och nackdelar givet de psykosociala omständigheter som karaktäriserar de tidiga vuxenåren.

## 11 ACKNOWLEDGEMENTS

Firstly, I would like to thank the patients who contributed with data to Studies I-IV.

Erik Hemmingsson, main supervisor, for believing in me and everything you taught me in the field of research; for your cool temper and most of all for continuously inspiring discussions on obesity and everything beyond (including tennis) as well as serving as a great role model for the tricky task of how to combine joy in life and work.

Signy Reynisdottir, co-supervisor, for having welcomed me to your obesity team already in year 3 in medical school and thereafter supported me with all your rich clinical experience and knowledge on obesity. I am ever so grateful that you inspired me to take the step to start my PhD studies in the field of obesity as the first PhD student at the Obesity Center.

Bo Angelin, co-supervisor, for always sharing your deep experience on research and quick replies to my emails.

Lena Backlund, mentor, for always inspiring discussions on life as a researcher and clinician.

Per Tynnelius, Finn Rasmussen, Anders Thorell and Jarl Torgersson for co-authorship.

All excellent colleagues at Överviktscentrum who helped out with data collection for Studies I-II. You are experts in the field of obesity and I learnt so much from all lunch discussions on obesity together with you. I would particularly like to thank my PhD colleague Anne Christenson for sharing this time together - for support, shared experiences and inspiration.

The steering committees for Folkhälsoenäten and SOReg for sharing their data.

Stockholms läns landsting for financing my PhD studies throughout.

Åke Kihlberg, former boss and supervisor at Capio Vårdcentral Lekeberg, for facilitating research when working as a registrar in general practice.

Madelene Andersson, director of ST studies, for helping out with administrative problems which appeared throughout when combining clinical and research work.

All my friends for being you and supportive during these years. An extra big thank you to Emelie, Eva, Andreas, Maja, Lotta, Helen, Matthew and Stina & Alex who all helped out with anything in between finding a place for me to stay while researching to helping out with tricky statistics, English language, Endnote and biochemical inquiries.

My parents for always believing in and supporting me.

Astrid, for your smile and never-ending optimistic and out-of-the-box outlook on life, for reminding me there is something else in life but work and for putting up with an extra family member, i.e. my computer, at weekends and holidays. Now, let's discover more of life together!

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