Health benefits two years after Roux-en-Y gastric bypass surgery and the effect of lifestyle intervention two to four years after surgery on weight regain and metabolic disturbances

Susanna Elisabeth Hanvold

Section of Nutrition and Dietetics
Department of Clinical Service
Oslo University Hospital

and

Faculty of Medicine
University of Oslo

Oslo 2018

Acknowledgements

The work presented in this thesis was performed at the Department of Morbid Obesity and Bariatric surgery and the Section of Nutrition and Dietetics, Oslo University Hospital. The research was supported by the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds, the Throne Holst Foundation, and the Norwegian Research Council.

I would like to thank my former chief, Ingunn Bergstad, who encouraged and facilitated the initiating of this project. I would also express my gratitude to my supervisors Anne-Marie Aas and Helga Refsum for their knowledge, support and patience for 10 long years. I am also very thankful to my co-supervisor Kathrine J Vinknes for her availability and for her consistently fast response to all my questions.

A lot of people have contributed to this work, and I am thankful to the co-authors and all others who have contributed to the project and the manuscripts. I would like to thank the master students who have contributed to collecting data and the staff at Diabetes Laboratory, and Central Laboratory, Oslo University Hospital, for blood samples and blood analysis. I would also like to thank University of Oxford and University of Oslo for blood analyses and the staff at Department of Nutrition, University of Oslo, for their help with analyses of dietary data. I am especially thankful to Elin B Løken for her availability and helpfulness with dietary data throughout this work. Further, I would like to thank Department of Psychology, University of Oslo, Patient Education Resource Centre and Section of Nutrition and Dietetics, Oslo University Hospital, for their contribution to the intervention. This work would not have been accomplished without their contributions.

I am grateful to all my colleagues at the Section of Nutrition and Dietetics for support and encouragement. I also want to thank my family for their support, especially my mother for proofreading all my work. Finally, I want to thank Fredrik for his technical advice and for taking care of our home and spending all of his leisure time with our wonderful children so that I could work late and finish this project. From now on, I look forward to spending more time with Fredrik, Alexander and Elise ☺

Oslo, April 2018

Susanna Hanvold

Summary

The aim of the thesis was to study the health benefits 2 years after Roux-en-Y gastric bypass surgery (RYGB) and the effects of a group-based lifestyle intervention program of moderate intensity on weight regain and metabolic disturbances 2 to 4 years post-surgery.

Paper I is a retrospective study where the health benefits achieved after RYGB is presented. The patients achieved great weight loss, and the prevalence of hypertension, type 2 diabetes mellitus, and metabolic syndrome were significantly reduced. Further, we investigated changes in employment status, and use of psychopharmaceutical drugs, including psychoanaleptics (antidepressants and psychostimulants) and psycholeptics (antipsychotics, anxiolytics and hypnotics, and sedatives) from before surgery until 2 years post-surgery. Despite great weight loss and remission of metabolic disturbances, no changes in the proportion of unemployed participants, or in the use of psychopharmaceutical drugs were found. Participants with body mass index (BMI) 43 kg/m^2 or lower at time of surgery had more health benefits compared with heavier participants. Hence, bariatric surgery should be considered before BMI exceeds 43 kg/m^2.

Paper II is a randomized study where the effect of a group-based lifestyle intervention program aimed at preventing weight regain between 2 and 4 years post-surgery was compared with a group that received usual care. Further, differences in metabolic disturbances, energy intake, and physical activity between the groups were investigated. Factors associated with weight regain regardless of group allocation were also identified. The intervention did not seem to have beneficial effects on any of the measured endpoints. Factors associated with weight regain were rapid weight increase from nadir, sedentary lifestyle, younger age and higher plasma concentrations of total cysteine (tCys) at 2 y. On the other hand, physical activity, high intake of artificially sweetened beverages and smoking were inversely associated with weight regain. Instead of offering a group-based intervention as standard treatment to prevent long-term weight regain after RYGB, a better strategy may be to selectively target patients at risk of future weight regain, and offer earlier and more frequent follow-up to these patients.

Paper III is a prospective study where the association between selected plasma amino acids with weight regain were investigated. We found that plasma aromatic amino acids, branched chain amino acids and tCys 2 years post-surgery were associated with BMI at 2 years post-surgery. Only plasma tCys at 2 years post-surgery was associated with weight regain from 2 to 4 years post-surgery. These results suggest that high plasma tCys may be used as a prognostic marker for future weight regain.

Overall, these papers show great weight loss and remission of hypertension, type 2 diabetes mellitus, and metabolic syndrome after RYGB. Best results are achieved in participants with pre-surgery BMI 43 kg/m^2 or lower. However, our findings indicate that this group-based lifestyle intervention program has no effect on weight regain or metabolic disturbances 2 to 4 years post-surgery.

List of papers

Paper I

Hanvold SE, Loken EB, Paus SF, de Brisis ER, Bjerkan K, Refsum H, Aas AM. Great Health Benefits But No Change in Employment or Psychopharmaceutical Drug Use 2 Years After Roux-en-Y Gastric Bypass. Obes Surg 2015;25:1672-9.

Paper II

Hanvold SE, Vinknes KJ, Løken EB, Hjartåker A, Klungsøyr O, Birkeland E, Risstad H, Gulseth HL, Refsum H, Aas AM. Does lifestyle intervention after gastric bypass surgery prevent weight regain? – A randomized clinical trial (submitted manuscript).

Paper III

Hanvold SE, Vinknes KJ, Bastani NE, Turner C, Loken EB, Mala T, Refsum H, Aas AM. Plasma amino acids, adiposity, and weight change after gastric bypass surgery: are amino acids associated with weight regain? Eur J Nutr 2017.

Abbreviations

AA	Amino acid
AAA	Aromatic amino acid
BCAA	Branched chain amino acid
BMI	Body mass index
CTG	Conventional treatment group
EWL	Excess weight loss
HbA_{1c}	Glycosylated haemoglobin A_{1c}
LIG	Lifestyle intervention group
MET	Metabolic equivalent
RYGB	Roux-en-Y gastric bypass
T2DM	Type 2 diabetes mellitus
tCys	Total cysteine
TWL	Total weight loss

List of Figures

List of Tables

Contents

1. Introduction

1.1. Classification of obesity

Body composition can be assessed using several different methods (1). Body mass index (BMI) is a weight for height measure that is commonly used to classify underweight, overweight and obesity (2). Obesity is further sub-classified into three categories according to severity (Table 1). A limitation of BMI index is that it cannot distinguish between fat and fat-free mass (1, 3). A waist circumference ≥94 cm and ≥102 cm for men and ≥80 cm and ≥88 cm for women indicates an increased and a substantially increased risk of metabolic complications, respectively (4). A high waist-hip ratio (>0.90 in men and >0.85 in women) indicates abdominal fat accumulation, and substantially increased risk of metabolic complications (4). Skinfold thickness is a tool used to assess subcutaneous fat in specific locations on the body (1). The need of skilled personnel to conduct the measurements, and the dependency of accurate measurements are limitations with waist, hip and skinfold thickness measurements (1). A Dual Energy X-ray Absorptiometry can be used to measure fat mass and fat-free mass, but are costly, and has a weight and width limit (1). Bioelectrical impedance analysis can be used to predict total body water and fat-free mass, and to calculate fat mass (1). Bioelectrical impedance analysis is inexpensive, safe and easy to use, but the accuracy of the measurement is uncertain because the bioelectrical impedance may not be high enough to penetrate all tissues (1).

Table 1: Classification of underweight, overweight and obesity according to BMI

Classification	**BMI(kg/m^2)**
Underweight	<18.5
Normal range	18.5 - 24.9
Overweight	≥25.0
Pre-obese	25.0 - 29.9
Obese	≥30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	≥40.0

1.2. Prevalence of obesity

More than 650 million people (13%) worldwide were reported to be obese in 2016, which is nearly a tripling since 1975 (5). In the United States, the obesity prevalence in 2013-2014 was reported to be 35% and 40% for men and women, respectively (6). An increase in obesity is also seen in the Norwegian population, with a prevalence in 2006-2008 in a large adult population of 23% and 22% for men and women, respectively (7).

1.3. Risk factors for obesity

The cause of obesity is energy imbalance, which is a multifactorial condition that includes individual factors (e.g., genetic factors), environmental factors (e.g., marketing and prices) and social factors (e.g., peer influences) (3, 8-11) (Figure 1). Childhood physical, verbal and sexual abuse (which belongs to the subgroup individual factor) is associated with adult obesity, and the risk is shown to increase with number and severity of each type of abuse (12-15).

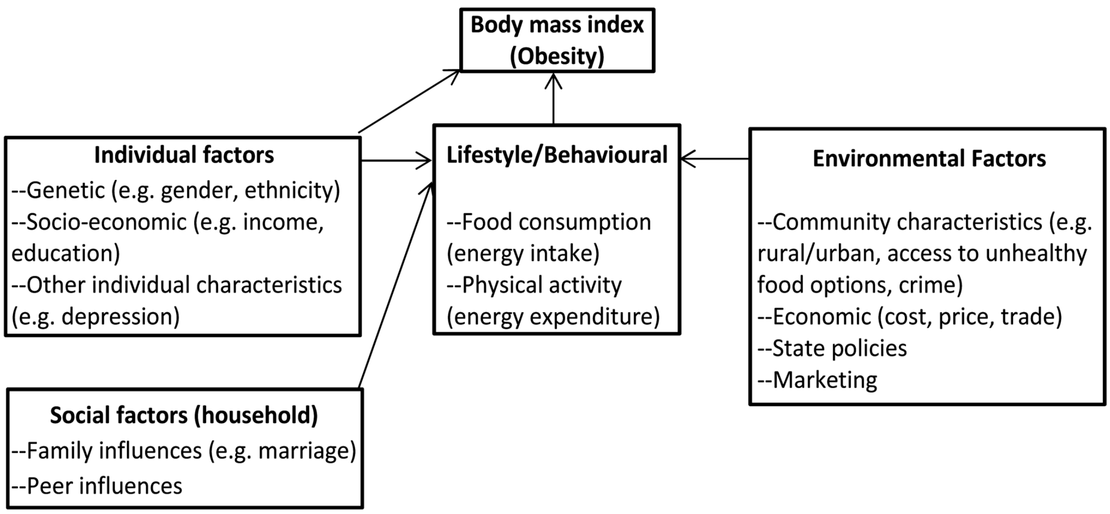

Figure 1: Factors that determine weight outcome. Reprinted from Sartorius et al 2015 (16) with permission from PLoSOne

Energy imbalance is a result of increased energy intake, decreased energy expenditure, or both (11). The change in lifestyle with less need to be physical active, together with highly available, palatable, energy-dense- and cheap food, creates an obesogenic environment (8, 10). The proportion of people who are physically active during leisure-time has decreased drastically over the last several decades (17) and the proportion of people who are sedentary has increased (10). At the same time people are less physically active at work (18). In an obesogenic environment, people with genetic susceptibility to obesity are more likely to overeat because of increased appetite and low sensitivity to satiety signals (10).

1.3.1. Amino acids as risk factor for obesity

In recent years, there has been increased interest in the association between plasma amino acids (AAs), including branched chain AAs (BCAAs), aromatic AAs (AAAs) and total cysteine (tCys), and obesity and obesity-related disorders (19-28). However, little is known about the prognostic value of plasma AAs and the risk of future weight gain.

The BCAAs, phenylalanine and tryptophan are essential AAs, whereas tyrosine and the sulphur-containing amino acid cysteine are conditionally essential AAs (28, 29). All AAs are available in our diet (19, 30), but cysteine can also be synthesized endogenously from methionine metabolism (31). The synthesis of cysteine (Figure 2) is regulated by several enzymes (including cystathionine β-synthase, cystathionine γ-lyase and cysteine dioxygenase) (28, 32) and micronutrients (including vitamin B6, vitamin B12 and folate) (33).

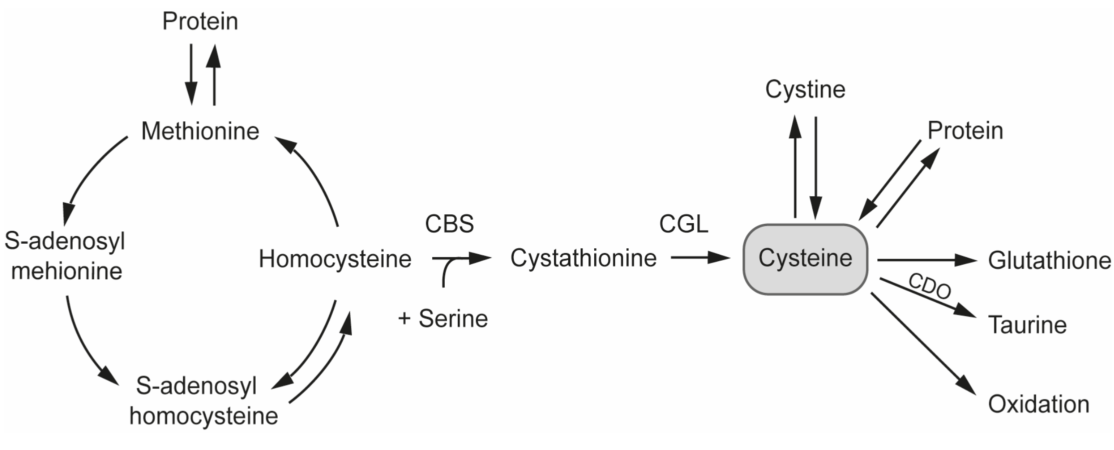

Figure 2: Cysteine metabolic pathways. *CBS* cystathionine β-synthase, *CDO* cysteine dioxygenase, *CGL* cystathionine γ-lyase. Reprinted with permission from Kathrine J Vinknes

A positive association of plasma AAs with insulin sensitivity, type 2 diabetes mellitus (T2DM), metabolic syndrome and cardiovascular disease is observed (20, 21, 23, 28, 34-37), and a reduction in plasma AAs may improve insulin resistance independent of weight loss (20). A reduction in plasma concentration of BCAAs and AAAs is described after bariatric surgery (34-36), whereas tCys remain approximately unchanged (38). Plasma AAs concentrations observed in three studies before and after Roux-en-Y-gastric bypass (RYGB) are shown in Table 2. The plasma concentrations of BCAAs and AAAs differ slightly between the studies, but the changes from pre to post-surgery have a similar trend. The reduction of plasma BCAAs and AAAs may be directly influenced by the amount of weight loss (in particular the reduction of visceral adiposity) (36), the reduced protein intake, the reduced degeneration of proteins or the increased catabolism of AAs (20, 34). In contrast to other AAs, plasma tCys does not change with weight loss, suggesting that tCys is a cause of obesity rather than a consequence (38, 39).

Table 2: Plasma AAs concentrations (µmol/L) reported in other studies before and after Roux-en-Y gastric bypass surgery

	Baseline	**1 y post-surgery**	***P*-value***
Aasheim et al 2011 (40)			
Total Cysteine	305	295	0.22[1]
Tan et al 2016 (38)			
Leucine/isoleucine	194.5	146.7	<0.001
Valine	331.8	260.3	<0.001
Phenylalanine	96.3	82.3	0.076
Tyrosine	86.3	63.4	<0.001
Tryptophan	60.8	57.0	0.24
	Baseline	**20% weight loss**	***P*-value****
Magkos et al 2013 (37)			
Leucine/isoleucine	167	139	<0.05
Valine	249	192	<0.05
Phenylalanine	62	42	<0.05
Tyrosine	63	44	<0.05
Tryptophan	–	–	

*Difference in plasma consentration pre to 1 y post-surgery
[1] Time effect (baseline, 6 weeks, 6 months, 1 y)
**Difference in plasma consentration pre to 20% weight loss

1.4. Consequences of obesity

Obesity is associated with morbidity and mortality (40-45), and common health consequences are cardiovascular disease, T2DM, musculoskeletal disorders and some types of cancer (40, 41, 43-49). Strong evidence is reported for the association between adiposity and cancer of the digestive organs and hormone related malignancies in women (41). Mortality among healthy non-smokers is reported to have a J-shaped relationship with BMI, and the lowest mortality is within the BMI range of 20.0-24.9 kg/m^2 (42). Severe obesity (BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with an obesity-related comorbidity) is associated with several years shorter life expectancy (44).

Stigma towards obesity is a problem, and it is reported that obese compared with non-obese individuals are less likely to be employed, often meet negative attitudes from family, friends and co-workers and are stigmatized in television and movies (50-52). Results from several studies suggest an association between obesity and depression (53-56). Obesity is found to increase the risk of depression, which may be caused by a negative self-image or somatic consequences (including hypertension, insulin resistance or dyslipidaemia), and depression is found to increase the risk of obesity through stress, and an unhealthy lifestyle (56, 57). The use of antidepressants may also increase the risk of obesity (58). Different antidepressants are available, and some increase the risk of weight gain more than others (59). The risk of developing depression increases with increasing obesity classification (53, 54, 60), and is higher in overweight and obese women, and in super obese men, compared with normal weight women and men (60).

Obesity is not only a physical and mental health problem, it also effects the healthcare system (61). A systematic review reported that obesity was estimated to account for 0.7-2.3% of the country’s healthcare expenditure, and that the medical cost was 30% higher for obese individuals than for normal weight individuals (61).

1.5. Treatment of obesity

Obesity can be treated with lifestyle changes (including energy restriction and increased physical activity), behavioural therapy, medication or bariatric surgery (62).

The Look AHEAD study was a large randomized controlled trial in the US designed to evaluate the effect of an intensive lifestyle intervention compared with usual care on cardiovascular morbidity and mortality in overweight and obese adults with T2DM

(63). The lifestyle intervention included several meetings every month the first year (individually and in groups), followed by a maintenance phase with monthly meetings from year 2-8 while usual care included three annual 1-hour group meetings the first 4 y, followed by one annual group meeting from year 5-8. After 1 y and 8 y, the participants in the lifestyle intervention program had lost 8.5% and 4.7% of initial weight, respectively, while the usual care group had lost 0.6% and 2.1%, respectively (63). Successful strategies for long-term weight maintenance was physical activity, energy restriction and self-monitoring of body weight weekly or more often (63). Still, the intervention had no effect on the primary endpoint of cardiovascular morbidity and mortality (64).

The National Weight Control Registry in US is an ongoing longitudinal study. It was funded to identify strategies for successful weight loss and weight maintenance after surgical and non-surgical weight loss (65). Criterion to be part of this registry is a weight loss of ≥13.6 kg for at least 1 y. A mean weight loss of 31.3 kg at baseline and 23.8 kg at 5 y was observed (66). The following behavioural changes from baseline to 1 y were found to be predictive for successful long-term weight outcome: A large initial weight loss, longer duration of weight maintenance, higher leisure time physical activity, energy- and fat restriction and self-monitoring of body weight (66). In the same registry, non-surgical participants were more physically active, they ate less fast-food and fat, were more dietary restrained, and had lower levels of depression and stress, compared with surgically treated patients (65).

Weight loss medications combined with behavioural therapy can also be beneficial to achieve weight loss (62, 67). According to The Norwegian Pharmaceutical Product Compendium, there are only two weight loss medications approved in Norway, Xenical, which reduces the fat absorption from the gut, and Mysimba, which reduces appetite and increases satiety (62, 67, 68).

Non-surgical patients participating in an intensive lifestyle intervention program (63), a weight loss camp (69) or combining weight loss medications with behavioural therapy (67) achieve better long-term weight loss than patients in usual care or no treatment (70, 71), but a greater weight loss is described after bariatric surgery compared with non-surgical obesity treatments (69, 72, 73).

1.6. Bariatric surgery

The indication for bariatric surgery is a BMI ≥40 kg/m^2 or a BMI ≥35 kg/m^2 with an obesity-related comorbidity (74-76). There are several bariatric procedures, which are either restrictive, malabsorptive or combined restrictive and malabsorptive (74). RYGB, sleeve gastrectomy, gastric banding and duodenal switch have been the most commonly used procedures (Figure 3), with sleeve gastrectomy as the currently most used procedure worldwide, followed by RYGB (74, 77).

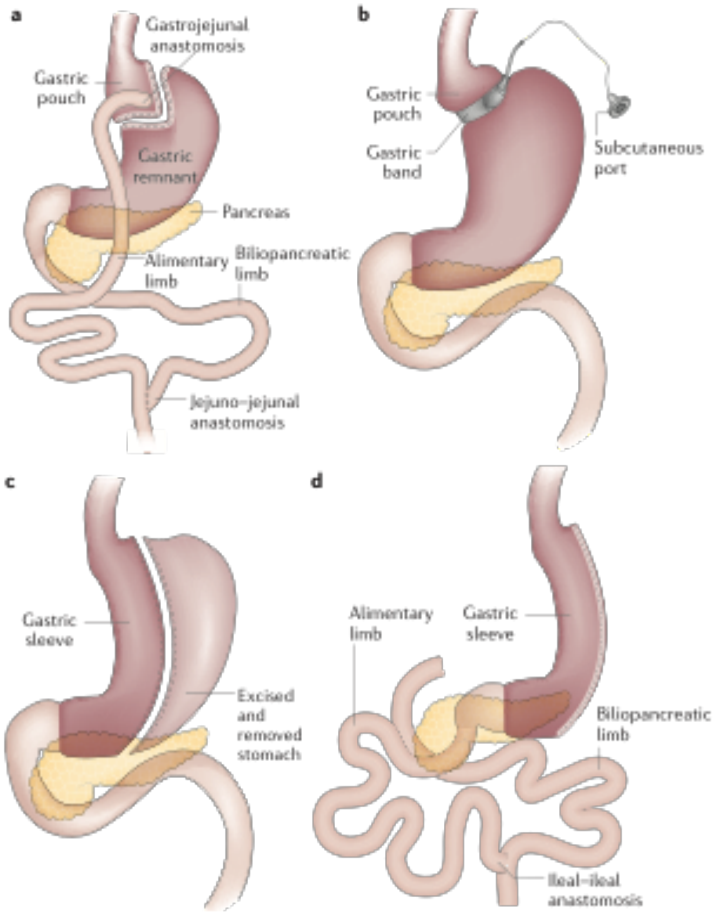

Figure 3: Bariatric surgical procedures. a| Roux-en-Y gastric bypass. b| Adjustable gastric banding. c| Sleeve gastrectomy. d| Biliopancreatic diversion with duodenal switch. Reprinted with permission from Nature (78)

Gastric banding is a restrictive procedure, where an adjustable silicon band is placed around the upper part of the stomach (78). Sleeve gastrectomy is also a restrictive procedure where ~80% of the stomach is removed (78). The restrictive and malabsorptive procedure that consists of a sleeve gastrectomy in addition to bypassing ~50% of the intestine is a duodenal switch procedure (78). RYGB is also a combined restrictive and malabsorptive procedure. It has been considered the "gold standard" in bariatric surgery, and it was for a long time the most frequently performed procedure (77, 78). RYGB consist of a small gastric pouch of ~30 ml. The duodenum is bypassed, and the Roux limb varies between 75-150 cm (78).

1.6.1. Health benefits and weight loss

A large Scandinavian registry, that included nearly 28000 patients previously operated with gastric bypass, described a mean total weight loss (TWL) 2 y post-surgery of approximately 32% (79). Remission of metabolic disturbances is described after surgery, with approximately 75% remission of T2DM (71, 80, 81) and 50-60% remission of hypertension (71, 80). Some relapse of metabolic disturbances is described from 1-2 y post-surgery, but remission is still observed to be significant 3 y (82), 6 y (71) and 10 y (83) post-surgery. Overall, life expectancy is described to increase post-surgery. According to calculations based on three large cohorts, an average female surgical patient age 45 y with T2DM and a pre-surgical BMI of 45 kg/m^2, will gain nearly 7 y of life expectancy with bariatric surgery (84).

Remission of depression and treatment of depression is observed post-surgery (85-87), but long-term outcome is inconsistent, with observed new onset (87), partial relapse (86) and complete relapse (85). Several studies show significantly greater weight loss, improvement in quality of life, and better remission of hypertension, T2DM and dyslipidaemia among surgical patients compared with non-surgical patients (69, 71, 73, 87), but a higher risk of complications (including gastrointestinal surgery, gastroduodenal ulcers, iron deficiency and abdominal pain) is observed in surgical patients (87).

No association of nausea, vomiting, dysphagia (88) or dumping syndrome (89, 90) with weight loss is described, but a greater weight loss is associated with abdominal pain (88). A review article that included 22 studies on malabsorption post-surgery described only some fat malabsorption and little or no malabsorption of carbohydrates and protein (91). Hence, it seems like weight loss is mainly achieved through reduced energy intake (91, 92). This may be mediated by the restricted volume of the stomach

(78, 93) or by changes in appetite seen post-surgery (94-96). An increase in the gut hormones peptide YY and glucagon-like peptide 1, and a decrease of ghrelin, which are reported after RYGB, are associated with decreased appetite and increased satiety (94-96). The role of bile acids, gut microbiota and microbiome are still unknown, but some studies have shown an association with weight loss post-surgery (96, 97).

1.6.2. Weight loss calculations

There is no standardized way of reporting weight loss, which makes it difficult to compare surgical studies, and surgical with non-surgical studies (98). Several definitions are used, including %TWL, TWL in kg, % excess weight loss (EWL) and % excess BMI loss (98). Percent EWL is a commonly used method to report weight loss after bariatric surgery. Percent EWL is usually defined as: weight loss/excess weight * 100 (98). Percent TWL is the usual way of reporting weight loss in non-surgical studies, and it is not associated with pre-surgery BMI (99).

1.6.3. Diet and physical activity recommendations

There are specific dietary recommendations that should be followed post-surgery. Clear liquid is recommended the first 1-2 days post-surgery, gradually followed by full liquid, pureed food and regular food (100, 101). Daily nutritional supplementations, including multivitamin plus minerals, calcium, vitamin D, vitamin B12, and additional iron supplementations if required, are recommended after RYGB to prevent nutritional deficiencies (75, 101, 102). A nutritional pyramid (Figure 4), including nutritional supplementations, physical activity and food choices, is suggested as a tool to help patients to follow the recommendations post-surgery (103). The patients are recommended small and frequent meals, a protein intake of at least 60 g/d, more than 1.5 l of fluids (consumed slowly and at least 30 min before the meal), limited intake of fat and sweets and physical activity of at least 150 min/week (75, 101).

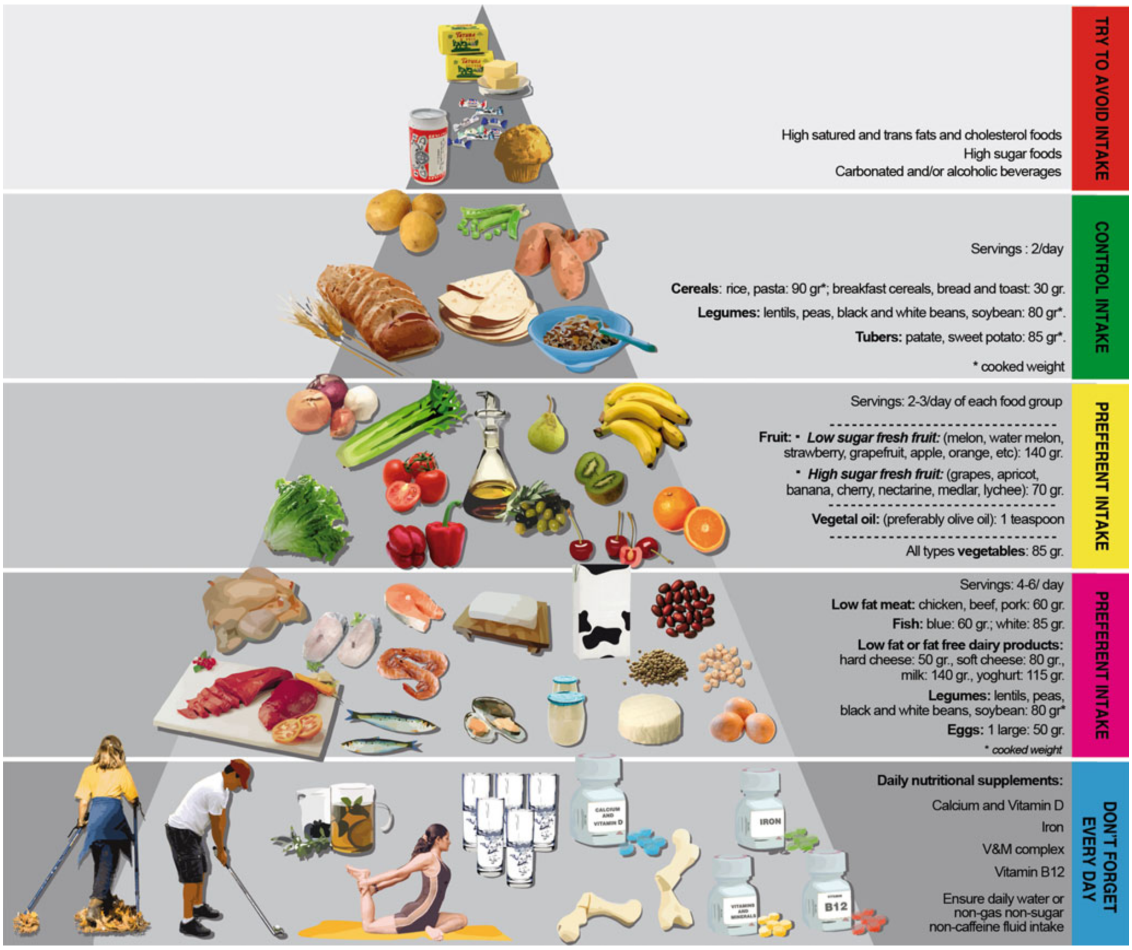

Figure 4: Nutritional pyramid after Roux-en-Y gastric bypass surgery. Reprinted with permission from Obesity Surgery (103)

1.6.4. Employment and use of psychopharmaceutical drugs

Several studies have shown an association between obesity and unemployment (51, 52, 104). Obesity may result in stigmatization and discrimination in the workplace (51, 52), disability, and in increased sickness absence (105-107). Both increase (108, 109) and no change (110) in employment have previously been reported after RYGB. Overall, it is suggested that bariatric surgery has a positive impact on occupational outcomes with fewer sick-days and/or a greater chance for an unemployed to return to work after undergoing surgery (111).

The prevalence of depression is observed to be higher among bariatric patients than in the general US population, with a depression prevalence of 19% and 8%, respectively (112). Evidence suggests that weight loss surgery is associated with a reduction in the prevalence, frequency and severity of depressive symptoms (85, 86, 112, 113). However, some studies have shown an increase of depressive symptoms with time (85-87). Depression post-surgery is associated with surgical pain (114), lower weight loss (113) and excess skin (115). Unrealistic expectations of weight loss and improvement in physical and mental health may lead to disappointment when not achieved (86, 116, 117).

The reported changes in use of antidepressant drugs are inconsistent. Results from studies on depressive symptoms post-surgery suggest both increased use of antidepressants (118), decreased use (86, 119), and decreased use followed by increased use (86).

1.6.5. Weight regain

Some weight regain is common after nadir (79, 120, 121), and relapse of metabolic disturbances post-surgery is observed parallel to weight regain (83). The Scandinavian Obesity Surgery registry from 2016, including almost 13000 patients 5 y post-surgery, described a weight regain of approximately 5 kg (79). Mean body weight from 0 to 5 y post-surgery is shown in Figure 5, and illustrates that body weight nadir is reached approximately 2 y after surgery.

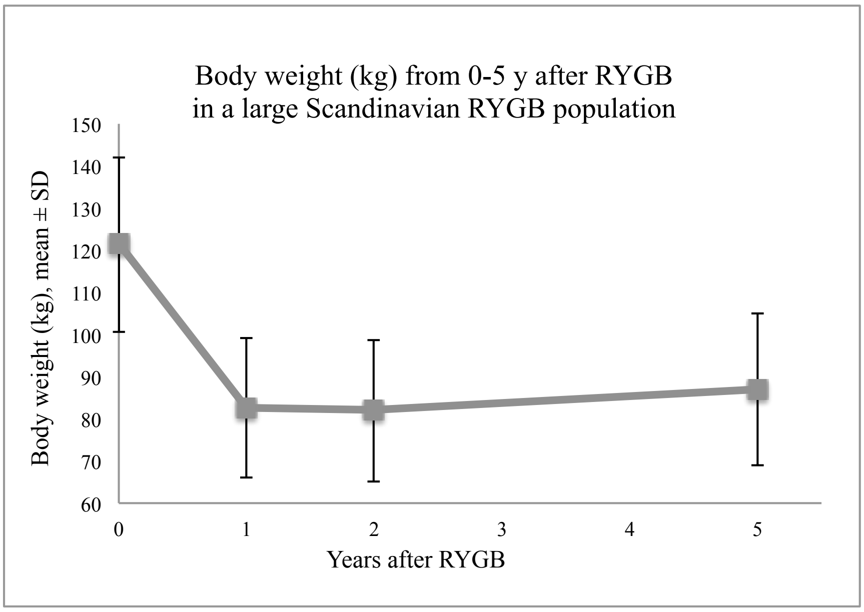

Figure 5: Mean body weight from pre-surgery until 5 y after RYGB reported in the Scandinavian Obesity Surgery Registry 2016 (79). *RYGB* Roux-en-Y gastric bypass

The absence of appropriate lifestyle changes after bariatric surgery, including poor dietary habits, lack of physical activity and lack of follow-up visits are factors that may influence weight regain (122). Control over food urges and eating habits, engagement in self-monitoring of body weight and keeping food records are factors that may improve weight outcome after bariatric surgery (123, 124).

1.6.6. Adverse events

Adverse events should be considered when deciding treatment of obesity (87). The prevalence of overall early complications after bariatric surgery are shown to be 8.3%, serious complications occur in 3.4% of patients within 30 days of surgery, and the 90 day mortality is shown to be 0.04% (125). The risk of serious early complications has been steady since 2011, while the risk of any early complications, including leakage, bleedings, abscesses and pulmonary complications, has decreased (126). Higher volume of bariatric surgeries and mostly laparoscopic procedures has improved the risk of complications post-surgery (125, 127). However, long-term complications are frequently reported, and include bowel obstruction, internal hernia, dumping syndrome and abdominal pain (128-130).

1.7. Rationale of this thesis

Obesity is associated with increased morbidity, mortality (40-45), decreased mental health (53-56) and more unemployment (51, 52, 104). The interest in the association between plasma AAs and obesity and obesity-related disorders is increasing (19-21), and it is suggested that plasma tCys may play a causal role in the regulation of obesity (28, 38). Still, little is known about the role of plasma AAs, including tCys, in weight regain.

Weight loss, improvements in health and a positive impact on occupational outcome are reported after bariatric surgery (69, 71, 73, 87, 111). Despite this, weight regain and some relapse of the achieved benefits is common (71, 82, 83). No randomized control trial has specifically focused on preventing weight regain after bariatric surgery. This intervention may provide information on strategies to maintain weight loss and prevent weight regain, as well as prognostic factors that can be used to identify subjects vulnerable for weight regain.

2. Aims

The aim of the thesis was to study the health benefits 2 y after RYGB and the effects of a group-based lifestyle intervention program on weight regain and health 2 to 4 y post-surgery.

The specific aims were:

1. To investigate health benefits 2 y after RYGB, including weight loss, and changes in metabolic disturbances, employment status and use of psychopharmaceutical drugs (Paper I).

2. To compare changes in weight and metabolic disturbances between a group that received usual care and a group that received a group-based lifestyle intervention program in addition to usual care (Paper II).

3. To identify lifestyle factors associated with weight regain, including dietary habits and physical activity (Paper II).

4. To investigate the relationship between plasma amino acids and weight regain (Paper III).

3. Methods

3.1. Study design

This thesis is based on a randomized controlled, non-blinded, single centre study conducted at Oslo University Hospital, comparing the effect of a lifestyle intervention program with usual care. The thesis consists of 3 papers (Table 3).

Table 3: Study design and number of subjects in Paper I-III. *CTG* Conventional treatment group, *LIG* Lifestyle intervention group

Paper	Study design	Participants (n)		
		Time of surgery	2 y after surgery	4 y after surgery
I	Retrospective	165	165	−
II	Randomized	−	85 (LIG) 80 (CTG)	77 (LIG) 65 (CTG)
III	Prospective	−	165	142

The PhD student designed the project under the supervision of experienced investigators and was responsible for the implementation of the intervention. The PhD student had been working with obesity treatment for several years before planning the intervention and had completed a theoretical education in treatment of obesity, as well as a communication course.

A clinical dietitian contributed to conducting the study and prepared, together with one of the master students, the dietary lectures. Some of the lectures had previously been used at single group meetings in overweight and obese surgical and non-surgical patients.

The PhD student was involved in the group meetings, together with other clinical dietitians, master students in clinical nutrition, a psychologist, an activity coach and an experienced user from the Patient Education Resource Centre.

A total of 7 master students in clinical nutrition, between 2008 and 2013, conducted the group meetings and physical exercise sessions, and/or were involved in the data collection through individual consultations, supervised by the PhD student. The master students received practical training at the Department of Morbid Obesity and Bariatric surgery supervised by clinical dietitians prior to the intervention, and they attended group meetings before starting up with their own groups. Some of the master students had experience from leading similar groups.

The study was approved by the Regional Committee for Medical and Health Research Ethics. All subjects signed informed consent before participation in the trial. The study is registered in ClinicalTrials.gov (NCT01270451).

3.2. Participants and randomization procedure

The participants were recruited from the Department of Morbid Obesity and Bariatric Surgery at Oslo University Hospital. A total of 630 study candidates were operated with RYGB between January 2006 and June 2009, and they received an invitation to participate in the study (Appendix 1). Flowchart for inclusion and implementation is shown in Figure 6. The intervention was conducted from August 2008-August 2012, and the participants were included in three batches from 2008 to 2010, and they were followed for 2 y. Mean duration from surgery to the beginning of the intervention was 21 months (range 14–32 months).

A total of 180 patients reported interest in the study. To be able to participate at group meetings and physical activity sessions, and to fill out questionnaires, we excluded immobile patients, and patients with an inability to read and understand Norwegian. One hundred and sixty-five participants (26%) were included in the study, and they were randomly assigned in a 1:1 allocation ratio to the lifestyle intervention group (LIG) or the conventional treatment group (CTG). A statistician prepared the list for randomization, which was managed by a researcher not directly involved in the study. The list for randomization was designed with blocks of four (for men) and six (for women) and stratified according to gender and EWL of more or less than 66%. The %EWL cut-off were chosen based on the mean EWL of 66% at 1 and 2 y post-surgery at Oslo University Hospital (unpublished data). The result of randomization was revealed to the patient and study personnel directly after the first individual consultation.

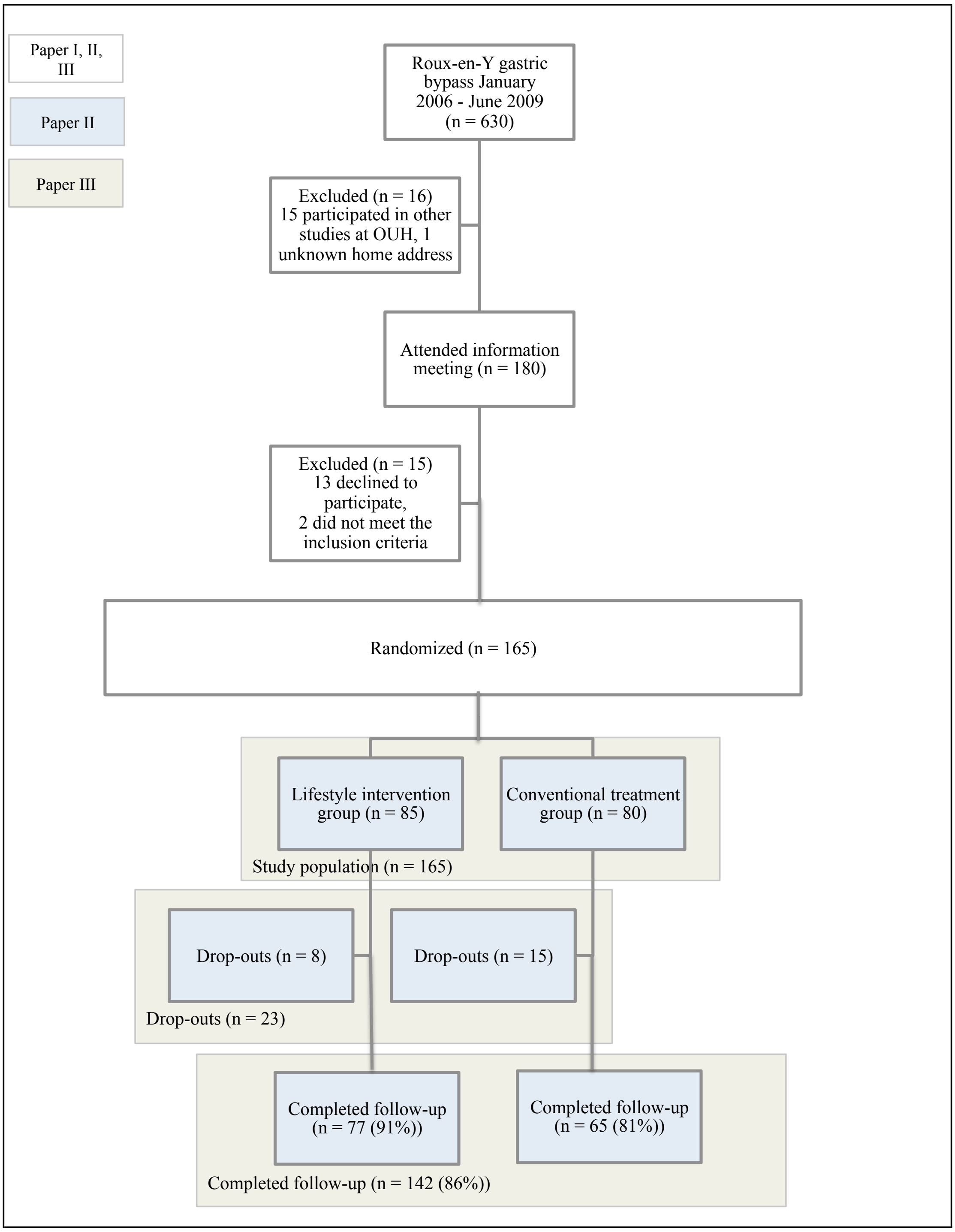

Figure 6: Flowchart for inclusion and implementation in the study. The white squares represents data used in Paper I, II and III (n = 165). The blue squares represents data used in Paper II (n = 77 in the lifestyle intervention group and n = 65 in the conventional treatment group). The beige square represents data used in Paper III (n = 142). *RYGB* Roux-en-Y gastric bypass

3.3. Surgical procedure

In this thesis all participants were operated with RYGB (Figure 3), which is a combined restrictive and malabsorptive procedure (74). The RYGB was performed with a gastric pouch of about 25-30 ml, and an alimentary and biliopancreatic limb of 150 and 50 cm, respectively.

3.4. The intervention

A Swedish program using techniques from behavioural treatment in weight reduction was used as a guiding tool when the intervention was designed (131). The lifestyle intervention program consisted of 16 meetings with a tapering dose, each lasting 2 h (Figure 7).

Table 4 shows an overview of topics and content at each group meeting. The meetings were based on The Norwegian Directorate of Health's recommendations (132) regarding level of physical activity and diet. Pedagogic models to increase physical activity and to optimize the nutritional quality of the meal were used. The participants were advised to choose food items labelled with the Keyhole symbol, which is used in the Nordic countries to help the consumers to identify the healthier options when buying food (133).

Each group meeting included measurements of body weight, a lecture on a given topic, group work and/or an assignment, and 30 min with supervised physical activity (Nordic walking, climbing stairs or strength training). The first year, the participants could choose to attend a day group or an evening group. Because of low attendance at the evening group, the day and evening group were joined the second year and replaced by one afternoon group. The participants were reminded by text message the day before every group meeting.

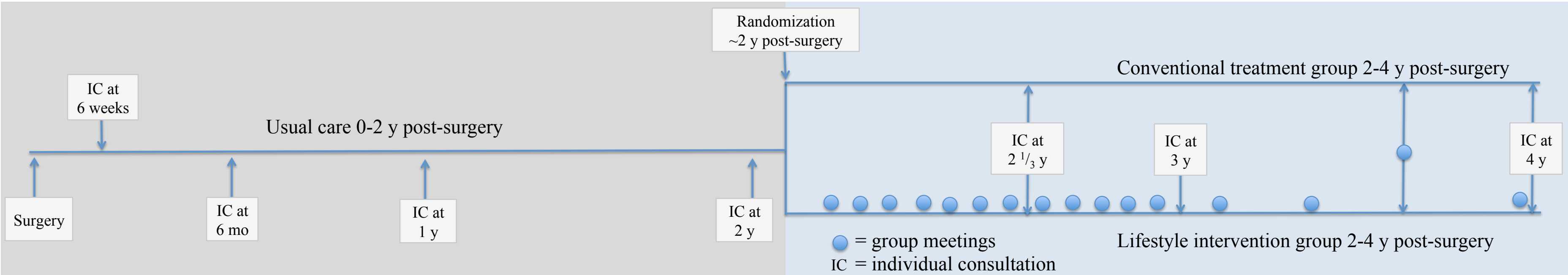

Figure 7: Usual care at Oslo University Hospital in 2008 (grey, left), and the design of the lifestyle intervention program (blue, right)

Dietary topics that were discussed were healthy food choices, meal frequency, portion size and energy density. Master students in clinical nutrition mainly held these lessons. The two lessons on physical activity were prepared and carried out by a clinical dietitian and activity coach. On the first of the two physical activity sessions, the participants were given a pedometer for self-monitoring number of steps per day and were instructed in the use of walking sticks. The participants were advised to decrease time spent on sedentary activity, and they were recommended ≥150 min/week with moderate activity or ≥75 min/week with high intensity activity, in accordance with Norwegian (132) and WHO (134) recommendations. The two sessions on body image were prepared and carried out by a psychologist and focused on self-esteem and body image. Halfway through the intervention, when the interval between the group meetings increased, an experienced user from Patient Education Resource Centre informed the participants about self-help groups. The last group meeting was a cooking class, which focused on healthy choices, and how to modify recipes.

In addition to the lifestyle intervention program the LIG received four extra individual consultations while the CTG received three extra individual consultations during the study (Figure 7).

Table 4: Description of the group meetings in the lifestyle intervention group

	Group meetings	Description of topics	Tasks and homework	Conducted the group meeting
1	Presentation and aims		Discuss individual goals, with time-perspective.	PhD student and master students
2	Physical activity I	Reasons to exercise, positive experience of physical activity and importance of activity concerning weight balance. Distribution of pedometers and guidance in use of walking sticks.	Physical activity: What do you want to change? Homework: Report activity on three active days and three non-active days	Clinical dietitian and activity coach
3	Fat and fat reduced products	How to read and how to understand food labelling and declarations. How to reduce the amount of fat.		Master students
4	Fibre, fruit and vegetables	How to increase the intake of fruits and vegetables, use more whole grain flour, and how to choose the most healthy food items? What is the Keyhole symbol?	How much fibre, fruits and vegetables do you consume? Discuss strategies to increase the intake. Homework: Increase the daily intake of fruits and vegetables, use more hole grain products.	Master students
5	Food during holidays and celebrations	Serving sizes, healthy eating and how to resist temptations.		Clinical dietitian
6	Low fat and low sugar	How to read and how to understand food labelling and declarations.		Master students
7	New Year's resolutions and cravings	Food choices, portion sizes, meals and in-between eating, healthy snacks and fast food. Reduce the amounts of sugar and fat as well as using alternatives, such as whole grain flour instead of white flour.	What is you're individual goal? How to achieve you're goal?	Master students
8	Self-help groups	Encourage the group to meet on their own, in between the group meetings.		Experienced user from Patient Education Resource Centre
9	Physical activity II	How to integrate physical activity in daily routine.	Advantage and disadvantage with physical activity and physical inactivity.	Clinical dietitian and activity coach
10	Sweeteners	Reducing amounts of sugar and alternatives to sugar.		Clinical dietitian
11	Body image I	Moods and feeling. How to handle changes in body and mind after bariatric surgery.		Psychologist
12	Summer food and challenges	Summer food and summer activities.	Strategies to make healthy choices in food and physical activity during the summer holidays.	PhD student
13	"Working groups/round table procedure"	Small working groups discuss challenges of daily life, triggers for dysfunctional strategies, and strategies to deal with cravings.		PhD student
14	Body image II			Psychologist
15	Food for the entire family (this group meeting was a regular meeting offered to all patients)	Regular mealtimes and planning. Recipes for healthy snacks.		Clinical dietitian
16	Cooking class	How to modify recipes, how to make healthy choices.	Healthy dishes prepared in small groups.	PhD student and clinical dietitian

3.5. Outcome measures

3.5.1. Data collection

Clinical data, including anthropometric measures and a clinical examination, were retrieved at the individual consultations 2 y, $2^{1}/_{3}$ y and 4 y post-surgery. A case report form designed for the intervention was used at the visits (Appendix 2). Pre-surgery data were retrospectively retrieved from the patient's hospital journals and from a prospective patient register at the Department of Morbid Obesity and Bariatric Surgery.

3.5.2. Anthropometric measurements and body weight

Body weight and body composition were measured by bioelectrical impedance analysis, using the Tanita BC418MA Body Composition Analyser (www.tanita.com). Body weight nadir was defined as the lowest weight until time of enrolment. This information was retrieved either from the patient's hospital journal, or the measured body weight from the individual consultation at time of enrolment, whichever was lowest. Fat mass (kg), fat mass (%), fat free mass (kg) and trunk fat (%) were estimated through bioelectrical impedance analysis. The maximum weight capacity of Tanita is 200 kg. Waist and hip circumference were determined by measuring tape to the nearest cm. The waist was measured at its largest circumference. The hip circumference was measured at the height of trochanter major. Height was measured to the nearest cm by Soehnle Professional height-measuring appliances (www.soehnle-professional.com). BMI was calculated as body weight (kg) divided by square height (m^2). Before surgery the patients were weighed on a flat Seca Vogel & Halke scale (www.seca.com). Otherwise the same measuring equipment was used pre and post-surgery.

3.5.3. Weight loss calculations

Different weight loss calculations were used in this thesis. In Paper I, %EWL was used to evaluate weight loss post-surgery, and an EWL ≥50% was considered a successful result. Percent EWL is dependent on three variables: pre-surgery body weight, post-surgery body weight, and ideal body weight (98). In our study, the ideal body weight was set to a BMI of 25 kg/m^2. Percent TWL and kg weight loss were used in Paper II and III. In Paper II weight maintenance from 2 to 4 y post-surgery was defined as weight gain less than 3%, while a weight change of +5% or more was considered clinically relevant (135). In Paper III, we defined relevant weight regain from 2 to 4 y as a regain of ≥2 BMI units.

3.5.4. Metabolic measurements and disturbances

Systolic and diastolic blood pressure was measured after 5 min of rest in the sitting position with a CAS 740 Vital Signs Monitor (www.casmed.com/740-vital-signs-monitor). The measurements were repeated twice and the average of the two measurements was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive drugs. T2DM was defined as HbA_{1c} ≥6.0% and/or use of hypoglycaemic agents. The prevalence of metabolic syndrome was assessed using criteria from the National Cholesterol Education Program (136). At least 3 of the following 5 criteria were required for the diagnosis of metabolic syndrome: 1, elevated waist circumference (≥102 cm for men, ≥88 cm for women): 2, elevated triglycerides (≥1.7 mmol/L) or drug treatment: 3, reduced HDL-cholesterol (<1.03 mmol/L for men, <1.3 mmol/L for women): 4, elevated blood pressure (≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure) or antihypertensive drugs: 5, elevated fasting glucose (≥5.6 mmol/L) or use of hypoglycaemic agents.

3.5.5. Use of medication

All use of drugs pre-surgery was collected from the prospective patient register at the Department of Morbid Obesity and Bariatric Surgery, while information about use of drugs post-surgery and during the intervention was retrieved from the case report form. Information about use of drugs for the cardiovascular system and hypoglycaemic agents was used in Paper I and II, while psychopharmaceutical drugs pre-surgery and 2 y post-surgery were described in paper I. Psychopharmaceutical drugs were divided into psychoanaleptics (ATC N06AB; antidepressants and psychostimulants) and psycholeptics (ATC N05ABC; antipsychotics, anxiolytics and hypnotics, and sedatives). Use of drugs in the adult population (20–64 years) in South-Eastern Norway was retrieved from the Norwegian Prescription Database 2010 (137) and was weighted to be comparable to the sex distribution in our study.

3.5.6. Laboratory analyses

Blood was collected after an overnight fast into tubes without anticoagulant (for serum) or with EDTA or lithium heparin (for plasma) and the samples were centrifuged at 3500×g, 10-15 min, at room temperature or 4 °C, respectively.

All samples were collected between autumn 2008 and autumn 2012. Blood analytes were measured in freshly collected samples using the hospital routine laboratory. Blood lipids, including cholesterol and triglycerides, were measured using Modular PE, modul P (Roche Diagnostics, Mannheim, Germany). Fasting plasma glucose was measured using the Gluco-quant Glucose/HK (Roche Diagnostics, Mannheim, Germany), whole blood HbA_{1c} was measured by HPLC on a Tosoh G7 analyser (Tosoh Corp. Tokyo, Japan). HbA_{1c} measured by Tosoh G7 analyser before March 2012 showed systematically higher values than reference methods. Measurements obtained before March 2012 have, therefore, been factor adjusted with 0.955 after recommendations from Norwegian Quality Improvement of Laboratory Examinations. Fasting serum insulin and C-peptide, collected before and after March 2012, were measured on an AutoDELFIA Insulin-kit (PerkinElmer Life and analytical Sciences, Wallac Oy, Mustionkatu 6, Turku, Finland) and on an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany), respectively. The newest analysing method was used on participants included in the last batch when analysing 4 y fasting serum insulin and C-peptide. These insulin and C-peptide results were converted with the following formulas Y(Modular) = 2.4 + 1.31 x X(DELFIA) and Y(Modular)=0.99X(DELFIA) + 85, respectively.

Due to haemolysis, fasting serum insulin data is missing from 15 participants at 2 y and 23 participants at 4 y post-surgery. Homeostatic model assessment of insulin resistance was estimated by the Oxford University homeostatic model assessment Calculator 2.2 from fasting glucose and insulin concentrations (138). An oral glucose tolerance test was performed at baseline and 4 y post-surgery in a subgroup of 21 and 22 non-diabetic participants from the LIG and the CTG, respectively. The 75 g oral glucose tolerance test was performed after an overnight fast and samples were obtained at 0, 30 and 120 min for determination of glucose and insulin. Insulin secretion was estimated using the insulinogenic index (Δinsulin 0-30 min /Δglucose 0-30 min).

Aliquots of serum and plasma samples were stored at −80 °C for later analyses of plasma AAs, including tCys, methionine, total BCAAs (sum of leucine, isoleucine, and valine), and total AAAs except histidine (sum of phenylalanine, tryptophan, and tyrosine). The concentrations of plasma AAs were measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) using a modified version of a previously described method (139). Plasma tCys was analysed at the University of Oslo in 2013, using a Sciex 4000 QTRAP MS/MS spectrometer (Framingham, MA, USA), while the other plasma AAs were measured at the University of Oxford in 2014. Details are further described in Paper III.

3.5.7. Questionnaires

Food diaries

Pre-coded food diaries (Appendix 3) and picture book (Appendix 4) (140) were used to assess energy intake and macronutrient distribution over a 4-day period before and after the intervention. The diary consists of a list with common foods and drinks, and empty lines where participants can enter foods and drinks not listed in the diary (140). The food diary has been validated among 9 y and 13 y old children, and the validity was found to be good or moderate in ranking individuals according to energy intake (141, 142). An example of the pre-coded food diary can be assessed at www.med.uio.no/imb/english/research/groups/dietary-research-nutritional-epidemiology/dietary-research/methods/. The diaries were administered by a clinical dietitian and master students and were scanned using the Teleform version 6 (Datascan Oslo, Norway). Energy intake and macronutrient distribution were estimated by a software system developed by the Department of Nutrition, University of Oslo Norway (143), that contained data based on the Norwegian food composition Table from 2006 (144).

Physical activity questionnaire including employment status

Validated 7-day physical activities recall questionnaire (Appendix 5) was used to calculate energy expenditure, physical activity level and time spent on physical activity of low, moderate or high intensity (145). The questionnaire has shown good correlation with ActiReg, which is an instrument used to calculate energy expenditure and physical activity (146). The questionnaire is designed based on the Hyrim physical activity questionnaire (147) and the International physical activity questionnaire (148), which both are developed to monitor physical activity and inactivity. The questionnaire includes 5 main categories about work, transportation, daily activity at home, leisure time activity and sedentary activity. It was designed to evaluate level of physical activity and adherence with the national guidelines for physical activity (132, 145). Physical activity level was calculated by dividing energy expenditure by the resting metabolic rate (149). The resting metabolic rate was calculated from weight, height, age and sex using Mifflin's formula (150).

Metabolic equivalent (MET) described the intensity of activities, which was divided into the categories: 1.0 MET (sleep), 1.1-3.0 MET (low), 3.1-6.0 MET (moderate), and >6 MET (high) (145). One MET is defined as the amount of energy expended during 1 min at rest, and is set to 3.5 mL oxygen per kg body weight per min (3.5 mL/kg/min) (149). Total MET-minutes were calculated by multiplying number of days and minutes used on the activity with the MET-value of the specific activity. The questionnaire covered all activity for a 24-hour-period. If the registered time did not add up to 24 h the residual time was registered as activity with low intensity (145).

In Paper II we investigated changes in employment from pre- to 2 y post-surgery. Information about pre-surgery work situation was collected from the prospective patient register at the Department of Morbid Obesity and Bariatric Surgery, while post-surgery information was collected using the physical activity questionnaire. Participants were registered as employed (including students), or unemployed; we did not distinguish between medical leave, disability, job seeking, or voluntary out of work.

Short-Form 36

The participants completed a short-form health survey version 2, consisting of 36 questions (SF-36). This is a generic measure, which yields an eight-scale profile score including physical health (consisting of physical functioning, role-physical, bodily pain and general health) and mental health (consisting of vitality, social functioning, role-emotional and mental health).

3.6. Statistical analyses

The sample size was calculated according to the primary endpoint of the study, which was a between-group difference in weight change 2 to 4 y post-surgery. A sample size of 65 subjects in each of the two treatment groups provided 80% power to detect a 2.5 kg difference in mean weight change from 2 to 4 y post-surgery. Due to lack of previous data to use as basis for the calculation we estimated a SD of 5 kg, and 5% type 1 error. In addition, the sample size provided a 20% allowance for dropouts.

SPSS version 21.0-25.0 (Chicago, IL) was used for the statistical analyses. In all Papers, descriptive statistics were reported as frequencies, median (25th–75th percentiles), or mean ± SD, and partial correlations were used to describe the linear relationship between two variables, adjusted for relevant covariates, including sex and age. Time from surgery to inclusion, study group allocation (Paper I and III), physical activity level, energy intake or macronutrients did not change the results significantly and were, therefore, not included in the adjustments. There were some outliers, and the analyses were done with and without these outliers. Since the results of these analyses were similar the outliers were included in the final analyses. If not otherwise stated, the combined data for men and women was presented.

In Paper I and III, two related samples were examined using Wilcoxon signed-rank test (skewed variables), paired samples t-test (normally distributed variables), or McNemar's test (categorical variables). In Paper II, two independent samples were examined using Mann-Whitney U (skewed variables), independent samples t-test (normally distributed variables), chi-square, or Fisher exact test (categorical variables). The between-group analyses were presented unadjusted. Analyses of covariance, which included all participants adjusted for age, sex and group allocation, were used to identify factors associated with weight regain 2 to 4 y post-surgery. These factors were selected based on univariate *P*-values <0.2, and included smoking status, plasma tCys, intake of artificially sweetened beverages and meat, and time spent on sedentary activities (reading, TV viewing and computer use). We used a linear mixed model for longitudinal analysis of changes in body weight at 2 y, $2^1/_3$ y and 4 y post-surgery. Only participants that attended the last individual consultation 4 y post-surgery were included in the other analyses. In Paper III, we investigated plasma AAs, all of which were normally distributed. Analyses of covariance, including age, sex and insulin as covariates, were used to compare differences between quartiles of plasma tCys at 2 y and ΔBMI 2 to 4 y. Binary logistic regression was used to examine the association of plasma AAs at 2 y with BMI regain ≥2 units 2 to 4 y.

P <0.05 (two-tailed) was considered statistically significant.

4. Main results – summary of papers

A total of 165 participants were included in the study approximately 2 y after RYGB. At inclusion, 75% of the participants were women, 96% were of Nordic ethnicity, mean duration since surgery was 21 mo (range 14–32 mo) and mean ± SD age was 45.7 ± 8.6 y. BMI was 30.9 ± 4.9 kg/m^2 and TWL 2 y post-surgery was 30.1 ± 8.2%. Further, 29% had hypertension, 10% had T2DM and 26% had metabolic syndrome.

4.1. Paper I

Great Health Benefits But No Change in Employment or Psychopharmaceutical Drug Use 2 Years After Roux-en-Y Gastric Bypass.

Great weight loss was achieved with a mean EWL of 71.4 ± 20.6%, which corresponds to a TWL of 30.1 ± 8.2%. The prevalence of T2DM, hypertension and metabolic syndrome were significantly reduced from time of surgery to 2 y post-surgery (P <0.001 for all). The use of antihypertensive drugs, oral hypoglycaemic agents, statins (P <0.001 for all) and insulin (P = 0.016) decreased significantly. No change in use of psychopharmaceutical drugs (P = 0.55) was found, but we found an increased use in the subgroup of drugs consisting of hypnotics and sedatives (P = 0.016). The use of antidepressants remained high (14.5%) compared with the use in the general population (8.4%). We did not find any association between use of antidepressant drugs before surgery and BMI or %TWL 2 y after surgery.

There were no changes in the proportion of unemployed participants from pre-surgery to 2 y post-surgery (P = 0.19).

Based on MET, the energy expenditure 2 y post-surgery was 10.0 ± 1.4 MJ for women and 13.3 ± 2.6 MJ for men, while reported energy intake for all participants was 7.3 MJ.

The health benefits were higher among participants with successful weight loss (defined as a EWL of ≥50%), and patients with lower pre-surgery BMI were more likely to achieve successful weight loss. None of the variables; age, energy intake, energy distribution, time used on physical activity, use of psychopharmaceutical drugs, or employment status were associated with successful weight loss.

4.2. Paper II

Does lifestyle intervention after gastric bypass surgery prevent weight regain? – A randomized clinical trial.

A total of 165 participants were allocated to lifestyle intervention (n = 85) or to usual care (n = 80). The LIG was offered 16 group meetings during a 2 y period. We found no significant difference in weight regain between the groups (LIG: 4.2 ± 6.4 kg and CTG: 3.9 ± 8.1 kg, $P = 0.82$.). During the study period 40% and 46% maintained or lost weight in the CTG and the LIG ($P = 0.51$), respectively, and 46% and 49% experienced a weight regain ≥5% ($P = 0.70$). There were no differences between the groups in changes in physical activity level, time spent on different activities, energy intake, macronutrient distribution, metabolic disturbances or metabolic markers 2 to 4 y post-surgery.

Mean participation at the group meetings was 49% (range 35-84%). There was no difference in weight regain between participants with high compared with low attendance rate.

Regardless of group allocation, we found a positive association between weight increase from nadir to 2 y and weight regain 2 to 4 y post-surgery (β = 0.5 (95% CI: 0.1-0.9)%, $P = 0.017$). Self-reported time used on moderate or high physical activity was 520 min/week, and participants who reported physical activity for ≥150 min/week had a lower weight regain compared with less active participants (β = −5.2 (95% CI: −9.1- −1.4)%, $P = 0.009$). Participants who were non-smokers had a lower %TWL 2 y post-surgery (β = −6.5 (95% CI: −9.5-−3.6)%, $P < 0.001$), and a higher weight regain 2 to 4 y post-surgery (β = 4.8 (95% CI: 1.4-8.3)%, $P = 0.006$) compared with smokers.

In analysis of covariance, we found that smoking, higher age, and higher intake of artificially sweetened beverages were inversely associated with % weight regain 2 to 4 y post-surgery, while high level of plasma tCys, and time spent on reading, TV viewing and computer use at 2 y were positively associated with % weight regain 2 to 4 y post-surgery.

4.3. Paper III

Plasma amino acids, adiposity, and weight change after gastric bypass surgery: are amino acids associated with weight regain?

In this paper, with 165 participants, we prospectively examined the relationship of plasma AAAs, BCAAs, and tCys 2 y post-surgery, with BMI at 2 y and with weight change 2 to 4 y post-surgery. Weight regain 2 to 4 y post-surgery was 4.0 ± 7.2 kg (P <0.001), and BMI change was 1.4 ± 2.5 kg/m^2 (P <0.001). All the investigated plasma AAs at 2 y correlated positively with BMI at 2 y ($P \leq 0.003$ for all). Plasma BCAAs and AAAs at 2 y correlated inversely with %TWL from 0-2 y ($P = 0.002$ and $P = 0.001$, respectively), while the association was not significant for tCys ($r = -0.139$, $P = 0.078$). Of all the investigated AAs, only plasma tCys at 2 y correlated positively with BMI at 4 y ($P = 0.010$) and with weight regain 2 to 4 years ($P = 0.015$).

In analyses of covariance, including age and sex as covariates, changes in BMI 2 to 4 y increased with 1.0 (95% CI 0.2, 1.8) kg/m^2 in the lowest plasma tCys quartile at 2 y compared with 2.3 (95% CI 1.5, 3.2) kg/m^2 in the highest quartile ($P = 0.025$). In binary logistic regression, we found an increased risk for gaining ≥2 BMI units 2 to 4 y when comparing the highest with the lowest plasma tCys quartile 2 y post-surgery (P for trend = 0.018).

5. Discussion of methods

5.1. Study design

The intervention is a single centre study and may not be representative for populations outside the region that our centre covers. On the other hand, a single centre study makes the practical implementation of the intervention and data collection easier and all blood samples are analysed at the same laboratory.

Eight people performed the measurements at the individual consultations. Thus, there was a risk for bias in manual measurements, including hip and waist circumference, at the different visits. However, personnel involved in the measurements were instructed in how to perform the measurements to limit the risk for errors. Furthermore, the methods were standardized, and the same measurement equipment was used.

Randomized clinical trial is the gold standard for evaluating interventions and blinding is recommended (151). In the present study, it was impossible to blind the participants due to group meeting attendance. The PhD student was responsible for the intervention, collected data and had to attend some of the group meetings. Consequently, the PhD student could not be blinded either.

5.2. Participants and randomization

The number of potential candidates was 630, but only 165 subjects were included in the study. Among those included, 91% and 81% completed in the LIG and CTG, respectively. A possible explanation of the slightly higher completion rate in the LIG is that most of the subjects in the CTG would have preferred to be in the LIG, or that participants in the LIG felt more committed to complete than participants in the CTG because of closer contact with the study personnel.

We have no information about the 465 patients who did not participate in the intervention, and no information from 4 y on those who did not complete the 4 y assessments. The baseline characteristics of the participants (age, sex and BMI) and the 2 y weight loss were similar to what is described in a review and meta-analysis from 2014 on bariatric surgery studies (152), but almost all of the participants in the present study were of Nordic ethnicity, and the findings may not be applicable to populations with other ethnic and cultural backgrounds. Those who volunteered to participate may also have been more motivated for lifestyle changes, and thus, regained less weight than other surgical patients. This is endorsed by an earlier publication from our hospital that observed a higher weight regain than in the present study (129).

Another possible bias may be the patients' geographical affiliation. Patients were located in South-Eastern Norway Regional Health Authority, which consist of 10 counties (153). Hence, travel distance to the hospital may have affected willingness to participate in the study. We have no record of patient's county affiliation at time of inclusion, but our impression is that most of the participants came from counties that were close to the hospital.

The randomization was stratified by EWL of more or less than 66%. Reported %EWL varies between studies: two systematic reviews of RYGB trials reported a mean EWL of 67.3% and 80.5% 1 and 2 y post-surgery, respectively (154, 155). This is higher than the cut-off level used to stratify by in the present study. However, we found no baseline differences in %EWL, or in other variables, between the groups and we assume the randomization to be successful.

The participants were included approximately 2 y after surgery, with a range from 14-32 months, and body weight nadir was reached between 1 and 2 y post-surgery. It is possible that the difference in time between surgery and study inclusion could have affected weight outcomes, because of differences in time of nadir. However, in analysis of covariance, we did not find that time of nadir or time between surgery and study inclusion were associated with weight regain 2 to 4 y post-surgery.

5.3. The intervention

We used a Swedish behavioural treatment program for weight reduction (131) as a guiding tool for designing the lifestyle intervention program. The original treatment program consisted of 25 meetings for a period of one year (131), whereas the present intervention consisted of 16 group meetings from 2 to 4 y post-surgery. The intervention was designed to maintain weight loss, and thus, the participants were

offered less frequent group meetings than the weight loss program used as a guiding tool.
Number and frequencies of group meetings in the present intervention were based on what was feasible with regards to hospital resources and what was practical for the patients. With more group meetings, or more frequent group meetings, participation at every meeting could be more challenging, and a lower attendance rate could possibly influence the group dynamic. It may have been easier to prioritize the scheduled meetings if there were fewer group meetings, but then the intervention may not have been sufficiently intense to prevent weight regain. The present intervention had group meetings biweekly the first 7 meetings, thereafter monthly until 12 months. Most weight loss interventions start with more frequent follow-ups, with weekly meetings in the weight loss phase and usually do not last longer than 6-12 months.

Follow-up in the weight maintenance phase is often less frequent than in the weight loss phase, but in The Look AHEAD study, the participants in the lifestyle intervention program were offered several meetings every month for several years (63). They observed a 7.9% higher 1 y weight loss than in the usual care group, while weight loss was 2.6% higher at 8 y when the intensity of the intervention was reduced, but still included several meetings every month (63). In an observational study including 4 cohorts, 2 of 3 non-surgical cohorts described a long-term significantly sustained weight loss even though some weight regain was shown when the intervention became less intensive (69). One of the cohorts consisted of participants attending 16 consecutive weeks at a weight loss camp followed by monthly telephone- or in person contact with health personnel. They described a 1 y and 5 y weight loss of 21% and 9%, respectively (69). In contrast, a weight loss study from the same camp, but without monthly follow-up, observed only 4.6% weight loss at 4 y, with a dose-response effect between the duration at the camp and long-term weight maintenance (156).

Another of the three cohorts described a 1 y weight loss of 14% followed by a significantly sustained 5 y weight loss of approximately 4% with 2 week residential stay every 6 months (after initial 14-16 week non-consecutive residential stay) (69). The last cohort received a 6 months intensive lifestyle intervention, a 6 months maintenance phase, and thereafter one yearly assessment (69). They observed a significant weight loss of approximately 7% after 1 y, but the weight loss was not sustained at 5 y (69). Thus, from these cohorts it seems like long-term and frequent follow-ups are important to sustain weight loss.

During the first year of the current intervention, two parallel group meetings were offered; a day group and an evening group. The second year of the intervention, only one group (early evening) was offered due to low participation at the evening group. The fact that it was only possible to attend one group meeting may have influenced the participation, and a significantly lower participation the second year was found. However, when comparing the attendance from the time when the interval between the group meetings increased (group meeting 8-12), with the second year (group meeting 13-16), no significant difference in participation was found.

Only two of the group meetings during the intervention focused on body image. The other group meetings focused on physical activity and dietary factors, and dietary changes to prevent weight regain. More focus on psychological factors in the group meetings could possibly have been beneficial in preventing weight regain.

The participants were encouraged to attend self-help groups in-between the scheduled group meetings, but there was no interest among the participants. This might be due to travel distance to the hospital, or that the participants were satisfied with the frequency of the scheduled group meetings.

5.4. Outcome measures

5.4.1. Weight change calculations

There is no standard way of reporting weight loss (98, 157) or weight regain (122, 123, 158-160), and we have used different calculations in Paper I, II and III to report weight outcome.

In Paper I, we used %EWL to report successful weight loss. Percent EWL may be useful to compare patients with very differing pre-surgery body weight (98), which in the present study varied between 87 kg and 192 kg. Percent EWL is commonly used in bariatric surgery studies, but there are methodological considerations with this method because it requires a definition of ideal weight, which may differ between studies (98, 161). Using %TWL as the prime outcome in bariatric weight loss studies has been suggested because it is less influenced by pre-surgery BMI and it is not dependent on ideal weight loss (157). Accordingly, we used %TWL as a measure of weight loss and weight change in Paper II and Paper III.

In Paper II, we defined weight maintenance 2 to 4 y based on a review by Stevens et al (135), where long-term weight maintenance after conservative weight loss is defined as a weight change of less than 3%, and a weight change of 5% or more as clinically relevant (135). In Paper III, we examined the odds of gaining ≥2 BMI units with quartiles of plasma tCys. When conducting the analysis using weight regain of more or less than 5% we found a similar trend as using ≥2 BMI units.

Definition of weight regain varies between studies, and in other publications the cut-offs for what was considered as weight regain has varied between 2% and 15% (122, 123, 158, 160). A regain of ≥2 BMI units corresponds to a 6.5% weight gain in this study population. This is slightly higher than the 5% defined as clinically relevant by Stevens et al (135). However, taking into account the initial large weight loss post-surgery, a weight regain of 6.5% may be acceptable.

5.4.2. Metabolic measurements and disturbances

Diagnosis of diabetes is based on level of HbA_{1c} with or without a cut-off for fasting glucose. HbA_{1c} ≥6.5% is commonly used while an HbA_{1c} 5.7-6.4% is used to identify individuals with high risk for future diabetes (162). Several models have been used to define remission of T2DM after RYGB (82, 163-167). Some define an HbA_{1c} <6.0% as full remission and HbA_{1c} <6.5% as partial remission (165, 166), while others define remission as HbA_{1c} <6.5% (82, 168). In this thesis we chose to define T2DM as HbA_{1c} ≥6.0% and/or use of hypoglycaemic agents.

Hypertension was defined as blood pressure ≥140/90 mmHg and/or use of antihypertensive drugs. Recently, American guidelines recommended a new definition of hypertension, with a threshold that shall not exceed 130/80 mmHg (169).

Table 5 presents the frequency of metabolic disturbances when using 2 different definitions of hypertension and T2DM. The prevalence of impaired glucose tolerance (defined as HbA_{1c} 5.7-6.4%) is also presented in Table 5. Significantly fewer had

T2DM pre-surgery when HbA_{1c} ≥6.5% was used compared with HbA_{1c} ≥6.0% (P = 0.016). A significant remission of T2DM was achieved within 2 y post-surgery, and there was no change from 2 to 4 y post-surgery independent of which definition was used.

We found a significantly higher frequency of hypertension at all time points when using the new definition, ≥130/80 mmHg (P<0.001 at all time points). Remission from hypertension was significant from 0-2 y independent of what definition was used, even though the frequency remained high with the new definition. From 2 to 4 y the frequency of hypertension with the new definition remained high and unchanged, whereas the frequency with the initial definition (≥140/90 mmHg) increased (Table 5).

Table 5: Prevalence of metabolic disturbances using different diagnostic criteria

	Before	2 years	*P*-value[1]	2 years	4 years	*P*-value[1]
Definition of type 2 diabetes mellitus	**n = 163**	**n = 163**	**(before-2 y)**	**n = 142**	**n = 142**	**(2-4 y)**
HbA_{1c} ≥6.0% and/or use of hypoglycaemic agents [n (%)]	51 (31.1)	16 (9.8)	<0.001	13 (9.2)	11 (7.7)	0.50
HbA_{1c} ≥6.5% and/or use of hypoglycaemic agents [n (%)]	44 (27.0)	11 (6.7)	<0.001	9 (6.3)	10 (7.0)	1.00
HbA_{1c} ≥5.7% and/or use hypoglycaemic agents [n (%)]	71 (43.6)	22 (13.5)	<0.001	17 (12.0)	26 (18.3)	0.004
Definition of hypertension	**n = 164**	**n = 164**		**n = 141**	**n = 141**	
≥140/90 mmHg and/or use of antihypertensive drugs [n (%)]	132 (80.5)	47 (28.7)	<0.001	41 (28.9)	53 (37.3)	0.012
≥130/80 mmHg and/or use of antihypertensive drugs [n (%)]	155 (94.5)	94 (57.3)	<0.001	84 (59.2)	84 (59.2)	1.0

[1] McNemar's test

5.4.3. Questionnaires

Food diaries

Four-days pre-coded food diaries were used to assess the dietary intake. Several methodological limitations are reported with all dietary self-reporting methods, including the risk of misreporting the intake of energy and macro- and micronutrients (170, 171), especially among obese and overweight individuals (170, 172, 173). However, there are studies showing no association between under-reporting and a BMI ≥25 kg/m^2 in 9-year old children and in adults (142, 174). There are several other methods to choose for dietary assessment, including food frequency questionnaire, 24-h recall and weighed records.

Food frequency questionnaire is a dietary assessment method used to assess the diet over a long period, and can provide information about food only eaten occasionally (170). With food frequency questionnaire more under-reporting of energy, and more over-reporting of healthy nutrient (e.g., vitamin C, vitamin K and carotenoids) is observed compared with 4-days pre-coded food diaries, which is described as a more accurate method to estimate intake of energy, protein and sodium (170). Repeated 24-h recall is shown to be a suitable method to estimate average energy intake and distribution (170, 175), but are described as costly considering scheduling, training interviewers and respondents and coding data (170). Weighed dietary records is described as the most accurate measure of dietary intake (176) where all foods and drinks consumed are measured with a food scale or household measures (177-179). Weighed dietary recording is an intensive and time-consuming method for the participants that may increase the risk of under-recording foods and drinks. The participants may also eat less or avoid certain food items to make recording easier (178). Food diaries are suggested to be the next best method after weighted records (176), and may overall be the best method since it is less invasive compared with weighed dietary records.

Under-reporting may be caused by inaccuracy in recording food intake and poor portion size estimations. It is observed more under-reporting of between-meal snacks than food consumed during a meal (179). A lower energy intake, lower intake of sweets, desserts and snacks, lower intake of sugary drinks and sucrose, and a higher energy percent from proteins are described in under-reporters (179). In a twin study using food diaries to assess food consumption and energy intake, under-reporting of energy and sweet- and fatty delicacies were described in the obese, but not in the non-obese co-twin (180). It was suggested that the obese co-twin under-reported unhealthy food without over-reporting the consumption of food that are generally perceived as healthy (180). Further, the obese tended to eat less fruits and berries (180). Similar results are described in The UK National Diet and Nutrition Survey where under-reporters, who were more likely to be obese, reported a lower intake of full fat dairy products, sugar and sweets, and also a lower intake of fruits, nuts and wholemeal bread and cereals (171).

Participants may modify their eating behaviour when they have to register and report to health professionals, which may explain the reported low energy intake (173). A reduced awareness of food consumption in the obese, or a reluctance to report the actual energy intake may be another explanation (173).

Different methods can be used to calculate misreporting of energy if body weight is stable (181, 182). In the present study, body weight was not stable, and these methods are, therefore, not applicable for assessment of misreporting in our study population.

Physical activity

The self-reported 7-day physical activity recall questionnaires have several limitations, with over-reporting of physical activity as a common problem (180, 183, 184). A high discrepancy in compliance with physical activity recommendations ≥150 min/week are shown in a study of 230 bariatric patients 1 y post-surgery, which observed a ~18% compliance with objective measurements compared with ~80% compliance with self-reported measurements (184). Other limitations may be difficulties with remembering all activity for the last 7 days, and difficulties with deciding the intensity of the activity. It is a major limitation that we do not have objective measurements in this study, and the main reason we did not implement objective measurements was the cost associated with the purchase of the instrument. However, it is likely that the participants over-reported their physical activity to the same extent as is reported in other intervention studies (183, 184). We also expect the extent of misreporting of energy and physical activity to be the same at both 2 y and 4 y post-surgery. Thus, changes in physical activity between 2 to 4 y should be possible to detect using this method.

Short-Form 36

The CTG and the LIG filled out the quality of life questionnaire short-form 36 (SF-36) before and after the intervention period. Long-term improvements in quality of life are observed after surgery, especially among patients with the largest weight loss (71, 185, 186), despite some weight regain 2 y onward (71, 186). The same quality of life improvements from pre-surgery to 2 y post-surgery are likely in the present study. The weight regain of approximately 4 kg during the 2 y intervention period in the present study is probably too small a change, in too short time to reveal any significant change in quality of life from 2 to 4 y post-surgery. Based on the fact that we did not expect to find any changes, the time-consuming work with the questionnaires, and the cost of the quality of life license, we did not prioritize analyses of the quality of life questionnaires.

5.5. Statistical analyses

No similar studies in preventing weight regain after bariatric surgery had been conducted when the current study was initiated in 2008, and the weight difference of 2.5 kg was based on the assumed outcome that the LIG would regain 2.5 kg less than the CTG. This 2.5 kg is comparable to the difference in weight regain observed in a non-surgical weight maintenance study lasting for 18 months, where the participants in the control group regained 2.4 kg more than participants in the face-to-face-group (187). The study had a similar design as the current intervention with weekly meetings the first month followed by monthly meetings the next 17 months to the face-to-face group, whereas the control group received quarterly newsletters with general information about diet and physical activity (187).

There are different methods to analyse results from randomized clinical trials. Per-protocol analyses include participants who strictly follows the protocol, all other participants are excluded (188). The main limitation with per-protocol analyses is that it may overestimate the effect of the intervention compared to a real life situation. It also may result in large number of excluded participants or missing data that will lead to reduced sample size and reduction in study power (188). The current study had low attrition rate, with a completion rate of 86% (n = 142) and only 23 of 165 participants did not attend the last visit. Per-protocol analyses may thus have had limited affect on the results. The intention to treat model is the recommended model in randomized controlled trials as it includes all randomized participants in the analyses (188). However, missing data is a challenge in these analyses as well (188). Last observation carried forward can be used to account for missing values, but the last observation could also be the baseline observation (189, 190). In the present study, with a mean weight regain of 4 kg, it will seem like participants who did not complete the intervention had less weight regain compared with completers. Thus, to replace missing values with the last observation carried forward would not be useful.

In the present study only participants who attended the last follow-up visit were included in the analyses, and they were analysed as part of the group they were randomized to. This model should not be confused with a per-protocol model since participants were included regardless of whether they followed the scheduled protocol or not, which in the LIG consisted of 16 group meetings.

With a linear mixed model, all observed data are included in the analysis (191), and analysis of the primary aim (difference in weight regain between the LIG and CTG) was repeated with this model. However, we had only one additional individual consultation and assessment, 4 months from study start, and thus, the linear mixed model analysis did not add substantially to the information given from the student independent sample t-test. This was confirmed by the fact that the findings from the linear mixed model analysis did not differ from the student independent sample t-test.

We found an association between plasma AAs 2 y post-surgery and fasting insulin 2 y post-surgery. As insulin was associated with both AAs and BMI, insulin could be a potential confounder distorting the relationship between AAs and BMI. Analyses in Paper III are therefore repeated adjusted for fasting $insulin_{2\ y}$. After this additional adjustment several of the results were weakened, even though the values were approximately unchanged. This may be explained by small insulin sample size due to loss caused by haemolysis in 15 and 23 participants at 2 and 4 y post-surgery, respectively.

Due to the small sample size for insulin we repeated the analysis adjusted for glucose or HbA_{1c}. This did not change the results, which suggest that glycaemic parameters do not confound the results.

6. Discussion of results

6.1. Health benefits 2 y after RYGB

6.1.1. Weight loss

Weight loss is described as %EWL (Paper I) and %TWL (Paper II and III), and we found an EWL of 71.4% and a TWL of 30.1% 2 y post-surgery. These results are in line with other publications (79, 118, 192). Several studies have demonstrated a substantial weight loss after bariatric surgery (70, 74, 118) and patients with lower pre-surgery BMI benefit most from surgery (193). In Paper I, we found that a pre-surgery BMI ≤43 kg/m^2 was associated with BMI <30 kg/m^2 2 y post-surgery. In line with this finding, a large retrospective study described an association between a pre-surgery BMI <40 kg/m^2 and a BMI <30 kg/m^2 1 y post-surgery (194).

Weight loss before surgery is usually recommended (195). However, the association between pre-surgery weight loss and post-surgery weight loss is inconsistent. Two review articles describe positive, inverse and no association between pre- and post-surgery weight loss (195, 196). No information on pre-surgery weight loss is available in the present study, and we do not know whether there is any beneficial effect of pre-surgery weight loss to reach a BMI <43 kg/m^2.

6.1.2. Metabolic disturbances

In line with several other studies (70, 118, 197), great health benefits were observed 2 y after surgery (Paper I). Despite some weight regain from 2 to 4 y after surgery, the remission of T2DM, hypertension and metabolic syndrome remained unchanged in the LIG and the CTG. However, a significant increase in hypertension from 2 to 4 y was observed in the overall population *(P* = 0.012) (Paper II). Others have described long-term sustained remission of metabolic disturbances from pre-surgery to 6 y onward, even though some relapse was observed from 2 y post-surgery (70, 71). In a large cohort study, including 4185 bariatric surgery patients with T2DM, life expectancy improved after bariatric surgery, but the improved life expectancy decreased with increasing BMI (84). The reduced benefit with increasing BMI may have several causes, including more surgical complications with higher BMI and longer duration of T2DM and thus, more difficulties to obtain remission (84).

It is described that patients who achieved a BMI <30 kg/m^2 have decreased need for medication for hyperlipidaemia, T2DM and hypertension compared with patients who remained obese (194). Similar findings are shown in Paper I, except for in the use of hypoglycaemic agents where we found no difference between participants with a BMI above or below 30 kg/m^2. To achieve a BMI <30 kg/m^2 post-surgery, early intervention should be emphasized, and surgical treatment should be considered for patients with a BMI lower than the current cut-off for surgery.

6.1.3. Employment

In Paper I, we did not find any changes in employment status 2 y post-surgery despite great weight loss and remission of metabolic disturbances.

One explanation may be that 2 y after surgery is too short a time to achieve an increased proportion of employed patients. However, we found the same proportion of unemployment 4 y after surgery (data not shown). In comparison, another Norwegian study including 224 patients observed no changes in employment status 5 y post-surgery, but they did find a significant reduction in number of days on sick leave (110). A study with only 38% employed patients pre-surgery observed an increase in the proportion of employment to 60% 3 y post-surgery (108). The improvement was not directly related to the weight loss, but the improved self-image, self-esteem and general confidence seen post-surgery were factors suggested to improve employment (108). Another study observed a proportion of unemployment before surgery as high as 66%, mainly related to morbid obesity (including depression, general pain and fatigue) (198). They observed that many did not return to work post-surgery despite weight loss and improvement in quality of life (198). However, the study participants in that US-study had a high pre-surgery BMI (53 kg/m^2), which may explain the high proportion of unemployment before surgery, and because of this the results may not be comparable to the results presented in Paper I.

Other studies outside Norway have shown an increased employment rate after surgery (108, 109). In a large retrospective study including 1011 patients from Europe and the US, the percentage of unemployed patients pre-surgery was 36.6% (104), which corresponds well to our findings of 37.7%. They observed an significant increase in employment after surgery, and showed that patients in employment pre- and post-surgery had lower pre-surgery BMI and less cardiovascular disease and arthritis (104). In addition, entering employment post-surgery was associated with younger age (104). The generous welfare benefits in Norway may explain why the proportion of employed patients did not increase post-surgery in the present study.

It is suggested that being unemployed or receiving disability pension before surgery are risk factors for not being employed after surgery (110), and that employment before surgery increases the chance for being employed after surgery (198). Thus, work ability should be implemented in the decision-making process for bariatric surgery.

6.1.4. Psychopharmaceutical drugs

In Paper I, we described that despite great health benefits, we found no change in the use of psychopharmaceutical drugs 2 y after surgery. Antidepressants, which in the present study were the largest subgroup of psychopharmaceutical drugs, are associated with obesity (58). Tricyclic antidepressants and monoamine oxidase inhibitors are more likely to cause weight gain than selective serotonin reuptake inhibitors (59, 199). In the present study, the antidepressant drugs were mostly selective serotonin reuptake inhibitors. This may explain the lack of association between use of antidepressants pre-surgery with BMI or %TWL 2 y post-surgery. The use of antidepressant drugs did not change 2 y post-surgery and remained high compared with the general population. It is suggested that it is difficult to stop using antidepressant drugs once initiated and this may explain why there is no or only small changes in the use of antidepressants after bariatric surgery (85). Thus, use of medications should be monitored and evaluated at every follow-up visit.

The use of drugs from the subgroup consisting of hypnotics and sedatives was lower than in the general population pre-surgery, and it remained lower 2 y post-surgery even though the prevalence significantly increased. Malabsorption of antidepressants is reported after surgery (200), and a possible reduced absorption of other medications may explain the increase in hypnotics and sedatives in the present study. However, knowledge of changes in bioavailability of medications after bariatric surgery is limited, and needs further research (101, 201).

Besides use of medications, information about mental health in the current study is lacking. Still, our finding regarding use of psychopharmaceutical drugs 2 y post-surgery indicates that mental health was stable the first 2 y post-surgery. In comparison, others have described short-time decreased prevalence of depression and decreased severity of depression until 1-2 y post-surgery (85, 86, 112, 113), followed by a new increase (85, 86).

6.2. The effect of the lifestyle intervention program

Weight regain after bariatric surgery is common (118, 120, 122), but studies on managing and preventing weight regain are lacking.

In Paper II, we evaluated the efficacy of a lifestyle intervention program of moderate intensity on weight regain 2 to 4 y post-surgery, and we found no difference in weight regain between the groups. Neither did we find any other differences between the groups from 2 to 4 y post-surgery, including physical activity, dietary habits and biochemical markers. Thus, it is not surprising that we did not find any differences between the groups in the proportion of T2DM, hypertension and metabolic syndrome. In contrast to most other studies that have focused on improving weight loss after bariatric surgery the aim of the present intervention was to prevent weight regain after bariatric surgery. Previous weight loss interventions have shown contradictory results (158, 159, 202-210). The review article of Kushner and Sorensen included 7 randomized controlled trials investigating the efficacy of behavioural, dietary or exercise counselling to improve weight loss. They concluded that lifestyle interventions after bariatric surgery had no or only modest effect in enhancing further weight loss (211).

It is shown that patients who attend post-surgery follow-ups achieve better long-term weight loss (212, 213). Thus, it is likely that additional follow-ups also may prevent weight regain. A randomized controlled trial with six nutritional and lifestyle meetings every other week, starting from 7 months post-surgery, observed better weight loss compared with a group that received brief printed lifestyle guidelines (205). A pilot study in US, including 84 participants directly after surgery, described a slightly better weight loss after 4 months with dietary group counselling compared with no counselling, but this difference was not statistically significant and was not maintained beyond the intervention (208). Another lifestyle intervention study starting directly after surgery (with 3 y duration) investigated the effect of 30 individual consultations with a dietitian in addition to 30 group sessions that were also offered to the control group (207). No difference in weight loss the first 9 months post-surgery (after 21 of 30 meetings) were observed, but a greater weight loss was observed after 12, 24 and 36 months compared with usual care (207). The lack of short time difference between the two groups is in line with another study that suggests that weight loss is a direct effect of surgery: Surgery reduces energy intake by changing food preferences, increases fullness, and reduces appetite and preoccupation with food (93). This may be explained by the restricted volume of the stomach (78, 93) and changes in hormones associated with appetite and satiety (94-96). The early direct effect of surgery may with time be impaired, which can explain weight regain from nadir. A suggestion is that changes in appetite hormones described shortly after RYGB not necessarily are obtained long-term. A cross-sectional study observed a higher plasma ghrelin level 3 y after RYGB compared with a pre-surgery group, and suggested that ghrelin do not contribute to long-term weight loss maintenance (214). In contrast, another study observed a sustained reduced ghrelin level 5 y post-surgery, with a slightly higher level in patients with weight regain (215). The genetic susceptibility to obesity (10), and the reduction in energy expenditure mediated through weight loss and reduced fat-free mass (216) and through adaptive thermogenesis (217, 218), may also increase the risk of weight regain. These are all factors that may have contributed to weight regain in our study, which the intervention was not able to effectively counteract.

In many of the above-mentioned studies, the main focus was weight loss, and the interventions started shortly after surgery (205-208, 210), lasted for ≤6 months (158, 159, 203-205, 209), included only participants with suboptimal outcome (158, 159, 202, 204, 209) or included ≤40 participants (158, 159, 202-204, 207, 209). Studies describing the efficacy of behavioural or lifestyle therapy on improving weight loss after bariatric surgery are summarized in Table 6. In contrast to our findings, some of these studies show weight loss with lifestyle follow-ups. The reason for this difference may by that these studies included patients shortly after surgery, or only patients with weight regain.

Table 6: Studies reporting the efficacy of behavioural or lifestyle therapy to improve weight loss after bariatric surgery. *EWL* excess weight loss

Author	Randomized controlled trials	Methods	Sample size	Inclusion criteria	Study start post-surgery	Time of follow-up	Weight loss	P-value*
Shah et al 2011 (209)	Exercise	Behavioural therapy, dietary counselling and weekly supervised exercise.	21	BMI ≥35 kg/m^2	$^1/_4$ y -8.5 y	12 weeks	−4.2 kg	0.46
	Control	Behavioural therapy and dietary counselling.	12		$^1/_4$ y -3.5 y		−4.7 kg	
Lier et al 2012 (210)	Cognitive therapy	6 weekly group sessions pre-surgery + 3 post-surgery group sessions.	49	All patients	0 y	1y	−46.1 kg	0.54
	Control	1 group meeting pre- and 1 group meeting post-surgery.	48				−42.9 kg	
Papalazarou et al 2010 (207)	Lifestyle interventions	30 lifestyle sessions + 30 x 40 min individualized sessions.	30	Females	0 y	3 y	−45.3 kg	**<0.05**
	Control	30 lifestyle sessions.					−30.8 kg	
Nijamkin et al 2012 (205)	Lifestyle intervention	6 session every second week for 12 weeks.	72	Hispanic-American	6 months	6 months	−17 kg	**<0.001**
	Control	Brief, printed lifestyle guidance.	72				−10 kg	
Kalarchian et al 2012 (202)	Behavioural intervention	12 weekly group meetings followed by 5 bi-weekly telephone session for 6 months.	18	EWL <50%	>3 y	1 y	EWL: 5.8%	0.32
	Control		18				EWL: 0.9%	
Ogden et al 2015 (206)	Behavioural intervention	3 x 50 min individual consultation (1 pre- and 2 post-surgery).	82	All patients	0 y	1 y	−16.6 kg/m^2	0.7
	Control	Brief, printed diet sheet information	80				−16.4 kg/m^2	
Sarwer et al 2012 (208)	Dietary counselling	15 minute dietary conselling every second week for 4 months.	41	All patients	0 y	2 y	−33.3%	>0.05
	Control	Monthly support group	43				−36.5%	
Author	**Interventions without control group**	**Methods**	**Sample size**	**Inclusion criteria**	**Study start post-surgery**	**Time of follow-up**	**Weight loss**	**P-value****
Faria et al 2010 (203)	Nutritional management	Dietary recommendations + physical activity. Follow-up every 15 days for ≥ 3 months.	30	Weight regain	>2 y	3 months	−4.3 kg	**<0.001**
Bradley et al 2017 (158)	Behavioural therapy	Remotely delivered behavioural therapy + telephone calls every 2 week for 10 weeks.	11	Weight regain	>1.5 y	3 months	−5.7%	**<0.05**
Bradley et al 2016 (159)	Behavioural therapy	75 min weekly group sessions	11	Weight regain	Mean 3.6 y	10 weeks	−3.3 kg	**0.01**
Himes et al 2015 (204)	Behavioural therapy	60 min weekly group meetings	28	Weight regain	Mean 4 y	6 weeks	−1.6 kg	**≤0.01**

*Between group changes **Within group changes

Participation in the study was voluntary, and the patients contacted study personnel to announce interest in the study. Hence, we assume that participants in both groups were motivated for lifestyle changes. The intervention was a weight maintenance study and we did not expect great changes during the intervention. However, we did not know the participants expectations', and some may have had unrealistic expectations of further weight loss and motivation might have deteriorated as this did not occur. A non-surgical weight loss intervention observed an increased likelihood of early drop-outs among participants with the lowest weight loss, suggesting that early success may motivate further participation (219). The fact that both groups may have been similarly motivated, may explain why we did not find any differences between the groups. In comparison, another study at our hospital found a weight regain of 8 kg from 2-5 y post-surgery (129). This supports the suggestion that also the CTG was motivated to prevent weight regain. Yet, a Scandinavian registry described a weight regain of approximately 5 kg from 2-5 y post-surgery (79), which is more in line with the 4 kg weight regain observed in the present study.

As described in the discussion of methods; a long-term more or less intensive intervention seems necessary to maintain weight loss. However, even though an 8 y intensive lifestyle intervention resulted in weight loss in adults with T2DM, it did not reduce cardiovascular events (64). A more intensive intervention may have resulted in better long-term weight outcomes in our study, but the frequency of the group meetings was based on hospital resources and what we thought was feasible for the patients.

Another possible explanation of no difference in weight regain between the groups may be the low attendance rate at the group meetings. Travel distance to the hospital may partly explain the low attendance rate at some of the meetings. However, no difference in weight regain between participants with high attendance compared with low attendance was observed. Hence, participation at group meetings did not seem to have effect on preventing weight regain.

6.3. Lifestyle factors associated with weight regain

Factors associated with weight regain 2 to 4 y post-surgery in the overall study population were rapid weight increase from nadir, sedentary lifestyle, younger age and higher concentration of plasma tCys at 2 y post-surgery, while most measurements of diet were not associated with weight regain.

6.3.1. Diet and physical activity

Energy intake is shown to decrease drastically directly after surgery, followed by a gradual increase (220). Lowest energy intake are seen 6 weeks (221) and 6 months (220) after surgery, and is shown to be lower at all time-points post-surgery compared with pre-surgery energy intake (220). The energy intake 6 months and 10 y post-surgery are reported to be 35-45% and 15-25% lower than before surgery, respectively (220). The estimated energy intake in the present study was ~1800 kcal 2 y post-surgery. This is in line with an observational study (222), but lower than in another observational study, which showed an energy intake of ~2400 kcal 2 y post-surgery even though they had a higher percentage of female participants (221). The reported energy intake in the present intervention is also lower than in the general adult population (223). It is reported that chronic dieting is common among obese and super obese (173, 224), which may explain the low energy intake observed in the present study as well as other studies. Food intolerance (88) and avoidance of certain foods (e.g., carbonated beverages, sweetened beverages, sweet desserts, dairy products, meat, bread, vegetables, grains, fats) is common after surgery (221, 225, 226).

One study found an association between increased energy intake from snacks, sweets and fatty foods with weight regain after bariatric surgery (122). This is in contrast to the under-reporting of energy, sweets and fatty food that often are described among obese subjects (179, 180).

One study showed that intake of energy from carbohydrate, fibre and proteins increased during the first 6 months post-surgery, while energy intake from fat decreased (220). However, these changes were partly or entirely lost by the 4 y and 6 y follow-up visit (220). In the current study, intake of energy remained unchanged, while intake of carbohydrate and sugar decreased, and fat intake increased from 2 to

4 y post-surgery. Unfortunately, we do not have pre-surgery dietary data in the present study.

In Paper II, we showed that artificially sweetened beverages at 2 y were inversely associated with weight regain. Similar observations is shown after conventional weight loss where participants who replaced artificially sweetened beverages with water lost less weight and regained more weight compared with participants who continued to consume artificially sweetened beverages (227). A possible explanation is that subjects who changed their drinking habits experienced a larger behavioural challenge than those who continued to drink artificially sweetened beverages (227). The association between artificially sweetened beverages and weight regain in the present study, was weak, and we cannot exclude that this is a chance finding.

Other possible dietary factors on weight regain are intake of proteins. Studies in this field have shown conflicting results. One study described an association between animal protein and obesity (228), while another study described a favourable effect of a high protein diet on weight loss maintenance (229). The possible beneficial effect of dietary protein is suggested to be mediated through increased satiety and thermogenesis (230). In the present study we did not find any association between dietary intake and weight regain besides intake of artificially sweetened beverages.

Self-monitoring of body weight as well as keeping food records are known to facilitate weight maintenance (123). This may be a simple and cheap tool to maintain weight loss and prevent weight regain. In the present study, food records were only used to evaluate energy intake and energy distribution at specific time points during the study.

In Paper II, the estimated energy expenditure was higher than the reported energy intake. The energy intake at 2 y post-surgery was not associated with weight regain 2 to 4 y, either unadjusted ($P = 0.19$) or adjusted for age, sex, and energy expenditure ($P = 0.23$). This is in line with another study observing no association between intake of energy and macronutrients and weight regain (222). This may be explained by under-reporting of energy and that the dietary assessment are not sufficiently reliable in overweight and obese subjects (173).

In Paper II, we reported that time spent on reading, TV viewing and computer use at 2 y were positively associated with weight regain 2 to 4 y post-surgery. The association between sedentary behaviour and weight regain in the current study is in line with others, which describe a higher BMI, less weight loss or more weight regain with sedentary behaviour (122, 231) or ≤150 min/week with moderate or high physical activity (232).

Every group meeting consisted of 30 min with supervised physical activity. Even though we did not systematically record participation rate at physical activity sessions, our impression is that a high proportion chose not to participate after the group meetings. This indicates that this population may have more barriers to engage in physical activity in general, and supports the finding that physical barriers (including asthma, body weight and injuries) and psychological barriers (including more depression and less motivation) are associated with obesity (233). The low participation in physical activity sessions after the group meetings is in contrast to the high proportion of participants (86%) who reported being in moderate or high physical activity ≥150 min/week 2 y post-surgery, which strengthens the suspicion that the participants in the current study over-reported their energy expenditure. Self-reported time used on moderate or high physical activity in the present study was 520 min/week at both 2 y and 4 y post-surgery, which is higher than the recommended level of at least 150 min/week (132, 134). However, reported time spent on moderate or high physical activity in the present study is in line with results from another Norwegian study using SenseWear Armband to register physical activity level, which indicate that the self-reported activity levels may be correct (222).

6.3.2. Weight regain from nadir, age and smoking

We found an association between weight increase from nadir and weight regain 2 to 4 y after surgery. This is in line with a weight loss intervention study including 36 patients with suboptimal weight loss, which suggested that patients with the least weight regain before the intervention started, achieved the best long-term body weight outcome (202). To implement strategies for weight maintenance at time of nadir (usually occurring 1 to 2 y post-surgery (79, 120)), including self-monitoring of body weight and food recordings, seems ideal. Thus, it may be beneficial to discuss these strategies with the patient at follow-up 1 and 2 y post-surgery. A previous suggestion is that a beneficial time to start dietary interventions in bariatric patients is 6 months post-surgery when maximal changes in diet are achieved, and when commitment to dietary changes is abandoned (which varies between subjects, but is seen from 6 months to 4 y post-surgery) (220).

Younger age is associated with better weight loss (193, 234), but also more weight regain from nadir (235). If younger age is beneficial regarding weight loss, bariatric surgery should not be delayed, despite the suggestion that younger age increases the risk of weight regain from nadir. Our observation that younger patients regained more weight should rather indicate that these patients might benefit from a closer follow-up from nadir to prevent weight regain.

It is described that smoking post-surgery is associated with greater weight loss (236), and that smoking cessation increases the risk for weight gain (237, 238). This is in line with findings in Paper II, where smoking is observed to be associated with increased weight loss and less weight regain. Nevertheless, patients should be encouraged to smoking cessation, as the health benefits from smoking cessation outweighs the increased risk of weight gain (237, 238).

6.4. The relationship between plasma amino acids and weight regain.

6.4.1. Plasma total cysteine

In Paper III, we showed a positive association between plasma tCys and future weight regain. It is suggested that plasma tCys might be a determinant of adiposity (28, 38), and that a decrease in tCys may be beneficial in enhancing weight loss. We do not know how to alter plasma tCys, and this needs to be investigated further. However, foods rich in cysteine and its precursor, methionine, could possibly contribute to increased plasma tCys.

Both methionine and cysteine are found in higher amounts in animal protein than in plant protein (239). A methionine restricted diet in rodents is shown to reduce body weight and fat mass (240). Cysteine supplementation to the methionine-restricted rats restored fat mass and caused weight regain (240). The mechanisms by which plasma tCys may increase fat mass is presently unknown, but one possibility may be through an influence on stearoyl-CoA desaturase-1, a fatty acid desaturase enzyme considered to be involved in development of obesity (240-242).

A diet low in methionine and cysteine, such as in a vegan diet may thus have beneficial effect on body weight. A total of 392 men from the EPIC oxford study (n = 65000), observed that vegans had a lower BMI, lower dietary intake of methionine and cystine and a lower plasma methionine concentration than meat-eaters (243). Plasma tCys was not measured in that study. A previous study in healthy humans (n = 36) showed that a plant and fish based diet lowered plasma BCAA and the AAAs phenylalanine and tryptophan, while plasma tCys and methionine remained unchanged (19). One explanation for the lack of reductions in plasma tCys and methionine may be a possible compensatory mechanism to maintain sulphur AAs, or that the methionine and cysteine intake was not sufficiently decreased on a plant-based diet that included fish (19).

Plasma tCys is associated with age (25, 27, 33, 244), serum creatinine (33, 244), diastolic blood pressure (27, 33), total cholesterol and coffee consumption (27, 244). However, little is known about the factors influencing plasma tCys. It seems that plasma tCys is tightly regulated under normal metabolic conditions, possibly to maintain plasma concentrations of tCys and tissue sulphur availability (245). Cysteine dioxygenase is an enzyme responsible for maintaining plasma tCys concentration by regulating the conversion of tCys to taurine. Dietary methionine and cysteine up-regulates cysteine dioxygenase, whereas low intake or concentrations result in degradation of this enzyme (245).

It is suggested that plasma tCys has a causal role in regulation of adiposity (28, 38). Knockout of the enzymes linked to the cysteine synthesis are characterized by decreased body weight (32). Reports of inborn errors of cysteine metabolism, with over-expression of the cysteine-synthesizing enzyme, cystathionine ß-synthase (28, 246) is suggested to be associated with obesity, whereas a defect in this enzyme result in decreased cysteine synthesis and very low body weight (28, 247). Taken together with our findings, plasma tCys may be used to selectively target patients in risk of future weight regain. Further, drugs that decrease cysteine synthesis, turnover or uptake have reported weight loss as a side effect (28). In mice on a high-fat diet, two drugs (registered for humans, but for different purposes) that influence cysteine metabolism significantly reduced plasma tCys and reduced weight gain (Elshorbagy, unpublished). The effects of these drugs on human energy metabolism have not been explored. If such drugs have the same effects in humans, anticysteine drugs may be useful for mediating weight loss in obese subjects with increased plasma concentration of tCys.

7. Key findings and conclusions

Health benefits 2 y after RYGB

- Despite great health benefits and weight loss 2 y post-surgery, employment status and use of psychopharmaceutical drugs did not change from pre-surgery to 2 y post-surgery (Paper I).
- The pre-surgery BMI should not exceed 43 kg/m^2 to achieve a BMI <30 kg/m^2 2 y post-surgery (Paper I).

The effect of the lifestyle intervention program

- A lifestyle intervention program 2 to 4 y post-surgery with 16 group meetings had no beneficial effect on weight regain, changes in metabolic disturbances, energy intake or physical activity compared with usual care (Paper II).

Lifestyle factors associated with weight regain

- Factors associated with weight regain 2 to 4 y post-surgery were rapid weight increase from nadir, sedentary lifestyle and higher concentration of plasma tCys (Paper II).

The relationship between plasma amino acids and weight regain

- Plasma BCAAs, AAAs and tCys at 2 y post-surgery were associated with BMI at 2 y post-surgery (Paper III).
- At 2 y post-surgery plasma tCys but not plasma BCAAs and AAAs was associated with weight regain from 2 to 4 y post-surgery (Paper III).

Based on the result of this study, it may be more beneficial to identify patients at risk of weight regain, instead of offering a lifestyle intervention program as standard treatment after surgery.

8. Future perspective

In the present study causes of obesity is not investigated, but previous studies have shown that psychological aspects are important. It is described that a history of abuse increases the risk of binge eating and psychiatric problems (248). The relationship of childhood abuse and outcomes after bariatric surgery are unknown, but one study suggests that childhood abuse has no negative impact on post-surgical outcomes (249). Psychological factors effect on weight regain should be further investigated. Other factors that should be investigated are the roles of gut hormones, gut microbiota and bile acids in obesity and weight management. Alteration in the gut microbiota may affect hormone status, and changes in satiety and food intake (250). RYGB is suggested to induce bile acids and changes in gut hormones, which contributes to weight loss and remission of T2DM (251).

An on-going randomized controlled trial in Portugal, with 180 participants, will evaluate the efficacy of an internet-based program on weight regain, including a self-help manual, weekly remotely delivered feedback and direct chat contact with a psychologist (252). Recruitment is planned to be completed by the end of 2019, and hopefully this study will reveal factors that can prevent weight regain.

Results from this study show that a group-based lifestyle intervention program as standard treatment after RYGB is not effective in preventing long-term weight regain. A better strategy may be to selectively target patients at risk of future weight regain. One such strategy could be implementation of plasma tCys as a prognostic marker to target the patient at risk of weight regain. Our study indicates that younger patients, smoking cessation, inactivity and rapid weight increase from nadir are factors that predispose for weight regain. Randomized controlled trials specifically targeting these groups are needed.

9. References

1. Beechy L, Galpern J, Petrone A, Das SK. Assessment tools in obesity - psychological measures, diet, activity, and body composition. Physiol Behav 2012;107:154-71.
2. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser, 2000:i-xii, 1-253.
3. Hebebrand J, Holm JC, Woodward E, Baker JL, Blaak E, Durrer Schutz D, Farpour-Lambert NJ, Fruhbeck G, Halford JGC, Lissner L, et al. A Proposal of the European Association for the Study of Obesity to Improve the ICD-11 Diagnostic Criteria for Obesity Based on the Three Dimensions Etiology, Degree of Adiposity and Health Risk. Obes Facts 2017;10:284-307.
4. World Health Organization. Waist circumference and waist–hip ratio. Report of a WHO expert consultation, Geneva, 8-11 December 2008. Internet: http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf?ua=1 (accessed 8th February 2018).
5. World Health Organization. Obesity and overweight - Fact sheet. Internet: http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 23rd November 2017).
6. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA 2016;315:2284-91.
7. Midthjell K, Lee CM, Langhammer A, Krokstad S, Holmen TL, Hveem K, Colagiuri S, Holmen J. Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study, Norway. Clin Obes 2013;3:12-20.
8. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804-14.
9. Manfredini R, De Giorgi A, Tiseo R, Boari B, Cappadona R, Salmi R, Gallerani M, Signani F, Manfredini F, Mikhailidis DP, et al. Marital Status, Cardiovascular Diseases, and Cardiovascular Risk Factors: A Review of the Evidence. J Womens Health (Larchmt) 2017;26:624-32.
10. Llewellyn C, Wardle J. Behavioral susceptibility to obesity: Gene-environment interplay in the development of weight. Physiol Behav 2015;152:494-501.
11. Scarborough P, Burg MR, Foster C, Swinburn B, Sacks G, Rayner M, Webster P, Allender S. Increased energy intake entirely accounts for increase in body weight in women but not in men in the UK between 1986 and 2000. Br J Nutr 2011;105:1399-404.
12. Williamson DF, Thompson TJ, Anda RF, Dietz WH, Felitti V. Body weight and obesity in adults and self-reported abuse in childhood. Int J Obes Relat Metab Disord 2002;26:1075-82.

13. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14:245-58.
14. Richardson AS, Dietz WH, Gordon-Larsen P. The association between childhood sexual and physical abuse with incident adult severe obesity across 13 years of the National Longitudinal Study of Adolescent Health. Pediatr Obes 2014;9:351-61.
15. Hemmingsson E, Johansson K, Reynisdottir S. Effects of childhood abuse on adult obesity: a systematic review and meta-analysis. Obes Rev 2014;15:882-93.
16. Sartorius B, Veerman LJ, Manyema M, Chola L, Hofman K. Determinants of Obesity and Associated Population Attributability, South Africa: Empirical Evidence from a National Panel Survey, 2008-2012. PLoS One 2015;10:e0130218.
17. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. Am J Med 2014;127:717-27 e12.
18. Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnest CP, Rodarte RQ, Martin CK, Blair SN, Bouchard C. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS One 2011;6:e19657.
19. Elshorbagy A, Jerneren F, Basta M, Basta C, Turner C, Khaled M, Refsum H. Amino acid changes during transition to a vegan diet supplemented with fish in healthy humans. Eur J Nutr 2017;56:1953-62.
20. Zheng Y, Ceglarek U, Huang T, Li L, Rood J, Ryan DH, Bray GA, Sacks FM, Schwarzfuchs D, Thiery J, et al. Weight-loss diets and 2-y changes in circulating amino acids in 2 randomized intervention trials. Am J Clin Nutr 2016;103:505-11.
21. Yamakado M, Nagao K, Imaizumi A, Tani M, Toda A, Tanaka T, Jinzu H, Miyano H, Yamamoto H, Daimon T, et al. Plasma Free Amino Acid Profiles Predict Four-Year Risk of Developing Diabetes, Metabolic Syndrome, Dyslipidemia, and Hypertension in Japanese Population. Sci Rep 2015;5:11918.
22. Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 2009;9:311-26.
23. Lee CC, Watkins SM, Lorenzo C, Wagenknecht LE, Il'yasova D, Chen YI, Haffner SM, Hanley AJ. Branched-Chain Amino Acids and Insulin Metabolism: The Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care 2016;39:582-8.
24. Bogl LH, Kaye SM, Ramo JT, Kangas AJ, Soininen P, Hakkarainen A, Lundbom J, Lundbom N, Ortega-Alonso A, Rissanen A, et al. Abdominal obesity and circulating metabolites: A twin study approach. Metabolism 2016;65:111-21.

25. Elshorbagy AK, Nurk E, Gjesdal CG, Tell GS, Ueland PM, Nygard O, Tverdal A, Vollset SE, Refsum H. Homocysteine, cysteine, and body composition in the Hordaland Homocysteine Study: does cysteine link amino acid and lipid metabolism? Am J Clin Nutr 2008;88:738-46.
26. Elshorbagy AK, Refsum H, Smith AD, Graham IM. The association of plasma cysteine and gamma-glutamyltransferase with BMI and obesity. Obesity (Silver Spring) 2009;17:1435-40.
27. El-Khairy L, Ueland PM, Nygard O, Refsum H, Vollset SE. Lifestyle and cardiovascular disease risk factors as determinants of total cysteine in plasma: the Hordaland Homocysteine Study. Am J Clin Nutr 1999;70:1016-24.
28. Elshorbagy AK, Smith AD, Kozich V, Refsum H. Cysteine and obesity. Obesity (Silver Spring) 2012;20:473-81.
29. Adams SH. Emerging perspectives on essential amino acid metabolism in obesity and the insulin-resistant state. Adv Nutr 2011;2:445-56.
30. Hoppe C, Molgaard C, Vaag A, Barkholt V, Michaelsen KF. High intakes of milk, but not meat, increase s-insulin and insulin resistance in 8-year-old boys. Eur J Clin Nutr 2005;59:393-8.
31. Brosnan JT, Brosnan ME. The sulfur-containing amino acids: an overview. J Nutr 2006;136:1636S-40S.
32. Elshorbagy AK. Body composition in gene knockouts of sulfur amino acid-metabolizing enzymes. Mamm Genome 2014;25:455-63.
33. Brattstrom L, Lindgren A, Israelsson B, Andersson A, Hultberg B. Homocysteine and cysteine: determinants of plasma levels in middle-aged and elderly subjects. J Intern Med 1994;236:633-41.
34. Laferrere B, Reilly D, Arias S, Swerdlow N, Gorroochurn P, Bawa B, Bose M, Teixeira J, Stevens RD, Wenner BR, et al. Differential metabolic impact of gastric bypass surgery versus dietary intervention in obese diabetic subjects despite identical weight loss. Sci Transl Med 2011;3:80.
35. Magkos F, Bradley D, Schweitzer GG, Finck BN, Eagon JC, Ilkayeva O, Newgard CB, Klein S. Effect of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding on branched-chain amino acid metabolism. Diabetes 2013;62:2757-61.
36. Tan HC, Khoo CM, Tan MZ, Kovalik JP, Ng AC, Eng AK, Lai OF, Ching JH, Tham KW, Pasupathy S. The Effects of Sleeve Gastrectomy and Gastric Bypass on Branched-Chain Amino Acid Metabolism 1 Year After Bariatric Surgery. Obes Surg 2016;26:1830-5.
37. Elshorbagy AK, Valdivia-Garcia M, Refsum H, Butte N. The association of cysteine with obesity, inflammatory cytokines and insulin resistance in Hispanic children and adolescents. PLoS One 2012;7:e44166.
38. Aasheim ET, Elshorbagy AK, Diep LM, Sovik TT, Mala T, Valdivia-Garcia M, Olbers T, Bohmer T, Birkeland KI, Refsum H. Effect of bariatric surgery on sulphur amino acids and glutamate. Br J Nutr 2011;106:432-40.
39. Elshorbagy AK, Kozich V, Smith AD, Refsum H. Cysteine and obesity: consistency of the evidence across epidemiologic, animal and cellular studies. Curr Opin Clin Nutr Metab Care 2012;15:49-57.

40. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working G. Body Fatness and Cancer--Viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-8.
41. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Martin-Hirsch P, Tsilidis KK. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017;356:j477.
42. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211-9.
43. Hjerkind KV, Stenehjem JS, Nilsen TI. Adiposity, physical activity and risk of diabetes mellitus: prospective data from the population-based HUNT study, Norway. BMJ Open 2017;7:e013142.
44. Poirier P, Cornier MA, Mazzone T, Stiles S, Cummings S, Klein S, McCullough PA, Ren Fielding C, Franklin BA, American Heart Association Obesity Committee of the Council on Nutrition PA, et al. Bariatric surgery and cardiovascular risk factors: a scientific statement from the American Heart Association. Circulation 2011;123:1683-701.
45. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.
46. Peltonen M, Lindroos AK, Torgerson JS. Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. Pain 2003;104:549-57.
47. Sorop O, Olver TD, van de Wouw J, Heinonen I, van Duin RW, Duncker DJ, Merkus D. The microcirculation: a key player in obesity-associated cardiovascular disease. Cardiovasc Res 2017;113:1035-45.
48. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, Zhao Y, Wang C. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291-7.
49. Jiang L, Rong J, Wang Y, Hu F, Bao C, Li X, Zhao Y. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2011;78:150-5.
50. Health at a Glance: Europe 2016. State of Health in the EU Cycle. Internet: http://www.oecd.org/health/health-at-a-glance-europe-23056088.htm (accessed: 28th November 2017).
51. Puhl RM, Heuer CA. The stigma of obesity: a review and update. Obesity (Silver Spring) 2009;17:941-64.
52. Puhl RM, King KM. Weight discrimination and bullying. Best Pract Res Clin Endocrinol Metab 2013;27:117-27.
53. Ma J, Xiao L. Obesity and depression in US women: results from the 2005-2006 National Health and Nutritional Examination Survey. Obesity (Silver Spring) 2010;18:347-53.
54. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2003;158:1139-47.
55. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Are the obese at greater risk for depression? Am J Epidemiol 2000;152:163-70.

56. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220-9.
57. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. Mol Psychiatry 2018.
58. Pratt LA, Brody DJ. Depression and obesity in the U.S. adult household population, 2005-2010. NCHS Data Brief 2014:1-8.
59. Aronne LJ, Segal KR. Weight gain in the treatment of mood disorders. J Clin Psychiatry 2003;64 Suppl 8:22-9.
60. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. Int J Obes (Lond) 2009;33:257-66.
61. Withrow D, Alter DA. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. Obes Rev 2011;12:131-41.
62. Ryan DH, Kahan S. Guideline Recommendations for Obesity Management. Med Clin North Am 2018;102:49-63.
63. The Look Ahead Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring) 2014;22:5-13.
64. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, et al. Look Ahead Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
65. Bond DS, Phelan S, Leahey TM, Hill JO, Wing RR. Weight-loss maintenance in successful weight losers: surgical vs non-surgical methods. Int J Obes (Lond) 2009;33:173-80.
66. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. Am J Prev Med 2014;46:17-23.
67. Saunders KH, Umashanker D, Igel LI, Kumar RB, Aronne LJ. Obesity Pharmacotherapy. Med Clin North Am 2018;102:135-48.
68. The Norwegian Pharmaceutical Product Compendium. Internet: https://www.felleskatalogen.no/medisin (accessed 2nd April 2018).
69. Ovrebo B, Strommen M, Kulseng B, Martins C. Bariatric surgery versus lifestyle interventions for severe obesity: 5-year changes in body weight, risk factors and comorbidities. Clin Obes 2017;7:183-90.
70. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273:219-34.
71. Adams TD, Davidson LE, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC, Strong MB, Vinik R, Wanner NA, Hopkins PN, et al. Health benefits of gastric bypass surgery after 6 years. JAMA 2012;308:1122-31.
72. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ 2013;347:f5934.

73. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med 2017;376:641-51.
74. le Roux CW, Heneghan HM. Bariatric Surgery for Obesity. Med Clin North Am 2018;102:165-82.
75. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, Heinberg LJ, Kushner R, Adams TD, Shikora S, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring) 2013;21 Suppl 1:S1-27.
76. Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, Yashkov Y, Fruhbeck G, International Federation for Surgery of O, Metabolic Disorders-European C, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 2014;24:42-55.
77. Angrisani L, Santonicola A, Iovino P, Vitiello A, Zundel N, Buchwald H, Scopinaro N. Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. Obes Surg 2017;27:2279-89.
78. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol 2017;14:160-9.
79. Scandinavian Obesity Surgery Registry. Annual Report SOReg 2016 Part 2: Follow-up weight changes, change in comorbidity, long-term complications and quality indicators on the clinical level. . Internett: http://www.ucr.uu.se/soreg/component/edocman/arsrapport-2016-del-2. Published August 2017 (accessed 10th November 2017).
80. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292:1724-37.
81. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 2009;122:248-56.
82. Purnell JQ, Selzer F, Wahed AS, Pender J, Pories W, Pomp A, Dakin G, Mitchell J, Garcia L, Staten MA, et al. Type 2 Diabetes Remission Rates After Laparoscopic Gastric Bypass and Gastric Banding: Results of the Longitudinal Assessment of Bariatric Surgery Study. Diabetes Care 2016;39:1101-7.
83. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
84. Schauer DP, Arterburn DE, Livingston EH, Coleman KJ, Sidney S, Fisher D, O'Connor P, Fischer D, Eckman MH. Impact of bariatric surgery on life expectancy in severely obese patients with diabetes: a decision analysis. Ann Surg 2015;261:914-9.

85. Booth H, Khan O, Prevost AT, Reddy M, Charlton J, Gulliford MC, Kings Bariatric Surgery Study G. Impact of bariatric surgery on clinical depression. Interrupted time series study with matched controls. J Affect Disord 2015;174:644-9.
86. Mitchell JE, King WC, Chen JY, Devlin MJ, Flum D, Garcia L, Inabet W, Pender JR, Kalarchian MA, Khandelwal S, et al. Course of depressive symptoms and treatment in the longitudinal assessment of bariatric surgery (LABS-2) study. Obesity (Silver Spring) 2014;22:1799-806.
87. Jakobsen GS, Smastuen MC, Sandbu R, Nordstrand N, Hofso D, Lindberg M, Hertel JK, Hjelmesaeth J. Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities. JAMA 2018;319:291-301.
88. Boerlage TC, van de Laar AW, Westerlaken S, Gerdes VE, Brandjes DP. Gastrointestinal symptoms and food intolerance 2 years after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Br J Surg 2017;104:393-400.
89. Banerjee A, Ding Y, Mikami DJ, Needleman BJ. The role of dumping syndrome in weight loss after gastric bypass surgery. Surg Endosc 2013;27:1573-8.
90. Laurenius A, Olbers T, Naslund I, Karlsson J. Dumping syndrome following gastric bypass: validation of the dumping symptom rating scale. Obes Surg 2013;23:740-55.
91. Mahawar KK, Sharples AJ. Contribution of Malabsorption to Weight Loss After Roux-en-Y Gastric Bypass: a Systematic Review. Obes Surg 2017;27:2194-206.
92. Odstrcil EA, Martinez JG, Santa Ana CA, Xue B, Schneider RE, Steffer KJ, Porter JL, Asplin J, Kuhn JA, Fordtran JS. The contribution of malabsorption to the reduction in net energy absorption after long-limb Roux-en-Y gastric bypass. Am J Clin Nutr 2010;92:704-13.
93. Ogden J, Clementi C, Aylwin S, Patel A. Exploring the impact of obesity surgery on patients' health status: a quantitative and qualitative study. Obes Surg 2005;15:266-72.
94. le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, Lonroth H, Fandriks L, Ghatei MA, Bloom SR, et al. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. Ann Surg 2007;246:780-5.
95. Schmidt JB, Pedersen SD, Gregersen NT, Vestergaard L, Nielsen MS, Ritz C, Madsbad S, Worm D, Hansen DL, Clausen TR, et al. Effects of RYGB on energy expenditure, appetite and glycaemic control: a randomized controlled clinical trial. Int J Obes (Lond) 2016;40:281-90.
96. Mulla CM, Middelbeek RJW, Patti ME. Mechanisms of weight loss and improved metabolism following bariatric surgery. Ann N Y Acad Sci 2017.
97. Risstad H, Kristinsson JA, Fagerland MW, le Roux CW, Birkeland KI, Gulseth HL, Thorsby PM, Vincent RP, Engstrom M, Olbers T, et al. Bile acid profiles over 5 years after gastric bypass and duodenal switch: results from a randomized clinical trial. Surg Obes Relat Dis 2017;13:1544-53.
98. Dixon JB, McPhail T, O'Brien PE. Minimal reporting requirements for weight loss: current methods not ideal. Obes Surg 2005;15:1034-9.

99. Hatoum IJ, Kaplan LM. Advantages of percent weight loss as a method of reporting weight loss after Roux-en-Y gastric bypass. Obesity (Silver Spring) 2013;21:1519-25.
100. Handzlik-Orlik G, Holecki M, Orlik B, Wylezol M, Dulawa J. Nutrition management of the post-bariatric surgery patient. Nutr Clin Pract 2015;30:383-92.
101. Busetto L, Dicker D, Azran C, Batterham RL, Farpour-Lambert N, Fried M, Hjelmesaeth J, Kinzl J, Leitner DR, Makaronidis JM, et al. Practical Recommendations of the Obesity Management Task Force of the European Association for the Study of Obesity for the Post-Bariatric Surgery Medical Management. Obes Facts 2017;10:597-632.
102. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. Surg Obes Relat Dis 2017;13:727-41.
103. Moize VL, Pi-Sunyer X, Mochari H, Vidal J. Nutritional pyramid for post-gastric bypass patients. Obes Surg 2010;20:1133-41.
104. Courtney MJ, Mahawar K, Burnell P, Jennings N, Balupuri S, Schroeder N, Small P, Carr W. Occupational Outcomes of Obesity Surgery-Do the Employed Return to Work, and Do the Unemployed Find Work? Obes Surg 2017.
105. Neovius K, Neovius M, Kark M, Rasmussen F. Association between obesity status and sick-leave in Swedish men: nationwide cohort study. Eur J Public Health 2012;22:112-6.
106. Harvey SB, Glozier N, Carlton O, Mykletun A, Henderson M, Hotopf M, Holland-Elliott K. Obesity and sickness absence: results from the CHAP study. Occup Med (Lond) 2010;60:362-8.
107. Neovius K, Johansson K, Rossner S, Neovius M. Disability pension, employment and obesity status: a systematic review. Obes Rev 2008;9:572-81.
108. Hawke A, O'Brien P, Watts JM, Hall J, Dunstan RE, Walsh JF, Slavotinek AH, Elmslie RG. Psychosocial and physical activity changes after gastric restrictive procedures for morbid obesity. Aust N Z J Surg 1990;60:755-8.
109. Hawkins SC, Osborne A, Finlay IG, Alagaratnam S, Edmond JR, Welbourn R. Paid work increases and state benefit claims decrease after bariatric surgery. Obes Surg 2007;17:434-7.
110. Andersen JR, Hernaes UJ, Hufthammer KO, Vage V. Employment status and sick-leave following obesity surgery: a five-year prospective cohort study. PeerJ 2015;3:e1285.
111. Sharples AJ, Cheruvu CV. Systematic Review and Meta-Analysis of Occupational Outcomes after Bariatric Surgery. Obes Surg 2017;27:774-81.
112. Dawes AJ, Maggard-Gibbons M, Maher AR, Booth MJ, Miake-Lye I, Beroes JM, Shekelle PG. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. JAMA 2016;315:150-63.
113. de Zwaan M, Enderle J, Wagner S, Muhlhans B, Ditzen B, Gefeller O, Mitchell JE, Muller A. Anxiety and depression in bariatric surgery patients: a prospective, follow-up study using structured clinical interviews. J Affect Disord 2011;133:61-8.

114. Ghoneim MM, O'Hara MW. Depression and postoperative complications: an overview. BMC Surg 2016;16:5.
115. Baillot A, Brais-Dussault E, Bastin A, Cyr C, Brunet J, Aime A, Romain AJ, Langlois MF, Bouchard S, Tchernof A, et al. What Is Known About the Correlates and Impact of Excess Skin After Bariatric Surgery: a Scoping Review. Obes Surg 2017;27:2488-98.
116. Homer CV, Tod AM, Thompson AR, Allmark P, Goyder E. Expectations and patients' experiences of obesity prior to bariatric surgery: a qualitative study. BMJ Open 2016;6:e009389.
117. Fischer L, Nickel F, Sander J, Ernst A, Bruckner T, Herbig B, Buchler MW, Muller-Stich BP, Sandbu R. Patient expectations of bariatric surgery are gender specific--a prospective, multicenter cohort study. Surg Obes Relat Dis 2014;10:516-23.
118. Sundbom M, Hedberg J, Marsk R, Boman L, Bylund A, Hedenbro J, Laurenius A, Lundegardh G, Moller P, Olbers T, et al. Substantial Decrease in Comorbidity 5 Years After Gastric Bypass: A Population-based Study From the Scandinavian Obesity Surgery Registry. Ann Surg 2017;265:1166-71.
119. Rutledge T, Braden AL, Woods G, Herbst KL, Groesz LM, Savu M. Five-year changes in psychiatric treatment status and weight-related comorbidities following bariatric surgery in a veteran population. Obes Surg 2012;22:1734-41.
120. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. Ann Surg 2006;244:734-40.
121. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, Ahlin S, Anveden A, Bengtsson C, Bergmark G, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307:56-65.
122. Freire RH, Borges MC, Alvarez-Leite JI, Toulson Davisson Correia MI. Food quality, physical activity, and nutritional follow-up as determinant of weight regain after Roux-en-Y gastric bypass. Nutrition 2012;28:53-8.
123. Odom J, Zalesin KC, Washington TL, Miller WW, Hakmeh B, Zaremba DL, Altattan M, Balasubramaniam M, Gibbs DS, Krause KR, et al. Behavioral predictors of weight regain after bariatric surgery. Obes Surg 2010;20:349-56.
124. Mitchell JE, Christian NJ, Flum DR, Pomp A, Pories WJ, Wolfe BM, Courcoulas AP, Belle SH. Postoperative Behavioral Variables and Weight Change 3 Years After Bariatric Surgery. JAMA Surg 2016;151:752-7.
125. Stenberg E, Szabo E, Agren G, Naslund E, Boman L, Bylund A, Hedenbro J, Laurenius A, Lundegardh G, Lonroth H, et al. Early complications after laparoscopic gastric bypass surgery: results from the Scandinavian Obesity Surgery Registry. Ann Surg 2014;260:1040-7.
126. Scandinavian Obesity Surgery Registry. Annual Report SOReg 2016 Part 1 - Operation statistics, case mix and early complications. Internet: http://www.ucr.uu.se/soreg/component/edocman/arsrapport-2016-del-1. Published April 2017 (accessed 4th February 2018).
127. Encinosa WE, Bernard DM, Du D, Steiner CA. Recent improvements in bariatric surgery outcomes. Med Care 2009;47:531-5.

128. Hogestol IK, Chahal-Kummen M, Eribe I, Brunborg C, Stubhaug A, Hewitt S, Kristinsson J, Mala T. Chronic Abdominal Pain and Symptoms 5 Years After Gastric Bypass for Morbid Obesity. Obes Surg 2017;27:1438-45.
129. Aftab H, Risstad H, Sovik TT, Bernklev T, Hewitt S, Kristinsson JA, Mala T. Five-year outcome after gastric bypass for morbid obesity in a Norwegian cohort. Surg Obes Relat Dis 2014;10:71-8.
130. Mehaffey JH, LaPar DJ, Clement KC, Turrentine FE, Miller MS, Hallowell PT, Schirmer BD. 10-Year Outcomes After Roux-en-Y Gastric Bypass. Ann Surg 2016;264:121-6.
131. Melin I. Obesitas: Handbok för praktisk klinisk behandling av övervikt baserad på beteendemodifikation och konventionell behandling, in Swedish. [Handbook for practical treatmet of obesity and metabolic syndrome based on cognitive behavior modification and conventional treatment], 1995.
132. The Norwegian Directorate of Health. Anbefalinger om kosthold, ernæring og fysisk aktivitet [Recommendations on diet, nutrition and physical activity] 2014. Internet: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/806/Anbefalinger-om-kosthold-ernering-og-fysisk-aktivitet-IS-2170.pdf (accessed 4th May 2017).
133. The Norwegian Directorate of Health. Keyhole, Healthy choices made easy. Internett: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1148/Enkelt-a-velge-sunnere-IS-0520E-engelsk.pdf (accessed 9th Oct. 2017).
134. World Health Organization. Global Recommendations on Physical Activity for Health. Internet: http://www.who.int/dietphysicalactivity/physical-activity-recommendations-18-64years.pdf?ua=1 (accessed 24th February 2017).
135. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. Int J Obes (Lond) 2006;30:391-9.
136. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. Crit Pathw Cardiol 2005;4:198-203.
137. The Norwegian Prescription Database. Internet: http://www.reseptregisteret.no (accessed 16th March 2014).
138. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.
139. Antoniades C, Shirodaria C, Leeson P, Baarholm OA, Van-Assche T, Cunnington C, Pillai R, Ratnatunga C, Tousoulis D, Stefanadis C, et al. MTHFR 677 C>T Polymorphism reveals functional importance for 5-methyltetrahydrofolate, not homocysteine, in regulation of vascular redox state and endothelial function in human atherosclerosis. Circulation 2009;119:2507-15.
140. Precoded food diary. Internet: http://www.med.uio.no/imb/english/research/groups/dietary-research-nutritional-epidemiology/dietary-research/methods/ (accessed 29th June 2016).

141. Andersen LF, Pollestad ML, Jacobs DR, Jr., Lovo A, Hustvedt BE. Validation of a pre-coded food diary used among 13-year-olds: comparison of energy intake with energy expenditure. Public Health Nutr 2005;8:1315-21.
142. Lillegaard IT, Loken EB, Andersen LF. Relative validation of a pre-coded food diary among children, under-reporting varies with reporting day and time of the day. Eur J Clin Nutr 2007;61:61-8.
143. Rimestad AH, Løken EB, Nordbotten A. Den norske matvaretabellen og beregningsdatabasen ved Institutt for ernæringsforskning, in Norwegian [The Norwegian food composition table and the database for nutrient calculations at the Institute for Nutrition Research]. Nor Epidemiol 2000;10.
144. The Norwegian Food Safety Authority, the Directorate of Helth and Social Affairs and the Department of Nutrition at the University of Oslo. The Norwegian Food Composition Table 2006. Internet: http://www.matportalen.no/verktoy/the_norwegian_food_composition_table/old_tables (accessed 12th of June 2014).
145. Solberg M, Anderssen SA. Utarbeidelse av målemetoder for måling av fysisk aktivitet. Utvikling og validering av spørreskjema for ungdom og voksne [Assessment of a method for measuring physical activity. Development and Validation of a questionnaire for adolescents and adults], 2002. Internet: http://helsedirektoratet.no/publikasjoner/utarbeidelse-av-malemetoder-for-maling-av-fysisk-aktivitet/Publikasjoner/utarbeidelse-av-malemetoder-for-maling-av-fysisk-aktivitet.pdf (accessed 24th March 2014).
146. Hustvedt BE, Svendsen M, Lovo A, Ellegard L, Hallen J, Tonstad S. Validation of ActiReg to measure physical activity and energy expenditure against doubly labelled water in obese persons. Br J Nutr 2008;100:219-26.
147. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. Atherosclerosis 2005;178:387-97.
148. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
149. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575-81.
150. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr 1990;51:241-7.
151. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG, Consort. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 2012;10:28-55.

152. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg 2014;149:275-87.
153. South-Eastern Norway Regional Health Authority. internett: https://www.helse-sorost.no/south-eastern-norway-regional-health-authority (accessed 16th November 2016).
154. Kang JH, Le QA. Effectiveness of bariatric surgical procedures: A systematic review and network meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017;96:e8632.
155. Osland E, Yunus RM, Khan S, Memon B, Memon MA. Weight Loss Outcomes in Laparoscopic Vertical Sleeve Gastrectomy (LVSG) Versus Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) Procedures: A Meta-Analysis and Systematic Review of Randomized Controlled Trials. Surg Laparosc Endosc Percutan Tech 2017;27:8-18.
156. Christiansen T, Bruun JM, Madsen EL, Richelsen B. Weight loss maintenance in severely obese adults after an intensive lifestyle intervention: 2- to 4-year follow-up. Obesity (Silver Spring) 2007;15:413-20.
157. Corcelles R, Boules M, Froylich D, Hag A, Daigle CR, Aminian A, Brethauer SA, Burguera B, Schauer PR. Total Weight Loss as the Outcome Measure of Choice After Roux-en-Y Gastric Bypass. Obes Surg 2016;26:1794-8.
158. Bradley LE, Forman EM, Kerrigan SG, Goldstein SP, Butryn ML, Thomas JG, Herbert JD, Sarwer DB. Project HELP: a Remotely Delivered Behavioral Intervention for Weight Regain after Bariatric Surgery. Obes Surg 2017;27:586-98.
159. Bradley LE, Forman EM, Kerrigan SG, Butryn ML, Herbert JD, Sarwer DB. A Pilot Study of an Acceptance-Based Behavioral Intervention for Weight Regain After Bariatric Surgery. Obes Surg 2016;26:2433-41.
160. da Silva FB, Gomes DL, de Carvalho KM. Poor diet quality and postoperative time are independent risk factors for weight regain after Roux-en-Y gastric bypass. Nutrition 2016;32:1250-3.
161. Montero PN, Stefanidis D, Norton HJ, Gersin K, Kuwada T. Reported excess weight loss after bariatric surgery could vary significantly depending on calculation method: a plea for standardization. Surg Obes Relat Dis 2011;7:531-4.
162. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 Suppl 1:S62-9.
163. Blackstone R, Bunt JC, Cortes MC, Sugerman HJ. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose, and medication status. Surg Obes Relat Dis 2012;8:548-55.
164. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, McLaughlin S, Phillips GL, 2nd, Robertson RP, Rubino F, et al. How do we define cure of diabetes? Diabetes Care 2009;32:2133-5.
165. Brethauer SA, Aminian A, Romero-Talamas H, Batayyah E, Mackey J, Kennedy L, Kashyap SR, Kirwan JP, Rogula T, Kroh M, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg 2013;258:628-36.

166. Lee WJ, Chong K, Chen SC, Zachariah J, Ser KH, Lee YC, Chen JC. Preoperative Prediction of Type 2 Diabetes Remission After Gastric Bypass Surgery: a Comparison of DiaRem Scores and ABCD Scores. Obes Surg 2016;26:2418-24.
167. de Oliveira VLP, Martins GP, Mottin CC, Rizzolli J, Friedman R. Predictors of Long-Term Remission and Relapse of Type 2 Diabetes Mellitus Following Gastric Bypass in Severely Obese Patients. Obes Surg 2018;28:195-203.
168. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:1577-85.
169. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017.
170. Park Y, Dodd KW, Kipnis V, Thompson FE, Potischman N, Schoeller DA, Baer DJ, Midthune D, Troiano RP, Bowles H, et al. Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers. Am J Clin Nutr 2018;107:80-93.
171. Cook A, Pryer J, Shetty P. The problem of accuracy in dietary surveys. Analysis of the over 65 UK National Diet and Nutrition Survey. J Epidemiol Community Health 2000;54:611-6.
172. Stea TH, Andersen LF, Paulsen G, Hetlelid KJ, Lohne-Seiler H, Adnanes S, Bjornsen T, Salvesen S, Berntsen S. Validation of a pre-coded food diary used among 60-80 year old men: comparison of self-reported energy intake with objectively recorded energy expenditure. PLoS One 2014;9:e102029.
173. Wehling H, Lusher J. People with a body mass index 30 under-report their dietary intake: A systematic review. J Health Psychol 2017.
174. Lindroos AK, Lissner L, Sjostrom L. Does degree of obesity influence the validity of reported energy and protein intake? Results from the SOS Dietary Questionnaire. Swedish Obese Subjects. Eur J Clin Nutr 1999;53:375-8.
175. Brussaard JH, Lowik MR, Steingrimsdottir L, Moller A, Kearney J, De Henauw S, Becker W, Group E. A European food consumption survey method--conclusions and recommendations. Eur J Clin Nutr 2002;56 Suppl 2:S89-94.
176. Bingham SA, Cassidy A, Cole TJ, Welch A, Runswick SA, Black AE, Thurnham D, Bates C, Khaw KT, Key TJ, et al. Validation of weighed records and other methods of dietary assessment using the 24 h urine nitrogen technique and other biological markers. Br J Nutr 1995;73:531-50.
177. Hagman U, Haraldsdóttir J, Seppänen R, Trygg K. Guidelines for the use of food record methods. Vår Föda 1990;42:supplement 3.

178. Broadfield E, McKeever T, Fogarty A, Britton J. Measuring dietary fatty acid intake:validation of a food-frequency questionnaire against 7 d weighed records. Br J Nutr 2003;90:215-20.
179. Svendsen M, Tonstad S. Accuracy of food intake reporting in obese subjects with metabolic risk factors. Br J Nutr 2006;95:640-9.
180. Pietilainen KH, Korkeila M, Bogl LH, Westerterp KR, Yki-Jarvinen H, Kaprio J, Rissanen A. Inaccuracies in food and physical activity diaries of obese subjects: complementary evidence from doubly labeled water and co-twin assessments. Int J Obes (Lond) 2010;34:437-45.
181. Westerterp KR. Doubly labelled water assessment of energy expenditure: principle, practice, and promise. Eur J Appl Physiol 2017;117:1277-85.
182. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord 2000;24:1119-30.
183. Bond DS, Jakicic JM, Unick JL, Vithiananthan S, Pohl D, Roye GD, Ryder BA, Sax HC, Wing RR. Pre- to postoperative physical activity changes in bariatric surgery patients: self report vs. objective measures. Obesity (Silver Spring) 2010;18:2395-7.
184. Bergh I, Kvalem IL, Mala T, Hansen BH, Sniehotta FF. Predictors of Physical Activity After Gastric Bypass-a Prospective Study. Obes Surg 2017.
185. Karlsson J, Taft C, Ryden A, Sjostrom L, Sullivan M. Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. Int J Obes (Lond) 2007;31:1248-61.
186. Kolotkin RL, Davidson LE, Crosby RD, Hunt SC, Adams TD. Six-year changes in health-related quality of life in gastric bypass patients versus obese comparison groups. Surg Obes Relat Dis 2012;8:625-33.
187. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. N Engl J Med 2006;355:1563-71.
188. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Intention-to-treat versus per-protocol analysis. Perspect Clin Res 2016;7:144-6.
189. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40.
190. White IR, Carpenter J, Horton NJ. Including all individuals is not enough: lessons for intention-to-treat analysis. Clin Trials 2012;9:396-407.
191. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2. ed: John Wiley and Sons Ltd, 2011.
192. Garb J, Welch G, Zagarins S, Kuhn J, Romanelli J. Bariatric surgery for the treatment of morbid obesity: a meta-analysis of weight loss outcomes for laparoscopic adjustable gastric banding and laparoscopic gastric bypass. Obes Surg 2009;19:1447-55.
193. Parri A, Benaiges D, Schroder H, Izquierdo-Pulido M, Ramon J, Villatoro M, Flores-Le Roux J, Goday A. Preoperative predictors of weight loss at 4 years following bariatric surgery. Nutr Clin Pract 2015;30:420-4.

194. Varban OA, Cassidy RB, Bonham A, Carlin AM, Ghaferi A, Finks JF, Michigan Bariatric Surgery C. Factors Associated With Achieving a Body Mass Index of Less Than 30 After Bariatric Surgery. JAMA Surg 2017;152:1058-64.
195. Gerber P, Anderin C, Thorell A. Weight loss prior to bariatric surgery: an updated review of the literature. Scand J Surg 2015;104:33-9.
196. Ochner CN, Dambkowski CL, Yeomans BL, Teixeira J, Xavier Pi-Sunyer F. Pre-bariatric surgery weight loss requirements and the effect of preoperative weight loss on postoperative outcome. Int J Obes (Lond) 2012;36:1380-7.
197. Adams TD, Pendleton RC, Strong MB, Kolotkin RL, Walker JM, Litwin SE, Berjaoui WK, LaMonte MJ, Cloward TV, Avelar E, et al. Health outcomes of gastric bypass patients compared to nonsurgical, nonintervened severely obese. Obesity (Silver Spring) 2010;18:121-30.
198. Velcu LM, Adolphine R, Mourelo R, Cottam DR, Angus LD. Weight loss, quality of life and employment status after Roux-en-Y gastric bypass: 5-year analysis. Surg Obes Relat Dis 2005;1:413-6; discussion 7.
199. Fava M. Weight gain and antidepressants. J Clin Psychiatry 2000;61 Suppl 11:37-41.
200. Roerig JL, Steffen KJ, Zimmerman C, Mitchell JE, Crosby RD, Cao L. A comparison of duloxetine plasma levels in postbariatric surgery patients versus matched nonsurgical control subjects. J Clin Psychopharmacol 2013;33:479-84.
201. De Smet J, Van Bocxlaer J, Boussery K. The influence of bypass procedures and other anatomical changes in the gastrointestinal tract on the oral bioavailability of drugs. J Clin Pharmacol 2013;53:361-76.
202. Kalarchian MA, Marcus MD, Courcoulas AP, Cheng Y, Levine MD, Josbeno D. Optimizing long-term weight control after bariatric surgery: a pilot study. Surg Obes Relat Dis 2012;8:710-5.
203. Faria SL, de Oliveira Kelly E, Lins RD, Faria OP. Nutritional management of weight regain after bariatric surgery. Obes Surg 2010;20:135-9.
204. Himes SM, Grothe KB, Clark MM, Swain JM, Collazo-Clavell ML, Sarr MG. Stop regain: a pilot psychological intervention for bariatric patients experiencing weight regain. Obes Surg 2015;25:922-7.
205. Nijamkin MP, Campa A, Sosa J, Baum M, Himburg S, Johnson P. Comprehensive nutrition and lifestyle education improves weight loss and physical activity in Hispanic Americans following gastric bypass surgery: a randomized controlled trial. J Acad Nutr Diet 2012;112:382-90.
206. Ogden J, Hollywood A, Pring C. The impact of psychological support on weight loss post weight loss surgery: a randomised control trial. Obes Surg 2015;25:500-5.
207. Papalazarou A, Yannakoulia M, Kavouras SA, Komesidou V, Dimitriadis G, Papakonstantinou A, Sidossis LS. Lifestyle intervention favorably affects weight loss and maintenance following obesity surgery. Obesity (Silver Spring) 2010;18:1348-53.
208. Sarwer DB, Moore RH, Spitzer JC, Wadden TA, Raper SE, Williams NN. A pilot study investigating the efficacy of postoperative dietary counseling to improve outcomes after bariatric surgery. Surg Obes Relat Dis 2012;8:561-8.

209. Shah M, Snell PG, Rao S, Adams-Huet B, Quittner C, Livingston EH, Garg A. High-volume exercise program in obese bariatric surgery patients: a randomized, controlled trial. Obesity (Silver Spring) 2011;19:1826-34.
210. Lier HO, Biringer E, Stubhaug B, Tangen T. The impact of preoperative counseling on postoperative treatment adherence in bariatric surgery patients: a randomized controlled trial. Patient Educ Couns 2012;87:336-42.
211. Kushner RF, Sorensen KW. Prevention of Weight Regain Following Bariatric Surgery. Curr Obes Rep 2015;4:198-206.
212. Gould JC, Beverstein G, Reinhardt S, Garren MJ. Impact of routine and long-term follow-up on weight loss after laparoscopic gastric bypass. Surg Obes Relat Dis 2007;3:627-30; discussion 30.
213. Sivagnanam P, Rhodes M. The importance of follow-up and distance from centre in weight loss after laparoscopic adjustable gastric banding. Surg Endosc 2010;24:2432-8.
214. Martins C, Kjelstrup L, Mostad IL, Kulseng B. Impact of sustained weight loss achieved through Roux-en-Y gastric bypass or a lifestyle intervention on ghrelin, obestatin, and ghrelin/obestatin ratio in morbidly obese patients. Obes Surg 2011;21:751-8.
215. Bohdjalian A, Langer FB, Shakeri-Leidenmuhler S, Gfrerer L, Ludvik B, Zacherl J, Prager G. Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin. Obes Surg 2010;20:535-40.
216. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995;332:621-8.
217. Camps SG, Verhoef SP, Westerterp KR. Weight loss, weight maintenance, and adaptive thermogenesis. Am J Clin Nutr 2013;97:990-4.
218. van Gemert WG, Westerterp KR, Greve JW, Soeters PB. Reduction of sleeping metabolic rate after vertical banded gastroplasty. Int J Obes Relat Metab Disord 1998;22:343-8.
219. Handjieva-Darlenska T, Handjiev S, Larsen TM, van Baak MA, Lindroos A, Papadaki A, Pfeiffer AF, Martinez JA, Kunesova M, Holst C, et al. Predictors of weight loss maintenance and attrition during a 6-month dietary intervention period: results from the DiOGenes study. Clin Obes 2011;1:62-8.
220. Kanerva N, Larsson I, Peltonen M, Lindroos AK, Carlsson LM. Sociodemographic and lifestyle factors as determinants of energy intake and macronutrient composition: a 10-year follow-up after bariatric surgery. Surg Obes Relat Dis 2017;13:1572-83.
221. Laurenius A, Larsson I, Melanson KJ, Lindroos AK, Lonroth H, Bosaeus I, Olbers T. Decreased energy density and changes in food selection following Roux-en-Y gastric bypass. Eur J Clin Nutr 2013;67:168-73.
222. Amundsen T, Strommen M, Martins C. Suboptimal Weight Loss and Weight Regain after Gastric Bypass Surgery-Postoperative Status of Energy Intake, Eating Behavior, Physical Activity, and Psychometrics. Obes Surg 2017;27:1316-23.

223. The Norwegian Directorate of Health. En landsomfattende kostholdsundersøkelse blant menn og kvinner i Norge i alderen 18-70 år, 2010-2011 [The third national dietary survey conducted among adults in Norway, 2010-2011]. Internet: http://helsedirektoratet.no/publikasjoner/norkost-3-en-landsomfattende-kostholdsundersokelse-blant-menn-og-kvinner-i-norge-i-alderen-18-70-ar/Publikasjoner/norkost-3-is-2000.pdf (accessed 24th March 2014).
224. Roehrig M, Masheb RM, White MA, Rothschild BS, Burke-Martindale CH, Grilo CM. Chronic dieting among extremely obese bariatric surgery candidates. Obes Surg 2009;19:1116-23.
225. Miller GD, Norris A, Fernandez A. Changes in nutrients and food groups intake following laparoscopic Roux-en-Y gastric bypass (RYGB). Obes Surg 2014;24:1926-32.
226. Silver HJ, Torquati A, Jensen GL, Richards WO. Weight, dietary and physical activity behaviors two years after gastric bypass. Obes Surg 2006;16:859-64.
227. Peters JC, Beck J, Cardel M, Wyatt HR, Foster GD, Pan Z, Wojtanowski AC, Vander Veur SS, Herring SJ, Brill C, et al. The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: A randomized clinical trial. Obesity (Silver Spring) 2016;24:297-304.
228. Bujnowski D, Xun P, Daviglus ML, Van Horn L, He K, Stamler J. Longitudinal association between animal and vegetable protein intake and obesity among men in the United States: the Chicago Western Electric Study. J Am Diet Assoc 2011;111:1150-5.
229. Aller EE, Larsen TM, Holst C, Karin Lindroos A, Kafatos A, Pfeiffer A, Martinez JA, Handjieva-Darlenska T, Kunesova M, Stender S, et al. Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12 months results. Int J Obes (Lond) 2014;38:1511-7.
230. Paddon-Jones D, Westman E, Mattes RD, Wolfe RR, Astrup A, Westerterp-Plantenga M. Protein, weight management, and satiety. Am J Clin Nutr 2008;87:1558S-61S.
231. Vatier C, Henegar C, Ciangura C, Poitou-Bernert C, Bouillot JL, Basdevant A, Oppert JM. Dynamic relations between sedentary behavior, physical activity, and body composition after bariatric surgery. Obes Surg 2012;22:1251-6.
232. Evans RK, Bond DS, Wolfe LG, Meador JG, Herrick JE, Kellum JM, Maher JW. Participation in 150 min/wk of moderate or higher intensity physical activity yields greater weight loss after gastric bypass surgery. Surg Obes Relat Dis 2007;3:526-30.
233. Adachi-Mejia AM, Schifferdecker KE. A mixed-methods approach to assessing barriers to physical activity among women with class I, class II, and class III obesity. Public Health 2016;139:212-5.
234. Talebpour A, Heidari R, Zeinoddini A, Talebpour M. Predictors of weight loss after laparoscopic gastric plication: a prospective study. J Laparoendosc Adv Surg Tech A 2015;25:177-81.

235. Shantavasinkul PC, Omotosho P, Corsino L, Portenier D, Torquati A. Predictors of weight regain in patients who underwent Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2016;12:1640-5.
236. Adams CE, Gabriele JM, Baillie LE, Dubbert PM. Tobacco use and substance use disorders as predictors of postoperative weight loss 2 years after bariatric surgery. J Behav Health Serv Res 2012;39:462-71.
237. Levine MD, Kalarchian MA, Courcoulas AP, Wisinski MS, Marcus MD. History of smoking and postcessation weight gain among weight loss surgery candidates. Addict Behav 2007;32:2365-71.
238. Filozof C, Fernandez Pinilla MC, Fernandez-Cruz A. Smoking cessation and weight gain. Obes Rev 2004;5:95-103.
239. Nimni ME, Han B, Cordoba F. Are we getting enough sulfur in our diet? Nutr Metab (Lond) 2007;4:24.
240. Elshorbagy AK, Valdivia-Garcia M, Mattocks DA, Plummer JD, Smith AD, Drevon CA, Refsum H, Perrone CE. Cysteine supplementation reverses methionine restriction effects on rat adiposity: significance of stearoyl-coenzyme A desaturase. J Lipid Res 2011;52:104-12.
241. Vinknes KJ, Dekker JM, Drevon CA, Refsum H, Nurk E, Nijpels G, Stehouwer CD, Teerlink T, Tell GS, Nygard O, et al. Plasma sulfur amino acids and stearoyl-CoA desaturase activity in two Caucasian populations. Prostaglandins Leukot Essent Fatty Acids 2013;89:297-303.
242. Hodson L, Fielding BA. Stearoyl-CoA desaturase: rogue or innocent bystander? Prog Lipid Res 2013;52:15-42.
243. Schmidt JA, Rinaldi S, Scalbert A, Ferrari P, Achaintre D, Gunter MJ, Appleby PN, Key TJ, Travis RC. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. Eur J Clin Nutr 2016;70:306-12.
244. El-Khairy L, Vollset SE, Refsum H, Ueland PM. Predictors of change in plasma total cysteine: longitudinal findings from the Hordaland homocysteine study. Clin Chem 2003;49:113-20.
245. Stipanuk MH, Dominy JE, Jr., Lee JI, Coloso RM. Mammalian cysteine metabolism: new insights into regulation of cysteine metabolism. J Nutr 2006;136:1652S-9S.
246. Pogribna M, Melnyk S, Pogribny I, Chango A, Yi P, James SJ. Homocysteine metabolism in children with Down syndrome: in vitro modulation. Am J Hum Genet 2001;69:88-95.
247. Morris AA, Kozich V, Santra S, Andria G, Ben-Omran TI, Chakrapani AB, Crushell E, Henderson MJ, Hochuli M, Huemer M, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis 2017;40:49-74.
248. Gustafson TB, Gibbons LM, Sarwer DB, Crerand CE, Fabricatore AN, Wadden TA, Raper SE, Williams NN. History of sexual abuse among bariatric surgery candidates. Surg Obes Relat Dis 2006;2:369-74, discussion 75-6.
249. Grilo CM, White MA, Masheb RM, Rothschild BS, Burke-Martindale CH. Relation of childhood sexual abuse and other forms of maltreatment to 12-month postoperative outcomes in extremely obese gastric bypass patients. Obes Surg 2006;16:454-60.

250. Khan MJ, Gerasimidis K, Edwards CA, Shaikh MG. Role of Gut Microbiota in the Aetiology of Obesity: Proposed Mechanisms and Review of the Literature. J Obes 2016;2016:7353642.
251. Sweeney TE, Morton JM. Metabolic surgery: action via hormonal milieu changes, changes in bile acids or gut microbiota? A summary of the literature. Best Pract Res Clin Gastroenterol 2014;28:727-40.
252. Conceicao EM, Machado PP, Vaz AR, Pinto-Bastos A, Ramalho S, Silva C, Arrojado F. APOLO-Bari, an internet-based program for longitudinal support of bariatric surgery patients: study protocol for a randomized controlled trial. Trials 2016;17:114.

10. Errata

Errata list, Susanna E Hanvold; Thesis: Health benefits two years after Roux-en-Y gastric bypass surgery and the effect of lifestyle intervention two to four years after surgery on weight regain and metabolic disturbances.

Page	Line	Original text	Type	Corrected text
3	20	insulin sensitivity	Correction	insulin resistance
44	31	an significant	Correction	a significant